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- Lack of Appetite
- Chronic Gastrointestinal Blood Loss
- Chronic Kidney Disease
Paraneoplastic Neurological Syndromes: What the Physician Should Know

Satish V Khadilkar¹, Bhagyadhan A Patel², Madhu Bala³

“It ain’t what you don’t know that gets you into trouble. It’s what you know for sure that just ain’t so”

Mark Twain

Introduction

Physicians deal with a wide variety of neurological conditions. Particularly in our country, where there is a great shortage of clinical neurologists, a large number of patients having neurological disorders are looked after by the physicians.¹ Common categories of diseases such as strokes, infections of the nervous system, epilepsies, headaches and movement disorders do not pose problems for the physicians. When it comes to uncommon conditions like the group we are discussing here, things get a little uncomfortable for most clinicians-physicians and neurologists alike! The spectre of rare but treatable conditions is always haunting the treating doctor. He knows that the common diseases are common and hence he will see large volume of these in his daily work, but the uncommon ones will fool him from time to time and he has to ‘catch’ these as well.

In this context, it is important to appreciate that para neoplastic neurological syndromes (PNS) exist and will make their appearance in consulting rooms of physicians once in a while. So, let us be conversant with these uncommon and intriguing neurological conditions that are potentially treatable. PNS are immune mediated manifestations of cancer and not direct results of the spread of cancer. Tumors express auto antigens that are shared with the nervous system and thus, result in antibody mediated damage to the central, peripheral or the autonomic nervous system. In the recent years, our abilities to characterize such antibodies and as a result the yield of PNS have improved.²

Is this a paraneoplastic syndrome?

In post graduate clinics and ward rounds, this question often comes up. Following are the clinical guidelines which help the diagnosis.

PNS generally precede the diagnosis of malignancy by a few months. Uncommonly, these develop in a patient known to have a cancer. The intervals between their appearance and that of cancer can be very long, stretching in years in some cases.

The clinical evolution of PNS exhibits a rapid tempo, evolving over weeks to months. Exceptionally, they are slow, going over years and such patients tend to be confused with neurodegenerative or genetic conditions.

PNS follow patterns of clinical involvements, within the central, peripheral or the autonomic nervous systems. Table 1 summarizes the well-recognized PNS. Out of these, Lambert Eaton myasthenic syndrome, sensory ganglionopathies, adult dermatomyositis and opsoclonus myoclonus syndrome are such that they evoke strong possibilities of a cancer in the body. On the other hand, presentations with ataxias and neuropathies have a wide differential diagnosis which the clinician will have to consider. In this issue of the journal authors make the important point of the clinical pattern of presentation and the tempo of the symptoms to be indicators of PNS and give illustrative cases of the classical PNS.³

A proportion of PNS are clinically less evident and are listed in table

Table 1: Well characterized PNS and associated malignancies

<table>
<thead>
<tr>
<th>Name of PNS</th>
<th>Malignancy</th>
<th>Antibodies (onconerual or neuronal cell surface)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central Nervous System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limbic encephalitis</td>
<td>SCLC, Testicular germ cell tumors, ovarian teratoma, thymoma and Hodgkin lymphoma.</td>
<td>Anti Hu, CV2/CRMP5, VGCC, Ma, Amphiphysin, AMPA, GABA, LGII, GAD-65, mGluR5.</td>
</tr>
<tr>
<td>Encephalomyelitis</td>
<td>SCLC, Breast, thymoma</td>
<td>Anti Hu, CV2/CRMP5, Amphiophyn</td>
</tr>
<tr>
<td>Cerebellar syndrome</td>
<td>Breast, SCLC, Ovary and Hodgkin lymphoma</td>
<td>Anti Hu, CV2/CRMP5, Ri, Yo, Tr, mGluR1, VGCC</td>
</tr>
<tr>
<td>Opsoclonus myoclonus syndrome</td>
<td>Neuroblastoma, SCLC, Breast and ovary</td>
<td>Anti Ri, Hu, Ma</td>
</tr>
<tr>
<td>Visual System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retinopathy</td>
<td>Melanoma, SCLC</td>
<td>Anti bipolar cell and anti-recoverin</td>
</tr>
<tr>
<td>Peripheral nervous system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensory ganglionopathy</td>
<td>SCLC, various other solid tumors</td>
<td>Anti Hu, CV2/CRMP5, VGCC</td>
</tr>
<tr>
<td>Neuromuscular junction and Muscle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lambert Eaton myasthenic syndrome</td>
<td>SCLC, lymphoma</td>
<td>Anti VGCC, Anti Hu, Sox1</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>SCLC, breast, ovarian, gastric cancer</td>
<td>Anti Tif y</td>
</tr>
</tbody>
</table>

¹Professor and Head, Department of Neurology, Bombay Hospital Institute of Medical Sciences, Mumbai, Maharashtra; ²Consultant Neurologist, Sterling Hospital, Ahmedabad, Gujarat; ³Resident, Department of Neurology, Bombay Hospital Institute of Medical Sciences, Mumbai, Maharashtra

SCLC, small-cell lung cancer; VGCC, voltage-gated calcium channel; NMDA, N-methyl-D-aspartate receptor; GABA, gamma-aminobutyric acid-B receptor; AMPA, alpha-amin-3-hydroxy-5-methyl-4-isoxazolopropionic acid receptor; VGKC, voltage-gated potassium channel, LGII, leucine-rich glioma inactivated protein-1; CASPR2, contactin-associated protein-like 2; GABA, gamma-aminobutyric acid-A receptor; mGluR5, metabotropic glutamate receptor 5; mGluR1, metabotropic glutamate receptor 1, GAD-65, glutamic acid decarboxylase
Table 2: Other presentations of PNS

<table>
<thead>
<tr>
<th>Name of PNS</th>
<th>Malignancy</th>
<th>Antibodies (onconerual or neuronal cell surface)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central nervous system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brainstem encephalitis</td>
<td>SCLC, Testicular germ cells tumors</td>
<td>Anti Hu, Ma, Ri</td>
</tr>
<tr>
<td>Characteristic Encephalitis</td>
<td>Ovarian teratoma, Rarely SCLC, breast, Hodgkin lymphoma, Testicular germ cell tumor.</td>
<td>Anti NMDA</td>
</tr>
<tr>
<td>PERM (Progressive encephalomyelitis with rigidity and myeloclonus)</td>
<td>Breast, SCLC and Hodgkin lymphoma</td>
<td>Anti amphiphysin, glycine receptor antibodies</td>
</tr>
<tr>
<td>Morvan syndrome</td>
<td>Thymoma</td>
<td>Anti-CASPR2 (VGKC)</td>
</tr>
<tr>
<td>Visual System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uveitis</td>
<td>SCLC</td>
<td>Anti CV2/CRMP5</td>
</tr>
<tr>
<td>Optic neuritis</td>
<td>SCLC</td>
<td>Anti CV2/CRMP5</td>
</tr>
<tr>
<td>Spinal cord</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stiff person syndrome</td>
<td>Breast, SCLC and Hodgkin lymphoma</td>
<td>Anti amphiphysin, glycine receptor antibodies, GAD-65</td>
</tr>
<tr>
<td>Myelitis</td>
<td>SCLC, Breast</td>
<td>Anti Hu, Amphiphysin</td>
</tr>
<tr>
<td>Peripheral nervous system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensorimotor neuropathy</td>
<td>SCLC, thymoma, breast, Multiple myeloma</td>
<td>Anti CV2/CRMP5</td>
</tr>
<tr>
<td>Mononeuritis multiplex</td>
<td>SCLC, Lymphoma, ca colon, kidney, bile duct, stomach and prostate</td>
<td>Anti Hu</td>
</tr>
<tr>
<td>CIDP with or without POEMS</td>
<td>Osteosclerotic myeloma</td>
<td>Anti VGKC (CASPR2)</td>
</tr>
<tr>
<td>Neuromyelotomy</td>
<td>Thymoma</td>
<td>Anti VGKC (CASPR2)</td>
</tr>
<tr>
<td>Neuromuscular junction and Muscle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Thymoma</td>
<td>Anti AchR, titin</td>
</tr>
<tr>
<td>Acute necrotizing myopathy</td>
<td>Solid tumor eg, SCLC, Bladder, breast, Gastrointestinal tract</td>
<td></td>
</tr>
</tbody>
</table>

SCLC, small cell lung cancer; NMDA, N-methyl-D-aspartate receptor; POEMS, polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes; CASPR2, contactin-associated protein-like 2; AChR, acetylcholine receptor.

Table 3: Differences in PNS resulting from intracellular or cell surface antigens

<table>
<thead>
<tr>
<th></th>
<th>Intracellular antigens</th>
<th>Cell surface antigens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenesis</td>
<td>T cell mediated</td>
<td>B cell mediated</td>
</tr>
<tr>
<td>Antibody specificity</td>
<td>React with all neurons of neuroaxis</td>
<td>Specific receptors</td>
</tr>
<tr>
<td>Cerebrospinal fluid inflammatory changes</td>
<td>Common</td>
<td>variable</td>
</tr>
<tr>
<td>Response to immunotherapy</td>
<td>Poor</td>
<td>Good</td>
</tr>
<tr>
<td>Cancer association</td>
<td>Always (Except GAD65)</td>
<td>Can occur with or without underlying cancer</td>
</tr>
<tr>
<td>Classical antibodies</td>
<td>Eg: Anti Hu, Ri, Yo, CV2/CRMP5, Amphiphysin, Ma, sox1, GAD65</td>
<td>Eg: NMDA, VGKC (LG1 and CASPR2), GABA-A, GABA-B, AMPA, mGluR5, mGluR1, Glycine, VGCC.</td>
</tr>
</tbody>
</table>

Table 4: Clinical clues to specific diagnosis

<table>
<thead>
<tr>
<th>Clinical clues</th>
<th>Specific antibody</th>
<th>Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young woman, psychosis, dystonia and autonomic instability</td>
<td>NMDA</td>
<td>Ovarian tumor</td>
</tr>
<tr>
<td>Older man, faciobrachial dystonic seizures</td>
<td>VGKC (LG1)</td>
<td>SCLC</td>
</tr>
<tr>
<td>Myokymia</td>
<td>VGKC (Caspr2)</td>
<td>Thymoma</td>
</tr>
<tr>
<td>Increased muscle tone, muscle spasms and hyperekplexia</td>
<td>Glycine receptor</td>
<td>Breast, SCLC</td>
</tr>
<tr>
<td>Sensory ataxia, gastroparesis and multiple regions of nervous system involved</td>
<td>Anti-Hu</td>
<td>SCLC</td>
</tr>
<tr>
<td>Daytime hypersomnolence and eye movement abnormalities</td>
<td>Anti-Ma</td>
<td>Testicular tumor</td>
</tr>
</tbody>
</table>

2. These have a wide differential diagnosis and are likely to be missed as compared to the classical syndromes. It is indeed this area where the clinician should be alert to the possibility of PNS and investigate, wading through the wide differential diagnosis.

A combination of two classical paraneoplastic syndromes in one patient is uncommon. Such combinations raise various possibilities besides PNS. A variety of system degenerations (e.g. spinocerebellar ataxias) and mitochondriopathies, more often than not, exhibit combinations of dysfunctions of parts of the nervous system. Also, when the central as well as the peripheral nervous systems are affected in the same individual, the categories of toxic, deficiency, metabolic and degenerative disorders are more likely.

Some of the antibody associated classical syndromes can occur with or without cancer, this is specifically true for antibodies against neuronal cell membrane as mentioned in Table 3, their response to treatment is better as compared to antibodies against neuronal intracellular antigens.4 5

The presence of risk factors for malignancy such as smoking or strong family history should prompt evaluation of underlying malignancy.

Some clinical clues can be useful for further workup and diagnosis of a suspected case of PNS as shown in Table 4.

How to prove PNS?

Once a paraneoplastic syndrome is clinically suspected, it is important to go over all the systems in the clinical history and examination if the patient is not already known to harbour a cancer. Appropriate antibody testing is the next step and Table 1 shows the antibody associations. In a proven case of cancer as well, we need to send the appropriate antibody studies to clarify the causal association. Presently, most laboratories offer panels of antibodies and while these are useful and cost effective, it is important to make sure that the antibodies of interest have been included. Patients with lung cancer tend to have higher proportion of incidental antibodies and thus, mere presence of antibodies is not enough to establish that a particular clinical presentation has a paraneoplastic cause. Hence, proper classification of clinical syndrome is of prime importance and antibody test results must be interpreted in this context. When serum antibodies are absent, testing antibody levels in CSF is preferred e.g. CSF NMDA level is gold standard as compared to serum assays. Table 5 mentions syndrome based evaluation.

When the clinical suspicion is strong and the cancer is not yet detected, in the present times, a whole body PET CT scan helps in the detection of the tumor. While PET CT scan can be used as a broad detection
measure, it is important to remember that all the tumors are not shown on this scan, for e.g, gonadal tumors, neuroblastoma, thymoma, prostatic carcinoma and mucosa predominant tumors can evade detection. Authors have had a patient with oesophageal carcinoma which hid from the PET CT; patient having presented with late age dermatomyositis. Another important point is that corticosteroid therapy can alter the antibody levels, which should be borne in mind.

**How to keep a vigil when PNS is suspected and cancer not detected?**

This situation calls for periodic clinical and investigative reviews. While there is no set pattern of follow-ups, one could begin with a three monthly clinical review of going over full history and clinical examination and performing clinically directed investigations. Repeating antibody levels may not serve much purpose as the severity of the syndrome does not consistently link with the antibody titers. How long to keep the follow up is a grey area and five years could be very broadly considered as adequate.

**How to treat PNS?**

PNS are not easy to treat and in the author’s experience, only a minority of patients has improved substantially. However, as there is a potential of improvement, therapy trials should be offered. Treatment of the neoplasm, (removal, chemotherapy or radiotherapy) can bring about some relief to the symptoms of PNS. While this is logical, as the tumor is believed to participate in the antibody production; there can be a lack of improvement. As PNS are antibody mediated diseases, logically, immunotherapies have been employed. When devastating neuro deficits exist, for rescue, plasma exchange or intravenous immunoglobulins can be gainfully employed, albeit for short lasting relief. Corticosteroids are the mainstay of long term maintenance of functionality; does titrated to produce best benefit and least encumbrance. The role of steroid sparing agents is unclear and has to be tailored to the individual situation which takes in to account the benefit potential and the total perspective of life expectancy and quality.

**What is the outlook?**

When a neurological paraneoplastic syndrome gets identified, it helps the search and detection of the malignancy which as yet has not announced itself and in that way, the patient may get benefits of early diagnosis. Dealing with the primary tumour and immunotherapy are known to reduce the impact of the disability but spectacular recovery or normalcy is not common. Hence the patient and family need counselling and rehabilitative programs for coping up with the disability. Chemotherapeutic agents and radiotherapies can add to the limitations (e.g neuropathy) and need to be kept in mind, while discussing the total outlook.

**References**

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Does the Tempo and Pattern of Neurological Syndrome Help Diagnose Paraneoplastic Etiology?

Pawan Ojha¹, Kamlesh Jagiasi¹¹, Akash Chheda², Girish Soni¹, Dhanashree Peddawad³, Nikhil Kadam², Sarika Patil³

Abstract

Background: Paraneoplastic neurological syndromes (PNS) are defined as remote effects of cancer that are not caused by the tumor and its metastasis, or by infection, ischemia or metabolic disruptions. In most patients, the neurological disorder is the manifesting condition and cancer is not detectable clinically at that time. Hence, most often it will be upon the neurologist and not the oncologist to detect paraneoplastic syndrome.

Aims and Objectives: To identify characteristic features of a neurological syndrome (presentation pattern and tempo of illness-onset, duration, progression and response to treatment) which indicate a paraneoplastic etiology.

Materials and Methods: This is a retrospective study. Medical records of all patients who were discharged/died in Neurology unit of a tertiary care center over a study period of two years with a diagnosis of Paraneoplastic neurological syndrome as per the diagnostic criteria given by F Graus et al¹ were studied.

Results: Seven PNS cases were identified of which, five had peripheral and two had central nervous system syndrome consistent with the anatomical localisation. Painful pure motor quadriaparesis was present in three cases. Subacute onset and rapid progression was seen in six out of seven patients. Ill sustained response to corticosteroid treatment was seen in three patients whereas the remaining four showed no response. In five patients, tumour was detected after the diagnosis of neurological syndrome, as against one patient which had an antecedent tumour and the remaining one patient had classical onconeural antibody without evidence of any detectable tumor. Average time to tumor diagnosis from neurological symptom was 3.5 months.

Conclusion: A subacute onset, rapidly progressive painful, pure motor quadriaparesis; Ganglionopathy in elderly and autoimmune encephalitis with ill sustained or no response to corticosteroids merits consideration of paraneoplastic etiology.

Introduction

Paraneoplastic neurological syndrome (PNS) is defined as remote effects of cancer that are not caused by the tumor and its metastasis, or by infection, ischemia or metabolic disruptions.² PNS is rare, affecting 1/10000 cancer patients.² PNS can present either as UMN or LMN syndrome, affecting different anatomical structures of the nervous system like brain parenchyma (Cerebellar degeneration, Encephalitis).³ In most patients, the neurological disorder is the manifesting condition and cancer is not detectable clinically at that time. Thus the neurologist has the charge of identifying a neurological disorder as paraneoplastic.² PNS are usually known to be severely disabling and so need prompt diagnosis to help early treatment of tumor.³ Many PNS are associated with antibodies (onconeural antibodies), suggesting the immune process. These antibodies are specific (more than 90%) but not sensitive, present in less than 50% patients with PNS. Thus absence of antibodies cannot rule out PNS.² Considering the rarity of PNS and the aforementioned difficulties, diagnosing PNS is challenging. Limited data is available on the characteristics of PNS from our country. The study was thus undertaken to understand the tempo and pattern of various PNS to help suspect the diagnosis of PNS which in turn can help early diagnosis of clinically occult tumour. Early diagnosis and treatment of tumor can change the tumor prognosis.

Aims and Objectives

To identify characteristic features of a neurological syndrome (presentation pattern and tempo of illness-onset, duration, progression and response to treatment) which indicate a paraneoplastic etiology.

Material and Methods

This is a retrospective study. Medical records of all patients who were discharged/died in Neurology unit of a tertiary care center over a study period of two years with a diagnosis of Paraneoplastic neurological syndrome as per the diagnostic criteria given by F Graus et al¹ were studied. The hospital protocol is to first diagnose the patient into clinical anatomical localisation syndrome based on history and examination, followed by search for etiology. Search for malignancy is done in all suspicious cases. Diagnostic modalities like CT chest, CT abdomen, whole body PET CT, MRI Brain,
serum onconeural antibodies and tissue biopsy as indicated are used in suspected cases.

Cases

1. LEMS: 32 years female had 4 months duration painful progressive asymmetric quadriparesis, diplopia, ptosis, nasal speech, facial weakness and generalised areflexia. She improved transiently with corticosteroids but later developed autonomic dysfunction i.e. postural dizziness, excess sweating and diarrhoea. NCS showed low amplitude CMAPs with normal SNAPs. RNS showed decremental response, CMAP improved post 10sec exercise and rapid RNS showed more than 100% increment thus confirming presynaptic neurotransmitter defect (Figure 1a). She improved with pyridostigmine and was continued on corticosteroids. CECT chest suggested tumour in lower lobe of left lung, biopsy confirmed small cell lung cancer (Figure 1b). She was referred to oncology centre.

2. Axonal polyradiculoneuropathy: 60 years female presented with 6 months history of painful progressive symmetric pure motor quadriparesis with generalised areflexia without cranial nerve involvement. She had skin hyperpigmentation (Figure 2b) and pedal edema. EMG-NCS showed severe axonal polyradiculoneuropathy. CSF proteins were raised. She had kidney injury (serum creatinine 2.4 mg%), anemia (Hemoglobin 7.1 gm%) and proteinuria (890 mg/24 hours). She showed good response to steroids transiently but later started deteriorating despite steroid therapy. Further evaluation with X-ray profile and whole body PET CT revealed multiple lytic bone lesions (Figure 2a), Serum protein electrophoresis with immunofixation showed M band in IgG region. Urine BJ proteins were present and serum calcium was 10.3 mg%. Bone marrow biopsy confirmed Multiple Myeloma (Figure 2c). She fulfilled the diagnostic criteria for POEMS syndrome.4 Multiple Myeloma treatment with chemotherapy showed mild improvement in her paraneoplastic syndrome.

3. Polymyositis: 62 years female was admitted with subacute history (1 month) of painful pure motor progressive symmetrical quadriparesis (mainly proximal lower limbs) with depressed deep tendon reflexes. Raised CPK 1042 IU and EMG showing myopathic
potentials with fibrillations were suggestive of myositis, which was confirmed on biopsy (Figures 3a and 3b). Patient continued to worsen despite treatment with IV steroids and developed bulbar weakness requiring feeding tube. CT chest and PET scan showed a thymoma, confirmed on open biopsy. She was referred to oncosurgery.

4. Ganglionopathy: 50 years female had subacute progressive incoordination with areflexia of upper limbs, then lower limbs and trunk over 1.5 months. NCS showed absent SNAPs in all four limbs with normal CMAP suggestive of ganglionopathy. Vitamin B12 levels, ANA blot, lip biopsy and MRI cervical spine were all normal. No response to corticosteroid therapy made us suspect a paraneoplastic etiology. PET scan revealed carcinoma breast (Figure 4) which was treated surgically. She showed mild improvement in PNS on follow up.

5. Motor Neuron Disease: 75 years male, diagnosed case of Carcinoma bladder since 1 year presented with subacute history (2 months) of progressive pure motor quadriparesis with wasting and fasciculations with exaggerated reflexes and bilateral extensor plantar responses. NCS EMG showed chronic denervation with reinnervation in cervical, lumbar and paraspinal muscles. Patient fulfilled El Escorial criteria for MND, patient showed rapid deterioration and succumbed.
in 9 months from onset of neurological symptoms. In view of subacute presentation and rapid deterioration with background history of tumour, diagnosis of paraneoplastic MND was made.

6. Auto immune limbic encephalitis: 45 years female presented with subacute (2 months) history of forgetfulness, language difficulty and change in behaviour. MRI brain showed bihemispheric fluffy hyperintense lesions without any mass effect affecting bilateral medial temporal (left more than right) and left frontal lobe (Figure 5a). CSF showed albumin- cytological dissociation, CSF NMDA and VIGK antibody were negative. She responded to immune therapy with corticosteroids and showed complete resolution of radiological lesions after 6 weeks (Figure 5b). Whole body PET CT showed anterior mediastinal hypermetabolic mass consistent with thymoma. Patient is advised thymectomy and is in remission on maintenance low dose steroids which is planned to be tapered and stopped after thymectomy.

7. Autoimmune Anti Ma Limbic encephalitis: 65 years female presented with subacute (3 months) rapidly deteriorating history of hyper-somnolesence, forgetfulness and behavioural changes. She had significant weight gain of 10 kg over last 3months. Her MRI showed bilateral medial temporal hyperintensity suggestive of limbic encephalitis and EEG showed FIRD consistent with encephalopathy (Figure 6). CSF examination was unremarkable. Anti Ma2 onconeural antibody was detected in serum. She did not have any evidence of tumour on whole body PET, CT chest and abdomen. She showed poor response to immune therapy (steroids and IVIG) and showed progressive deterioration in attention and orientation.

Paraneoplastic neurological syndrome cases have been summarised in Table 1 with regards to onset, progression and response to treatment.

**Discussion**

The study gives experience of Paraneoplastic Neurological syndrome from a tertiary care centre in India over a period of 2 years. Though PNS is rare, it can be severely disabling. Knowing the characteristics of PNS can help suspect them early and early diagnosis can improve tumour prognosis. There is not much literature on PNS from India except the case series from a centre in South India. Therefore this study is important as we bring out key features in our cases which help characterise PNS, increasing the awareness of these entity.

**Challenges in the diagnosis of PNS**

i. **Diagnosis of Tumor:** Tumor diagnosis often follows PNS diagnosis as the tumor is not apparent at presentation. In our study, only one patient was diagnosed with malignancy at presentation whereas in other patients, tumour was revealed after active search following suspicion of paraneoplastic etiology. In one patient, no tumor could be identified and patient had only presence of onconeural antibody.

ii. **Sensitivity and specificity of Diagnostic tests:** Onconeural antibody- Less than 50% patients with PNS have onconeural antibodies, however these are highly specific (>90%) for PNS.

iii. **Delay in recognition of PNS:**

a. **Lack of facilities/ experts:** Quite often the patients present to non-specialists. Rarity of this condition causes delay in diagnosis even at the hands of trained neurologists. In our study, five patients came from Interiors of state and had significant disability at the presentation.

b. **Treatment response:** Two of the five in whom steroids were started before admission showed improvement initially on treatment, but one deteriorated after 4 weeks of steroids and other worsened while steroid tapering was attempted after 6 weeks. Steroid response can delay the suspicion and diagnosis of PNS. As PNS is associated with antibodies against the neural antigens produced by the tumour, immune mechanism is suggested in some PNS and so the response to steroids or other immunotherapies can occur.

c. **Lack of awareness.** Tempo and pattern of clinical syndrome is varied, PNS can affect any part of the neuro axis. Characteristics of PNS are described below to improve awareness and increase PNS recognition.

**LEMS** is due to presynaptic neuro transmission defect, it can be paraneoplastic and is present in 1% of small cell lung cancer. It is characterised by triad of proximal painful pure motor weakness, areflexia and autonomic dysfunction. Electrophysiologically, it is triad of low amplitude CMAPs, decremental response on slow RNS and incremental response on fast RNS. Ocular and bulbar features are seen in 30% and autonomic dysfunction in 60% within 3 months of onset. Hyporeflexia/ areflexia is usually universal (90-100%), however post exercise facilitation of reflexes can be observed in only 40% of patients with LEMS. Our patient had ocular, bulbar and autonomic involvement within 4 months of onset. She had areflexia but did not show post exercise facilitation. LEMS usually responds to pyridostigmine and immune therapy, however long-term clinical and pharmacological remission has been reported in patients following successful tumour resection.

**Paraneoplastic polyneuropathies:** It can be confused with chronic inflammatory demyelinating polyneuropathy (CIDP) and in lymphomas with direct infiltration of nerves (neurolymphomatosis). Sensorimotor polyneuropathies may antedate the diagnosis of multiple myeloma and sclerotic myeloma, which are typically associated with IgG or IgA paraproteins. Recent neurophysiological studies indicate that the polyneuropathy of POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M component, and skin changes) can be differentiated from CIDP by the presence of diffuse demyelination and more severe axonal loss as was seen in our case. Lenalidomide and dexamethasone are effective to control the neuropathy of POEMS patients who are not suitable for or progress after autologous stem cell transplantation.
Sensory Ganglionopathy may present with symptoms that do not raise the suspicion of a paraneoplastic origin. A recent study on sensory ganglionopathies of different causes identified paraneoplastic cases in a group of older (>60 years) male patients with subacute onset early pain, and frequent involvement of the arms. It is a rapidly progressive autoimmune disorder commonly associated with small cell cancers due to relentless destruction of dorsal root ganglion cells by cytotoxic T cells. Because neuronal damage is irreversible, early recognition may be the only means to prevent severe neurologic disability.7

An association between polymyositis and various cancers has been reported in the literature13 but it is still debated, as the published data lacks either lung cancer histologic differentiation or biopsy-based delineation between polymyositis and dermatomyositis.14 Polymyositis should be considered as a potential presentation of paraneoplastic syndrome, especially in patients who are at risk for lung cancer. The clinical course of myopathy is closely linked with the course of cancer.14

Paraneoplastic MND has been described in the literature. It is rare and assessing for paraneoplastic ALS/MND with antibody panels does not appear useful.15,16 There is little evidence supporting a pathogenic role of cancer, lymphoma, or monoclonal gammopathy in patients with amyotrophic lateral sclerosis (ALS)/MND.17 Until there is more evidence showing benefits of immune therapy in paraneoplastic ALS, its use should be avoided.17

Limbic encephalitis: Several autoantibodies have been described in limbic encephalitis, i.e. the classical ‘onconeural’ antibodies including Anti Hu, Yo, Ri antibo...diseases.18

References

Quality of Hypertension Management in Type 2 Diabetes in India: A Multisite Prescription Audit

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Abstract

Background and Objective: Renin-angiotensin system (RAS) blockers (angiotensin converting enzyme inhibitors ACEI, angiotensin receptor blockers, ARB) are preferred drugs to control hypertension among diabetic patients. To determine frequency of RAS blocker use in hypertensive patients with type 2 diabetes, we performed a multisite study in India.

Methods: We evaluated physician prescriptions in consecutive patients with type 2 diabetes at 9 sites in India. Details of socio-demographic characteristics, clinical findings and prescription medicines were obtained. Descriptive statistics are reported.

Results: Hypertension treatment details were available in 8056 of 8699 diabetic patients (4829 men, 3227 women). No hypertension was in 3300 (40.9%), hypertension in 3625 (45.0%), and hypertension with vascular disease in 1131 (14.0%). In diabetics with no hypertension, hypertension, and hypertension with vascular disease, respectively, prescriptions of antihypertensive drugs was: RAS blockers in 19.4, 48.2 and 58.1%, beta-blockers in 4.8, 31.6 and 38.8%, calcium channel blockers in 0.4, 27.4 and 14.3% and diuretics in 0.6, 36.4 and 17.1%. ACEIs were prescribed more frequently than ARB’s in hypertensive diabetics (60.7 vs 39.2%) as well as in diabetics with vascular disease (58.6 vs 41.4%). In diabetics with hypertension (n=3625) prescription of one, two or three antihypertensive drugs was 49.8%, 33.7% and 3.5% while statins were prescribed in 54.1%.

Conclusion: Use of RAS blockers (ACEI or ARB) in uncomplicated as well as complicated hypertensive patients with type 2 diabetes is sub-optimal. Most of the patients are on one drug and prescription of ≥3 drugs are rare. Statins are prescribed in only a half.

Introduction

Hypertension management in patients with type 2 diabetes is crucial to prevent vascular complications. There is strong clinical trial and meta-analytical evidence that systolic blood pressure (BP) >140 mmHg is harmful and guidelines suggest prompt initiation and titration of therapy to achieve and maintain systolic BP <140 mmHg in most patients with diabetes.1 A meta-analysis reported that each 10 mmHg reduction of systolic BP was associated with significantly lower risk of mortality, cardiovascular events, coronary heart disease, stroke, albuminuria and retinopathy in patients with diabetes.2 Strong evidence also exists from randomized clinical trials that diastolic BP <90 mmHg is associated with decreased adverse vascular complications.2 Control of systolic and diastolic BP to these levels in all patients with diabetes has been recommended by US, European, British and many other guidelines.1,3,5 All these guidelines also advise that apart from lifestyle management, first line treatment for BP control among diabetes patients should be renin-angiotensin system (RAS) blockers, either angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs).1,3,5 Other drugs for BP control in diabetes are diuretics, calcium channel blockers (CCBs) and beta-blockers.5,6 On the other hand, some recent reviews have observed no difference in outcomes using any of the available classes of anti-hypertensive drugs and suggest use of any of these compounds.6,9 It has also been reported that most patients with diabetes need more than one drug for appropriate BP control. Guidelines also recommend use of statins in all diabetics, especially hypertensive diabetics for lowering cardiovascular risk.1

Diabetes in epidemic in India and is an important cause of morbidity and mortality.10 Global Burden of Diseases Study has reported that in India diabetes led to 3.37% of all deaths in the year 2015, up from 1.23% in 1990.11 In terms of metabolic risk factors, it is the second most important cause for loss of disability adjusted life years in India after high blood pressure.12 Better BP control can prevent 20-30% of cardiovascular mortality in patients with diabetes.1 The Oxford University based Blood Pressure Lowering Trialists’ Collaboration has reported that BP control in diabetes can lead to reduced mortality at every level of BP.13 This group also reported that use of RAS blockers (ACEIs or ARBs, but not both) is associated with 20% lower mortality compared to other drugs such as beta blockers and CCBs.14

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Received: 14.01.2017; Accepted: 18.04.2018
Hypertension management in India is characterized by low awareness, treatment and very poor control.15,16 In India Heart Watch-1 study we reported that among population-based urban subjects with diabetes, hypertension awareness was in 79.9%, treatment in 48.7% and control to BP <140/90 mmHg was in 40.7%.17 This is much more than general population based studies in India.18 In India Heart Watch-2 study we obtained treatment patterns in patients with type-2 diabetes at various sites in the country and reported a low use of statins in these patients.19 In the present prescription-audit report we report prevalence of hypertension in clinic-based patients with type-2 diabetes, types of anti-hypertensive medications in these patients and use of combination therapies.

**Methods**

We performed a multisite (n=9) registry based study in eight cities across India to determine prescription pattern of antihypertensive drugs in patients with type-2 diabetes.19 Institutional ethics committee at the central coordinating centre at Jaipur (India), approved the study. Requirement of informed consent from each patient was waived by the ethics committee because anonymized data were used for analyses. Details of methodology has been reported.19 We obtained data on successive patients attending the out-patients department as respective centres until the target of 500 patients was reached at each site. A larger sample size was available at the primary site where the proforma was piloted.

Demographic and clinical details were obtained similar to the previous India Heart Watch study.17 An abbreviated version useful for a disease registry was used in the present study.19 Socio-demographic factors were education, occupation and socioeconomic status and lifestyle factors included details of smoking and tobacco use, physical activity patterns and diet. Details of concomitant risk factors- overweight or obesity (body mass index, BMI ≥25 kg/m²), hypertension, hypercholesterolemia, hypertriglyceridemia and low HDL cholesterol as well as duration of diabetes were also obtained. Presence of microvascular diseases were ascertained from medical records with focus on diabetic retinopathy, chronic renal disease (serum creatinine ≥2.0 mg/dL) and overt diabetic foot disease. We did not obtain details of presence of microalbuminuria, proteinuria, albumin-creatinine ratio or ankle-brachial index due to lack of uniform data at all sites. Presence of macrovascular disease was obtained from the patients and included history of overt coronary heart disease, history of stroke or symptomatic peripheral arterial disease with claudication as reported earlier.19

Patients were categorized based on absence or presence of hypertension into 3 groups: Group 1 had no hypertension; Group 2 had hypertension without cardiovascular complications and Group 3 had diabetes with evidence of micro-or macro- cardiovascular disease with or without hypertension. Prescriptions were audited for various medications including anti-diabetic, anti-hypertensive and lipid lowering medications. We obtained details of type of antihypertensive medicines. These medicines were classified into drug classes including RAS blockers (ACEIs or ARBs), CCBs, beta-blockers, diuretics and others (mineralocorticoid receptor blockers (spironolactone, epleronone, etc.), alpha blockers (prazosin, etc.), centrally acting drugs (clonidine, moxindine, etc.) and others. Use of other drugs was low and hence details are not reported.

**Results**

We obtained detailed prescriptions in in 8699 patients with type 2 diabetes (men 5292, women 3407) as reported earlier.19 Details of hypertension status and anti-hypertensive therapies were available in 8056 patients (men 4829, women 3227). Recruitment at different sites has been reported19 and was Jaipur (3 sites, 42.7%), Nagpur (17.7%), Madurai (11.2%), Dibrugarh (9.2%), Lucknow (9.1%), Udaipur (6.3%) and Jodhpur (3.9%). Demographic and clinical details of the study participants have been reported.19 12% study participants were less than 40 years of age. Most of the patients had diabetes for more than 2 years and a third for

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**Table 1: Demographic and clinical characteristics of the study cohort**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Numbers with data</th>
<th>Total (N = 8699)</th>
<th>Men (N = 5292)</th>
<th>Women (N = 3407)</th>
<th>X2 test p value (male/female differences)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age-groups</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>8699, 5292/3407</td>
<td>1016(11.7)</td>
<td>625(11.8)</td>
<td>391(11.5)</td>
<td>0.635</td>
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<tr>
<td>40-49</td>
<td></td>
<td>2288(26.3)</td>
<td>1385(26.2)</td>
<td>903(26.5)</td>
<td>0.731</td>
</tr>
<tr>
<td>50-59</td>
<td></td>
<td>2815(32.3)</td>
<td>1728(32.6)</td>
<td>1087(31.9)</td>
<td>0.466</td>
</tr>
<tr>
<td>60+</td>
<td></td>
<td>2580(29.7)</td>
<td>1554(29.3)</td>
<td>1026(30.1)</td>
<td>0.558</td>
</tr>
<tr>
<td>Smoking/tobacco use</td>
<td>7695, 4678/3017</td>
<td>1633(21.2)</td>
<td>1201(25.6)</td>
<td>432(14.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Regular physical activity</td>
<td>7029, 4372/2657</td>
<td>3150(44.8)</td>
<td>2122(48.5)</td>
<td>1028(38.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Obesity, BMI ≥25 kg/m²</td>
<td>8699, 5292/3407</td>
<td>3070(35.3)</td>
<td>1773(33.5)</td>
<td>1293(37.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>8673, 5275/3398</td>
<td>4464(51.5)</td>
<td>2583(48.9)</td>
<td>1881(55.3)</td>
<td>&lt;0.001</td>
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<tr>
<td>Cholesterol≥200 mg/dL</td>
<td>3979, 2469/1510</td>
<td>1390(34.9)</td>
<td>824(33.4)</td>
<td>566(37.5)</td>
<td>0.008</td>
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<tr>
<td>LDL cholesterol ≥100 mg/dL</td>
<td>3979, 2469/1510</td>
<td>1989(50.0)</td>
<td>1193(48.3)</td>
<td>796(52.7)</td>
<td>0.007</td>
</tr>
<tr>
<td>Triglycerides ≥150 mg/dL</td>
<td>3979, 2469/1510</td>
<td>1403(35.2)</td>
<td>866(35.0)</td>
<td>537(35.5)</td>
<td>0.754</td>
</tr>
<tr>
<td>HDL&lt;40 mg/dL</td>
<td>3979, 2469/1510</td>
<td>1945(48.9)</td>
<td>1025(41.5)</td>
<td>920(60.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>Macrovascular complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Coronary heart disease</td>
<td>7131, 4391/2740</td>
<td>1099(15.4)</td>
<td>720(16.4)</td>
<td>379(13.8)</td>
<td>0.003</td>
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<tr>
<td>Others (stroke, PAD)</td>
<td>372(3.2)</td>
<td>232(3.5)</td>
<td>140(5.1)</td>
<td>0.743</td>
<td></td>
</tr>
<tr>
<td>Microvascular diseases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retinopathy</td>
<td>4851, 2992/1859</td>
<td>298(6.1)</td>
<td>183(6.1)</td>
<td>115(6.1)</td>
<td>0.994</td>
</tr>
<tr>
<td>Others</td>
<td>670(13.9)</td>
<td>424(14.2)</td>
<td>246(13.2)</td>
<td>0.357</td>
<td></td>
</tr>
<tr>
<td>Chronic renal disease (serum</td>
<td>6381, 3915/2466</td>
<td>356(5.6)</td>
<td>267(6.8)</td>
<td>89(3.6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Numbers in parentheses are percent; BMI body mass index; LDL low density lipoprotein; HDL high density lipoprotein; PAD peripheral arterial disease;
longer than 5 years. Risk factor details were available in most patients (Table 1) and showed that smoking and/or tobacco use was one-fifth while moderate to high physical activity in less than half. Hypertension was in 51.5%, total cholesterol ≥200 mg/dl in 34.9%, LDL cholesterol ≥100 mg/dl in 50.0%, triglycerides ≥150 mg/dl in 35.2% and low HDL cholesterol in 48.9%. Macrovascular complications such as coronary heart disease was in 15.4% and others (stroke, large vessel peripheral arterial disease) in 5.2% while macrovascular complications such as retinopathy, diabetic foot or advanced chronic renal disease (creatinine ≥2.0 mg/dl) was in 6.1%, 13.9% and 6.8% respectively.

Clinical characteristics in those without hypertension (n=3300, 40.9%), with hypertension (n=3625, 45.0%) and with cardiovascular disease with/without hypertension (n=1131, 14.0%) are shown in Table 2. Patients with hypertension with or without cardiovascular disease were significantly older and had greater diabetes duration. Prevalence of various risk factors was lower in group with hypertension and cardiovascular disease (Table 2).

Prescription of various classes of anti-hypertensive drugs in the total cohort was: RAS blockers (ACEIs or ARBs) in 3045 (37.8%), beta-blockers in 1705 (21.2%), calcium channel blockers 1163 (14.4%), and diuretics in 1523 (18.9%). Details of prescriptions of various classes of anti-hypertensive drugs in diabetics without hypertension, with hypertension and with macrovascular or microvascular cardiovascular disease are shown in Table 3. Among hypertensive diabetics, the commonest anti-hypertensive drug prescribed were RAS blockers followed by diuretics, calcium channel blockers and beta-blockers. Among diabetics with cardiovascular disease, the commonest antihypertensive drugs were also RAS blockers followed by beta blockers, calcium channel blockers and diuretics. RAS blockers were prescribed in 19.4% non-hypertensive diabetics, 48.2% hypertensive diabetics and 58.1% diabetics with cardiovascular disease (Figure 1). ACE inhibitors were prescribed more frequently as compared to ARB’s in all the three groups. Ratio of ACEI:ARB in various groups was 64:36 in non-hypertensive diabetics, 56:44 in hypertensive diabetics, 59:41

Table 2: Demographic and clinical characteristics of diabetic patients without hypertension, with hypertension and hypertension with cardiovascular disease

<table>
<thead>
<tr>
<th>Variables</th>
<th>Without hypertension</th>
<th>Hypertension</th>
<th>Hypertension and CVD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men (N=2075)</td>
<td>Women (N=1225)</td>
<td>Total (N=3300)</td>
</tr>
<tr>
<td></td>
<td>Men (N=2050)</td>
<td>Women (N=1575)</td>
<td>Total (N=3625)</td>
</tr>
<tr>
<td></td>
<td>Men (N=704)</td>
<td>Women (N=427)</td>
<td>Total (N=1131)</td>
</tr>
<tr>
<td>Age-groups</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>318(15.3)</td>
<td>164(13.4)</td>
<td>482(14.6)</td>
</tr>
<tr>
<td>40-49</td>
<td>628(30.3)</td>
<td>408(33.3)</td>
<td>1036(31.4)</td>
</tr>
<tr>
<td>50-59</td>
<td>645(31.1)</td>
<td>378(30.9)</td>
<td>1023(31.0)</td>
</tr>
<tr>
<td>60+</td>
<td>484(23.3)</td>
<td>275(22.4)</td>
<td>759(23.0)</td>
</tr>
<tr>
<td>Diabetes duration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2yr</td>
<td>209(10.1)</td>
<td>149(12.1)</td>
<td>358(10.8)</td>
</tr>
<tr>
<td>2-5yr</td>
<td>570(27.4)</td>
<td>339(27.6)</td>
<td>909(27.5)</td>
</tr>
<tr>
<td>&gt;5yr</td>
<td>372(17.9)</td>
<td>211(17.2)</td>
<td>583(17.7)</td>
</tr>
<tr>
<td>Smoking/tobacco use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>520(25.1)</td>
<td>185(15.1)</td>
<td>705(21.3)</td>
</tr>
<tr>
<td>Physical active</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>834(40.2)</td>
<td>383(31.2)</td>
<td>1217(36.9)</td>
</tr>
<tr>
<td>Obesity, BMI ≥25 kg/m²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>751(36.2)</td>
<td>502(41.0)</td>
<td>1253(37.9)</td>
</tr>
<tr>
<td>Cholesterol≥200 mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>399(19.2)</td>
<td>264(21.5)</td>
<td>663(20.1)</td>
</tr>
<tr>
<td>LDL cholesterol ≥100 mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>656(31.6)</td>
<td>424(34.6)</td>
<td>1080(32.7)</td>
</tr>
<tr>
<td>Triglycerides ≥150 mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>371(17.9)</td>
<td>198(16.1)</td>
<td>576(17.2)</td>
</tr>
<tr>
<td>HDL&lt;40/50 mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>504(24.3)</td>
<td>435(35.5)</td>
<td>939(28.4)</td>
</tr>
</tbody>
</table>

Table 3: Antihypertensive and other medications in various groups of diabetics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Without hypertension</th>
<th>Hypertension</th>
<th>Hypertension and CVD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men (N=2075)</td>
<td>Women (N=1225)</td>
<td>Total (N=3300)</td>
</tr>
<tr>
<td></td>
<td>Men (N=2050)</td>
<td>Women (N=1575)</td>
<td>Total (N=3625)</td>
</tr>
<tr>
<td></td>
<td>Men (N=704)</td>
<td>Women (N=427)</td>
<td>Total (N=1131)</td>
</tr>
<tr>
<td>Anti-hypertensive drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAS blockers</td>
<td>410(19.8)</td>
<td>231(18.9)</td>
<td>641(19.4)</td>
</tr>
<tr>
<td>ACEI</td>
<td>283(69.0)</td>
<td>127(55.0)</td>
<td>410(63.9)</td>
</tr>
<tr>
<td>ARB</td>
<td>127(30.9)</td>
<td>104(45.0)</td>
<td>231(36.0)</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>84(5.2)</td>
<td>38(4.1)</td>
<td>122(4.8)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>04(0.2)</td>
<td>03(0.5)</td>
<td>07(0.4)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>05(0.2)</td>
<td>05(0.8)</td>
<td>10(0.6)</td>
</tr>
<tr>
<td>Other drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-diabetes drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>242(11.7)</td>
<td>115(9.3)</td>
<td>357(10.8)</td>
</tr>
<tr>
<td>OAD</td>
<td>1029(49.5)</td>
<td>600(49.0)</td>
<td>1629(49.3)</td>
</tr>
<tr>
<td>Anti-platelets</td>
<td>400(19.3)</td>
<td>210(17.1)</td>
<td>610(18.5)</td>
</tr>
<tr>
<td>Lipid lowering</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>1195(57.6)</td>
<td>662(54.0)</td>
<td>1857(56.3)</td>
</tr>
<tr>
<td>Fibrates</td>
<td>55(2.6)</td>
<td>25(2.0)</td>
<td>80(2.4)</td>
</tr>
</tbody>
</table>

22 Journal of The Association of Physicians of India • Vol. 66 • September 2018
in diabetics with cardiovascular disease (Table 3). Beta-blockers were prescribed in almost similar proportions in hypertensive diabetics without or with cardiovascular disease while CCB’s and diuretics were prescribed more in simple hypertensives without cardiovascular disease (Table 3). Prescription of insulin was low in all the three groups. Anti-platelet drugs were prescribed mostly in diabetics with cardiovascular disease (61.3%). Statin prescriptions were significantly greater in those with cardiovascular disease (62.0%) as compared to diabetics without hypertension (56.3%) and with hypertension (54.1%) (p<0.05).

**Mono-therapy with an antihypertensive drug** was the most frequent type of prescription in all the three groups and was in 18.1% in diabetics without hypertension, 49.8% in hypertensive diabetics and 42.5% in diabetics without hypertension, 49.8% in hypertensive diabetics and 42.5% in diabetics without hypertension (Group 1), with cardiovascular disease (Group 2), and with/without hypertension (Group 3) (Figure 2).

![Fig. 1: Prescriptions of various anti-hypertensive drug classes in diabetics without hypertension (Group 1), diabetics with hypertension (Group 2), and diabetics with cardiovascular disease and with/without hypertension (Group 3)](image1)

![Fig. 2: Prescriptions of one drug, two drugs or three drugs in diabetics without hypertension (Group 1), with hypertension (Group 2), and with cardiovascular disease (Group 3)](image2)

Discussion

This multisite prescription audit among diabetes patients in India shows that renin-angiotensin system blocking drugs, ACE inhibitors or ARBs, are the most frequently prescribed anti-hypertensive drugs in these patients. The prescription of this class of drugs is much lower than optimal compared to various international clinical practice guidelines (Table 3). Mono-therapy is the most common and BP control is observed in only a third of diabetic patients with hypertension.

Blood pressure control in diabetics can be achieved by combination of health-promoting lifestyles (regular physical activity, healthy diet, smoking cessation) and drug therapies. Most of the current guidelines advise that RAS blockers should be the first line treatment of hypertension in these patients (Table 3). On the other hand, some meta-analysis suggest that any class of drugs is appropriate as long as BP is under control.8 Our study shows that there is a low use of RAS blockers (ACEIs or ARBs) in patients with uncomplicated hypertension in diabetics in India. Although the prescriptions of RAS blockers was greater in diabetic hypertensives than diabetic patients with hypertension. Controlled BP was in 387 (31.7%) diabetic hypertensives. When BP control was defined by systolic BP less than 140 mmHg it was in 425 (34.8%) patients.

![Table 4: Quality gaps in management of hypertension in diabetes in the present study compared to international guidelines](table4)

<table>
<thead>
<tr>
<th></th>
<th>ADA 2016</th>
<th>EASD 2016</th>
<th>JNC-8 2014</th>
<th>ESC/ESH 2013</th>
<th>British NICE 2011</th>
<th>Present study</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAS blockers</td>
<td>&gt;90%</td>
<td>&gt;90%</td>
<td>&gt;90%</td>
<td>&gt;90%</td>
<td>&gt;90%</td>
<td>48.2</td>
</tr>
<tr>
<td>Statins in high risk diabetes</td>
<td>&gt;90%</td>
<td>&gt;90%</td>
<td>&gt;90%</td>
<td>&gt;90%</td>
<td>&gt;90%</td>
<td>54.1</td>
</tr>
<tr>
<td>Aspirin in uncomplicated diabetes</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>15.8</td>
</tr>
</tbody>
</table>

practice.24 Only a few studies in India have reported prescription patterns in patients with hypertension25,26 but we could not find any recent study that has focused on anti-hypertensive drugs in diabetics, hence our data are not locally comparable. A study among elderly diabetics with hypertension in China has reported much greater use RAS blockers.27 In this study, the most commonly prescribed drugs were RAS blockers (77%), followed by CCBs (65%) and β-blockers (45%). Combinations of two drugs was the most common way in antihypertensive medication (41%) and three drugs or more was in 29%. In contrast to our study, combinations of CCB and ARB were the more common in the Chinese study.

The ACCORD study has reported that level of BP control in patients with diabetes should be 130–140 mm Hg systolic and 85–90 mmHg diastolic and lower levels are associated with greater cardiovascular events.28 A tighter control has been suggested in the past by various international guidelines5,7 but following the publication of ACCORD study most have revised the targets for BP control in patients with diabetes.12 In the ACCORD study the most common anti-hypertensive drugs were RAS blockers followed by thiazide-like diuretics and CCBs.29 However, more than 80% of patients were on RAS blockers, much more than the present study.

Our study has a number of limitations. We have evaluated prescription patterns of qualified endocrinologists, diabetologists and physicians at secondary and tertiary care.19 To really assess the prescriptions of various anti-hypertensive drugs in diabetes there is a need for audit of larger number of physicians in primary and secondary care. Hypertension is very common in primary care and there are large variations in practice patterns.29 Secondly, we did not inquire reasons for low use of RAS blockers as well as poor diabetes control in these patients. The study was targeted at practices where reliable data are quickly available and a larger study involving many more physicians is planned to overcome this study limitation Thirdly, level of control of BP can only be assessed by a prospective registry and we used data obtained in a cross sectional study. The current clinic BP may not be the ideal one and a study has reported that home BP or ambulatory BP are more reliable that office BP in predicting outcomes.30 Poor control of BP could be due to non-adherence to anti-hypertensive medication. This is an important problem not only in low- and middle-income countries where it has been reported in more than half of patients (63%).31 Non-adherence to antihypertensive medication is also observed in Western European countries and the US.32 Other indications are small and non-uniform number of patients at each site, lack of standardized treatment, unavailability of drug dose and absence of outcomes data. These data can be obtained only in a larger and well-funded study and ours is a pragmatic study (registry) with limited budget. Our study shows that there is a need to disseminate healthcare related information to practicing physicians so that optimal drug/s are prescribed and targets are achieved in diabetic patients. This is all the more important at primary care and secondary care levels where it is likely that in patients with diabetes the prescriptions of RAS blockers are lower and BP control is poorer that the present study.33

In conclusion this is one of the first large multi-city study that has evaluated anti-hypertensive drug prescriptions, use of combination therapy and level of BP control in patients with diabetes. The results show a sub-optimal prescriptions of RAS blockers (ACE inhibitors or ARBs). Single drug use is high and there is a poor control of hypertension. Policies focused on physician education and continuous prescription audits are needed to better control hypertension not only in diabetics but in all patients with hypertension.

References

Outcomes of Implementing the Central Venous Catheter Bundle at a Tertiary Care Hospital in North India, at AIIMS, New Delhi

Shanmugam Krishnan1, Arvind Kumar2, Prayas Sethi3, Manish Soneja3, Immaculata Xess4, Arti Kapil5, RM Pandey6, Naval K Vikram7, Ashutosh Biswas7, Naveet Wig7*

Abstract

Introduction: Central venous catheter (CVC) associated infection are many times higher in India compared to western countries. A group of interventions called as CVC bundle, if implemented effectively prevents CVC related complication.

Methodology: Our study was a prospective quasi-experimental study. The study evaluated the level of compliance with the central venous catheter bundle in the management of patients in our Medicine wards and Intensive care unit (ICU).

Results: In the study, the incidence of central line associated bloodstream infection (CLABSI) was zero and the incidence of pneumothorax was 5%. Most of the patients had higher Acute physiology and chronic health evaluation (APACHE II) at baseline and multi organ dysfunction. The compliance with whole CVC bundle improved from 0% at baseline to 10% in post-intervention phase. Compliance of many components increased significantly in the post intervention period. These were Hand washing before insertion (15% to 72.5%, p<0.001), Maintenance (0% to 52.5%, p<0.001), Prompt removal of catheters (40% to 70%, p=0.007), Skin antisepsis with chlorhexidine increased approaching significance (0% to 12.5%, p=0.055). Avoidance of femoral catheters was done in more than 95% of the cases. The predictors of mortality were higher APACHE II (OR 1.23 [CI 1.03-1.47], p=0.020) and duration of hospital stay (OR 0.87 [CI 0.78-0.97], p=0.022).

Conclusion: This study done at All India Institute of Medical Sciences showed improved outcome in terms of catheter infection and mechanical complications. CVC bundle compliance increased significantly though adherence to full bundle was less. In future, with rectification of barriers to bundle completion, the compliance with CVC bundle can be further improved.

Introduction

Healthcare – associated infection (HAI) as defined by CDC is a localized or systemic condition resulting from an adverse reaction to the presence of an infectious agent or its toxin that was not present on admission to the acute care facility.1 Healthcare-associated infections from invasive medical devices in the intensive care unit (ICU) particularly CLABSI has been shown to pose the greatest threat to patient safety, hospital cost and stay.2 Device associated infections in developing countries are up to 13 times higher than in USA.3 Studies done in the developed countries have shown that strict institutional protocol

33. Gupta N, Kedar HS, Pawan RB. Strategies for better hypertension control in India and other lower-middle income countries. J Assoc Physicians India 2016; 64:38-64.
with frequent quality evaluation for aseptic control practices decreases the incidence of CLABSI. A bundle is a group of interventions related to a disease process, that when executed together, produce better outcomes than when implemented individually. Numerous studies done in the developed countries have shown that proper implementation of evidence based practices grouped together as central venous catheter bundle had brought a dramatic reduction in the incidence of CLABSI. Studies to evaluate compliance of the same in Indian settings. Indian studies have limited and there are no studies to evaluate compliance of the same in Indian settings.

**Methods**

**Setting**

The study was conducted in Medicine ICU and Emergency wards of All India Institute of Medical Sciences, New Delhi after getting an ethical clearance from hospital ethical committee. It was conducted from January 2013 to October 2014, as quality improvement interventional study on a Quasi-Experimental pre-post Design model with three phases; Pre-intervention phase (Nine months of assessment of current practices in the CVC insertion, maintenance and removal), Quality improvement or Intervention phase (Three months of sensitisation, education and feedback to residents regarding guideline based protocol in CVC insertion, maintenance and removal via discussion, lectures, posters, notes distribution, What’s app on Institute for Healthcare Improvement (IHI) bundle and American Society of Anaesthesiologists (ASA) insertion checklist. Each quality indicator was assigned as 1 if graded correctly, 0 if not done correctly.

**Description and definitions**

The Quality indicators were defined for the comparison between pre-intervention and post-intervention phases. Quality indicators were based on Institute for Healthcare Improvement (IHI) bundle and American Society of Anaesthesiologists (ASA) insertion checklist. Each quality indicator is described here in detail separately. Blood cultures and central line tips were sent for cultures at the time of removal or when there was a suspicion for CLABSI.

**Quality Indicators used in the study**

1. **Hand washing:** Hand washing was considered as optimal when alcohol based rub was used optimally as defined by WHO and CDC guidelines during central line insertion.

2. **Full barrier precautions:** Full barrier precautions included the use of sterile body drape, cap, mask, gown and sterile gloves and the status was maintained throughout the procedure. No contact with aseptic devices were allowed.

3. **Cleaning the skin with povidone iodine/ Chlorhexidine:** Cleaning the skin was considered optimal when the insertion site was cleansed with alcoholic chlorhexidine which was allowed to dry before insertion. In case of non-availability of chlorhexidine, povidone iodine 10% aqueous solution which was available commonly was assessed with the use of alcoholic disinfectant.

4. **Maintenance:** In maintenance parameters assessed were dressings at the site of catheter, dressing changes made in accordance with the current recommendations. Along with assessment of ports in which aseptic technique was followed with proper hand washing and cleaning the hub with alcohol soaked swab or gauze before access to the ports.
5. **Prompt removal of catheters**: Prompt removal of catheters was assessed by a daily assessment of catheter need and the delay to removal in days was also noted.

6. **Avoidance of femoral catheters**: Catheter site of insertion was noted.

### Complications

**Pneumothorax**

Pneumothorax is air in the pleural cavity. It can be diagnosed by chest x ray or USG chest. In our study, pneumothorax was diagnosed by a radiologist with chest x rays.

**Arterial puncture**

Arterial punctures were defined in our study when bright red pulsatile flow was noted during needle insertion. ABG and USG were also used if doubt arises.

**Hematoma**

Hematoma was defined in our study as an area greater than 3 cm of bruising or swelling around the site of insertion.

### Statistical Analysis

All data collected were entered in Microsoft Excel spreadsheet and the data was analysed using STATA software version 11.0. Pearson Chi-square test/ Fischer exact test was used for analysis of categorical data. Unpaired student t-test was used for analysis of continuous data in normal distribution. Wilcoxon Mann–Whitney test was used to compare data in skewed distribution. For skewed variables, data were presented as median (minimum-maximum). Univariate and multivariate logistic regression was performed for predictors of mortality. Multivariate analysis was done for variables with a p value of less than 0.20 on Univariate logistic regression. A p value of less than 0.05 was considered significant.

### Results

A total of 156 patients were screened in both the phases and 76 patients were excluded as 52 patients had a dialysis catheter in addition to triple lumen catheter and 24 patients had central line inserted by others (Figure 1). The mean age of the study population was 43.75 years and 48.78 years in the pre-intervention and post-intervention group respectively. The male and female sex distribution in pre-and post-intervention phase was 52.5%, 47.5% and 55%, 45% respectively.

The characteristics of both the groups like APACHE II, hemoglobin, total leucocyte count, platelet count and diastolic BP were comparable in both groups except for systolic BP, creatinine and urea which were significantly higher in the post intervention group at the time of admission (Table 1).

Comorbidities in both the phases like hypertension, hypothyroidism, connective tissue disease, Coronary artery disease, tuberculosis, Malignancy, congestive heart failure, cerebrovascular accident and COPD were comparable and the difference wherever was not significant.

The most common indication of central line at the time of insertion in pre-intervention and post-intervention group was hypotension (62.5% and 52.5%) requiring central venous (CVP) pressure monitoring and inotropic requirement followed by acute kidney injury (AKI) requiring CVP (30 and 40%) for fluid administration. Absence of peripheral lines constituted 6 cases in 7.5 and 7.5% respectively in two phases. Central lines were inserted most commonly in ward followed by ICU and in emergency ward around 42.5%/45%,30%/27.5% and 27.5%/27.5% respectively in pre/post intervention phase. There was no significant difference between the places of insertion. USG guidance during central line insertion was used only for internal jugular insertion in 78.57% and 96.88% in both the phases.

**Comparison of Bundle implementation phases and compliance**

Patient characteristics were summarized as previously described. Parameters were comparable except for creatinine, urea, systolic BP and COPD. Indications for central line were similar in both the phases.

At baseline, compliance with all the 6 parameters in combination were nil. There was vast scope of improvement in each and every sector of the bundle. The only indicator which was above 50% was avoidance of femoral catheters which was done in all the patients except for one patient in each of the groups (Figure 7); the site of insertion in phase 1/phase II were IJV,subclavian and femoral were 35%/80%, 65% /17.5% and 2.5% /2.5% respectively. Out of the six individual components of the bundle three showed statistically significant improvement in the post intervention period. These bundle components were hand washing before insertion (15% in phase 1 to 72.5% in phase 2, p<0.001) as shown in figure 2,
Maximum sterile barrier precautions (n = 80)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proper skin antisepsis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>with chlorhexidine/ povidone iodine (n=80)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dressing</td>
<td>28(70%)</td>
<td>36(90%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Dressing change</td>
<td>22(55%)</td>
<td>33(82.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>Ports</td>
<td>0(0%)</td>
<td>22(55%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Trendelenburg position</td>
<td>35(87.5%)</td>
<td>32(80%)</td>
<td>0.36</td>
</tr>
<tr>
<td>Patency checked</td>
<td>32(80%)</td>
<td>33(82.5%)</td>
<td>0.77</td>
</tr>
<tr>
<td>No of attempts</td>
<td>1(1-6)</td>
<td>1(1-3)</td>
<td>0.034</td>
</tr>
<tr>
<td>(Median min-max) by USG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>X ray done</td>
<td>36(90%)</td>
<td>37(92.5%)</td>
<td>0.69</td>
</tr>
<tr>
<td>Documentation</td>
<td>10(25%)</td>
<td>27(67.5%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Days delayed for removal</td>
<td>1(0-6)</td>
<td>0(0-4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Median (min-max)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Complications

Insertion complications

Insertion complications assessed in the study were hematoma, arterial puncture, pneumothorax and tip malposition. Although all the complications decreased in the post intervention period, only tip malposition (26 vs 25 with p value =0.041) achieved statistical significance. All 4 pneumothoraxes (3 in pre-intervention period vs. 1 in the post intervention period, p=0.615) that occurred in the study were diagnosed by chest X rays and required ICD insertion. There was a total of 3 hematomas in pre-intervention period ascompared to 2 in the post intervention period (p≠ 1.0).

Arterial punctures occurred in both the phases (5 in phase 1 vs. 4 in phase 2, p=1.0). None of the arterial punctures had a significant hematoma or complication. Tip malposition also occurred frequently in the study (52.5% in phase 1 vs. 37.5% in phase 2, p=0.041). The most common tip malposition was tip below the level of carina for right sided catheters. The only significant individual predictor of insertion complications was number
of attempts (number of attempts>1, p<0.001).

The mean number of attempts in pneumothorax was 3.25±1.89 as against 1.33±0.08 in patients who did not have a pneumothorax. The mean number of attempts in arterial punctures was 2.78±0.52 as against 1.28±0.07 in patients who did not have it. The mean number of attempts in hematoma was 3.2±0.73 as against 1.33±0.07 in patients who did not have it. The mean number of attempts were significantly higher in patients who developed insertion complications. There were no independent predictors of arterial punctures or tip malposition.

**Maintenance complications**

Infectious complications were also assessed. There was no CLABSI or Catheter-related bloodstream infection (CRBSI) observed in this study. However, catheter infection as defined above decreased from 3 to 1 in the post intervention period, even though it did not attain statistical significance (Figure 10). In the catheter infection, two were diagnosed by clinical criteria and their fever responded promptly within 48 hours of removal of the catheter and empirical antibiotics. Another two patients grew MRSA on catheter tip and these two patients were treated with vancomycin for 2 weeks. There was 1 case of Enterobacter colonization and one case of Candida colonization in pre-intervention period, 1 case of Acinetobacter colonization in post intervention period, 2 cases of contamination in intervention period and 2 in the post intervention with all being Gram positive cocci. Blood cultures were sterile in all patients with catheter infection, colonization and contamination. There were only 4 blood cultures positive in the entire study as blood cultures before antibiotics were sent only in 15% of patients. All the 4 cases were secondary bloodstream infections with pneumonia, 2 being community acquired, 1 each of VAP and HAP.

None of the predictors of catheter tip infection were statistically significant except for the number of attempts which was more in patients who developed catheter tip infection. Even though improper hand washing, improper skin antisepsis and number of attempts were more in the catheter tip infection these were not statistically significant probably due to the low incidence of catheter tip infection and small sample size. The whole bundle compliance increased from 0% to 10% in the post intervention period. However, if proper skin antisepsis with povidone iodine is included, it improved from 0% to 17.5%.

**Impact on Hospital mortality**

None of the catheter complications had a significant impact on hospital mortality. The independent predictors of hospital mortality for all the patients combined were AKI, septic shock at admission, higher APACHE II and intubated patients. The mean duration of hospital stay was lower in the patients who died probably due to higher APACHE II at admission and hence the mean duration of catheter days was also lower in the patients who died. Univariate and multivariate logistic regression was also done for mortality predictors. All patients who died were on ventilators and hence logistic regression was not possible. Each unit increase in APACHE II conferred an odds ratio of 1.23 for mortality. Duration of hospital stay and number of catheter days correlated inversely with mortality probably due to early deaths as expected in septic shock patients. On multivariate logistic regression, only APACHE II and duration of hospital stay were independent predictors of mortality.

**Discussion**

This study was conducted in the medicine wards and ICU of All India Institute of Medical Sciences, New Delhi, a tertiary level hospital in India to assess the level of compliance at the baseline with CVC bundle. The study also assessed the improvement in compliance with bundle quality indicators following intervention in the form of physician education and feedback. Baseline characteristics were comparable for both the groups. Quality indicators improved from 0% in the baseline to 10% in the post intervention phase. Proper hand washing, prompt removal of catheters and maintenance improved significantly in the post intervention period.

Evaluation of the data collected in the baseline phase revealed that compliance with individual bundle components was low for most of the components. Compliance was greater than 50% only for avoidance of femoral catheters. This parameter was achieved in 97.5% of all cases. Prompt removal of catheters was relatively better than other parameters, being practiced in 40% of all patients. Proper hand washing was practiced in only 12.5% of all catheter insertions during pre-intervention period. This is in accordance with multiple studies emphasizing that proper hand washing is done in less than 40% of all insertions. During the post intervention period, hand washing improved significantly to 72.5%. This is in accordance with a study done by Zingg et al. who observed that hand washing improved from 59% in baseline to 65% in intervention period, even though proper hand washing in that study improved from 22.5% to 42.6%, p= 0.003. A quasi-experimental study conducted by Apisarnthanarak et al. in Thailand also showed improved adherence to central line bundle particularly hand hygiene improved significantly after intervention from 8% to 54% and CABSI decreased significantly from 14 per 1000 catheter days to 1.4 per 1000 catheter days. Maximum sterile barrier
precautions were practiced in 10% of catheter insertions only. This is in accordance with a study done by Perez Parra et al. who reported that maximum sterile barrier precautions were the least practiced and was less than 50% even among experienced physicians and it improved significantly after educational intervention. In the post intervention period, it improved to only 22.5% probably due to the limited availability of gown and cap in emergency and wards. The use of mask, however improved significantly from 30% to 72.5% in the post intervention period. Proper skin antisepsis with chlorhexidine was not practiced in any patient during pre-intervention period. This was partly due to poor availability of 2% chlorhexidine in emergency and medicine wards of our hospital. This was in accordance with a study done in Yemen which showed that none of the ICU units had 2% chlorhexidine solutions. However, even povidone iodine was not used correctly.

International Nosocomial Infection Control Consortium (INICC) study done in 15 developing countries also showed improvement in chlorhexidine antisepsis from 7% to 27%, p<0.001. In our study, although chlorhexidine usage increased to 12.5%, still povidone iodine was used most commonly due to ease of availability of povidone iodine.

Maintenance parameters significantly improved from 0% in the baseline to 52.5% in the post intervention period. Proper dressing was done in 65% of all catheter insertions. This is in accordance with a study conducted in Yemen by Al-Sayaghi who found that the most frequently practiced correct parameter in central line bundle was hand washing and dressing materials. The use of ports defined as scrubbing the hub with alcohol based scrub improved significantly from 0% in the pre-intervention period to 52.5% in the post intervention period. Miller et al. conducted a prospective study in 29 pediatric ICUs and found that maintenance bundle improved significantly from 65% in the baseline to 82% in the post intervention period, resulting in a decrease in CLABSI rates by 43% with maintenance bundle being the only independent predictor. In our study, maintenance bundle compliance was less probably due to increased workload of the residents and the nursing staff. Prompt removal of catheters was done in 40% of cases in pre-intervention period, which improved significantly to 70% in the post intervention period. The number of idle catheter days decreased significantly from a mean of 1.65 catheter days from the baseline to 0.5 catheter days in the post intervention period. Burdeu et al. conducted a study in which approximately 26.2% of CVC days were idle, thus prompt removal of catheters was not done. In a similar study done by Ilan et al., there was a significant decrease in the proportion of patients with nonessential CVC days from 51% to 26% after the intervention.

Pneumothorax occurred in 4 cases (5%) more frequent in subclavian insertions than internal jugular vein insertions and also the chances of pneumothorax were more when the number of attempts were more. This is in accordance with multiple studies and a recent study conducted by Vinson et al. in community emergency centers also revealed a higher incidence of pneumothorax with subclavian rather than internal jugular vein insertions (2.3% vs. 0.1%, p<0.001) and also with failure at the first attempt (2.5% vs. 0.3%, p=0.05). In this study, the risk of pneumothorax also increased with positive pressure ventilation. However, in our current study, there was no significant relation of pneumothorax with ventilator probably due to the small sample size. Arterial punctures occurred in 22.5% in our study, more in subclavian (18.75%) than in the internal jugular (6.5%). This is in accordance with an Indian study done by Jha et al who observed that arterial punctures were the most common complication and it occurred more commonly in subclavian (16.6% vs. 4.5%) as against internal jugular vein. Even though previous studies have shown that the risk of arterial punctures is higher with internal jugular than the subclavian route, the use of USG guidance during IJV insertions has been shown to decrease the rate of complications. Thus, the low rate of arterial punctures in IJV seen in our study is likely due to USG guided internal jugular insertions.

Hematomas occurred in 5 cases (12.5%), 3 in pre-intervention period and 2 in post intervention period. The incidence of hematomas is higher than the study conducted by Jha et al. who found an incidence of 2.5% with IJV and 4.5% with subclavian insertions. This suggests a great chance of improvement in this area pertaining to our experts.

Infectious complications

There was no CLABSI documented in our study in both the phases. This was a peculiar observation compared to previous studies. This may be due to the multitude of antibiotics received by our patients, including MRSA cover which was given in over 70% of patients and most of the patients had sepsis with a known focus of infection. A recent study in our ICU by Deepit et al. also revealed zero CLABSI in our ICU despite hospital acquired infections being present in 38.8% of cases.

Catheter tip infection occurred in 4 cases (5%), 3 in pre-intervention period decreasing to 1 in post intervention period, even though the decrease was not statistically significant thus contributing to a total of 5.03/1000 catheter days, 2.15/1000 catheter days in IJV, 6.28/1000 catheter days in the subclavian and catheter colonization rate of 3.78/1000 catheter days. Deshpande et al. in an epidemiologic prospective observational study observed a rate of catheter infection of 4.01/1000 catheter days and catheter colonization rate of 5.07/1000 catheter days. The higher incidence of catheter tip infection in our current study is likely due to poor compliance with the CVC bundle. Mortality in our study was 36.25% high due to sepsis with septic shock being the majority of our cases. However, the mortality of severe sepsis and septic shock is likely higher than our estimates since AKI requiring dialysis was excluded from our study. Mosaics study, a prospective cohort study done in Indian ICU also showed a similar mortality rate of 38.3% in sepsis patients admitted in ICU. The study conducted by Todii et al. in four ICUs in India over a 3-year period showed that in-hospital mortality in patients with severe sepsis was 65.2%. The study did not calculate the percentage of septic shock or the mortality in septic shock subgroup.

The hospital stay was significantly more in patients who survived rather than patients who died likely due to higher APACHE II and organ dysfunction at diagnosis thereby resulting in early deaths. The average hospital stay in our study was 20.01 days. The national analysis of severe
sepsis patients in Canada for 12 years also revealed a similar hospital stay of 20 days in severe sepsis patients. There was no relation of hospital stay with catheter tip infection or insertion complications. However, 2 patients with MRSA infection received antibiotics vancomycin for 2 weeks and the other 2 patients with clinical catheter tip infection received empirical antibiotics for 1 week. One patient with mediastinal hematoma was admitted for 5 extra days for observation of hematoma. There was no significant difference in ICU stay between both the phases and also in the patients who developed complications.

**Limitations of our Study**

Our study had a small sample size. A larger study population could have shown CLABSI, CLRSI with an impact on hospital mortality and hospital length of stay.

Our study had a quasi-experimental design. We could not perform an RCT in our study population of patients because of ethical constraints as the CVC insertion bundle is the current standard of care in these patients. Also, CVC post insertion bundle is obtaining important role to further decrease rate of CLABSI.

With our study design, we were able to control most of the threats to both internal and external validity. Our study has a strong external validity and the study results can be applied to the general population. The study was designed to minimize threats to internal validity. Even with a organized study, we were able to increase the compliance with the CVC bundle from 0% at the baseline to only 10% by the end of the study period. This means that there are many variables involved in the process improvement. But in our study, we did not measure these barriers to bundle compliance improvement including the contribution of physician behavior and CVC insertion cart. Identifying and rectifying these variables could have led to a better rate of compliance with the CVC bundle in our study.

**Conclusions**

The study done at All India Institute of Medical Sciences showed there were zero CLABSI events. Successful completion of the CVC bundle with quality indicators along with USG guidance during insertion is associated with improved outcome in terms of catheter infection and mechanical complications, although the difference was not significant. USG guided IVJ insertion improved significantly in the post intervention period. CVC bundle compliance increased significantly for hand washing, maintenance and prompt removal of catheters. Special attention needed to be given to maximum sterile barrier precautions and chlorhexidine skin antisepsis as compliance related to these measures were the hardest to improve. The study showed that a CVC bundle could be implemented in our emergency setting. Repeated feedback to clinicians and training was crucial in improving compliance. In future, with identification and rectification of barriers to bundle completion, probably with separate CVC cart, the compliance with CVC bundle can be further improved.

**References**

Early Intensified Insulin Therapy in Newly Diagnosed Type 2 Diabetes Leads to Sustained Improvement in Glycemic Control and Improved Beta Cell Function

Jatinder Kumar Mokta1*, Vishwanathan Mohan2, Kiran Mokta3, Ramesh4

Abstract

Aim: Type 2 diabetes (T2D) is a progressive disease characterized by relentless deterioration of pancreatic β-cell function. Traditionally, insulin is used in later stages of T2DM. This study looks at use of insulin at time of diagnosis of T2DM and its effect on glycemic control and beta cell function.

Methods: This is a prospective observational study conducted in symptomatic newly diagnosed type 2 diabetes adults (>18 years) who presented with glycated hemoglobin (A1C) levels > 9%. For the initial 8 weeks, patients were treated with pre-mix insulin after which they were changed over to oral agents, and followed up for next three years.

Results: Amongst 122 study participants, who completed the study, 50% were female and 90% were from rural areas. Average age of participants was 51.4 ± 9.6 years. Baseline mean fasting plasma glucose (FPG), post prandial plasma glucose (PPPG) and A1C were 267 ± 76 mg/dl, 408 ± 101 mg/dl and 11.5 ± 1.4% respectively. At the end of insulin therapy (8 weeks), the mean FPG, PPG and A1C reduced to 107 ± 10 mg/dl, 145 ± 24 mg/dl and 7.3 ± 0.8% respectively all of which were highly significant. The mean post-prandial C-peptide significantly increased from 1.8± 0.6 to 2.8± 0.9 ng/dl. An average of 1.7 kg weight gain and 0.97 episodes of mild to moderate hypoglycemia were observed. At the end of study (156 weeks), the mean FPG, PPG and A1C were 99 ± 14 mg/dl, 152 ± 12 mg/dl and 6.7 ± 0.4%.

Conclusion: Early insulin therapy in treatment naïve patients with type 2 diabetes results in rapid improvement of glycaemia thus helps to maintain long term normoglycemia and improves β-cell function.

Introduction

Diabetes mellitus currently affects 69 million people in India and this number is expected to rise to 109 million by 2030. Moreover, the age at onset of T2D is decreasing. The shift of age at onset of diabetes at younger ages means that their chances of developing complications at middle age are substantially higher.

The primary objective of treatment of type 2 diabetes (T2DM) is to achieve and maintain good glycemic control in order to minimize the long-term micro- and macro vascular complications. Current clinical guidelines recommend a stepwise approach to glycemic management in newly diagnosed T2D, starting with lifestyle changes followed by sequential use of one, and then several, oral hypoglycemic agents (OHA) and finally insulin treatment when all OHA fail. Although insulin is effective in all stages of the natural course of T2D and is ultimately necessary to achieve glycemic control, it is currently the most underused anti-diabetic agent as a mere 12% of patients with type 2 diabetes use insulin alone while another 14% use insulin along with OHA. As stated above, typically, insulin is recommended when dual or triple OHA therapy does not achieve the targeted glycemic goals. Unfortunately, research has shown that by this time, many patients have lived 5 years with A1C levels greater than 8%, and 10 years with A1C levels greater than 7%.

Extreme hyperglycemia creates “glucose toxicity” - a state of very high and sustained glucose levels that paradoxically worsens both insulin secretion and insulin resistance. Therefore at the time of diagnosis, if there is marked hyperglycemia and glucotoxicity, temporary insulin therapy may help restore physiologic function and this help conversion to non-insulin treatment later for sustained period of time. Unfortunately, there is very little data on early insulin therapy in T2DM for India. Herein, we describe the initiation of insulin in T2D 33 patients with marked hyperglycemia at the time of diagnosis for a period of eight weeks followed by sustained maintenance of targeted glycemic target for next 36 months on oral hypoglycemic agents.

Material and Methods

Study design and study setting

We conducted this study in newly diagnosed type 2 diabetes (treatment naïve) adult (>18 years) patients who presented to the outpatient internal medicine clinic of Indira Gandhi Medical College and Hospital (IGMC), Shimla from January 2012 through June 2016. Patients enrolled in the study fulfilled the inclusion criteria: Age > 18 years, newly diagnosed type 2 diabetes patients with A1C levels higher than 10% and /or A1C levels higher than 9% with

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symptoms of hyperglycemia. This study complies with WHO diagnostic criteria for diabetes mellitus, i.e., a random or casual plasma glucose concentration ≥ 200 mg/dl or fasting plasma glucose ≥ 126 mg/dl or 2-hour plasma glucose ≥ 200 mg/dl during standard 75g oral glucose tolerance test. Patients were excluded if they had: type 1 diabetes, acute complications (hyperglycemic hyperosmolar state or diabetic ketoacidosis), renal or hepatic dysfunction, acute infection, congestive heart failure, acute coronary syndrome, age < 18 years or > 80 years or if they were pregnant. At baseline, the patient’s history was recorded and a thorough physical examination conducted. Anthropometric measurements: weight, height, waist (at the level of anterior superior iliac spine in standing position) and body mass index (weight in kilogram divided by height in meter square) were recorded. Fasting plasma glucose, post prandial plasma glucose, A1C and blood pressure were recorded. Post-prandial C-peptide was measured at base line and at the end of two-month. Plasma glucose levels were measured by using glucose oxidase and A1C and C-peptide was measured by radioimmunoassay. All patients underwent routine blood tests i.e. complete haemogram, liver and kidney functions and lipid profile at base line. X-ray chest and thyroid function functions were done where clinically indicated. Patient’s telephone number and address were recorded and they were advised to follow at 2-month intervals. At base line, patients were educated regarding the symptoms of hypoglycemia and about the corrective measure if hypoglycemia occurs. Patients were advised to contact the treating physician in case of emergency i.e. unconsciousness.

**Study duration and follow up**

Patients were enrolled from January 2012 through June 2013 and were followed up for 3 years from the month of enrollment. Due to difficult geographical terrain, patients were advised to come for follow up between 3 to 6 months at their convenience.

Study participants were followed up at 2 month, 6 month, 12 month, 18 month, 24 month, 30 month and 36 month; respectively. Patients were reminded telephonically for their follow up visits. At each follow up visits, fasting plasma glucose, post-prandial plasma glucose and A1C were measured. Symptoms of hypoglycemia (minor as well as major included hospitalization) and subjective feeling of well being were recorded.

Hypoglycemia: “Any abnormally low plasma glucose concentration that exposes the subject to potential harm” and defined as:

- **Biochemically:** Based on documented blood glucose levels < 70 mg/dl.
- **Overall hypoglycemia:** any event classified by study investigators as such (from history: patient had one or other symptom of hypoglycemia and symptom resolved on taking sugar without knowing the blood glucose level).
- **Hypoglycemia was classified:**
  - Mild: An event associated with symptoms (autonomic symptoms) and individuals are able to self-treat.
  - Moderate: An event associated with symptoms (both autonomic and neuroglycopenic) and the individual is able to self-treat.
  - Severe: An event requiring assistance of another person to actively administer carbohydrates, glucagon or take other corrective actions and unconsciousness may occur.

**Treatment protocol and follow up**

We obtained a written informed consent from each participant before subjecting to clinical examination and treatment. All participants who gave their consent to participate in the study were treated with pre-mix human insulin (30:70) at dose 0.5 IU/Kg twice daily and metformin 500 mg twice daily and increased to 1000 mg twice daily after one week.12 We preferred pre-mix insulin to basal insulin because twice-daily pre-mix insulin provided lower A1C level compared with once daily and post-prandial glucose level is better controlled with twice-daily pre-mix insulin.9 All participants were advised to adopt healthy life style. The treating physician taught insulin injection technique to each study participant before prescribing insulin to remove injection phobia and to build patient’s confidence. For co-morbidities (hypertension and dyslipidemia) patients were treated as per the standard guidelines.

At the end of two months (first follow-up) insulin was discontinued and patients were switched over to oral anti-diabetic drugs. The choice of oral antidiabetic agents (metformin, Pioglitazone, and secretagogue and DPP-4 inhibitor in single and / or in combination) was at the discretion of treating physician. At subsequent follow up (6, 12, 18, 24, 30 and 36 month) visits, the oral agents were modified (dose increased or decreased; and new oral agent and / or insulin added) depending on the A1C level and at the discretion of the treating physician.

**Statistical analysis**

Discrete values were expressed as percentage and continuous variables as mean± SD. Student t test was applied to assess the significance of difference in mean values and chi-square test applied for assessing the significance of the difference between groups. ‘P’ value < 0.05 was considered significant.

**Results**

One hundred and eighty three (183) patients fulfilled the eligibility criteria and were enrolled the study, of whom 41 patients agreed for the insulin therapy while 142 patients refused for insulin therapy at the first contact (Figure 1). Fear of habituation was the commonest reason for refusal of insulin therapy in 84 patients followed by fear of injection and not confident in injecting insulin seen in the other 43 patients. In addition, 15 patients voiced their concerns about inconvenience of insulin therapy (particularly while traveling) as they believed that insulin needed to be refrigerated and said that a refrigerator was not available in villages. All the 142 patients who initially refused insulin were briefly educated about insulin. They were specifically told that insulin would be given for the initial 2 months to control the very high blood glucose and were assured that after 2 months they will be switched to oral drugs. After this brief insulin education period, 105 (73.9%) patients agreed for insulin therapy but 37 (26.1%) patients still refused. Then, 37 patients were excluded from the study, and were treated with oral agents. Insulin injection technique was demonstrated to all patients who accepted insulin therapy. In virtually, patient’s injection phobia went away after the first injection. The most common response after insulin demonstration was, “Oh it is
Study duration: January 2012 to June 2013
Inclusion: A diabetic naïve with hyperglycemic symptoms with A1C < 9 without hyperglycemia having A1C > 10

Total number of patients enrolled=183
41 patients (22.40%) agreed for Insulin therapy at first contact
142 patients (77.59%) refused for Insulin therapy
Brief education
105 patients (73.94%) agreed for Insulin now
37 patients (26.05%) still refused, thus excluded
Ultimately 146 patients (79.78%) patients were put on Insulin
17 patients (11.64%) lost to follow up at 2 months
7 patients (4.79%) lost to follow up between 6 to 24 months
Thus 122 patients were analyzed at the end of study

Table 1: Demographic profile at baseline (n = 122)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean (± SD)</th>
<th>p value</th>
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<tbody>
<tr>
<td>Age(years) Male</td>
<td>53.7 (± 9.6)</td>
<td>0.012</td>
</tr>
<tr>
<td>Female</td>
<td>49.0 (± 9.1)</td>
<td></td>
</tr>
<tr>
<td>Sex Male</td>
<td>61 (50%)</td>
<td>NA</td>
</tr>
<tr>
<td>Female</td>
<td>61 (50%)</td>
<td></td>
</tr>
<tr>
<td>Height(cm) Male</td>
<td>168.5 (± 5.3)</td>
<td>0.000</td>
</tr>
<tr>
<td>Female</td>
<td>155.5 (± 4.8)</td>
<td></td>
</tr>
<tr>
<td>Weight(kg) Male</td>
<td>70.6 (± 9.1)</td>
<td>0.000</td>
</tr>
<tr>
<td>Female</td>
<td>64.7 (± 10.1)</td>
<td></td>
</tr>
<tr>
<td>Waist(cm) Male</td>
<td>93.7 (± 6.2)</td>
<td>0.04</td>
</tr>
<tr>
<td>Female</td>
<td>91.5 (± 7.2)</td>
<td></td>
</tr>
<tr>
<td>BMI(kg/m²) Male</td>
<td>24.9 (± 2.6)</td>
<td>0.003</td>
</tr>
<tr>
<td>Female</td>
<td>26.6 (± 3.5)</td>
<td></td>
</tr>
<tr>
<td>SBP (mmHg) Male</td>
<td>139 (±15)</td>
<td>0.50</td>
</tr>
<tr>
<td>Female</td>
<td>137 (± 14)</td>
<td></td>
</tr>
<tr>
<td>DBP (mmHg) Male</td>
<td>84 (± 7)</td>
<td>0.71</td>
</tr>
<tr>
<td>Female</td>
<td>84 (± 9)</td>
<td></td>
</tr>
</tbody>
</table>

NA= Not Applicable; Number of patients with BP ≥140/90 mmHg are 28

so simple and it does not hurt”. It took an average of 5 minutes to educate and demonstration of insulin technique in the busy OPD. Thus, final the number of patients who accepted the insulin therapy was 146 (79.8%) (Figure 1).

Of 146 patients who accepted insulin therapy, 17 (11.6%) patients were lost to follow up at first visit at 2-month and seven (4.79%) patients left treatment between 6 month and 24 months and were excluded from the study. Thus, finally, 122 subjects completed the three year study period and were included in the study for the final analysis (Figure 1).

The demographic profile of 122 study participants who completed the study is shown in Table 1. Ninety-one (74.6%) patients had history of osmotic symptoms. Sixteen (13.11%) patients were diagnosed during routine laboratory work up, 10 (8.2%) patients were diagnosed before undergoing preoperative check up prior to various different surgeries.

At baseline, FPG of study subjects ranged between 160 - 525 mg/dl with a mean of 267 ± 76 mg/dl, the PPPG ranged between 229-750 mg/dl with a mean of 408 ± 101 mg/dl and A1C ranged from 9.4 - 15.5% with a mean of 11.4%. The post–prandial C-peptide levels could only be measured in 39 study subjects due to financial reasons and it ranged between 0.8 ng/dl – 2.7 ng/dl with mean of 1.8± 0.6 ng/dl. The systolic blood pressure ranged between 110 - 192 mmHg with a mean of 137 ± 15 mmHg (male: 138 ± 16 mmHg; women: 136 ± 14 mmHg). Diastolic pressure ranged between 60 - 110 mm Hg with a mean of 83 ± 8 mm Hg (male: 83 ± 7 mm Hg; women: 83 ± 9 mm Hg) and 28% were found to be hypertensive at base line (Table 1).

First follow-up visit at 2-months

The fasting plasma glucose levels of study participants at 2-month follow up ranged from 76 - 178 mg/dl with a mean of 106 ± 10 mg/dl. The postprandial plasma levels ranged from 102 - 238 mg/dl with a mean of 144 ± 24 mg/dl (Figure 2). The A1C at the end of two-month insulin treatment ranged from 5.5 – 9% with a mean A1C of 7.3% (Figure 3). The reduction in the mean FPG, PPPG and A1C was highly significant at 2-months (p < 0.001). The post-prandial C-peptide levels measured in 39 study subjects at 0 month was 1.81 ± 1.0 ng/dl which increased to 2.78 ng/dl at the
end of 2-months (p = 0.01). There was an average 1.7 kg increase in the weight of study participants from 67.7 kg to 69.4 kg. Overall, there were 0.97 episode/patient of hypoglycemia. However, all episodes of hypoglycemia were minor except for seven, which were of moderate intensity. 113 patients (92.62%) were satisfied with the treatment and reported improvement in the quality of life after insulin treatment. The ‘feel good phenomenon’ was attributed to relieving of osmotic symptoms and feeling more energetic.

**Treatment changes at 2-month follow-up**

At two-month, the insulin injection was discontinued and participants were treated with oral antidiabetic agents. Twelve (9.8%) patients were treated with the combination of metformin (2000 mg) and pioglitazone (15 mg), 36 (29.5%) patients were treated with the combination of Sitagliptin (50 or 100 mg) and metformin (2000 mg) and 74 (60.7%) patients were treated with combination of glimepiride (1 or 2 mg) and metformin (2000 mg). Subsequent follow up was planned at 6, 12,18,24,30 and 36 month.

**Follow-up at 6, 12, 18, 24 and 30 months**

The mean FPG of study subjects ranged from 95 ± 12 mg/dl to 102 ± 12 mg/dl, the mean postprandial plasma glucose ranged from 145 ± 19 mg/dl to 153 ± 10 mg/dl and the mean A1C ranged from 6.3 to 7.3% at 6, 12, 18, 24 and 30 month respectively (Fig. 2 and 3). The reduction in mean FPG, PPG and A1C at 6, 12, 18, 24 and 30 months were highly significant (p < 0.001). In four patients (2 in sitagliptin and 2 in glimepiride arm) another short course of insulin was required at 12, 18 and 24 months respectively, for deteriorating plasma glucose and rising A1C (> 9%) despite maximum dose of oral agents. In all four patients, plasma glucose was normalized in 4 to 6 weeks, and was later reverted to oral agents, and subsequently their plasma glucose remained well controlled on oral agents.

**Follow up results at 36 months**

At 36 month, the fasting plasma glucose ranged from 70 - 153 mg/dl with a mean of 99 ± 13 mg/dl and post-prandial plasma glucose ranged from 124 - 178 mg/dl with a mean of 152 ± 12 mg/dl and the A1C ranged from 5.2 – 9.9% with a mean of 6.6% (Figures 2 and 3). The reduction in all three parameters (FPG, PPG and A1C) remained significantly lower at 36 months compared to the base line levels. At the end of 36 month, 93 (76.2%) had A1C 7%. The baseline A1C and reduction in A1C after treatment was similar in male and female participants.

At the end of 36 months, the majority of patients were on two drug OHA regimens while few needed three drug regimens.

**Discussion**

In the natural course of type 2 diabetes, early, intensive and strict glycemic control is clinically important because it limits exposure to high glucose level and consequently its toxic effects with substantial reduction in risk of development both microvascular and macrovascular complications in long term. This phenomenon of long term protective effects on micro vascular and macrovascular complications with short burst of intensive therapy soon after the diagnosis is termed as “metabolic memory”.

The natural history of diabetes reflects two abnormalities: a gradual increase in the insulin resistance and a progressive decline in insulin secretory response, over a decade or more, to a point that 50-80% of β-cell functions is lost by the time diabetes is diagnosed. Prolonged exposure to hyperglycemia results in glucotoxicity and oxidative stress of β-cells, culminating in β-cell destruction. Early level of insulin secretion (first-phase) is key determinant of pancreatic β-cell function and loss of first phase insulin secretion is crucial defects in the pathogenesis of type 2 diabetes. The rapid acquisition of glycemic control with transient intensive insulin therapy (TIIT) has been demonstrated to have beneficial effect on β-cell function in a number of studies and this has been confirmed by a meta-analysis. The statistically significant increase in the level of C-peptide after short course of insulin therapy suggests improvement of β-cell function in our study subjects and extends support to these previous studies. The probable underlying mechanism in the improvement of β-cells function with insulin therapy is that insulin therapy keeps the pancreatic β-cells in a resting state and thereby eases the burden of the pancreatic β cells and also possibly accelerates β cell repair by suppressing glucotoxicity and lipotoxicity. Further, by directly enhancing the insulin sensitivity in the peripheral tissues (free fatty acid antagonizes the action of insulin on peripheral cells and Insulin reduces free fatty acid production), insulin therapy has demonstrated improvement in the insulin resistance in number of studies.

Significant reduction in glycemic levels (FPG, PPG and A1C) at the end of insulin therapy in this study is suggestive of effectiveness of early use of insulin in the treatment of newly diagnosed type 2 diabetes with marked hyperglycemia and extends support to a number of previous studies. The rapid acquisition of glycemic control with short intensive insulin therapy helps in maintaining long-term glycemic control has been demonstrated in a number of studies. Sustained glycemic control after use of early insulin therapy was seen in this study, as 73.7% of patients had A1C 7% at the end of 3 years compared to 33% of patients treated with oral agents from the time of diagnosis in...
United Kingdom Prospective Diabetes Study. Guidelines recommended glycemic control (<7%) early in the natural course of diabetes has been demonstrated to have a beneficial effect on cardiovascular events compared to strict glycemic control in the later part of natural course of diabetes.15

Hypoglycemia and weight gain are two commonly associated adverse effects of insulin therapy.16 However, since insulin is used only for 2 months, these are not an issue compared to late addition of insulin in the usual treatment paradigm.16

In this study, 77.6% of patients initially refused to have insulin therapy; this confers the patient’s resistance in starting insulin therapy and supports the findings of previous studies.17 However, identifying these barriers and addressing the patient’s fears crucially important for the timely initiation of insulin therapy.18 We are pleased that 73.9% of patients ultimately accepted the insulin therapy after a brief education session of only about 5 minutes. This is feasible even a busy outpatient clinic. Furthermore, patients with a positive attitude about insulin therapy are more likely to achieve higher remission rates. However, in some patients preconceived fears and beliefs are stronger than their health care provider’s advice and may have difficulty in changing their opinion.19 This is shown by the 26.1% of our patients who did not agree for insulin therapy despite their health care provider’s advice.

The treatment satisfaction and improvement in the quality of life seen after insulin therapy in this study extend support to the results of previous studies18 and serve as encouragement for an introduction of insulin therapy at an earlier stage in the natural course of type 2 diabetes. Education as well as increased level of support from medical personnel during treatment initiation to patient, positively influences the patients perception and reduces their fear of treatment leading to acceptance of insulin therapy.

The U.K. Prospective Diabetes Study (UKPDS) and Diabetes Control and Cardiovascular Trial (DCCT) and the follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) studies provide rational that aggressive glycemic control early in the natural course of diabetes (at time of diagnosis) will dramatically lessen the burden of cardiovascular disease many years down the road.2 However, tight glycemic control late in the natural course of diabetes with long standing T2D with established cardiovascular disease may actually increase mortality rates.19 It has been reported that less than one third of physicians in India prescribe insulin compared to OADs.20 Based on our experience, we suggest that patients with newly diagnosed T2DM and A1C > 9% (with symptoms) could be given short time intensive insulin therapy to rapidly obtain normoglycemia. This insulin treatment can be stopped as soon as stable glycemic control is achieved and they can then be moved into standard care according to a patient-centered treatment approach. This also makes it easier to restart the insulin treatment in the natural course of disease when insulin is needed as shown by four of our patients who readily accepted insulin when their glycemic control deteriorated later. Finally, education about the initiation of insulin treatment at first contact influences the patients’ psychological condition positively and reduces the fear of insulin therapy.

In summary, a more proactive approach in the management of severe uncontrolled diabetes early in the natural course of diabetes with transient use of intensive insulin therapy has the potential of achieving and maintaining effective glycemic control and improving beta cell function. This could also potentially reduce the risk of long-term complications compared with later addition of insulin in the treatment paradigm of diabetes, although admittedly long term follow up studies are needed in this aspect as currently we do not have the data to support prevention of diabetes complications based on early and aggressive treatment with insulin in T2 patients.

Acknowledgement

Authors are thankful to Principal, Indira Gandhi Medical College, Shimla for providing basic facilities to carry out the study. Authors gratefully acknowledge the participation of all the patients in the study.

References

A Crossover Study Evaluating Effect of Timing of Levothyroxine on Thyroid Hormone Status in Patients of Hypothyroidism

Swati Srivastava1*, Gunjan Sharma2, Monika Rathore3, Ashutosh Chaturvedi4, Prakash Keswani1, GN Saxena5, Aradhana Singh6, Raman Sharma7

Abstract

Objective: Current literature shows a definite benefit of fasting state Levothyroxine administration. However, superiority of any specific timing is not yet established. Our study was designed to compare the effect of timing of levothyroxine administration, morning versus evening dose, on thyroid profile control in patients of hypothyroidism.

Methodology: A randomized double-blind crossover study was performed on 60 patients with primary hypothyroidism, euthyroid on stable levothyroxine regime of 100 µg daily, randomized into two sequence groups, morning dose first (AB sequence) versus evening dose first (BA sequence) with switch over after 6 weeks. Primary endpoints were change in thyroid function tests.

Results: There was an insignificant rise in TSH in morning dose first group (AB) at 6 weeks which reduced significantly in evening dose, [2.36(1.11) to 2.45(1.19) mIU/L (p=0.56)], [2.07(0.99) (p=0.006)] respectively. Levothyroxine evening dose first group (BA) showed significant reduction of TSH levels at 6 weeks followed by non significant increase [2.63(0.96) to 1.85(1.35) mIU/L, (p=0.002)], [2.14(1.16), (p=0.15)]. Group AB showed mild followed by significant rise in FT3 at 6 and 12 weeks respectively, [1.06(0.30) to 1.14(0.33) ng/dl (p=0.18)], [1.24(0.36) (p=0.008)]. FT3 of BA sequence significantly increased at 6 weeks followed by mild increase, [1.10(0.29) to 1.20(0.28) ng/dl (p=0.01)] [1.23(0.31) ng/dl (p=0.58)]. FT3 of AB revealed initial reduction (p=0.87), followed by significant rise (p=0.02). Group BA showed a significant rise (p=0.04) in FT3 followed by fall (p=0.63).

Conclusion: Bedtime dosing of Levothyroxine showed improved thyroid hormone status control and could be a viable option in treatment of patients with hypothyroidism occurring in the small intestine, may vary significantly to the tune of 50-80% being absorbed. Strict instructions regarding taking levothyroxine on empty stomach, early morning may be associated with compliance issues. Patients’ lifestyle and consumption of other medications advised to be taken empty stomach could make it inconvenient for the patients leading to failure to follow this advice. An alternative regimen for ideal timing of the drug needs to be reviewed.

We hypothesize that Thyroid hormone status is controlled better if Levothyroxine is administered in evening then in morning among patients of hypothyroidism. Hence our study was designed to compare the effect of timing of levothyroxine administration over thyroid profile control in the Indian Subcontinent.

Methodology

Study Design

A randomized double-blind crossover study was performed among patients with primary hypothyroidism who visited Medicine wards and Out-patient Department, S.M.S. hospital, Jaipur. Crossover study was ideal as inconveniencing for the patients leading to compliance issues. In addition our study’s objective was to evaluate a slight modification of standard treatment. Uniformity regarding sequence of treatment regimes and period was kept in this 2x2 crossover design. We did not keep washout period as same dose of same drug was given, but only on different time of the day.

Introduction

Hypothyroidism, a commonly encountered disorder, is characterized by reduction in thyroid hormones. The effects of hypothyroidism are largely correlated with the severity of hormone deficiency whatever be the etiology. The consistent potency and long half life of levothyroxine make it an ideal modality of treatment in Hypothyroidism. The fact that the medicine has a very narrow therapeutic range, an accurate adjustment is required for target Thyrotropin (TSH) controls. For a good control of thyroid function, compliance and adherence to accurate prescription instructions is important. However in the face of several factors influencing the absorption of the drug, the optimal drug effects may be altered.

There are no specific guidelines regarding timing of levothyroxine intake. Usual recommendations for the drug are that it should be taken on an empty stomach, usually in the morning, before breakfast. Studies have shown fasting conditions to be most suitable for consistent and optimal absorption of the drug, with higher and variable TSH levels when taken with breakfast. The absorption of levothyroxine,
with plain water. Folic acid tablets of dose at least two hours after dinner one hour before breakfast and bedtime instructed to take morning dose at least sequence group”). Patients were

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group AB</th>
<th>Group BA</th>
<th>Test statistics</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (in years)</td>
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<td>39.72 (14.02)</td>
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<tr>
<td>Female</td>
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<td>25</td>
<td></td>
<td></td>
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<tr>
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<td>BMI (kg/m$^2$)</td>
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<td>24.65 (1.97)</td>
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<tr>
<td>Lipid profile:</td>
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<td>TC (mg/dL)</td>
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<td>172.50 (39.97)</td>
<td>1.78</td>
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</tr>
<tr>
<td>HDL (mg/dL)</td>
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<td>47.16 (1.71)</td>
<td>0.81</td>
<td>0.42</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
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<td>0.26</td>
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<tr>
<td>S. Creatinine (mg/dL)</td>
<td>0.93 (0.20)</td>
<td>0.99 (0.17)</td>
<td>1.24</td>
<td>0.22</td>
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</table>

Table 2: Comparison of mean of difference at (between 6 and 12 weeks) of variables in two sequence groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean of difference (SD)</th>
<th>t Statistics</th>
<th>P Value</th>
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</thead>
<tbody>
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<td>TSH (mIU/L)</td>
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<td>2.86</td>
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<td>FT$_3$ (pg/mL)</td>
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<td>-0.08 (0.92)</td>
<td>-1.54</td>
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<td>-0.03 (0.30)</td>
<td>-1.07</td>
</tr>
<tr>
<td>BMI (Kg/m$^2$)</td>
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<td>-0.04 (0.14)</td>
<td>-0.76</td>
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<tr>
<td>TC (mg/dL)</td>
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<td>-10.87 (26.76)</td>
<td>1.95</td>
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<tr>
<td>TG (mg/dL)</td>
<td>3.86 (26.48)</td>
<td>2.98 (55.34)</td>
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<td>LDL (mg/dL)</td>
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<td>HDL (mg/dL)</td>
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<td>-0.40 (5.72)</td>
<td>0.37</td>
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<tr>
<td>S. Creatinine (mg/dL)</td>
<td>0.05 (0.17)</td>
<td>-0.003 (0.12)</td>
<td>1.38</td>
</tr>
</tbody>
</table>

Table 2: Results of two sequence groups at baseline, 6 weeks, 12 weeks: Mean (SD)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group – AB (n=30) (Morning dose 1st group)</th>
<th>Group – BA (n=29) (Evening dose 1st group)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH (mIU/L)</td>
<td>2.36 (1.11)</td>
<td>2.45 (1.19)</td>
</tr>
<tr>
<td>FT$_4$ (ng/dL)</td>
<td>1.06 (0.30)</td>
<td>1.10 (0.29)</td>
</tr>
<tr>
<td>FT$_3$ (pg/mL)</td>
<td>4.07 (0.98)</td>
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</tr>
<tr>
<td>BMI (Kg/m$^2$)</td>
<td>23.84 (2.16)</td>
<td>24.65 (1.97)</td>
</tr>
<tr>
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</tr>
<tr>
<td>S. Creatinine (mg/dL)</td>
<td>0.93 (0.20)</td>
<td>0.99 (0.17)</td>
</tr>
</tbody>
</table>

Study population

Inclusion criteria consisted of patients of primary hypothyroidism of age 18 years or more, who were euthyroid on stable levothyroxine regime of 100 µg daily for at least 6 months. Pregnant females, patients suffering from gastrointestinal disease and those on medication known to interfere with the uptake of Levothyroxine were excluded. Patients were taken for study after taking informed consent. The medical ethics committee of the S.M.S. Hospital, Jaipur, approved the study protocol.

Study protocol

60 patients satisfying inclusion criteria were randomized into one of the two sequence groups of 30 each, one group taking 100µg levothyroxine in the morning and placebo at bedtime (Morning Dose First Group which we will refer to as “AB sequence group”), and the other group taking levothyroxine at bedtime and placebo before breakfast (Evening Dose First Group which we will refer to as “BA sequence group”). Patients were instructed to take morning dose at least one hour before breakfast and bedtime dose at least two hours after dinner with plain water. Folic acid tablets of 5mg strength, which had appearance similar to levothyroxine tablets were used as placebo. After 6 weeks, patients in the Morning Dose First Group were switched to placebo in the morning and levothyroxine at bedtime for next 6 weeks. Similarly, after 6 weeks, patients in Evenning Dose First Group were shifted to levothyroxine in the morning and placebo at bed time for another 6 weeks.

Patients' assessment

Patients were assessed at baseline, 6 weeks and 12 weeks. Clinical examination including Body Mass Index and biochemical parameters were conducted on each visit. Blood samples were drawn on the morning of the every planned visit and patients were instructed not to withhold levothyroxine tablets on the day of blood sampling. Blood samples were collected after overnight fasting and analyzed for Thyrotropin (TSH), free triiodothyronine (FT$_3$), free thyroxine (FT$_4$), serum creatinine and lipid Profile. All tests were done in Central Laboratory, S.M.S. Hospital, Jaipur.

Patients' data was collected at every planned visit, and was analyzed at the end of study.

Laboratory methods of estimation of parameters

Total cholesterol, triglycerides, high density lipoprotein were estimated using Beckman Cx4 auto analyzer. LDL cholesterol was calculated using Friedewalds formula. Chemiluminescent assay with fully automated ImmunoLyte 2000 machine in Thyroid lab of SMS Hospital was used for measurement of FT$_3$, FT$_4$, and TSH level.

Statistical analysis

The Primary aim of the study was to see the change occurring in Thyrotropin and Thyroid hormone levels when levothyroxine was taken at bedtime versus in the morning. The effect of bedtime Vs morning regime of levothyroxine on serum creatinine, lipid levels and Body Mass Index constituted the secondary objective of the study.

The direct treatment effect among primary end points was measured by performing an independent t test between the differences of 6 and 12 weeks in the AB sequence group (levothyroxine morning dose first) and the BA sequence group (levothyroxine evening dose first). The presence of carryover effect from one period to other was measured by performing an independent t test on sum of the variables at 6 weeks and 12 weeks. All p values were two sided.

Baseline characteristics of two sequence groups were analyzed. For count data chi-square test was used and independent t test was used for continuous data.

Results

One out of 30 cases in Evenning dose first group (BA) was lost to follow up and excluded from analysis, while all 30...
cases from AB group remained in the study till end. Baseline characteristics including BMI of both the sequence groups were comparable (Table 1).

**Primary outcomes: (Table 2, 3)**

Within group and Inter group Analysis

1. Mean(SD) Thyrotropin levels (mIU/L): Levothyroxine morning dose first group, showed a non significant rise in Mean (SD) Thyrotropin levels (mIU/L) from 2.36 (1.11) to 2.45 (1.19) mIU/L (p=0.56) at 6 weeks but when changed over to evening doses, levels reduced significantly from 2.45 (1.19) to 2.07 (0.99) (p=0.006) at 12 weeks. Levothyroxine evening dose first group showed a significant reduction of Mean (SD) TSH levels (mIU/L) from 2.63 (0.96) to 1.85 (1.35) mIU/L, (p=0.002) in first 6 weeks. On switching over to morning doses, there was a non significant increase in levels from 1.85(1.35) to 2.14(1.16), (p=0.15) (Figure 1).

Intergroup comparison of Mean of difference of TSH at the end of 6 weeks (p=0.002) and 12 weeks were statistically significant (p=0.006).

2. Mean (SD) FT4 (ng/dl) levels: Group AB showed a negligible increase in Mean (SD) FT4 (ng/dl) levels, from 1.06(0.30) to 1.14(0.33) ng/dl (p=0.18) at 6 weeks but on crossover to evening doses, FT4 levels significantly increased from 1.14 (0.33) to 1.24 (0.36) at 12 weeks (p=0.008). Group BA showed a significant increase in FT4 from 1.10(0.29) to 1.20(0.28) ng/dl (p=0.01) at 6 weeks when on evening Levothyroxine dose, which on crossover to morning dose regimen, resulted in a mild increase to 1.23(0.31)ng/dl at 12 weeks(p=0.58) (Figure 2).

3. Mean (SD) FT3 levels (pg/ml): Group AB, revealed a negligible reduction from 4.07(0.98) to 3.98(1.21) pg/ml (p=0.87). On crossover to evening levothyroxine regimen FT3, significantly increased (p=0.02). Group BA showed a significant rise in FT3 when they were on evening doses from 3.93(0.87) to 4.34(0.77) (p=0.04). On crossover to morning doses, FT3 levels decreased slightly, (p=0.63) (Figure 3).

**Direct Treatment and Carryover effect of 2 sequence groups**

Pre test done using two sample Independent t test on sum of variables at 6 weeks and 12 weeks revealed that there was a negligible carryover effect (p=0.42, 0.77 and 0.34 respectively for FT3, FT4, TSH. The independent t test done for differences between treatment effect of both the groups revealed that Evening dose group had significantly better control of TSH than morning dose group with a mean difference of 0.66 mIU/L (confidence interval 0.19 to 1.13) (p=0.006). (Table-3) but there was no significant difference in FT3 (p=0.13) and FT4 level (p=0.29) in both groups.

**Secondary outcomes**

**BMI:** Both the sequence groups (AB and BA) showed a mild but insignificant increase in BMI (P= 0.32, 0.08 respectively). Serum creatinine did not show any significant variation in both the groups. On analyzing changes in triglycerides, total cholesterol, serum HDL, serum LDL in each group at 6 and 12 weeks the difference was found to be statistically insignificant. Intergroup analysis also showed insignificant difference.

**Discussion**

Current literature shows a definite benefit of fasting state Levothyroxine ingestion over non-fasting state, but superiority of any specific timing of Levothyroxine administration over other is not yet established. It is consistently inferred that whatever be the timing of Levothyroxine, it should be well separated from meal times, it should not need much change in patients routine lifestyle and food practices and it should not interfere with other drugs the patient may be taking. In this regard, bedtime Levothyroxine intake could be more convenient for many patients, as they do not have to postpone breakfast and can easily adjust intake of other medications to be taken on empty stomach.

The benefit of cross-over design adapted in our study was that it avoids the problem of comparability of cases and control with regards to confounding variables as each crossover case becomes his/her own control. The inter subject variability issue is overcome in this design.

Only those patients who were stable on 100 µg levothyroxine for at least past 6 months were included in our study so as to exclude the variability occurring due to dose differences. In addition, individual patient’s response to medications may vary, so new patients were excluded and only those who were well controlled with the levothyroxine were selected.
Elimination of these confounding variables brought precision for evaluating direct treatment effects of bedtime versus morning dosages.

The improvement of thyroid function tests when on evening dose of Levothyroxine observed in our study could be explained by several factors. The pulsatile nature of TSH release with maximum levels at night favors bedtime levothyroxine supplementation. Physiologically, a high nocturnal gastric acid secretion would lead to better drug absorption at night. Also, reduced gut motility gives more time for absorption at this time improving its bioavailability. The patients when on evening dose were instructed to take levothyroxine at least two hours post dinner. This was not difficult for many as not ingesting anything after dinner was customary for them. Also, there would be ample time for drug absorption at night. Contrary to this, in the morning, patients tend to have morning tea or coffee and an early breakfast is also a routine for many. Our patients were instructed to remain fasting for one hour following morning levothyroxine ingestion.

Reviewing literature we find similar results in some studies investigating the effects of timing of levothyroxine on thyroid profile. Effect of timing of levothyroxine, investigated by Nienke Bolk et al in a randomized double blind study revealed definite benefit with bedtime levothyroxine dose resulting in a significant fall in Thyrotropin levels and an increase in free thyroid hormone levels with bedtime doses. These results are consistent with the favourable outcome of evening dose levothyroxine obtained in our study. Elliot DP conducted a retrospective review of data in 15 elderly residents of a nursing home who underwent a change in timing of levothyroxine from morning to midnight. They found a reduction in TSH following night time dosage of levothyroxine which was however, not significant statistically. The author concluded the possibility of post breakfast levothyroxine administration. Another study comparing morning and evening dose of levothyroxine was conducted by Rajesh Rajput et al. The authors included newly diagnosed patients of primary hypothyroidism and observed the thyroid hormone status, and quality of life parameters following treatment with levothyroxine in morning and evening time dosages. Similar dose requirement in both groups of patients to achieve normal thyroid hormone status was observed. Their study concluded that evening dose administration of levothyroxine could be an effective alternative to the usual practice of morning dosage. However, not all studies showed a benefit with evening dose levothyroxine. Thien-Giang Bach-Huynh et al studied the thyroid hormone status achieved with levothyroxine dosing taken on empty stomach, along with breakfast and at bedtime. Best results of Thyrotropin control were seen when levothyroxine was taken in fasting conditions as compared to when taken with food or at bedtime. They found variability in control of thyroid profile with levothyroxine taken in other than fasting states. Another recent study comparing Thyrotropin levels when taken fasting as compared to with breakfast also reported variability in TSH levels and requirement of closer observation in patients taking levothyroxine with breakfast.

Quality of life parameters are of importance in management of hypothyroidism. No objective evaluation was done in this regard in our study and biochemical parameters were mainly considered. This aspect was studied by Nienke Bolk et al where they did not find any difference in quality of life in patients with morning or evening dose of levothyroxine. Changes in BMI did not show any difference in both the regimes in our study. As seen in clinical practice, while dealing with patients of hypothyroidism, reduction or gain of weight is an important matter of concern for the patient. Other parameters including lipid profile and serum creatinine levels did not show any difference in both the groups.

Conclusion

Considering a better biochemical thyroid hormone status control and the secondary outcomes not showing any adverse changes gives us encouraging ground to consider bedtime doses of levothyroxine administration as a viable option. In the present scenario with an extremely busy and fast morning lifestyle schedule, bedtime doses could prove to be very convenient and be instrumental in improving compliance. Also, patients who are not adequately controlled with morning dose levothyroxine could be shifted to bedtime doses for a better Thyrotropin reduction. Further studies including larger patient population and for longer duration need to be conducted to establish whether these beneficial effects sustain for long duration.

References

Assessment of Pituitary Gonadal Axis and Sperm Parameters in Anemic Eugonadal Males Before and After Correction of Iron Deficiency Anemia

Sudhir Mehta\(^1\), Laxmikant Goyal\(^2\), Manohar Lal Meena\(^3\), Sandhya Gulati\(^4\), Nidhi Sharma\(^5\), L Harshvardhan\(^6\), Gunja Jain\(^2\), Shaurya Mehta\(^7\)

Abstract
Iron deficiency anemia (IDA) is one of the most common nutritional anemia worldwide. Anemia imposes a significant hypoxic environment in different organs and tissues including the testes. This study evaluated the effect of treatment of IDA on the pituitary gonadal axis (Serum FSH, LH, Testosterone) and sperm parameters in adult eugonadal males.

Methodology: A hospital based interventional, analytic study was conducted at a tertiary care center among 25 eugonadal males (fully sexually developed, fertile) with newly diagnosed and untreated IDA, admitted in medicine wards and not suffering from any inflammatory disorders (excluded by C-reactive protein) after exclusion of patients having other forms of anemia/ hemoglobinopathies/ any malignancy/having MCV >80 fL, aplastic anemia and primary hypogonadism. Sexual maturation was assessed according to maturity stages 5. Investigations were performed before and 6 weeks after treatment of IDA with intravenous iron sucrose included CBC, peripheral blood smear, serum ferritin, serum iron, TIBC, serum FSH, serum LH, serum Testosterone and semen analysis (Semen volume, Sperm count, Sperm motility and Sperm morphology).

Results: The change in mean Hb level before (5.66 ± 1.97gm/dl) and after treatment (11.96 ± 0.87 gm/dl) was statistically significant. (P<0.001) Patients who had subnormal and normal serum level of FSH, LH, Testosterone and sperm parameters before treatment were divided into group A and group B respectively. Serum levels of FSH, LH and testosterone along with sperm parameters significantly improved after correction of anemia (p<0.01). The mean change in these parameters was significantly higher in patients having subnormal value of these parameters before treatment (Group A) than in patients having normal pre-treatment level (Group B) (p<0.01). The level of anemia (hemoglobin) had significant positive correlation with serum FSH, serum LH, serum testosterone levels and sperm parameters (semen volume, sperm count, sperm morphology, RPM and sperm motility) (p<0.001).

Conclusion: IDA had significant negative association with the pituitary gonadal axis (Serum FSH, LH, Testosterone) and sperm parameters in adult eugonadal males. The serum levels of FSH, LH and testosterone along with sperm parameters significantly improved after correction of anemia, especially in patients having subnormal value of these parameters.

Introduction
Iron deficiency anemia (IDA) is one of the most common nutritional anemia worldwide.\(^1\) Anemia imposes a significant hypoxic environment in different organs and tissues including the testes. Spermatogenesis in the seminiferous tubules of the testes occurs under a high proliferation rate, which demands considerable oxygen consumption.\(^2,3\) Hence spermatogenesis is affected considerably by hypoxia.\(^2,3\)

Morphological studies in animals reveal that hypoxia causes damage to germinal epithelium, folding of the basal membrane, degeneration, sloughing of spermatogenic cells in lumen of seminiferous tubules and lipid droplet deposition in sertoli cells and spermatogonia degeneration with chromatin margination.\(^4\) Studies indicate that hypoxia reduces the fertility of male rats, rhesus monkeys and men by decreasing sperm count and sperm motility in semen.\(^5,8\)

Up to best of our knowledge, there is no Indian literature available which has assessed pituitary gonadal axis and sperm parameters in anemic eugonadal males before and after correction of anemia. Hence, we undertook the present study to evaluate the effect of treatment of IDA on the pituitary gonadal axis (Serum FSH, LH, Testosterone) and sperm parameters in adult eugonadal males.

Methodology
This hospital based interventional, analytic study was conducted at a tertiary care center in Rajasthan, during one calendar year, after obtaining due permission from Research Review board/ Institutional Ethics committee and informed written consent of the study participants. Twenty five eugonadal males (fully sexually developed, fertile) with newly diagnosed and untreated iron deficiency anemia (Hb<10g/dl), admitted in medicine wards and not...
suffering from any inflammatory disorders (excluded by C-reactive protein) were included in this study. Patients having other forms of anemia/hemoglobinopathies/any malignancy/having MCV >80 fL and aplastic anemia were excluded from this study.

All cases of primary hypogonadism were excluded from the study. Sexual maturation was assessed according to maturity stages 5. All patients were married and had children (21). Investigations were performed before and 6 weeks after treatment of IDA with intravenous iron sucroses included CBC, peripheral blood smear, serum ferritin, serum iron, TIBC, serum FSH, serum LH, and serum Testosterone in a fasting venous sample and semen analysis (Semen volume, Sperm count, Sperm motility and Sperm morphology). Semen collection was done by masturbation after minimum 3 days of abstinence and was analyzed as per WHO criteria. Blood samples were drawn from patients in EDTA vials for CBC including peripheral blood smear; and in plain vials for serum ferritin, serum iron and TIBC. Patients having microcytic hypochromic anemia, serum ferritin below 20 ng/ml and transferrin saturation < 20% were selected. Patient’s clinical history, findings of physical examination and other relevant data, including lab test results, were recorded in structured forms. CBC was done on Sysmex XT 4000i automated analyzer. Serum ferritin was measured on IMMULITE 2000 Systems analyzer using a solid-phase, two-site chemiluminescent immunometric assay. Serum iron was measured using colorimetric assay. TIBC was measured using saturation – precipitation method. Transferrin saturation (TSAT) was calculated as TSAT = (serum iron/TIBC) x100 and expressed as percentage. Hormonal analysis was done by chemiluminescent immunometric assay in our institutional lab. Semen analysis was done by single pathologist who was blinded to the study and clinical state of the patients. All lab workers were blinded to the study and clinical state of the patients.

**Statistical analysis**

Microsoft Excel® and SPSS® 17 for Windows® were used for data storage and analysis. Continuous variables were expressed as mean ± standard deviation. Student’s t test was used to determine statistical difference between variables. Correlation analysis was done by using Pearson correlation coefficient and linear regression was performed. Statistical significance was set at P value ≤ 0.05.

**Results**

Out of 25 eugonadal anemic male patients with IDA, 14 patients (56%) were below 25 years, and 11 (44%) patients were more than 25 years (age range 23-45 years). All patients had iron deficiency with Hb <10 gm/dl at the time of recruitment. The change in mean Hb level before (5.66 ± 1.97gm/dl) and after treatment (11.96 ± 0.87 gm/dl) was statistically significant. (P<0.001)

Patients who had subnormal and normal serum level of FSH, LH, Testosterone and sperm parameters before treatment were divided into group A and group B respectively.

**Semen parameters (Table 1)**

<table>
<thead>
<tr>
<th>Total Sperm Motility (%)</th>
<th>RPM (%)</th>
<th>Normal Sperm Morphology (%)</th>
<th>Semen volume(ml)</th>
<th>S. Testosterone (ng/dl)</th>
<th>Total Sperm Motility (%</th>
<th>RPM (%)</th>
<th>Normal Sperm Morphology (%)</th>
<th>Semen volume(ml)</th>
<th>S. Testosterone (ng/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>34.63 ± 3.29</td>
<td>51.40 ± 0.4</td>
<td>51.21 ± 1.52</td>
<td>75.83 ± 0.30</td>
<td>25.66 ± 1.33</td>
<td>5.86 ± 0.87</td>
<td>7.63 ± 0.69</td>
<td>3.27 ± 0.96</td>
<td>19.0 ± 0.27</td>
<td>6.42 ± 1.56</td>
</tr>
<tr>
<td>1.65 ± 0.02</td>
<td>1.36 ± 0.08</td>
<td>1.92 ± 0.07</td>
<td>3.01 ± 0.159</td>
<td>0.54 ± 0.05</td>
<td>0.54 ± 0.05</td>
<td>0.54 ± 0.05</td>
<td>0.54 ± 0.05</td>
<td>0.54 ± 0.05</td>
<td>0.024 ± 0.01</td>
</tr>
<tr>
<td>28.17 ± 20.30</td>
<td>296.3 ± 17.12</td>
<td>62.14 ± 2.68</td>
<td>62.14 ± 2.68</td>
<td>62.14 ± 2.68</td>
<td>3.01 ± 0.159</td>
<td>3.01 ± 0.159</td>
<td>3.01 ± 0.159</td>
<td>3.01 ± 0.159</td>
<td>3.01 ± 0.159</td>
</tr>
</tbody>
</table>

**Serum ferritin, serum iron, TIBC, IDA with intravenous iron sucrose**

*TSAT = (serum iron/TIBC) x100 and expressed as percentage. Hormonal analysis was done by chemiluminescent immunometric assay in our institutional lab. Semen analysis was done by single pathologist who was blinded to the study and clinical state of the patients. All lab workers were blinded to the study and clinical state of the patients.

**Table 1: Study parameters in participants before and after treatment of anemia and mean change in parameters after treatment of iron deficiency anemia**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A (n=6)</th>
<th>Group B (n=19)</th>
<th>Mean change after treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td>After treatment</td>
<td>After treatment</td>
<td>Before treatment</td>
</tr>
<tr>
<td>S. FSH (mIU/ml)</td>
<td>0.65 ± 0.014</td>
<td>1.65 ± 0.02</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>S.LH (mIU/ml)</td>
<td>0.54 ± 0.05</td>
<td>1.36 ± 0.08</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>S. Testosterone (ng/dl)</td>
<td>62.14 ± 2.68</td>
<td>159.14 ± 34.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Semen volume(ml)</td>
<td>1.08 ± 0.124</td>
<td>3.01 ± 0.159</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Total sperm count (million/ ml)</td>
<td>34.63 ± 3.29</td>
<td>91.62 ± 52.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Normal Sperm Morphology (%)</td>
<td>20.25 ± 1.92</td>
<td>52.25 ± 1.92</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>RPM (%)</td>
<td>15.66 ± 0.75</td>
<td>51.40 ± 0.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Total Sperm Motility (%)</td>
<td>25.66 ± 1.33</td>
<td>75.83 ± 0.30</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hemoglobin (gm/dl)</td>
<td>3.27 ± 0.96</td>
<td>10.9 ± 0.27</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

S. FSH= Follicle stimulating hormone, S.LH= Luteinizing hormone, RPM= Rapid progressive sperm motility, * = Highly Significant, ! = Significant
in group A than group B (1.93±0.08, 1.63±0.08 respectively) (p <0.01).

Total sperm count in group A was significantly high after correction of anemia (91.62±5.829million/ml) compared to pre-treatment level (34.63±3.29million/ml) (p <0.001). Similarly in group B, after treatment sperm count was significantly higher (91.18±5.84) compared to pre-treatment level (50.12±7.90million/ml) (p <0.001). The mean change in sperm count was significantly of larger magnitude in group A than group B (50.12±1.07, 33.16±0.82 respectively) (p <0.01).

**Correlation of hemoglobin and study parameters in participants, after treatment for iron deficiency anemia**

<table>
<thead>
<tr>
<th>Correlation</th>
<th>r-value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb and serum FSH</td>
<td>0.975</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hb and serum LH</td>
<td>0.985</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hb and serum testosterone</td>
<td>0.978</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hb and semen volume</td>
<td>0.976</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hb and sperm count</td>
<td>0.852</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hb and normal sperm morphology</td>
<td>0.891</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hb and RPM</td>
<td>0.901</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hb and total sperm motility</td>
<td>0.981</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Discussion**

In this study, the effect of treatment of IDA on the pituitary gonadal axis (Serum FSH, LH, Testosterone) and sperm parameters in adult eugonadal males was evaluated. It was found that serum levels of FSH, LH and testosterone along with sperm parameters significantly improved after correction of anemia. The mean change in these parameters was significantly higher in patients having subnormal value of these parameters before treatment (Group A) than in patients having normal pre-treatment level (Group B). The level of anemia (hemoglobin) correlated well with all these parameters.

One possible explanation for improvement in study parameters after anemia correction is hypoxic effect of anemia which results in impairment in hormonal and sperm parameters. Various studies are described in literature supporting hypoxia as a cause of impaired hormonal and sperm parameters.

**Correction of anemia**

Correction of anemia was also found to be associated with gonadotropin hormones levels and sperm parameters in sickle cell disease. Similarly in thalassemia major patients, improvement in hormone levels (serum FSH, LH, Testosterone) and semen parameters (sperm count and sperm morphology) were significantly associated with increase in haemoglobin after packed red cell transfusion.

In mountain trekkers, the effect of chronic hypoxia due to high altitude (2000-5600 meters above sea level) resulted in alteration of human spermatogenic parameters (oligospermia) and these spermatogenic alterations restored 1-6 months after returning to sea level. Thus oxygen supply had some role in physiological mechanisms of spermatogenesis and male fertility. High altitude might affect spermatogenesis and Leydig cell function, negatively but reversibly. Hypobaric hypoxia (high altitude) also inhibits the spermatogenesis in rats and decreases primary spermatocytes and thus suppress spermatogenesis. High altitude (hypobaric hypoxia) was also found to be associated with fall in LH, FSH and Testosterone levels in adult male and these hormones returned to normal level when the persons came to low land.

One pilot study was in echo with our study as this pilot study evaluated semen parameters and hormone levels (serum FSH, LH, Testosterone) before and 12 weeks after iron therapy in adults with iron-deficiency anemia. They found that after correction of anemia, a significant increase of Hb was associated with an increase of Testosterone, FSH and LH. Semen volume, sperm count, sperm motility and sperm morphology improved significantly after anemia correction. In current study, after correction of anemia, significant positive correlation of hemoglobin levels were found with serum FSH, LH, Testosterone levels and sperm parameters (sperm count, semen volume, sperm morphology, sperm motility). Similar findings were reported in previous study in IDA.

Previous reports also had shown significant positive correlation of hemoglobin levels with serum FSH, LH, Testosterone levels and sperm parameters in sickle cell anemia and in...
Physiologically, the testes are at risk of hypoxia as they have high metabolic requirements due to spermatogenesis and peculiar blood supply as approximately 50% of incoming arterial blood is siphoned off via arterio-venous anastomoses in the spermatic cord. Blood vessels are located exclusively between the tubules, and oxygen reaches the lumen of the seminiferous tubules only by diffusion. So, seminiferous tubules operate in a state of relative hypoxia. Whenever oxygen delivery to testes became hampered as in anemia, it would negatively affect spermatogenesis. The deleterious effect of anemia on hormone levels may partially limit the significant findings of this study. We included only IDA patients in our study. We did not include patients with megaloblastic/dimorphic anemia as vitamin B12, and folate can impair spermatogenesis per se, apart from the hypoxic effect of anemia. Larger studies are required to enforce these results.

**Limitations**

The sample size of patients included in our study is smaller (n=25), which may partially limit the significant findings of this study. We included only IDA patients in our study. We did not include patients with megaloblastic/dimorphic anemia as vitamin B12, and folate can impair spermatogenesis per se, apart from the hypoxic effect of anemia. Larger studies are required to enforce these results.

**Conclusion**

IDA had significant negative association with the pituitary gonadal axis (Serum FSH, LH, Testosterone) and sperm parameters in adult eugonadal males. The serum levels of FSH, LH and testosterone along with sperm parameters significantly improved after correction of anemia, especially in patients having subnormal value of these parameters.

So anemia has independent effect on pituitary-gonadal axis and spermatogenesis and should be kept in mind in evaluating patients with suboptimal sperm parameters.

**References**

Obstructive Sleep Apnea in Bronchial Asthma Patients: Assessment of Prevalence and Risk Factors

Ramakant Dixit\textsuperscript{1}, Satyadeep Verma\textsuperscript{2}, Neeraj Gupta\textsuperscript{3}, Amit Sharma\textsuperscript{2}, Arjun Chandran\textsuperscript{2}

Abstract

Background: Sleep-related breathing disorders are group of respiratory disease among them obstructive sleep apnea (OSA) is highly prevalent and seen among those having recognized risk factors. Recent studies have shown that asthma and OSA contribute bi directional relationship where each disorder adversely influences the other one. This study was planned to assess OSA among bronchial asthma patients.

Methodology: This study was conducted at Sleep lab of our department among adult patients of bronchial asthma after institutional ethical committee approval. Eligible and willing to participate patients were subjected to clinical assessment protocol that included history, clinical examination, measurement of Sleep Score, BMI, neck circumference etc followed by overnight Level 1 polysomnography.

Results: 50 patients with age range 30 to 68 years constituted the study population with mean age of 48.16 years. 70% patients were female with male female ratio of 1:2.3. The prevalence of OSA in asthma patients was 46%. 12% patients had mild OSA, 14% had moderate while 20% were having severe OSA. Mean BMI in our study was 27.87 Kg/m\(^2\). OSA patients were associated with more BMI compared to patients without OSA (42% vs. 30%) (p value 0.04). Asthma patients who were smokers had more OSA symptoms compared to non-smokers (p value 0.002). Asthma patients with OSA were also associated with higher neck circumference and more snoring at night time as compared to non OSA population. Uncontrolled asthma was seen in 18 patients and 16 of them were having OSA (p=0.001). Most common co morbid illness in patients with OSA was GERD (78.26%) followed by allergic rhinitis (56%). Most of these patients (82%) were not having associated major local anatomical defect.

Conclusions: OSA is not uncommon in asthma patients. Careful assessment of sleep related symptoms and demographic parameters of asthma patients are essential to suspect diagnosis of OSA. Additional factors like smoking, obesity, GERD and allergic rhinitis are important contributing factor for higher risk of OSA among asthma patients. Early diagnosis of OSA in asthma patients by polysomnography may have a clinical benefit in the management of both diseases.

Introduction

Obstructive sleep apnea (OSA) is characterized by intermittent obstruction of the upper airway during sleep leading to early morning awakening, difficulty in maintaining sleep, hypoxemia and sleep fragmentation. Important risk factors for development of OSA are old age, obesity, smoking, anatomical factors, metabolic disorders etc.\textsuperscript{1} Asthma is recently recognized as an independent risk factor for OSA.\textsuperscript{2} The pathophysiology of these two conditions seems to overlap significantly, as airway obstruction, inflammation; obesity, metabolic syndrome etc. are associated with development of both these diseases. It also suggested that asthma co morbidities, like GERD, nasal polyp and medications for asthma control like oral and inhaled steroid may also contribute to development of OSA. This frequent coexistence of OSA and asthma is also referred as “Alternate Overlap syndrome” now a days.\textsuperscript{3}

Patients with asthma who are at high risk of OSA are more likely to have worse daytime and night time asthma symptoms. Interestingly, patients who are diagnosed with OSA and treated with Continuous Positive Airway Pressure (CPAP) seem to have better asthma control.\textsuperscript{4} There is scanty literature on association between bronchial asthma and obstructive sleep apnea from our country. This study was therefore planned to assess clinical, demographic profile and risk factors for OSA in patients having bronchial asthma at our institution.

Methods

This was a cross sectional study on adult patients presenting with signs, symptoms and history suggestive of asthma and willing to participate in the study after institutional ethical committee approval. The diagnosis of bronchial asthma was based on the Global Initiative for Asthma (GINA) guidelines.\textsuperscript{5} The enrolled patients were assessed by detailed clinical history, clinical assessment for OSA based on day night symptoms, smoking status, Berlin Questionnaire,\textsuperscript{6} measurement of neck circumference and Mallampatti score etc. COPD was ruled out in these patients by suggestive clinical background, radiological assessment and spirometry.

The Body mass index (BMI) was calculated by measurement of height...
in meter and weight in kilogram using following formula:

\[
\text{AHI} = \frac{\text{Total no of Apneas + Total no of Hypopneas}}{\text{Total sleep time (in hours)}}
\]

Based on the AHI, the OSA was classified as following:

- Mild OSA: AHI ≥5/hr and <15/hr
- Moderate OSA: AHI ≥15/hr and ≤30/hr
- Severe OSA: AHI >30/hr

### Results

In the present study, 50 patients of Bronchial Asthma constituted the study population. Most of the patients (40/50, 80%) were between the age group 30-60 years. 13 patients were between 30-40 years, 14 patients were 41-50 years, 13 patients were 51-60 years and 10 patients were >60 years of age. The mean age of patients was 48.16 years. There were 15 male (30%) and 35 female (70%) patients with male:female ratio of 1:2.3.

Most of the patients (56.52%) and hypertension (47.83%). In non OSA group also similar trend was seen in frequency of co morbid illness although their number was less but statistically not significant (Table 4).

Most common co morbidity in OSA group was GERD (78.26%) with statistically significant association (p value 0.03), followed by allergic rhinitis (56.52%) and hypertension (47.83%). Five patients each (21.73%) in OSA group were having Diabetes mellitus and hypothyroidism. In non OSA group also similar trend was seen in frequency of co morbid illness although their number was less but statistically not significant (Table 4).

### Table 1: Severity of OSA in asthma patients

<table>
<thead>
<tr>
<th>OSA</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>4</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Moderate</td>
<td>3</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Severe</td>
<td>4</td>
<td>6</td>
<td>10</td>
</tr>
</tbody>
</table>

### Table 2: Demographic and anthropometric profile of Asthma patients with or without OSA

<table>
<thead>
<tr>
<th>Parameters</th>
<th>No OSA (n=27)</th>
<th>OSA (n=23)</th>
<th>Total (n=50)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>45.74</td>
<td>50.82</td>
<td>48.16</td>
<td>0.573</td>
</tr>
<tr>
<td>Male: female ratio</td>
<td>4:23</td>
<td>11:12</td>
<td>15:35</td>
<td>0.26</td>
</tr>
<tr>
<td>Smoker</td>
<td>1</td>
<td>10</td>
<td>11</td>
<td>0.002</td>
</tr>
<tr>
<td>Mean BMI</td>
<td>27.10</td>
<td>28.11</td>
<td>27.87</td>
<td>0.04</td>
</tr>
<tr>
<td>Mean neck circumference in cm</td>
<td>34.48</td>
<td>36.30</td>
<td>35.14</td>
<td>0.192</td>
</tr>
</tbody>
</table>

### Table 3: Comparison of clinical symptoms in asthma patients with or without OSA

<table>
<thead>
<tr>
<th>Clinical symptoms</th>
<th>No OSA (n=27)</th>
<th>OSA (n=23)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daytime Symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morning headache</td>
<td>16</td>
<td>19</td>
<td>0.137</td>
</tr>
<tr>
<td>Morning dry mouth</td>
<td>6</td>
<td>8</td>
<td>0.503</td>
</tr>
<tr>
<td>Fatigue</td>
<td>23</td>
<td>21</td>
<td>0.82</td>
</tr>
<tr>
<td>decrease concentration</td>
<td>10</td>
<td>13</td>
<td>0.274</td>
</tr>
<tr>
<td>Excessive day time sleepiness</td>
<td>8</td>
<td>11</td>
<td>0.304</td>
</tr>
<tr>
<td>Night symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Snoring</td>
<td>18</td>
<td>21</td>
<td>0.08</td>
</tr>
<tr>
<td>Witness apnea</td>
<td>11</td>
<td>15</td>
<td>0.149</td>
</tr>
<tr>
<td>Disturb sleep</td>
<td>19</td>
<td>15</td>
<td>0.932</td>
</tr>
<tr>
<td>Nocturnal thrust</td>
<td>6</td>
<td>8</td>
<td>0.503</td>
</tr>
<tr>
<td>Nocturnal diuresis</td>
<td>16</td>
<td>15</td>
<td>0.888</td>
</tr>
<tr>
<td>Nocturnal sweating</td>
<td>12</td>
<td>19</td>
<td>0.013</td>
</tr>
</tbody>
</table>

### Table 4: Comparison of co-morbidities in asthma patients with or without OSA

<table>
<thead>
<tr>
<th>Co-morbid illness</th>
<th>No OSA (n=27)</th>
<th>OSA (n=23)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>5</td>
<td>11</td>
<td>0.056</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>3</td>
<td>5</td>
<td>0.526</td>
</tr>
<tr>
<td>Hypothyroid</td>
<td>4</td>
<td>5</td>
<td>0.79</td>
</tr>
<tr>
<td>Allergic Rhinitis</td>
<td>8</td>
<td>13</td>
<td>0.103</td>
</tr>
<tr>
<td>GERD</td>
<td>12</td>
<td>18</td>
<td>0.032</td>
</tr>
</tbody>
</table>
Table 5: Comparison of level of asthma control in patients with or without OSA

<table>
<thead>
<tr>
<th>OSA status</th>
<th>Well controlled (n=13)</th>
<th>Partial controlled (n=19)</th>
<th>Uncontrolled (n=18)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma with OSA</td>
<td>1</td>
<td>6</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Asthma without OSA</td>
<td>12</td>
<td>13</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Prevalence of OSA</td>
<td>7.69%</td>
<td>31.57%</td>
<td>88.88%</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Discussion

23 patients (46%) of bronchial asthma were having OSA confirmed by level 1 polysomnography in the present study. A wide variation in prevalence of Obstructive sleep apnea ranging from 27% to 74% has been found in different studies among asthma patients worldwide. This could possibility due to difference in sample size and selection criteria of study patients. To best of our knowledge we could not found Indian literature on prevalence of OSA among asthma patients evaluated by level 1 polysomnography.

Mean age of asthma patients having OSA was 50.82 years while non OSA group it was 45.74 year. Mean age in OSA group was 52.1±5.9 compared to non OSA group (47.3±21.21 years) in a study by Zidan et al. Another studies by Byun et al and Guven et al also found higher mean age in OSA group. These studies suggest that OSA is more common in middle age group among asthma patients.

Asthma is a female predominance disease. In present study 52.17% female patients were having associated OSA. The female predominance of asthma patients having OSA is also observed by other worker i.e. 59.2% by Madama et al and 66.66% by Zidan et al.

Smoking and obesity are strong predictor of OSA in general as well as in asthma patients. 90.91% smoker asthmatics were also having OSA in present study. Byun et al observed 60.4% smoker having OSA among asthma patients. Several possible factors for development of OSA in smokers include upper airway inflammation, stimulant effects of nicotine on upper airway muscles and increased production of mucus.

In present study, we screen asthma patients for OSA by Berlin Questionnaire and 59.5% patients suspected by Berlin Questionnaire score were found to have OSA on polysomnography. This figure is superior to 39.5% observed by Auckley et al.

Mean BMI in asthma patients with OSA was 28.11 in our study. Zidan et al and Julien et al also observed a higher BMI i.e. 29.2±3.28 and 27.8±1.1 kg/m² respectively among asthma patients having associated OSA. Obesity causes collapsibility of upper air way due to excess fat deposition which contributes to more risk of OSA. Excess weight gain in asthma patients may also occur due to limited ability to exercise, sleep deprivation with increased insulin resistance or the use of oral steroids.

Most common day time symptom in OSA group was fatigue (91.30%) followed by morning headache and decreased concentration. Most common night symptom in OSA group was snoring (91.30%). These findings are consistent with other studies in the literature.

GERD was most common co morbid illness among OSA patients in our study with 78.26% prevalence. Zidan et al found 56% of asthmatic patients with OSA having GERD symptoms. Green et al and Valipour et al reported GERD in 62% and 58% patients respectively. This situation may be due to increased trans diaphragmatic pressure and decreased intra thoracic pressure occurring during the apneic episodes. Proximal migration of gastric acid and prolonged clearance of acid during sleep further causes upper airway dysfunction and tendency to collapse during sleep.

Allergic rhinitis not only causes poor asthma control but is also an associated risk factor for OSA. In a large population based study by Braido et al in 2014, over 1941 patients were evaluated for risk of OSA in asthma patients with or without allergic rhinitis. 47.3% patients with asthma alone were having OSA while 55.9% asthma patients with allergic rhinitis had associated OSA. Zidan et al, Guven et al and Shen et al also found similar results. Allergic rhinitis causes nasal as well as upper airway obstruction in asthma patients, that in turn increases the negative pressure at upper airway during inspiration, ultimately increasing the risk of OSA.

Effect of anatomical factors over incidence of OSA is not clearly defined. There is paucity of data about anatomical defect and its effect on OSA. In current study only 18% OSA patients were having some kind of anatomical defect. Isono et al found adenoid hypertrophy in 57% patients, abnormal hard palate in 29% patients and enlarged palatine tonsil in 14% asthma patients having OSA. Teodorescu and co workers in 2012 found nasal polyps in 15% patient of bronchial asthma. Upper airway inflammation and rhinitis in asthma patients facilitates deviated nasal septum and polyp formation that may block normal air flow and fluid drainage which in turn causes more obstruction at upper airway especially during sleep and may contributes to higher occurrence of OSA in such patients.

Mallampatti score could be an important screening tool for OSA and essential part of pre-test physical examination. However, its role in predicting severity of OSA remains doubtful and needs further study. A cross sectional study by Hukins et al over 953 patients concluded that there was no statistically significant correlation between AHI and Mallampatti score. Our study also could not found a significant correlation between OSA and higher Mallampatti score especially at score 3 and 4 in asthma patients.
There are several studies that links obstructive sleep apnea (OSA) with the level of asthma control and shows that OSA is associated with poor asthma control. Repeated upper airway obstruction results in increased intrathoracic pressure, frequent arousal, sleep fragmentation and intermittent hypoxemia that contributes to activation of inflammatory process both at upper as well as lower respiratory tract. Poor asthma controlled was also observed more commonly in asthma patients having OSA in our study.

There are few limitations in this study. Firstly the study participants were selected from hospital settings who were willing to participate. Secondly there were only few young asthmatic patients. More so, we adopted convenient sampling where all the asthma patients of different age group from community did not have equal chance of selection, therefore findings of this study can’t be generalized. Large sample sizes with multicentre data’s are needed to estimate an actual burden of OSA among asthma patients and explore further details in this association that largely remains under recognized at present.

Despite these limitations our study first time highlights the OSA as important co morbidity in patients of bronchial asthma and its risk factor from our country. We conclude with a remark that careful assessment of sleep related symptoms and demographic parameters of asthma patients is important to sensitize the clinician towards the diagnosis of possible OSA. Additional factors i.e. smoking, obesity, GERD and allergic rhinitis are important contributing factor to suspect higher risk of OSA among asthma patients. In present study, there was no difference in symptoms of excessive day time sleepiness and snoring in the two groups, therefore, the critical symptoms of OSA may not be sufficient to predict the diagnosis of OSA in routine clinical practice. Polysomnography is therefore an important tool for confirming OSA in asthma patients especially among those with poor symptom control despite optimal medical management.

References

Clinical Spectrum and Etiological Evaluation of Patients with Pulmonary Hypertension in Municipal Corporation Hospital of Ahmedabad City

Zalak Malav Gadani1*, Prashant M Bhansali1

Abstract

Objectives: To study the demographical profile and etiological evaluation of patients with pulmonary hypertension

Materials and methods: Total 66 patients coming to medical OPD and admitted in medical wards having pulmonary hypertension were enrolled in study after obtaining approval from ethics committee of our institute. Demographic profile of all these patients and detailed general and systemic examination was done as per the performed proforma. We have utilized multiphase investigative approach for etiological evaluation.

Results: Involvement of younger age group, gender reversibility, housewives and labourers contributing as major occupational etiological factor, were few of the surprising observations in our study. Left sided heart disease and lung parenchymal diseases were most frequent causes of PH.

Conclusion: This study provides some novel information on PH in Indian population. There is, however, a definite need to conduct a large-scale study involving urban as well as rural population to reconfirm the above mentioned new observations concluded in our study.

Introduction

Pulmonary hypertension (PH) is a serious disorder that affects the functional quality of patients in form of disabling the patient in performing routine day to day activities and decreases their life span. If diagnosed early, a better quality of life can be provided. A stepwise approach for investigation of patients suspected of pulmonary hypertension is essential to initiate appropriate treatment. The routine workup of a patient suspected to have pulmonary hypertension could easily be carried out in any well-equipped peripheral hospital in many advanced countries. However, in developing countries the necessary work up can only be done in major tertiary hospitals. The typical patient who diagnosed in a developing country such as India or China often has advanced disease and poor prognosis.1,2

About 20 to 25 million people or more suffering from PH of different causes in the developing world.3 There are regional differences regarding the etiology of PH; for instance, in France, the frequency of PH due to anorexigenic drugs is higher. In one study from Brazil, 30% of PH was due to schistosomiasis.4,5 Therefore, it is likely that there is a strong regional influence in PH aetiologies, justifying the reproduction of these prevalence studies in our country.

Patients presenting with dyspnoea on exertion and pedal oedema are not infrequent in medical OPD. Few of them have no common identifiable cause. On detailed evaluation significant number of such patients is found to have pulmonary hypertension to account for their symptoms. Based on this observation we have decided to systematically study series of such patients and try to conclude some meaningful conclusion that may help in diagnosis and management of such patients in future.

There is a need to study PH in Indian scenario in view of several unique characteristics like high prevalence of certain diseases (as has been well demonstrated in other chronic diseases), attitudes and cultural beliefs of the people which are quite different from the western population. So it is necessary to study demographic profile and etiological evaluation of patient in India to know the disease etiology and course for further management of patients.

Objectives of Study
1. To study the demographical profile of patients with pulmonary artery hypertension
2. Etiological evaluation of patients with pulmonary artery hypertension.

Material and Methodology

It is an observational cross-sectional study, conducted for 1 year duration from May 2013 to May 2014

Inclusion Criteria
Patients admitted in medical wards with symptomatology suggestive of pulmonary hypertension and confirmed by echocardiography (RVSP >40MMHG).

Exclusion Criteria
• Pediatric patients
• Pregnant patients
• Patients having no PH on echocardiography

All patients attending medical OPD and admitted to medical wards having clinical suspicion of PH were subjected to 2dimension echocardiography after obtaining written informed consent from the patient. Pulmonary
hypertension was suspected on the basis of following clinical features. The symptoms and signs suggestive of pulmonary hypertension are Exertional dyspnea, Chest pain, Fatigue, Abdominal discomfort, Pedal Oedema, Hypoxia, Cyanosis, Clubbing, Fatigue, Abdominal discomfort, Pedal Oedema, Oxygen saturation above 90%, Pao2 < 60 found in 13.63%, emphysema in 10.60%, most common ECG finding is p pulmonale (42.42%) followed by non-tricuspid regurgitation (50%).

Most common ECG finding is p pulmonale (42.42%) followed by non-specific ST/T changes (31.81%) and specific ST/T changes (31.81%) and right axis deviation (19.70%).

In systemic examination signs of right side heart failures like congestive hepatomegaly (72.73%), clinically ascites (46.97%), loud s2 (21.21%), presence of gallop (12.12%), murmur of tricuspid regurgitation (50%).

Effects of PH on right side heart failure include right ventricular hypertension (60.6%), right heart dilatation (46.97%), right atrial dilatation (25.76%), right ventricular dilatation (21.21%), right ventricular hypertrophy (12.12%), and tricuspid regurgitation (50%).

In CXR findings, cardiomegaly was found in 80.30%, blunting of cardiophrenic angle in 30.30%, dilated pulmonary artery in 22.72%, tuberculosis in 19.70%, bronchiectasis in 13.63%, interstitial lung disease in 13.63%, emphysema in 10.60%. Most of patients were able to maintain saturation above 90%. Pao2 < 60 found in 15.16%, and Paco2 >45 found in 50%.

Table 1: Clinical features

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnoea</td>
<td>64 (96.97%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>62 (93.93%)</td>
</tr>
<tr>
<td>Pedal oedema</td>
<td>57 (86.36%)</td>
</tr>
<tr>
<td>Coughing</td>
<td>44 (66.67%)</td>
</tr>
<tr>
<td>Abdomen distension</td>
<td>30 (45.46%)</td>
</tr>
<tr>
<td>Abdomen discomfort</td>
<td>23 (34.84%)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>15 (22.72%)</td>
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Table 2: NYHA grading of dyspnoea at time of presentation

<table>
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<th>NYHA grade</th>
<th>Number of patients</th>
</tr>
</thead>
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<tr>
<td>NYHA 3</td>
<td>38 (57.58%)</td>
</tr>
<tr>
<td>NYHA 4</td>
<td>19 (28.79%)</td>
</tr>
<tr>
<td>NYHA 2</td>
<td>07 (10.60%)</td>
</tr>
</tbody>
</table>

Table 3: General examination

<table>
<thead>
<tr>
<th>General examination</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raised jugular venous pressure</td>
<td>59 (89.34%)</td>
</tr>
<tr>
<td>Jaundice</td>
<td>17 (25.76%)</td>
</tr>
<tr>
<td>Use of accessory muscles</td>
<td>17 (25.76%)</td>
</tr>
<tr>
<td>Pallor</td>
<td>07 (10.60%)</td>
</tr>
<tr>
<td>Clubbing</td>
<td>06 (9.09%)</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>04 (6.06%)</td>
</tr>
<tr>
<td>Kyphoscoliosis</td>
<td>03 (4.55%)</td>
</tr>
<tr>
<td>Barrel shape chest</td>
<td>02 (3.03%)</td>
</tr>
</tbody>
</table>

PAH: Pulmonary artery hypertension; PFT: Pulmonary function test; COPD: Chronic obstructive pulmonary disease; HRCT: High resolution computerized tomography; ILD: Interstitial lung disease; CBC: Complete blood count; ANA: Anti nuclear antibody; HIV: Human immune virus; TSH: Thyroid stimulating hormone; LFT: Liver function test.

Fig. 1: An algorithm for workup of patients with PH

Total 66 patients were studied in this study; age group most commonly affected is 51 to 60 years. Mean age group is 53 years. In present study there is slight male preponderance. Most commonly affected group is housewives followed by labours. Smoking was found as risk factor in 20% of patient. Chulha exposure was found as a risk factor in 21%.

Out of 66 patients, 12 patients were hypertensive, 10 patients were of ischemic heart disease, 9 patients had past history of tuberculosis and 8 patients were known case of chronic obstructive pulmonary disease.

In systemic examination signs of right side heart failures like congestive hepatomegaly (72.73%), clinically ascites (46.97%), loud s2 (21.21%), presence of gallop (12.12%), murmur of tricuspid regurgitation (50%).

Most common ECG finding is p pulmonale (42.42%) followed by non-specific ST/T changes (31.81%) and right axis deviation (19.70%).

In CXR findings, cardiomegaly was found in 80.30%, blunting of cardiophrenic angle in 30.30%, dilated pulmonary artery in 22.72%, tuberculosis in 19.70%, bronchiectasis in 13.63%, interstitial lung disease in 13.63%, emphysema in 10.60%. Most of patients were able to maintain saturation above 90%. Pao2 < 60 found in 15.16%, and Paco2 >45 found in
The incidence of PH in global population is 1%. With increase in the age the incidence of PH increases and goes up to 10% in age group >65 years.

Age group most commonly affected in our study is 6th decade of life. Mean age group is 53 years. Mean age in earlier studies were higher (7th decade onwards) than the mean age in present study. This could be explained by fact that previous studies were conducted in western population where incidence of infectious disease like rheumatic heart disease, tuberculosis, COPD, viral infections etc are less as compared to our country and approximately 33% of patients in our study have developed PH secondary to these aetiologies.

Contrary to standard medical literature gender preponderance is reversed in our study. It is generally been shown to have female preponderance in almost all registries. Male: Female ratio was 1.7 in NIH (national institute of health) and 1.9 in French registry data. Male outnumbers females in present study probably due to history of smoking, exposure to fumes and dusty work environment is common in male gender explaining higher incidence of PH in Indian male. Higher rate of illiteracy and lack of health awareness coupled with higher symptom tolerance of average Indian woman could also be a factor for gender reversibility.

For obvious reason our study also confirms that labourers are commonly affected, as reported by previous studies on PH. Additionally, our study also found that high number of females who are housewives, have developed PH. This is probably due to their exposure to chulha run by kerosene fumes, cow dung, and is more prone to develop lung parenchyma disease and pulmonary hypertension compared to smoking as a risk factor in western women.

It is well accepted fact that chronic smoking leads to COPD and COPD itself is an established etiological factor for PH, hence habit of smoking makes person more vulnerable to pulmonary hypertension. Exposure to smoke either due to smoking or any other means (Chulha, passive smoking) has led to PH in 45 patients (67%).

As far as presenting symptoms of PH are concerned (Table 1), Most common complaints of patients were dyspnea on exertion (96.97%) follow by fatigue (93.93%), pedal oedema (86.36%), coughing (66.67%). This is in concert with previous studies those have also reported dyspnea on exertions the most common symptom at presentation. Rich et al1 have reported 60% incidence of dyspnea in patients of pulmonary hypertension, followed by fatigue (19%) and syncope (13%). Total 13 patients were overweight and obese.

NYHA class at time of presentation remains vital prognostic parameter (Table 2). It can also be used as a surrogate marker of general awareness of patient about his health. Most of the patients had NYHA grade 3 breathlessness (57.58%) on presentation indicating lack of health consciousness and relatively poor treatment outcome.

The unique mechanism of pulmonary hypertension in obese individual include obstructive sleep apnoea, obesity hypoventilation syndrome, anorexic agents, cardiomyopathy of obesity and pulmonary thromboembolic disease. Novel mechanisms of pulmonary hypertension in obese are endothelial dysfunctions and hyperuricemia. In our study about 20% of the patients had obesity. However, unlike sleep apnoea and hypoventilation syndrome, ILD and LV dysfunctions probably secondary to

### Table 4: Echocardiography findings

<table>
<thead>
<tr>
<th>Echocardiographic finding</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tricuspid regurgitation</td>
<td>66 (100%)</td>
</tr>
<tr>
<td>RVSP &gt;2.5</td>
<td>66 (100%)</td>
</tr>
<tr>
<td>TR velocity &gt;2.6</td>
<td>57 (86.36%)</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>32 (48.48%)</td>
</tr>
<tr>
<td>RVOT &gt;2.3</td>
<td>28 (42.42%)</td>
</tr>
<tr>
<td>Left ventricle systolic dysfunction</td>
<td>23 (34.84%)</td>
</tr>
<tr>
<td>Right ventricle dysfunction</td>
<td>19 (28.79%)</td>
</tr>
<tr>
<td>Regional wall motion abnormality of left ventricle</td>
<td>16 (24.24%)</td>
</tr>
<tr>
<td>IVC &gt;2.3</td>
<td>12 (18.18%)</td>
</tr>
<tr>
<td>Right atrium area &gt;28 cm2</td>
<td>12 (18.18%)</td>
</tr>
<tr>
<td>Pulmonary regurgitation</td>
<td>11 (16.67%)</td>
</tr>
<tr>
<td>Size of left atrium &gt;4.5</td>
<td>06 (9.09%)</td>
</tr>
<tr>
<td>Congenital anomaly</td>
<td>05 (7.58%)</td>
</tr>
<tr>
<td>Left ventricle diastolic dysfunction</td>
<td>04 (6.06%)</td>
</tr>
<tr>
<td>Rheumatic heart disease</td>
<td>03 (4.55%)</td>
</tr>
</tbody>
</table>

10.60%.

### Table 5: Etiological distributions

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricle dysfunction</td>
<td>16 (24.24%)</td>
</tr>
<tr>
<td>Interstitial lung disease</td>
<td>09 (13.63%)</td>
</tr>
<tr>
<td>Tuberculosis + bronchiectasis</td>
<td>06 (9.09%)</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>05 (7.58%)</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>05 (7.58%)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease + Congestive cardiac failure</td>
<td>04 (6.06%)</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>03 (4.55%)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>03 (4.55%)</td>
</tr>
<tr>
<td>Rheumatic heart disease</td>
<td>03 (4.55%)</td>
</tr>
<tr>
<td>Undiagnosed</td>
<td>02 (3.03%)</td>
</tr>
<tr>
<td>Fibrotic lung disease</td>
<td>02 (3.03%)</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>02 (3.03%)</td>
</tr>
<tr>
<td>Restrictive lung disease</td>
<td>01 (1.51%)</td>
</tr>
<tr>
<td>Chronic thromboembolism</td>
<td>01 (1.51%)</td>
</tr>
<tr>
<td>Obstructive sleep apnoea</td>
<td>01 (1.51%)</td>
</tr>
<tr>
<td>Thryotoxicosis</td>
<td>01 (1.51%)</td>
</tr>
<tr>
<td>Lymphangitis carcinomatosis</td>
<td>01 (1.51%)</td>
</tr>
</tbody>
</table>

### Table 6: Classifications according to type of pulmonary hypertension

<table>
<thead>
<tr>
<th>Type of pulmonary hypertension</th>
<th>Number of patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>10</td>
<td>15.15%</td>
</tr>
<tr>
<td>Type 2</td>
<td>24</td>
<td>36.36%</td>
</tr>
<tr>
<td>Type 3</td>
<td>31</td>
<td>46.97%</td>
</tr>
<tr>
<td>Type 4</td>
<td>1</td>
<td>1.51%</td>
</tr>
</tbody>
</table>

Pulmonary function test was performed in 30 patients, out of which 12 reports were inconclusive due to poor effort, obstructive pattern in 13.64%, and restrictive pattern in 13.64%.

HRCT Thorax performed in 28 patients. Bronchiectasis found in 8 patients, tuberculosis in 8 patients, interstitial lung disease in 7 patients, fibrosis in 2 patients, chronic thromboembolism in 1 patient.

In present study, left ventricle dysfunction was most common cause. Among respiratory causes, interstitial lung disease, tuberculosis, and bronchiectasis predominate over COPD. Thryotoxicosis and Lymphangitis carcinomatosis are rare cause of pulmonary HTN. There has been no patient of familial PAH.

Most common type of pulmonary hypertension in present study is type 3 (46.97%). Type 2 pulmonary hypertension found in 36.36%. Type 1 pulmonary HTN found in 15.15%. There has been no patient of familial PAH. Chronic thromboembolism found only in one patient. The absence of patients of type V PH (miscellaneous causes like sarcoidosis, histiocytosis X, etc.) is probably due to rarity of these conditions and under detection due to lack of knowledge about the association with PH in these conditions.

**Discussion**

The incidence of PH in global population is 1%. With increase in the age the incidence of PH increases and goes up to 10% in age group >65 years.
Obesity associated cardiomyopathy were major etiological factors in our study. Thromboembolism was found to be least important aetiology for PH in obese patients.

Presenting signs, symptoms and systemic examination findings do not reveal anything special to confirm the diagnosis of PH on clinical basis (Table 3). However, pedal oedema not responding adequately to diuretic therapy in absence of significant CCF and liver dysfunction was found to be a reasonable ground to suspect PH and subject such patients to ECHO for final confirmation of PH (Table 4).

In developing countries 80% of cases are due to congenital heart disease, valvular heart disease and infections and most of these cases are younger (age <65 years).Left sided ventricular dysfunction or valvular dysfunction result in chronic left atrial hypertension leading to passive backward transmission of this pressure to pulmonary vasculature leading to pulmonary hypertension (Tables 5 and 6).

Left sided heart diseases and lung parenchymal diseases are most frequent cause of pulmonary hypertension in our study, matching with the etiological factors in younger population (< 65 years) of western world. There has been no patient of familial PAH. This is quite understandable considering the relative rarity of condition, cost and availability of genetic testing and feasibility of invasive procedure like cardiac catheterization as well as small number of study population. Connective tissue diseases are also less common as compared to western studies, a finding difficult to explain.

Conclusion

This study provides some novel information on PH in the subcontinent. Total 66 patients presenting with pulmonary hypertension were studied for demographic, clinical, etiological and echocardiographic data. Some of the findings are quite similar to the western world but few interesting observations have also emerged. Male outnumbers females in present study. Mean age group is 53 years, much younger than western world. Housewives and labourers are commonly affected. Left sided heart diseases and lung diseases are most frequent cause of pulmonary hypertension. Pulmonary thromboembolism is infrequent.

Limitation of study

Right heart catheterization is gold standard for diagnosis of pulmonary hypertension, but this facility is not available in our institute, so it is not done – is the main limitation of our study.

A definite need to conduct a large-scale study involving urban as well as rural population to reconfirm the above mentioned etiological and gender differences found in our study compared to western literature data.

Abbreviations

OPD – Out door patient department; PH – Pulmonary Hypertension; RVSP – Right ventricle systolic pressure; ECG – Electrocardiogram; 2D ECHO – 2 dimension echocardiography; CBC – Complete blood count; RBS – Random blood sugar; RFT – Renal function test; LFT – Liver function test; CXR (PA) – Chest X-ray postero-anterior view; NYHA – New York heart association; BMI – Body mass index; IVC – Inferior vena cava; COPD – Chronic obstructive pulmonary disease; ILD – Interstitial lung disease; CCF – Congestive cardiac failure

References

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Metformin Hydrochloride 850 mg SR + Glimpiride 2 mg

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8th - 10th March, 2019 (Friday - Sunday)

With Faculty From
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City ___________________________ Pincode ___________________________ State / Country ___________

Mobile Number / Contact No (with area code) ___________________________ Email-id ___________________________

PAYMENT DETAILS

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* Includes PHFI/CDI course participants
# Health care providers Non MBBS / Para Medics / Researchers.
Note: Final decision on registration will be taken by Organizing Committee.
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Young Hearts go Ischemic too

Amit Gulati¹, Cinosh Mathew², Rajneesh Calton³*

Abstract

Introduction: Young presentation of acute coronary syndrome (ACS) has been poorly described in literature. We hereby evaluate patients younger than 30 years.

Material and Methods: In this prospective study we enrolled 1377 patients who underwent coronary angiography for symptoms concerning for acute coronary syndrome over a period of one year.

Results: Male predominance (100%) was seen among the young patients (less than 30 years) with most common presentation being chest pain. Incidence of ST elevation myocardial infarction (STEMI) was significantly higher (75%) than non-ST elevation myocardial infarction/ unstable angina (NSTEMI/UA). Most common associated risk factor was current smoking (41.6%). As compared to elderly, young patients were seen to have better outcome with percutaneous coronary interventions (PCI) and thrombolysis.

Conclusions: Very young <30 years suffer from ischemia too and may differ in presentation, risk factors and outcome as compared to old. Primary prevention of avoidable risk factors should be aggressively promoted among young.

Introduction

Considering the potential years of life lost, acute coronary syndrome (ACS) is becoming a major concern in young population. ACS is a term that is applied to various manifestations of ischemic heart disease which can range from unstable angina, non ST elevation Myocardial infarction (NSTEMI) to ST elevation MI (STEMI). Various risk factors that can contribute to an early occlusion of coronary vessels include diabetes mellitus, hypertension, obesity, smoking, dyslipidemia, various genetic factors and a hereditary prevalence. ACS manifests most commonly as sudden onset chest pain due to ischemia caused by occlusion of one or more main coronary arteries or its branches. Though the overall prevalence of coronary syndrome is much more in middle aged and elderly population but presently it is no more an exception in young.

Considering the morbidity and mortality burden associated with ACS, we certainly need to draw our attention towards its clinical presentation, management and outcome in young patients.

This prospective study was designed with an aim to assess acute coronary syndrome: its various manifestations, risk factors, treatment measures and the clinical outcome with a short term follow up in young patients aged 30 years or less. The usual study of ACS in young has been for population <45 years or in 30-45 year range. To the best of our knowledge ours is among the very few studies in medical literature where such a young presentation of ACS has been evaluated.

Material and Methods

Patient selection

Consecutive 1377 patients admitted with ACS who underwent coronary angiography over a span of one year were studied. Majority of patients were over 40 years of age (1303/1377) while 74 patients were under 40 years. 62 out of 74 were in the age group 30-40 years and 12 out of 74 were under 30 years. All these 12 young patients were males. In our series, these 12 patients were evaluated for the clinical presentation, various cardiovascular risk factors, prompt management measures and their clinical response. Review of the history and physical examination recorded at the time of admission yielded information about risk factor and presentation. Data collected included demographics, smoking habits, drug use, family history of cardiovascular disease, hypertension, glucose intolerance or hyperlipidemia and physical activity at the onset of myocardial infarction. Location of infarction, angiographic results, complications, and other follow-up data were added as they were collected.

Clinical diagnosis

ACS comprised of one of the following diagnosis: unstable angina, NSTEMI and STEMI. The clinical diagnosis of ACS was based on few parameters such as presenting symptoms and the initial electrocardiogram findings. A change in the level of cardiac biomarkers (creatinine kinase, CK-MB, troponin) with one value being above the 99th percentile of upper reference limit (URL) is required for diagnosing MI. In addition to symptoms and ECG changes, new regional wall abnormality also point towards the diagnosis of MI. Based on the ST segment elevation on initial ECG along with elevated cardiac markers, diagnosis of STEMI was made while patients falling into the category of NSTEMI presented with cardiovascular symptoms or ECG changes suggesting ACS or both with elevated cardiac markers while unstable angina was diagnosed when patient presented with symptoms but the level of cardiac markers was within the normal range.

Cardiovascular risk factors analysis

The various cardiovascular risk factors were analysed. Hypertension and diabetes mellitus were considered...
Table 1: Summarises symptoms, signs and angiographic findings amongst the young ACS patients (< 30 years)

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>12</th>
<th>30 M</th>
<th>Chest pain</th>
<th>Smoking</th>
<th>At rest</th>
<th>Double Vessel PCI with Stenting to Proximal LAD</th>
<th>Recovered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation of Pain</td>
<td>8.3%</td>
<td>(1/12)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>25%</td>
<td>(3/12)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Signs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bradycardia</td>
<td>8.3%</td>
<td>(1/12)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>16.6%</td>
<td>(2/12)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cardiogenic Shock</td>
<td>8.3%</td>
<td>(1/12)</td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Risk Factors</td>
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<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>25%</td>
<td>(3/12)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Diabetes</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>41.6%</td>
<td>(5/12)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Angiographic Findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal Coronaries</td>
<td>16.6%</td>
<td>(2/12)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single Vessel Disease</td>
<td>50%</td>
<td>(6/12)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Double Vessel Disease</td>
<td>16.6%</td>
<td>(2/12)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triple Vessel Disease</td>
<td>0</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Ectasic Coronaries</td>
<td>16.6%</td>
<td>(2/12)</td>
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</tr>
</tbody>
</table>

to be present if diagnosed in accordance with the defined practice guidelines. History of tobacco smoking as well as current smoking was another risk factor that was analysed due to its adverse cardiovascular effects. A positive family history of coronary artery disease (CAD) was considered if CAD was seen in first degree relative.

Baseline investigations and coronary angiogram analysis

An initial electrocardiogram (ECG) formed the common baseline investigation for all patients. An echocardiography was performed to further analyse the cardiac chambers and cardiac wall abnormalities along with analysing ejection fraction. Baseline coronary angiogram was performed and analysed on Seimens Axiom Artis Zee cathlab. The digital angiograms were analysed using QCA at the cardiology catheterization lab of Christian Medical College, Ludhiana. Various quantified parameters included reference vessel’s diameter, point of maximum stenosis, percentage diameter stenosis and length of stenotic segment.

Intervention and post-intervention analysis

An overall assessment of the severity and nature of coronary stenosis was performed to further decide the need of percutaneous coronary intervention (PCI). PCI with stenting was done depending upon degree of stenosis.

Statistical analysis

Statistical analysis was done with Statistical Package for Social Sciences (SPSS, version 16.0, SPSS, and Chicago, IL, USA). A descriptive analysis primarily focusing on percentage distribution and incidence of clinical presentation, various risk factors and treatment outcome was performed.

Results

A total of 1377 patients admitted with ACS underwent coronary angiogram. Young patients aged < 30 years accounted for 0.87% of the total coronary angiograms performed in our institution during the study period.

A clear male predominance (100%) was seen with none of the young patient aged <30 being female. Among these young males various presentations were analysed. Most frequent presenting symptom observed was chest pain though with a variable duration with or without radiation of chest pain. However bradycardia (8.3%), dyspnoea (25%) and signs of cardiogenic shock (8.3%) were less commonly observed among young. Amongst the young, incidence of STEMI was significantly higher (75%) than NSTEMI/UA (25%). The most common risk factor seen was current smoking (41.6%) while hypertension was seen in 25% of young patients.

Coronary angiographic findings were assessed. A typical picture of diffuse atherosclerotic lesions involving multiple vessels was less common. Single vessel disease was the most common angiographic finding seen in 50% of young ACS patients while 16.6% showed a double vessel coronary artery disease.

Different therapies were based on the angiographic findings and the clinical diagnosis. PCI with stenting and thrombolysis were more commonly used in patients with STEMI (88.8%) while a conservative management and symptom based approach was a common line of action for patients with NSTEMI/UA. A good clinical outcome was seen in young patients from both PCI as well as thrombolysis. Only one patient presenting late with cardiogenic shock expired during hospitalisation while the rest showed a good response.

Discussion

Our analysis emphasises various
differences in presentation, risk factors, clinical outcome of ACS among young patients as compared to the old patients. Firstly, the commonest presenting complaint was chest pain as against older age group where signs of frank heart failure are more commonly seen. Secondly, higher incidence of STEMI was found in young patients (75%).

As seen by Tuzcu et al, smoking was the commonest risk factor (41.6%) adding to the early occlusion of coronaries in our analysis too. A favourable clinical outcome was the most positive difference analysed in our study. All our patients less than 30 years of age were males. This is in accordance with the study conducted by LM Branco et al. This may be due to the more widespread prevalence of risk factors like smoking and hypertension among young males. The low incidence of MI in young women limited our ability to investigate this entity adequately in young females. None of our patients who had ACS at less than 30 years of age was a female. Risk factors associated with MI in men had similar implications in women, with oral contraceptives being an additional consideration.

Schoenenberger et al. showed that chest pain is the commonest presentation of ACS in young. Our study affirms this statement and further shows that in comparison to signs of frank heart failure, chest pain was the most frequent presentation with a high incidence of 91.6%. Other symptoms such as bradycardia, hypotension were a less common presentation of ACS.

Morillas et al found STEMI to be the presenting feature in 80% of young patients. Our study is in accordance with their study as STEMI was seen in 75% of patients and NSTEMI/UA in 25% of patients. This could be attributed to the commoner single vessel involvement with plaque rupture among young as compared to a more diffuse atherosclerotic disease in the older patients.

As previously analysed and reported regarding the cardiovascular risk factors, we saw similar high risk prevalence with tobacco smoking. Diabetes and hypertension were less commonly seen as against the older age group. Family history of premature CAD was present in none of our patients as compared to 40.2% by Mark et al in American population. This may be due to the changing lifestyle and eating habits among Indians.

Studies conducted previously have shown high prevalence of eliciting substance abuse leading to cardiovascular manifestations. One of the most common among these was cocaine. In our study none of the patients had history of cocaine abuse, though this may be underreported due to social taboos.

In young patients sudden rupture in a previously insignificant plaque may lead to acute presentation. An acute physical stress or an emotional strain leads to a sudden increase in the coronary shear forces. Along with the genetic predisposition vasospastic component predisposes to the sudden plaque rupture. It has been seen that exertion prior to myocardial infarction is more common in younger patients or in those with normal coronaries, suggesting coronary spasm as a possible etiology. If we successfully characterize and understand the mechanism of disease in young, the preventive and curative measures will be vastly improved. Although no firm association could be established, one of our patients presented with sudden onset chest pain while playing cricket. Coronary angiogram showed dissection and occlusion of proximal LAD.

In our study only 16.6% of young presenting with ACS had normal coronary vessels. Majority had a single vessel involvement as previously seen by Schoenenberger et al. Single vessel disease is a major target of reperfusion therapies and thrombolysis. A favourable outcome was seen in majority of our patients which is in accordance with the mortality analysis reported previously. A probable explanation could be less extensive disease among young and a prompt pharmacological or catheter intervention. Percutaneous stenting as well as thrombolysis showed a good response in STEMI and NSTEMI patients with a quick recovery in majority of young.

Arzamendi et al studied the cause of sudden cardiac death (SCD) among young and found that CAD was the main cause leading to 37% of deaths among 21-30 year old and a major share of 80% deaths in 31-40 year old. In our study majority of patients showed a good response to various treatment measures while only one patient presenting late with cardiogenic shock expired during hospitalisation. There was no young patient with sudden cardiac death in our study.

The gender differences between smoking in males and females has been declining in the recent years and smoking prevalence among young is increasing specially in developing countries. It has been analysed that maintaining a healthy lifestyle throughout young adulthood does lower the cardiovascular disease risk profile during middle age. Strong public health and individual efforts are essential to improve and maintain healthy lifestyles in young adult.

Conclusions
To conclude, very young <30 years suffer from ischemia too and may differ in presentation, risk factors as well as outcome of ACS as compared to old. Symptoms pointing towards cardiac ischaemia should not be ignored in the young patients and it needs an early intervention and treatment. Awareness about heart attack, early referral and evaluation is important as a quick response to reperfusion therapy can be life saving. Every effort should be made to spread awareness about avoidable risk factors especially smoking in the young.

Sources of Funding
The authors declare no source of funds for research support.

References
Severe Thrombocytopenia in Dengue Fever and Vitamin B12 Level

Sandeep Tak1*, Geethu Chachappan2, Jagdambe Singh Rathore2, Sheshkaran Singh Charan2, Ramniwas Bijarniya1, Manoj Lakhotia3

Abstract

Objective: To document correlation between vitamin B12 deficiency and severity of thrombocytopenia, platelet recovery and duration of hospital stay in dengue fever patients.

Methods: This prospective observational study was done in dengue fever patient with severe prolonged thrombocytopenia (<20,000 µl and > 2 days duration). Patient with underlying malignancy, hematological disorders, septicemia, or use of any drug which may cause thrombocytopenia, were excluded. Standard statistical methods were used.

Results: Total 40 subjects were included in current study. Twenty one were male and mean age was 25±12 years. Forty percent subjects were having B12 level < 200 pg/L and mean B12 level was 336.9±362.36 pg/L. SDS requirement was highest in B12<100 pg/L group (3±1.41) as compared to other groups. Time required for recovery of plateletes to 20000/µl threshold, was also highest in B12<100 pg/L group (5.75±0.95days) as compared to other groups. Duration of hospital stay was also highest in B12<100 pg/L group (5.25±1.25days) as compared to other groups. There was no relation between B12 levels and other complications of dengue like bleeding, serositis, and shock.

Conclusion: Our study suggests that B12 deficiency may responsible for severe thrombocytopenia; slower platelates count recovery and prolonged hospitalisation in dengue fever patients.

Introduction

Dengue is one of the most significant arboviral diseases of humans worldwide. It is predominantly distributed in tropical and subtropical regions that are the natural home for its vector, mosquitoes of the genus Aedes.1 The causative aetiological agent is the Flavivirus genus of family Flaviviridae, otherwise called dengue virus (DENV).2 Infection with DENV may be subclinical or symptomatic. Dengue fever clinical illness is traditionally classified, in order of increasing severity, as either dengue fever (DF), dengue haemorrhagic fever (DHF) or dengue shock syndrome (DSS). More recently, the WHO proposed a revised classification of clinical infection: dengue; dengue with warning signs; and severe dengue.1 DF is due to primary infection with any of the serotypes and is typically mild and self-limiting. Recovery from infection is generally complete and confers lifelong homotypic immunity. DF manifests as a fever for 2–10 days, headache, retroorbital pain, joint and muscle pain with skin rashes.2 Secondary infection with a other serotype generates cross-reactive antibodies, which increases the potential risk of antibody-dependent enhancement of disease, a form of immunopathology. Hence, recurrent infection is the major risk factor for the serious, often fatal, complications of DHF and the rarer DSS. These are marked by problems of capillary permeability, a decrease in platelet count, disordered blood clotting, severe bleeding, and for DSS alongside systemic shock leading to organ failure.1,3

There are no large epidemiological study to assess B12 level in Indian population but few studies suggest that Vitamin B12 deficiency is common in Indian populations with prevalence range of 35% to 60%.8,9 Vitamin B12 is an important factor required for erythropoiesis and thrombopoiesis. Approximately 10 % of patients with symptomatic B12 (cobalamin deficiency) have significant thrombocytopenia.5 There are case reports associating B12 deficiency with thrombotic thrombocytopenic purpura (TTP) like picture.6,7

However, search on pubmed has failed to reveal any study/case report looking in B12 level in patients with dengue and severe thrombocytopenia.

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4. Corresponding Author
Received: 02.08.2017; Accepted: 20.03.2018
Table 1: Vitamin B12 level and single donor platelets requirement

<table>
<thead>
<tr>
<th>B12 group (number)</th>
<th>SDP</th>
<th>ANOVA</th>
<th>P-value</th>
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<tr>
<td>B12&lt;100 pg/L (4)</td>
<td>3.00</td>
<td>1.414</td>
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<tr>
<td>B12 101-200 pg/L (12)</td>
<td>1.17</td>
<td>.835</td>
<td></td>
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<tr>
<td>B12 201-300 pg/L (13)</td>
<td>1.46</td>
<td>1.12</td>
<td>2.145</td>
</tr>
<tr>
<td>B12&gt;300 pg/L (11)</td>
<td>1.36</td>
<td>1.286</td>
<td>.096</td>
</tr>
<tr>
<td>Total (40)</td>
<td>1.50</td>
<td>1.198</td>
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Table 2: Vitamin B12 level and platelet recovery time

<table>
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<th>B12 group</th>
<th>Platelet Recovery</th>
<th>ANOVA</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>B12&lt;100 pg/L (4)</td>
<td>5.75</td>
<td>.957</td>
<td></td>
</tr>
<tr>
<td>B12 101-200 pg/L (12)</td>
<td>4.08</td>
<td>1.165</td>
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<tr>
<td>B12 201-300 pg/L (13)</td>
<td>3.38</td>
<td>0.96</td>
<td>9.072</td>
</tr>
<tr>
<td>B12&gt;300 pg/L (11)</td>
<td>3.00</td>
<td>.000</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>3.73</td>
<td>1.716</td>
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Table 3: Vitamin B12 and hospital stay

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<th>Correlation between</th>
<th>Pearson correlation</th>
<th>P-value</th>
<th>Interpretation</th>
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</thead>
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<tr>
<td>B12 group and SDP</td>
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<td>.239</td>
<td>No correlation</td>
</tr>
<tr>
<td>B12 group and number of hospital stay</td>
<td>-0.468</td>
<td>.002</td>
<td>Correlation exist</td>
</tr>
<tr>
<td>B12 group and platelet recovery</td>
<td>-0.644</td>
<td>.000</td>
<td>Correlation exist</td>
</tr>
</tbody>
</table>

Table 4: Vitamin B12 level and duration of hospital stay

<table>
<thead>
<tr>
<th>B12 group (number)</th>
<th>Duration of hospital stay</th>
<th>ANOVA</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>B12&lt;100 pg/L (4)</td>
<td>5.25</td>
<td>1.258</td>
<td></td>
</tr>
<tr>
<td>B12 101-200 pg/L (12)</td>
<td>4.67</td>
<td>1.435</td>
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</tr>
<tr>
<td>B12 201-300 pg/L (13)</td>
<td>4.0</td>
<td>1.10</td>
<td>2.796</td>
</tr>
<tr>
<td>B12&gt;300 pg/L (11)</td>
<td>3.64</td>
<td>.505</td>
<td></td>
</tr>
<tr>
<td>Total (40)</td>
<td>4.23</td>
<td>1.209</td>
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</table>

Material and Methods

We conducted a prospective observational study in the Department of Medicine at Dr. Sampoorna Nand Medical College, Jodhpur. Admitted patients who were positive for NS1 antigen/IgM/ELISA for dengue along with platelet counts less than 20000/µl and were showing slow recovery of platelets i.e., persisting below 20000/µl for 2 days or more, were included in the study. Patients with underlying malignancy, hematological disorder, sepsis, or use of any drug which may cause thrombocytopenia, were excluded from study.

Clinical features, hematological and biochemical parameters were noted and vitamin B12 levels were measured. Single donor platelets (SDP) transfusion was done if patient was actively bleeding or if platelet levels were less than 10000/µl. For the analysis purpose patients were divided into four groups according to B12 level, viz, B12<100 pg/L (n=4), B12 101-200 pg/L (n=12), B12 201-300 pg/L (n=13), and B12>300 pg/L (n=11).

SDP requirement was highest in B12<100 pg/L group (3±1.41) as compared to other groups (Table 1), but it was not statistically significant (p-value=0.96, ANOVA=2.14). Time required for recovery of platelets to 20000/µl threshold, was also highest in B12<100 pg/L group (5.75±0.95 days) as compared to other groups (Table 2 and Figure 4), and it was statistically significant (p-value=0.0, ANOVA=9.07). Duration of hospital stay was also highest in B12<100 pg/L group (5.75±0.95 days) as compared to other groups (Table 3), and it was statistically significant (p-value=0.04, ANOVA=2.79) (Table 4).

There was no relation between B12 levels and other complications of dengue like bleeding, sepsis, and shock.

Results

Total forty subjects were included in study. Twenty-one were male and remaining were female subjects. Mean age of the patients were 25±12 year. Twelve patients were non-vegetarian rest all were vegetarian. Forty percent subjects were having B12 level < 200 pg/L and 72% of the patients had B12 level < 300 pg/L and mean B12 level was 336.9±362.36 pg/L. Mean lowest platelet count was 8090±3968/µl (Figure 1). Mean duration of hospital stay was 4.23±1.20 days and mean single donor platelets (SDP) transfusion was 1.5±1.19 (Figures 2 and 3).

For the analysis purpose patients were divided in to four groups according to B12 level were, viz, B12<100 pg/L (n=4), B12 101-200 pg/L (n=12), B12 201-300 pg/L (n=13), and B12>300 pg/L (n=11).

SDP requirement was highest in B12<100 pg/L group (3±1.41) as compared to other groups (Table 1), but it was not statistically significant (p-value=0.96, ANOVA=2.14). Time required for recovery of platelets to 20000/µl threshold, was also highest in B12<100 pg/L group (5.75±0.95 days) as compared to other groups (Table 2 and Figure 4), and it was statistically significant (p-value=0.0, ANOVA=9.07). Duration of hospital stay was also highest in B12<100 pg/L group (5.75±1.25 days) as compared to other groups (Table 3), and it was statistically significant (p-value=0.04, ANOVA=2.79) (Table 4).

Discussion

Often primary reason for admission in dengue patients is thrombocytopenia and fear factor associated with thrombocytopenia. Duration of admission is also often determined in India by recovery of platelet counts to “safe level” i.e., > 20000/µl. In several studies, there was no direct correlation between severity of thrombocytopenia and dengue complication. In some subset of dengue patients recovery from thrombocytopenia is swift, while in other subset it may take several days. We started this study with presumption that there may be other factors that may be contributing to thrombocytopenia and its slow recovery, during acute hematological/hematopoietic stress. Identifying and correcting contributory factor may probably cutdown duration of admission in patients with dengue fever and severe thrombocytopenia. Severe vitamin B12 deficiency may be associated with thrombocytopenia apart from anemia and leukopenia. Vitamin B12 deficiency is common in Indian population; therefore, we planned this pilot study to test the hypothesis that vitamin B12 level may have correlation with prolonged and severe thrombocytopenia in some patients.

In current study requirement for SDP was highest (3.0±1.41) in a group with vitamin B12 level less than 100pg/L compared to group B12>300 pg/L (1.36±1.2860), although it was not statistically significant. This suggest that severe B12 deficiency may prolong severity of thrombocytopenia, as in current study SDP was transfused only if platelets persisted below 10000/µl.

This was confirmed by another parameter measured i.e., platelet recovery time (time taken to recover to >20000/µl). This parameter was selected as during in-patient managemnt as the platelets recover beyond 20000/µl and if patient is otherwise fit, she/he is considered for discharge. Platelet recovery time was also maximum in B12<100 pg/L group (5.75±0.95 days) as compared to group with B12>300 pg/L (3.0±0 days) and it was statistically...
significant. As it is clear from Table 2 more severe, the B12 deficiency was more prolonged was platelet recovery time.

As discussed earlier, duration of hospital stay is often associated with severity of thrombocytopenia and time it takes to recover to relatively safer level. Similar trend was seen in duration of hospital stay: Hospital stay (in days) was also highest in vitamin B12<100 pg/L group (5.25±1.25days) as compared to group with B12>300 pg/L (3.64±0.5days) and it was statistically significant. As it is obvious from Table 3 as the severity of vitamin B12 deficiency increased so does the hospital stay.

There are no published studies measuring these parameters against vitamin B12 level so we cannot compare with any other study.

Limitation of study: We measured vitamin B12 level only in patients with severe thrombocytopenia as we were testing our hypothesis. Therefore, it had limited number of patients. A larger study is required to confirm these preliminary findings. Best approach would be to measure vitamin B12 level in large cohort of dengue patients and plot it against platelet level. Next logical step should be to see response to injectable B12 supplementation in such patients.

**Conclusion**

Vitamin B12 deficiency may be a contributing factor to development of severe thrombocytopenia in dengue fever, particularly in Indian population. Severe vitamin B12 deficiency may prolong the hospital stay and increase the requirement of platelet transfusion.

**References**

Qualitative Analysis of the Most Cited Publications from Leading Indian Medical Institutions

Anita S Malhotra¹, Nusrat Shafiq², KK Talwar³, Samir Malhotra⁴*

Abstract

Background and Objectives: The most important responsibility of physicians is research - advancement of medical knowledge is the core on which the other responsibilities, patient care and research, are based. This study was planned to conduct a qualitative analysis of the major publications from the the country’s leading medical institutions.

Methods: We used Scopus to generate a list of total number of publications from the topmost institutions, the number of citations, and citations per article. We calculated the h-index, g-index, i-10 index, and h5-index for these institutions. A more detailed analysis was carried out for the top 20 most cited papers in each of the institutions. Only descriptive statistics were used.

Results: Among the top 10 medical institutions included, AIIMS, Delhi and PGIMER, Chandigarh were the top institutes, accounting for more publications and citations than the next eight institutions combined. The other institutions also managed to publish a large number of highly-cited papers. AIIMS was the leading institution when other indices were calculated. Among the most-cited articles, >80% had first/corresponding authors from outside India. A large number papers remained uncited, even after many years of publication.

Interpretation and conclusions: Uncited papers could be a result research conducted with the purpose of getting the numbers needed for promotion (NPN). Importance of collaborative research was seen to be an important factor when citations are considered. Even with the huge resource deficit, our institutes managed to publish a decent number of highly cited articles, which can be boosted if funding situation is improved.

Introduction

The word doctor is derived from the Latin word ‘docere’, meaning, ‘to teach’. From where do we get the teaching matter?

It has recently been shown that lower levels of serum calcium, even within the normal range, increase the risk for sudden cardiac arrest. These findings need to be ‘taught’, with the accompanying editorial stating, “Low serum calcium levels may be considered a potential risk factor for sudden cardiac arrest...........” with the remark that these findings should be interpreted with caution.

Similarly, when we choose to use a drug in the treatment of some illness, the confidence that the drug works comes only from research.

Consequently, although the World Medical Association Declaration states, “....... THE HEALTH AND WELL-BEING OF MY PATIENT will be my first consideration ........”, neither healthcare, nor teaching can occur without research.

Therefore, we believe that the most important responsibility of physicians is to do research - advancement of medical knowledge forms a core component of physicians’ work, as the various Codes of Ethics state.

Research in India is highly dichotomized – on the one hand, more than half of our medical institutions did not publish even a single paper over a ten-year period between 2005 to 2014, on the other hand, some institutions have continued to produce hundreds of publications annually, as seen in several studies over the last decades.

Similar patterns were observed when we recently analyzed data in two specific areas – Clinical Pharmacology and Chemotherapy as part of the International Council for Science National Committee-commissioned Status Report on Pharmacological Research in India for the past 5 years.

A preliminary analysis of publications emanating out of some of the leading institutions of the country by us showed that less than 0.5% of the publications in these top institutions were cited >100 times. However, this was not a systematic study and we did not thoroughly analyze topmost publications from the leading institutions of the country.

This study was thus planned to conduct a qualitative analysis of the major publications from the the country’s leading medical institutions.

Methods

We included medical institutions which are widely considered to be the best in India. We used Scopus to generate a list of total number of publications from each of these institutions, year-wise list in the last 5 years, the number of citations, and citations per article. We also noted the year for which Scopus has the first entries of publications from these institutions.

For each of the selected institutes, we calculated the h-index, the g-index,
The top 10 medical institutions widely considered to be the best are: the three institutions of national importance, namely, All India Institute of Medical Sciences, Delhi (AIIMS), Postgraduate Institute of Medical Education and Research, Chandigarh (PGIMER), Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry (JIPMER), Christian Medical College, Vellore (CMCV), Sanjay Gandhi Postgraduate Institute, Lucknow (SGPGI), King George Medical University, Lucknow (KGMU), Maulana Azad Medical College, Delhi (MAMC), Kasturba Medical College, Manipal (KMC), Seth GS Medical College and KEM Hospital (KEM) and Banaras Hindu University, Varanasi (BHU).

Table 1: Details of number of publications, citations and indices in the top 10 medical institutions of India

<table>
<thead>
<tr>
<th>Institute</th>
<th>Total number of publications</th>
<th>Total number of citations</th>
<th>h index</th>
<th>g index</th>
<th>h5 index</th>
<th>h5 median</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIIMS</td>
<td>29394</td>
<td>304929</td>
<td>10.4</td>
<td>150</td>
<td>264</td>
<td>61</td>
</tr>
<tr>
<td>PGIMER</td>
<td>20707</td>
<td>197179</td>
<td>9.5</td>
<td>110</td>
<td>175</td>
<td>51</td>
</tr>
<tr>
<td>CMCV</td>
<td>8432</td>
<td>85547</td>
<td>10.1</td>
<td>93</td>
<td>147</td>
<td>40</td>
</tr>
<tr>
<td>SGPGI</td>
<td>6874</td>
<td>83627</td>
<td>12.2</td>
<td>86</td>
<td>168</td>
<td>37</td>
</tr>
<tr>
<td>KGMU</td>
<td>6424</td>
<td>45407</td>
<td>7.1</td>
<td>70</td>
<td>111</td>
<td>29</td>
</tr>
<tr>
<td>MAMC</td>
<td>5518</td>
<td>35731</td>
<td>6.5</td>
<td>62</td>
<td>91</td>
<td>22</td>
</tr>
<tr>
<td>KMC</td>
<td>5392</td>
<td>33368</td>
<td>6.2</td>
<td>61</td>
<td>86</td>
<td>18</td>
</tr>
<tr>
<td>JIPMER</td>
<td>4732</td>
<td>254094</td>
<td>5.4</td>
<td>47</td>
<td>70</td>
<td>21</td>
</tr>
<tr>
<td>BHU</td>
<td>5564</td>
<td>58908</td>
<td>10.6</td>
<td>88</td>
<td>144</td>
<td>33</td>
</tr>
<tr>
<td>KEM</td>
<td>4612</td>
<td>43779</td>
<td>9.5</td>
<td>71</td>
<td>120</td>
<td>30</td>
</tr>
</tbody>
</table>

Abbreviations: All India Institute of Medical Sciences, Delhi (AIIMS), Postgraduate Institute of Medical Education and Research, Chandigarh (PGIMER), Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry (JIPMER), Christian Medical College, Vellore (CMCV), Sanjay Gandhi Postgraduate Institute, Lucknow (SGPGI), King George Medical University, Lucknow (KGMU), Maulana Azad Medical College, Delhi (MAMC), Kasturba Medical College, Manipal (KMC), Seth GS Medical College and KEM Hospital (KEM) and Banaras Hindu University, Varanasi (BHU).

Table 2: Various research metrics of the top 10 medical institutions of the country

<table>
<thead>
<tr>
<th>Institution</th>
<th>i-1000 index, n (%)</th>
<th>i-100 index, n (%)</th>
<th>i-10 index, n (%)</th>
<th>i-zero index, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIIMS</td>
<td>8 (0.027)</td>
<td>304 (1.03)</td>
<td>6990 (24)</td>
<td>9393 (32)</td>
</tr>
<tr>
<td>PGIMER</td>
<td>2 (0.001)</td>
<td>130 (0.63)</td>
<td>4223 (20)</td>
<td>6251 (30)</td>
</tr>
<tr>
<td>CMCV</td>
<td>1 (0.012)</td>
<td>85 (1.01)</td>
<td>2102 (25)</td>
<td>2287 (27)</td>
</tr>
<tr>
<td>SGPGI</td>
<td>3 (0.044)</td>
<td>64 (0.93)</td>
<td>1939 (28)</td>
<td>1852 (27)</td>
</tr>
<tr>
<td>KGMU</td>
<td>1 (0.016)</td>
<td>31 (0.48)</td>
<td>1106 (17)</td>
<td>2279 (35)</td>
</tr>
<tr>
<td>MAMC</td>
<td>0 (0)</td>
<td>23 (0.42)</td>
<td>923 (17)</td>
<td>1783 (32)</td>
</tr>
<tr>
<td>KMC</td>
<td>0 (0)</td>
<td>22 (0.41)</td>
<td>819 (15)</td>
<td>2017 (37)</td>
</tr>
<tr>
<td>JIPMER</td>
<td>0 (0)</td>
<td>7 (0.15)</td>
<td>690 (15)</td>
<td>1713 (36)</td>
</tr>
<tr>
<td>BHU</td>
<td>1 (0.018)</td>
<td>72 (1.29)</td>
<td>1319 (24)</td>
<td>1561 (28)</td>
</tr>
<tr>
<td>KEM</td>
<td>0 (0)</td>
<td>33 (0.71)</td>
<td>1012 (22)</td>
<td>1273 (28)</td>
</tr>
</tbody>
</table>

Abbreviations: All India Institute of Medical Sciences, Delhi (AIIMS), Postgraduate Institute of Medical Education and Research, Chandigarh (PGIMER), Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry (JIPMER), Christian Medical College, Vellore (CMCV), Sanjay Gandhi Postgraduate Institute, Lucknow (SGPGI), King George Medical University, Lucknow (KGMU), Maulana Azad Medical College, Delhi (MAMC), Kasturba Medical College, Manipal (KMC), Seth GS Medical College and KEM Hospital (KEM) and Banaras Hindu University, Varanasi (BHU).

Results

The year-wise number of publications in the last 5 completed years from 2012 to 2016 was also noted.

A more detailed analysis was carried out for the top 20 most cited papers in each of the institutions. We estimated the total number of citations for the top 20 articles, calculated number of citations per paper, and noted the maximum/minimum citations received. A cumulative impact factor of the institutions was calculated by summing up the journal impact factors in which the top 20 most cited papers were published. The median and range of the cumulative impact factor were also estimated.

In addition, for the top 20 articles, we looked at who was the first/ corresponding author, how many of them were research/review articles and checked whether the papers were part of collaborative research or single-institutional.

For the sake of comparison, we chose one of the top international medical institutions (Harvard Medical School) and a few Indian medical colleges that can be considered to be somewhere in-between the top-most and the bottom ones.

Statistical analysis: We presented the data as numbers, percentages, means or medians. Only descriptive statistics was used. Figures were made using MS Excel.

The i-10 index, 14 and the h5-index with h5-median.15 Although these indices are author level metrics, we used them for institutions. The h-index was defined as: An institute is said to have an index of h if it has published h papers each of which has been cited at least h times. The g-index was calculated as the largest number such that the top g articles of an institute received at least g² citations. The i10-index was calculated as the number of publications of an institute with 10 or more citations. We extended the concept of i-10 index to very highly cited papers using i-1000 index and i-100 index. In addition, we used another index, i-zero, to denote the number of papers that have not received any citations.

The h5-index was defined as the h-index of an institute for articles published in the last 5 years. The h5-median was estimated as the median number of citations for articles constituting the institutional h5-index.
third of all publications did not receive a single citation and the single largest category of citations was between 1 to 9 (Figure 1).

A detailed analysis of the top 20 papers with respect to the number of citations (number, maximum/minimum), total impact factor of the journals, and median (range) of impact factor followed a pattern similar to that seen for the overall publication scenario with AIIMS and PGIMER leading followed by the other institutions (Table 3).

In most of the top papers, the corresponding authors and the first authors matched belonged to the same institutions, but for the top 5 among the selected 10 institutions more than 80% of the papers had first/corresponding authors from outside, in most cases USA or UK (Table 4). These were also the institutions whose papers received the highest numbers of citations and were published in high impact factor journals. On the other hand, in general, the lower placed institutions had less of collaborative articles, and also received less number of citations (Table 4). Less than a quarter of all papers were research articles, others being research papers primarily (Table 4).

We looked at the research output of some of the established, older medical colleges of India (Table 5). These institutions produced nearly 50 papers per year per institute. In contrast, one of the newer institutions, namely, GMCH, Chandigarh, to which one of the authors belongs, publishes more than 100 papers per year (Table 5). When the number of publications over the last five years from these institutions was combined, there was a trend towards decline (Figure 2). The top institutions, barring BHU, had very few publications listed in Scopus in their earlier years (Table 6).

The Medical Council of India website\(^1\) lists 477 colleges out of which 218 are Government and 218 are managed by Trusts, most of which are old colleges. The MCI list shows that in the last few years three new categories of medical colleges have come up – ‘Private’, 10 colleges; ‘Society’, 22 colleges and ‘Govt-Society’, 9 colleges (Table 7). We did not analyze research output from these newer institutions. Among the top ten institutions that we evaluated, nine are government institutions.

**Discussion**

We conducted a qualitative analysis of the most cited papers of the top institutions of the country. It is interesting to note that although
these institutions are ranked at the top based on their medical education and patient-care strengths, they were top performers in research too, denoting the inseparableness of the three major roles. This study adds to the earlier work\(^1\) showing more than half of the medical colleges did not publish a single paper in a year by looking into more details at the other extreme of the spectrum – the best performers.

As expected, and as seen previously, AIIMS and PGIMER retained their two top positions, managing to keep the wide gap between them and the next-placed institutions. We used several metrics to evaluate the research impact, namely, number of publications, total number of citations, number of citations for the most cited paper, impact factor of the journals in which research was published, h-index, the g-index, the i-10 index, and the h5-index with h5-median. We extended the concept of i-10 index to i-100 and i-1000 to look at the heavily cited articles. Although some of these metrics are author or journal level metrics, we used them to calculate institutional indices, which we believe is a reasonable way to make comparisons nationally as well as internationally.

The reason for using a number of metrics is that none of them is perfect and all are prone to misuse, keeping in mind the Goodhart’s law which states that “when a feature of the economy is picked as an indicator of the economy, then it inexorably ceases to function as that indicator because people start to game it”.\(^8\)

The most-cited paper of the country in the medical field received 4625 citations. To gain some perspective, the all time most cited paper is by Lowry et al which describes how to measure protein concentration\(^9\) with more than 200,000 citations. Also, the top 10 most cited papers in the world have been cited 40,000 times whereas the top hundred are cited more than 12,000 times.\(^10\)

About 0.016% articles from the top institutions received more than 1000 citations, which appears to be a small figure, but compares with the worldwide data (~0.026%).\(^11\) The i-1000 index which we obtained can be considered to be the national i-1000 index in medicine as it is doubtful there will be publications with more than 1000 citations from other institutions.

Journal impact factors represent the number of citations per article in the last two years and has been commonly used as a measure of quality of a journal. The sum total of the impact factors of journals in which the top 20 publications of AIIMS were published was more than 700. In contrast, Harvard Medical School, considered the world’s topmost medical institute, had impact factor totaling 661, less than that of AIIMS, and impact factor median of 37,205 as against 47,831 for AIIMS, although on other parameters it scored much higher. For example, the total number of publications is 261,006 (AIIMS – 29394), the most cited paper has 15960 citations (AIIMS – 4625) and the top 20 articles were cited 1,41,111 times (AIIMS – 25,436).

Harvard Medical School publishes more than 12,000 papers a year, ten times more than our leading institutions. This comparison was done to highlight several important aspects. The Scopus database shows the first entry of Harvard as 1884 whereas in case of AIIMS it is 1950. Second, Harvard Medical School has 2,900 faculty members and more than 5,000 instructors\(^12\) whereas AIIMS has about 500 faculty members.\(^13\)

Thirdly, the majority of the top research publications in Harvard and the Indian institutions are outcomes of public-funded research. In this regard, some perspective can be obtained by the following figures: the annual budget of National Institutes of Health (NIH, USA) is nearly US$ 32 billion whereas the budget of ICMR for the year 2017-18 was US$232 million, a multiplicative factor of nearly 140.\(^14\)

Government funding for research is critical – even in fields considered to be typically industry-based, that is new drug discovery/development, it has been estimated that a large proportion of drugs and almost all the vaccines in the past few decades were created with public funding.\(^15\)

This aspect is probably the most important reason why India has not been able to make an impact in the field of medical research of which it is capable of. The abundant skilled manpower, well versed in the intricacies

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**Table 6: Number of publications in the first 5 years of the top medical institutions of India**

<table>
<thead>
<tr>
<th>Institute</th>
<th>Total number of publications in the first five years</th>
<th>Year since record shown in Scopus</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIIMS</td>
<td>1</td>
<td>1950</td>
</tr>
<tr>
<td>PGIMER</td>
<td>20</td>
<td>1963</td>
</tr>
<tr>
<td>CMCV</td>
<td>0</td>
<td>1886</td>
</tr>
<tr>
<td>SGPGI</td>
<td>37</td>
<td>1986</td>
</tr>
<tr>
<td>KGGMU</td>
<td>1</td>
<td>1914</td>
</tr>
<tr>
<td>KMC</td>
<td>6</td>
<td>1963</td>
</tr>
<tr>
<td>MAMC</td>
<td>17</td>
<td>1959</td>
</tr>
<tr>
<td>JIPMER</td>
<td>20</td>
<td>1966</td>
</tr>
<tr>
<td>KEM</td>
<td>7</td>
<td>1934</td>
</tr>
<tr>
<td>BHU</td>
<td>319</td>
<td>1971</td>
</tr>
</tbody>
</table>

**Table 7: State-wise distribution and year of MCI inspection of the three newer categories of management of the medical colleges as per the MCI website**

<table>
<thead>
<tr>
<th>State</th>
<th>Year of inspection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Management: Private</td>
<td></td>
</tr>
<tr>
<td>Rajasthan</td>
<td>2016</td>
</tr>
<tr>
<td>Chattisgarh</td>
<td>2013</td>
</tr>
<tr>
<td>Andhra Pradesh</td>
<td>2015</td>
</tr>
<tr>
<td>Uttar Pradesh</td>
<td>2015</td>
</tr>
<tr>
<td>Uttar Pradesh</td>
<td>2013</td>
</tr>
<tr>
<td>Rajasthan</td>
<td>2016</td>
</tr>
<tr>
<td>Telangana</td>
<td>2013</td>
</tr>
<tr>
<td>Gujarat</td>
<td>2016</td>
</tr>
<tr>
<td>Uttar Pradesh</td>
<td>2016</td>
</tr>
<tr>
<td>Maharashtra</td>
<td>2017</td>
</tr>
<tr>
<td>Management: Society</td>
<td></td>
</tr>
<tr>
<td>Haryana</td>
<td>2017</td>
</tr>
<tr>
<td>Madhya Pradesh</td>
<td>2016</td>
</tr>
<tr>
<td>Madhya Pradesh</td>
<td>2016</td>
</tr>
<tr>
<td>Rajasthan</td>
<td>2016</td>
</tr>
<tr>
<td>Andhra Pradesh</td>
<td>2016</td>
</tr>
<tr>
<td>Andhra Pradesh</td>
<td>2016</td>
</tr>
<tr>
<td>West Bengal</td>
<td>2016</td>
</tr>
<tr>
<td>Delhi</td>
<td>2012</td>
</tr>
<tr>
<td>Uttar Pradesh</td>
<td>2015</td>
</tr>
<tr>
<td>Uttar Pradesh</td>
<td>2016</td>
</tr>
<tr>
<td>Telangana</td>
<td>2016</td>
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<tr>
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<td>2013</td>
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<tr>
<td>Madhya Pradesh</td>
<td>2015</td>
</tr>
<tr>
<td>Kerala</td>
<td>2014</td>
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<td>Andhra Pradesh</td>
<td>2016</td>
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<tr>
<td>Rajasthan</td>
<td>2015</td>
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<tr>
<td>Chattisgarh</td>
<td>2016</td>
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<tr>
<td>Madhya Pradesh</td>
<td>2014</td>
</tr>
<tr>
<td>Andhra Pradesh</td>
<td>2016</td>
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<tr>
<td>Madhya Pradesh</td>
<td>2016</td>
</tr>
<tr>
<td>Telangana</td>
<td>2005</td>
</tr>
<tr>
<td>Uttarakhand</td>
<td>2006</td>
</tr>
<tr>
<td>Management: Govt-Society</td>
<td></td>
</tr>
<tr>
<td>Gujarat</td>
<td>2012</td>
</tr>
<tr>
<td>Gujarat</td>
<td>2011</td>
</tr>
<tr>
<td>Gujarat</td>
<td>2012</td>
</tr>
<tr>
<td>Gujarat</td>
<td>2015</td>
</tr>
<tr>
<td>Gujarat</td>
<td>2017</td>
</tr>
<tr>
<td>Gujarat</td>
<td>2011</td>
</tr>
<tr>
<td>Gujarat</td>
<td>2015</td>
</tr>
<tr>
<td>Assam</td>
<td>2012</td>
</tr>
<tr>
<td>Gujarat</td>
<td>2012</td>
</tr>
</tbody>
</table>
of research, places India in a unique position to be among the world leaders in research if research fund allocation is substantially enhanced.25

Another area of concern is that nearly a third of all papers from even the topmost institutions remained uncited, even after many years of publication. While the contribution of discipline-dependence26 and inherent shortcomings of the databases,27 cannot be ruled out, this can also be due to conduct of “me-too” type of research, or research that is not answering a relevant question and is conducted just for the sake of gaining a publication, most likely with the purpose of getting the numbers needed for promotion (NNP).

On the positive side, many of the papers, at least from the topmost institutions, were highly cited, gaining thousands of citations. When we analyzed these publications we noticed that nearly 80% were a result of collaboration, especially with international organization. As a result the first and the corresponding authors were from outside India. It is widely believed that collaborations are important in research and our data provides direct evidence of the same. The institutions among the lower half of the top 10 did not manage to get much collaborations going, and as a result, their papers did not receive a large number of citations.

Review articles are known to receive many citations28 but our data show that less than a quarter of the most highly cited papers were reviews.

We also looked at some of the older medical colleges to have some assessment of their status of research. Prior to looking at the data, we were under the impression, based on the earlier papers, that the number of publications from these institutions will be very few. However, it was not the case and most of these colleges were publishing and were getting cited. There was a worrying trend of fall in the number of publications from these institutions over the past five years, which probably requires further detailed evaluation to see if there is a systematic feature so that some intervention can be planned. We did not look at the least performing colleges, as had been recently done,29 and there was no reason to suspect a dramatic change in that situation.

We also did not look at data from some of the newer colleges, specifically whose managements are mentioned in the MCI website as “Private”, “Society”, or “Government-Society”. Although we suspect that their research output would be insubstantial, it may be too early to expect more. Even the institutions which are now leading, had published very few papers during their initial years. It would be interesting to follow-up on this work, say 5-10 years later, and look at the research output from these newly established colleges under novel management categories and may be compare with the government ones.

Another limitation of the study is that some of the metrics used are actually meant for individual researchers and we used them for institutions. We hope this kind of compilation does convey the message regarding research output of the institutions evaluated.

Our comparison with other institutions was also not a randomized comparison, nor did we age-match institutions. However, we did not cherry pick the institutions for comparison just to prove a point and believe that they present a fairly representative picture of the medical research scenario in the country.

Some of the landmark medical research carried in India in the fields of iodine deficiency, cholera, other diarrheal disorders, tuberculosis, poliomyelitis, and leprosy has been described previously.11 To this can be added the important work in the field of malaria from Osmania University, Hyderabad,29 and heart valves from Sree Chitra, Trivandrum,30 besides others. It would be a good idea to conduct a thorough review of such qualitatively important research from India in future.

In conclusion, our analysis of the best publications from the topmost institutions shows that these institutions are capable of competing with the best in the world, as even with the huge resource deficit, they managed to publish a decent number of highly cited articles. The study also highlights the importance of research collaboration, with collaborative papers being the most cited ones. Lastly, several of the middle-rung colleges that we looked at, did not point to a dismal picture, which allows us to end with hope, especially if funding situation is improved.

Acknowledgment
The authors wish to acknowledge the secretarial assistance of Mr. Swarnjit Saini.

References
INnOvative GLiptin for All T2DM patients

Robust Glycemic Control\(^1\)
Minimal Hypoglycemia\(^1\)
Weight neutral\(^1\)
No dosage adjustment needed in renal impairment\(^1\)


Making strides through Innovation for your Patients with Diabetes

Glaritus
- Launched in 2009
- 1st Glargine of Indian Origin
- Launched in 2003
- India’s 1st Recombinant Human Insulin

Wosulin
- Launched in 2017
- World’s 1st 200 IU Human Insulin

CONSEGNA

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Glycemic Control in Patients with Diabetic Kidney Disease; Time to Recognize Perils of Iatrogenic Hypoglycemia? Moving away from Intensive Glycemic Control

Puneeta Gupta¹, Rajesh Gupta², Anil K Gupta³

Abstract
The chronic complications of Diabetes Mellitus (DM), which may be present in as many as 50% of the patients at the time of diagnosis, are a major burden for both individuals with the disease and health systems and it has been estimated that as much as 60–70% of healthcare expenditure related to diabetes (about 670 billion dollars a year) is currently attributable to chronic complications of the disease. These high prevalence rates are widely acknowledged to further rise as poor lifestyle choices and their consequences continue to rise. Adding to that is an aging population and urbanization that together will make situation even more challenging. Type 2 diabetes affects about 90-95% of newly diagnosed patients of diabetes and accounts for majority of cases of Chronic Kidney Disease (CKD). In other words, CKD affects about 20-40% of individuals with diabetes making it one of the most common complication related to the disease. The risk of renal failure is 25 times higher in diabetic patients than in the non-diabetic population. Thus patients with diabetes and renal failure represent a special risk group as they have higher morbidity and mortality and are at a higher risk of hypoglycaemia than diabetic individuals with normal renal function. In addition, for all the physicians who are taking care of patients of diabetes and kidney disease, formulation of comprehensive plan of management directed at modification of risk factors of cardiovascular disease (CVD) is of utmost importance as majority of patients with CKD die as a result of cardiovascular complications rather than progression to ESRD, (accounting for about 70% of deaths over the age of 65). The contrasting results available from clinical trials in recent years have generated perplexity amid concerns that glucose-lowering therapies, under certain circumstances, might even be detrimental; in light of the fact that intensive glycemic control increased the risk for death by 22% in the ACCORD trial. Moreover it should be pooled data of some extensive reviews which has been carried in last one and half year have demonstrated that intensive glycemic control significantly increases the risk of cardiovascular and all-cause mortality in patients of CKD. So it is increasingly problematic for clinicians to continue aggressive glycemic control for the treatment of renal outcome in patients of advanced renal insufficiency with multiple co-morbidities. Thus, a lower survival benefit due to multiple co-morbidities combined with general lower life expectancy necessitates a balanced approach. Suggesting the need for revised and extended target of HbA1C in this patient population.

Introduction
Diabetes was first recognized 3500 years ago by the Ancient Egyptians. One of the first clinical description was given by Aretaeus, who practiced in the city of Cappadocia around 120 AD. He wrote that the condition was ‘fortunately rare’, but ‘short will be the life of the man in whom the disease is fully developed’.¹ Now in 21st century, as we struggle with explosive population growth and changing lifestyles, the first part of the statement is no longer relevant as incidence of diabetes has doubled every 20 years since 1945. The figures available in 7th world diabetes atlas released by International Diabetes Federation (IDF) showed that approximately 415 million adults were living with diabetes in 2015. Further, five million people died because of diabetes related causes, accounting for more mortality than that resulted from malaria, tuberculosis, and HIV combined together.² The World Health Organization estimates that prevalence of diabetes (DM) will increase from 415 million to 642 million in 2040; with two countries, China and India accounting for largest numbers of patients with diabetes.³ The second part of our introducing statement is as true today as it was almost 2000 years ago, as approximately 44% of patients with type 2 diabetes are likely to succumb to their disease within 10 years of diagnosis. The chronic complications of diabetes, which may be present in as many as 50% of the patients at the time of diagnosis, are a major burden for both individuals with the disease and health systems and it has been estimated that as much as 60–70% of healthcare expenditure related to diabetes (about 670 billion dollars a year) is currently attributable to chronic complications of the disease.⁴ These high prevalence rates are widely acknowledged to increase further as poor lifestyle choices and their consequences continue to rise. Adding to that is an aging population and urbanization that together will make situation even more challenging.
A bout 90–95% of those afflicted with DM are diagnosed with type 2 diabetics and Type 2DM is the main cause of chronic kidney disease (CKD). Affecting about 20–40% of individuals with diabetes, making it one of the most common complications related to the disease. The risk of renal failure is 25 times higher in diabetic patients than in the non-diabetic population. Patients with diabetes and renal failure represent a special risk group as they have higher morbidity and mortality and are at a higher risk of hypoglycaemia than diabetic individuals with normal renal function. In addition, for all physicians who are taking care of patients of diabetes and kidney disease, formulation of comprehensive plans of management directed at modification of risk factors for cardiovascular disease (CVD) is of utmost importance as majority of patients with CKD die as a result of cardiovascular complications rather than progression to ESRD (End Stage Renal Disease). About 70% of people over the age of 65. Also there is graded inverse relationship between CVD risk and glomerular filtration rate (GFR) that is independent of age, sex and other risk factors, thus making CKD an independent risk factor for CVD events. Altogether, knowledge regarding the prevention and management of diabetic nephropathy, along with other aspects of diabetes care, is part of the comprehensive care of any patient with diabetes and nephropathy.

Discussion

Intensive versus conventional glycemic control and long term complications of the diabetes.

It has been recognized for quite some time now that uncontrolled hyperglycemia has pathogenic role in micro- and macrovascular complications of the diabetes. Still debated, however, is the level of glucose lowering necessary to reduce complications, balanced by the risk and costs of the means used. There have been numerous studies over the past 20 years or so that have attempted to clearly address the benefits, risks, and complications of intensive versus standard glycemic control. The core data for target setting of blood glucose in type 1 and type 2 diabetes initially came from two landmark trials published in the last decade of 20th century; the Diabetes Control and Complications Trial (DCCT, 1993) and the United Kingdom Prospective Diabetes Study (UKPDS, published in 1999) which aimed to prove the benefit of tight glucose control in terms of diabetic complications. Although tight glucose control was already suspected to be beneficial in terms of chronic complications, these two studies formally demonstrated such a hypothesis. Since then, the evidence provided by these studies has guided clinical practice and medical decisions for several years. Thus, based on the trials results, the American Diabetes Association (ADA) recommended a target HbA1C < 7.0% for prevention of renal disease and other microvascular complications which was also endorsed by National Kidney Foundation Kidney Disease Outcome Quality Initiative (KDOQI) Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease. Although both DCCT and UKPDS studies showed a trend toward an improvement in cardiovascular complications with intensive glycemic control, as, yet this debate between intensive versus conventional control refused to die as this difference was not statistically significant. So, several long-term trials were started in the past decade to compare the effects of intensive versus standard glycemic control on chronic complications especially the cardiovascular mortality. These trials were expected to show more favorable results in reducing the chronic complications of the diabetes with intensive glucose control as participants here were relatively high risk with established type 2 diabetes. In both DCCT and UKPDS studies enrolled patients were younger or recently diagnosed with diabetes with no history of cardiovascular events and absence of other cardiovascular risk factors apart from diabetes. With those differing characteristics of selected population in both trials were believed to be main reason for less desirable result seen as far as cardiovascular mortality was concerned.

In 2008, two of these trials, Action to Control Cardiovascular Risk in Diabetes (ACCORD), terminated its glycemic control study due to the finding of increased mortality in participants randomized to a strategy of very intensive glycemic control with a target AIC of <6. Thus this unexpected outcome and results of other two trials reduced the enthusiasm generated by the aforementioned studies and forced the representatives of the American Heart Association (AHA) and the American College of Cardiology (ACC), to reexamine the recommendations for glycemic targets in patients with diabetes, the majority of whom have type 2 diabetes.

Simultaneously, when this point about intensive glycemic control and cardiovascular mortality was being actively debated, many researchers also started questioning the actual benefit of intensive glycemic control in preventing clinical renal endpoints (e.g., progressive loss in glomerular filtration rate) beyond albuminuria in type 2 diabetics. In a significant paper, which reviewed data from 7 trials involving 28,065 adults and encompassing 163,828 patient-years of follow up, between January 1, 1950, and December 31, 2010; conventional and intensive glycemic control in patients with T2DM and its effect on renal outcome was evaluated. The points evaluated by the researchers were the development of micro- or macroalbuminuria, and the clinical endpoints were doubling of serum creatinine level, ESRD, and renal related deaths suggesting that intensive glycemic control reduces albuminuria (referred to as surrogate end point by these and many researchers) but evidence was lacking that it prevented clinically meaningful renal outcome in patients with T2DM measured during the 3.5 to 10.7 years of the published trials.

Thus various questions remain to be answered as far as glycemic management of patients of diabetic kidney disease is concerned. Should we aim to lower HbA1C by tighter glycaemic control in patients with diabetes and advanced stages of CKD (eGFR <45 mL/min)? (estimated Glomerular Filteration Rate).
2. Is an aggressive treatment strategy (in number of injections and controls and follow-up) superior to a more relaxed treatment strategy in patients with diabetes and CKD?

3. Is any oral drug superior to another in terms of mortality/complications/glycaemic control in patients with diabetes type 2 in advanced CKD (GFR <45 mL/min/1.73 m²)?

4. In patients with diabetes type 2 and CKD (GFR <45 mL/min/1.73 m²), is maximal oral therapy better than starting/adding insulin at an earlier stage?

5. Are there better alternatives than HbA1c to estimate glycaemic control in patients with diabetes and CKD stage 3b or higher (GFR <60)? Before discussing these points with available evidence from clinical trials, following paragraph, the anti-diabetic drugs use in chronic kidney disease is reviewed.

**Metformin**

Metformin which is recommended as the initial pretermmed pharmacological agent for type 2 diabetes is eliminated via the kidneys and its clearance decreases 75% when the GFR falls to less than 60; without any further change when the GFR declines to 30 mL/min/1.73 m². Thus to minimize the risk of lactic acidosis, various guidelines have advised against using this compound in men with serum creatinine more than or equal to 1.5 and normally aren’t recommended in patients with CKD stage 3b or higher (GFR <60). However, certain individual variation in metabolism and clearance of these molecules can be effectively used when prescribing these drugs for CKD patients. Glipizide is metabolized by the liver into several inactive metabolites and its clearance and elimination half-life are not affected by a reduction in GFR so can be used in almost all the patients of CKD in whom sulfonylureas are under consideration.\(^\text{18,19}\)

**Glitazones**

These are potent insulin sensitisers which have been available for the management of type 2 diabetes for over a decade. The pharmacokinetics of pioglitazone are not altered by renal impairment, and there is no need for dose adjustment in this setting. Despite this advantage also lack of hypoglycemia as side effect, the drug should still be used with caution in CKD because of the risk of water and sodium retention and heart failure. Data regarding its safety in dialysis patients is as yet very limited.\(^\text{18,20}\)

**Gludeine**

Out of two available drugs repaglinide has been used in CKD. Although renal impairment may slightly prolong its half-life, the use of repaglinide is not contraindicated in patients with renal impairment or in dialysis patients. A preprandial dose of 0.5–4 mg should be titrated according to the postprandial blood glucose response.\(^\text{18,20}\)

**Glucagon like peptide-1 (GLP-1) analogue**

Incretin mimetics include glucagon-like peptide 1 (GLP1) analogs and agonists (exenatide, lixisenatide and liraglutide), which are injectable and increase insulin secretion and suppress glucagon secretion in a glucose-dependent manner, with reduced risk of hypoglycemia. These drugs show diuretic effect via GLP-1 receptors expressed in renal tubules and may aggravate renal impairment, especially in patients treated with renin-angiotensin system inhibitors or diuretics.\(^\text{18,20}\)

**The DPP-4 inhibitors**

The commonly used DPP-4 inhibitors, also known as “gliptins”, despite their common mechanism of action have structural heterogeneity that translates into different pharmacological properties and different metabolism and excretion pathways. Sitagliptin is mostly eliminated unchanged in the urine and can be used with appropriate dose reduction in all chronic kidney stages. The usual dose of 100 mg once per day is reduced to 50 mg/day for patients with moderate renal impairment (GFR 30-50 mL/min), which is further reduced to 25 mg once a day in end-stage renal disease (ESRD) requiring dialysis. The Vildagliptin dose is reduced by half (to 50 mg/day) for both moderate and severe CKD. The dose of Saxagliptin (5 mg once daily) should be reduced to 2.5 mg once daily in patients with moderate or severe renal impairment (GFR 30-50mL/m²) and is not recommended for patients with ESRD requiring dialysis. Presently, Linagliptin is the only DPP-4 inhibitor that is eliminated nearly entirely via the bile, thus making this agent a possible treatment choice for patients in all stages of CKD, and even stage 5 (GFR <15 mL/min/1.73 m²), without dose adjustments. The safety of this therapeutic class has been questioned after the release of a phase 4 trial showing increase in hospitalization for HF. Certain risk factors are associated with this higher HF rate, such as previous HF, a GFR of <60 mL/ min and increased levels of N-terminal pro-B-type natriuretic peptide (BNP).\(^\text{21,22}\)

Sodium-Glucose Cotransporter-2 (SGLT-2) Inhibitors (canagliflozin, dapagliflozin, emplagliflozin) are novel hypoglycemic agents.\(^\text{3}\)

**SGLT2 Inhibitors**

The kidney plays an important role in glucose homeostasis, mostly by the reabsorption of filtered glucose. In the kidney, filtered glucose is actively reabsorbed by specific transporters located on the apical (brush-border) membrane of proximal tubular cells. A new generation of drugs called SGLT2 inhibitors, decreases the capacity for renal glucose reabsorption and reduces the renal threshold at which glucose is excreted resulting in net loss of excess glucose in the urine thus directly reducing plasma glucose concentrations in patients with hyperglycemia. This therapeutic class has been approved for the treatment of patients with T2DM with an GFR of ≥45 mL/min/1.73 m², but only one drug canagliflozin has been evaluated in this setting, however use of canagliflozin in patients with moderate CKD is less effective in improving glycemic control and is associated with a higher occurrence of adverse reactions compared to patients with mild renal impairment or normal renal function. The SGLT-2
inhibitors are only effective with some degree of kidney function and are not recommended in dialysis patients.23

Insulin Treatment

Regardless of the fact that insulin is considered as the best choice to improve glycemic control in patients with renal failure, specific information about dose adjustment and differences in insulin profiles in this population is still limited because of few studies carried out in patients with advanced renal insufficiency.17-20 There is no a consensus about the choice of various preparation of insulin in patients with CKD. However the principles of insulin therapy for CKD patients are not different from general diabetic patients.

1. In type 2 diabetic subjects with the early stage of CKD, all hypoglycaemic agents can be applicable. Once the estimated glomerular filtration rate (eGFR) falls below 60 mL/min, a subject’s anti-diabetic therapy needs to be re-evaluated as some oral antidiabetic drugs are formally contraindicated and others require dose reduction.

2. As in CKD stage 3b or higher, the risk of hypoglycaemia is enhanced and hypoglycemia from antidiabetic drug therapy is among the four leading causes of hospitalization for adverse drug reactions in the elderly and the survival benefit is probably lower due to the general lower life expectancy; therefore, a balanced approach, taking into account the specific condition of this patient is needed suggesting that the target of HbA1c can be extended above 7.0% in this patient population. Hypoglycemia triggers a cascade of physiologic effects, inducing adrenergic activation, oxidative stress, and cardiac arrhythmias, and may contribute to sudden death and ischemic cerebral damage.25

3. In an extensive review26 of adults with type 2 diabetes using various hypoglycemic therapy, reviewers observed no significant differences in the associations between any of available classes of glucose-lowering drugs (alone or in combination) and the risk of cardiovascular or all-cause mortality or in terms of nephroprotection26 thus the first concern on the part of prescribing practitioner should always be not to increase the risk for severe hypoglycaemia. As a consequence, preference should go to drugs with a low risk for hypoglycaemia and risk was reported to be low with metformin, glipizide, acarbose, DPP-IV inhibitors and the SGLT2 inhibitors. Sulfonylureas and glinides are associated with an increased risk of hypoglycaemia and when sulfonylureas are combined with insulin, the risk of hypoglycaemia may increase more than 14-fold.24,26

4. For CKD patients with type 2 diabetes, many physicians are of the opinion that initial treatment with an oral agent rather than insulin is appropriate because of the lack of pharmacokinetic studies for the various types of insulin in patients with different degrees of renal insufficiency and the absence of therapeutic guidelines that define insulin adjustments based on GFR making it difficult to advocate ideal insulin therapies in these patients. Moreover, because intensive insulin therapy is associated with more episodes of hypoglycaemia and weight gain indirectly raising blood pressure. However, the patients who fail therapy with oral agents or have frequent episodes of hypoglycemia are treated with insulin.

5. After the publication of various encouraging reports on safety of metformin in patients of chronic kidney disease, it was concluded that although metformin is mainly cleared by the kidneys, the drug levels generally remain within the therapeutic range and lactate concentrations are not substantially increased when used in patients with mild to moderate renal insufficiency (estimated glomerular filtration rates, 30-60 mL/min) thus making overall incidence of lactic acidosis in metformin users generally indistinguishable from the background rate in the population with diabetes. Observational studies suggest a potential benefit from metformin on macrovascular outcome, even in patients with prevalent renal contraindications for its use. So many experts are of the opinion that metformin use can be considered in patients with GFR of up to 30 mL/min/1.73 m², with dose reduction advised at 45 mL/min.27,28 However, there is indirect evidence that a rapid drop of GFR can lead to a sudden accumulation of metformin. Therefore, patients should be instructed to reduce or stop metformin in conditions with enhanced risk of acute kidney injury, e.g. severe bouts of diarrhoea, dehydration or fever.

6. In patients with a GFR >45 mL/min, in whom the glycaemic target has not been achieved with
metformin, it can be combined, either with a DPP4 inhibitor or repaglinide. However, When cost is an issue, a short-acting second-generation sulphonylurea, with no active metabolites could be considered, as these drugs are commonly cheaper than other drugs. If the control is still not adequate, basal insulin should be added as a third agent. There is little experience with triple oral therapy in CKD and also combination of insulin with secretagogue drugs increases the risk of hypoglycaemic episodes, and therefore, should be avoided.

7. In patients with a GFR <30ml/min/1.73m² or who are on dialysis, the experience with non-insulin anti-diabetic drugs has been very limited, and as such the treatment of choice should be insulin. However, some clinicians prefer to continue oral agents which are approved in this setting rather than switching to insulin, in patients who have already achieved acceptable glycemic control on these agents and both repaglinide and DPP4 inhibitors are alternatives to be assessed.

8. As renal clearances of different agents might differ, combining drugs in a one pill formulation can lead to overdosing of one of the constituents in patients with CKD these formulations should be avoided in patients with CKD stage 3b or higher (eGFR <45 mL/min/1.73 m²), as the two components may have different dose adaptation requirements.

9. Glycated hemoglobin may not be as accurate among ESRD patients as in the general population due to biological and patient-specific factors. HbA1c values may be falsely elevated or decreased in those with CKD. The factors associated with a lower than expected HbA1C are decreased red blood cell survival and increased red blood cell formation (use of iron, erythropoitin). The accumulation of uraemic toxins may be responsible for a higher than expected HbA1C values. The fructosamine level and glycated albumin level are proposed as a better measure of glycemic control in patients with CKD in future.34

9. The presence of albuminuria in patients with T2DM is a predictor of chronic renal failure, with the mean time from the start of proteinuria until end-stage kidney disease being 7 years. Therefore, a strategy to detect diabetic kidney disease earlier by screening for albuminuria and reduced glomerular filtration rate is important to prevent progression of diabetic nephropathy.

Conclusion

The assumption that treatment of hyperglycemia can prevent all diabetes complications, including CVD, has been an “act of faith” in the medical fraternity for many decades. The contrasting results available from clinical trials in recent years have generated perplexity amid concerns that glucose-lowering therapies, under certain circumstances, might even be detrimental; in light of the fact that intensive glycemic control increased the risk for death by 22% in the ACCORD trial. Moreover, pooling the data from all these studies did not produce the expected outcome of decreased cardiovascular-related death or all-cause mortality in many high-risk cohorts. The reasons for the lack of clinical benefits are unclear. The possible explanation for this is that many like, intensive control may have been initiated too late in the course of the disease (the legacy effect), there may have been insufficient duration of glycemic treatment, or once HbA1c levels reach a certain point (e.g. <7%), further reduction does not result in greater benefits. A recent study demonstrated that despite substantial increases in the use of glucose-lowering medications (and inhibitors of the renin-angiotensin-aldosterone system) from 1988 to 2008, the prevalence of CKD in patients with diabetes has actually increased. So it is increasingly problematic for clinicians to continue aggressive glycemic control for the treatment of renal outcome in patients of advanced renal insufficiency with multiple co-morbidities. Thus it can be concluded that the selection of a glycemic goal in a person with diabetes is a compromise between the documented upside of glycemic control—the partial prevention or delay of microvascular complications—and the documented downside of glycemic control—the recurrent morbidity and potential mortality of iatrogenic hypoglycemia causing harmful effects on the patient’s safety. Some extensive reviews which have been carried out in last one and half year have reported that intensive glycemic control significantly increases the risk of cardiovascular and all-cause mortality in patients of CKD.30,31 In other words, the goal should be to keep the blood glucose within the narrow range to reduce the progression of the disease and improve quality of life, minimizing comorbidities and cardiovascular risks. However, to date, the real benefits and impact of tight glycemic control in patients with long-standing diabetes and advanced CKD in particular are not yet fully known. Patients with type 2 diabetes are heterogeneous for age, duration of disease, comorbidity, and genetic background. Glucose-lowering therapy should be adapted to this complexity, with an attempt at improving, or at least avoidance of worsening of associated cardiovascular risk factors and thus HbA1c goal between 7% and 8% is perhaps more appropriate. The latest guidelines of ADA35 advises less stringent HbA1c goals in patients with long duration of disease, limited life expectancy, presence of important comorbidities and established vascular complication. It further states that patient attitude and expected treatment efforts, available resources and support system should also be taken into consideration while setting glycemic targets.

Suggestions for further research

1. More studies are required to evaluate whether it is glycaemic variability and specifically the recurrent episodes of hypoglycaemia, that contribute to increased cardiovascular risk, rather than the average blood glucose level.

2. A study of intensive versus standard control (HbA1c <53 mmol/mol versus <69 mmol/ mol), specifically in patients with diabetes and CKD stage 3–5 using drugs with very low risk of inducing hypoglycaemia, is warranted.

Conflict of interest

The all three authors declare that there is no conflict of interest.
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Fish Envenomation: Neglected Hazard in Aquariums

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Abstract
Around 1200 species of marine fish are venomous. Venomous fishes pose a significant health problem to certain populations in the world and are important neglected environmental diseases. Keeping fish in an aquarium is a popular hobby throughout the world. One in ten households possesses aquariums as their hobby. Aquariums are a convenient option for those living in flats and, more generally, those in rented accommodation, where keeping cats, dogs and caged animals is often banned. These tanks are stocked with wildlife extracted from the world’s freshwater sources and also from oceans. Rapid growth of marine ornamental industry has made available a lot of marine and venomous fishes in the markets and being marketed as an aquarium fish. This can lead to potential envenomation among general public. Fortunately, most of the incidents were trivial and require no medical attention. However, a few fish stings cases may be serious and sometimes fatal outcomes may occur if they are not managed properly. Fish venoms possess cardiovascular, neuromuscular, oedematous and cytolytic activity. This paper reviews the presenting symptoms and treatment options for envenomation from the most common and deadly marine specimens, aquarists are likely to encounter and their preventive measures.

Introduction

Fish constitute almost half the numbers of vertebrates on earth and approximately 22,000 species of fish are contained in some 50 orders and 445 families.¹ They live in all types of water, but over 90% of species live in the marine environment. Many people over the world depend on fishes or products made from fishes for their food and economic livelihood. The beauty of many fish species are highlighted in aquariums, fish stores and in home collections. As of 1996, aquarium keeping is the second-most popular hobby in United States. The 2015-2016 APPMA National Pet Owners Survey reported that Americans own approximately 95.5 million freshwater fish and 9.5 million saltwater fish. An estimated 13.3 million US household owned an aquarium.² Around 36 million fishes were estimated to be kept in aquaria in Germany. The hobby has a strong popularity in Europe, Asia, and North America. In the United States, 40% of aquarists maintain two or more tanks.³ Aquariums are a convenient option for those living in flats and, more generally, those in rented accommodation, where keeping cats, dogs and caged animals is often banned. These tanks are stocked with wildlife extracted from the world’s freshwater sources and also from oceans. In contrast, to the previous estimates of 200 venomous fishes, around 1,200 fishes in 12 clades are presumed to be venomous based on a phylogenetic study.⁴ The rapid growth of marine ornamental industry has placed potentially dangerous marine specimens at the hands of the general public increasing the chances of severe envenomation in them.

Epidemiology of Fish Envenomation

Around 40,000 to 50,000 marine envenomation occur worldwide each year.⁵ The American Association of Poison Control Centers 2010 estimates about 1800 aquatic exposures every year,⁶ although the actual number of envenomation that results from home aquarium specimen remains unknown as these cases are mostly under reported. Several factors contribute to under-reporting. Victims of marine envenomation who are unaware of the toxicity of some marine animals may not seek medical attention unless the condition is severe. Moreover, treating physicians may not consult or they report these injuries to the toxicology center. While fatalities are rare, some exotic aquarium specimens had also been reported to cause death in humans. Moreover, hobbyists, unsuspecting adults and children are at risk for envenomation from venomous fishes in aquariums.⁷

Problem Statement

There are no studies specifically considering the injuries taking place in aquariums but there are ample case reports and few studies on marine envenomation to highlight this potential environmental hazard in the present era of increasing marine adventure leisure activities and growing aquarium industries.

A 3-year retrospective review on venomous fish sting cases reported to the Hong Kong Poison Information Centre (HKPIC) showed that out of the 33 cases of marine envenomation, twelve were confirmed to be stung by catfish (Plotosus lineatus), 7 by stonefish (Synanceia verrucosa) and 4 by lionfish (Pterois volitans). The remaining cases included waspfish (Hypodytes rubripinnis), stingrays (Taeniura meyeni), rabbitfish (Siganus canaliculatus), silver cat (Selenotocota multifasciata) and other unknown fish. Most patients were stung on the hands (n=30). All patients complained of pain at the sting site. Other presenting symptoms were wound swelling (n=28), erythema (n=13) and numbness (n=13). In terms of complications, there were

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Fishermen were the common victims who get stung while emptying their nets or removing fish from a fishhook. Bathers and divers are another group at risk. They are usually stung in the foot by bottom-dwelling venomous fish while wading in water. However, accidents do also occur when victims needlessly touch or bother venomous fish. On the other hand, accidents may also occur outside of the water, while preparation of edible fish and in aquariums while cleaning their fish tanks. 

### Venomous Fishes

Fishes are generally regarded as venomous if they possess a traumatizing apparatus such as spines which are capable of both puncturing the skin and depositing venom within wound. Around 1200 species of fish are considered as venomous. Fish represent a superclass, comprising of 3 classes, Cyclostomata (cyclostomes or jawless fishes), Chondrichthyes (cartilaginous fishes, sharks, rays, skates and chimaeras) and Osteichthyes (bony fishes). Fish with venomous spines are found mostly among the cartilaginous fishes (in particular rays and skates, less so sharks and chimaeras) and among the bony fishes. Venoms are complex mixtures of species, subspecies, or even geographic-variant–specific substances that are pharmacologically highly active and can cause a wide range of clinical signs and symptoms which can be grouped into 7 classes: local, auto-pharmacological, anti-hemostatic, neurological, muscular, cardiac, and renal effects. Venom effects are predominantly species-specific, which makes it difficult to transfer observations from animals to humans. Unlike venomous animals, animals classified as poisonous lack an injection device, instead they possess toxins that are dispersed in their body tissues and get activated when the animal is ingested.

#### Venom Apparatus

In order to be classified as venomous, a fish must not only secrete a noxious substance from specialized secretory glands, but also possess some form of specialized delivery apparatus. With
the exception of the sabre-toothed blenny fish (Meiacanthus nigrolineatus) which possesses venomous canine teeth, the venom apparatus in most fishes invariably consists of spines that may be located on the dorsal (the most common), pectoral, operculum, shoulder, pelvic, anal and caudal areas of the fish, depending on the species. Venomous spines are those which remain in close association with cells containing venom and are capable of entering a wound when the spine sheath gets ruptured. The spines may have a median dorsal or a median ventral ridge with venom glands arranged along the grooves. Some venomous fishes have serrated grooves which can produce lacerations in victims. Most other spines are hollow to allow passage of the venom into the wound. 

Venom glands are comprised of concentrations of unicellular glands, three types of glands are found, a) mucus glands b) clavate glands c) sacciform glands. Mucus glands have a slimy secretion and clavate cells have a proteinaceous secretion, both these glands need to be ruptured before their contents are released. These secretions get released on damage to the gland while fish handling. Sacciform glands release their venom through an apical pore without the gland being ruptured. In some species e.g. stonelfish (Synanceja spp.), these venomous spines are highly developed, with distinct venom glands and venom ducts closely associated with the spine. In other species, the venom apparatus is poorly developed with a spine which is loosely associated with the venomous secretory products. Almost, the venom apparatus of all venomous fish consists of the same basic structure of a spine, associated with venom secreting cells covered by an integumentary sheath. Venom is delivered when the spine pierces the tissue of the victim, rupturing the integumentary sheath enclosing the spine. In addition to venom apparatus, many species of fish are able to secrete substances from their skin, known as Icthyocrinotoxins. These substances are capable of repelling or incapacitating other marine animals and are also thought to possess antibiotic activity, protecting fish from the invading microorganisms in the marine environment. Although it has been suggested that these ichthyocrinotoxins may also enter a wound during the envenomation process, the lack of specialized delivery apparatus makes it difficult to classify these secretions as venoms. 

**Aquarium Fishes Causing Potential Envenomation**

**Lion Fish**

The most dangerous among the venomous fishes known, belong to Scorpaenidae family and, they are divided in to three groups typified by different genera: Pterois (lionfish), Synanceja (stonelfish) and Scorpaena (scorpionfish). Lionfish are originally inhabitants of tropical waters of the Indo-Pacific region. In recent years it has disseminated over the Atlantic Ocean, USA, in several Caribbean countries (Bermuda, Bahamas, Cuba, Dominican Republic, Jamaica, Puerto Rico, Turks and Caicos, Cayman Islands, Belize, Haiti, U.S. Virgin Islands, Mexico, Aruba, Curacao, and Bonaire) and more recently in South America (Colombia and Venezuela). They are known by other names like Turkey fish, Dragon fish, Scorpion fish, Fire fish, Feather fishes, Butterfly fishes, Zebra fishes and Devilfishes. Lionfish can have different colours (red, green, red, navy green, brown, orange, yellow, black, maroon or white) and present with long and slender spines covered by an epithelial sheath that contains venom glands in the grooves of upper two-thirds of the spine. The venom flows to the wound when the ray of the fin penetrates the skin of the victim and the epithelium is broken. There are 12 to 13 rays or spines in the dorsal fin, two in the pelvic fin and three in the anal fin. The pectoral spines do not have venom. Lionfishes are popular aquarium fish and thus envenomening is common in aquarium handlers. The majority of the reported envenomation occurs in the upper extremities of the victims. The main symptom is the excruciating local pain, the pain increases in 1 to 2 hours and typically persists for 6 to 12 hours. It may radiate throughout the root of the affected limb. Moreover, the painful process can last even for weeks. There is marked inflammation, with erythema, edema and warmth. In some cases, there can be local cyanosis, paleness, vesicles and blisters. Rarely, the sting site can present with skin necrosis. Lionfish venom may provoke systemic manifestations such as cardiac effects and blood pressure changes and are thought to be due to nitric oxide release. In humans, Pterois venom usually causes systemic symptoms like nausea, vomiting, cold sweating, fever, dyspnea, convulsions, abdominal pain and syncope. Paralysis of the limbs and cardiac failure are observed infrequently. There are no published reports of death, as the venom has not shown to be lethal to healthy humans. The development of anaphylaxis and severe infections are always a possibility and require immediate emergency medical treatment.

**Rabbit Fish**

Siganidae family are popularly called as rabbit fish, fox face or spine foot. There are 30 species all over the world and are distributed in reefs among sea grasses, mangroves, and estuaries and also in shallow lagoons of tropical and subtropical coastal environments including southern Korea, Japan, Southeast Asia, Australia, Indo–Pacific regions, Hong Kong, Taiwan and Red Sea. These fish are appreciated as food items by people in the Indo-pacific and eastern Mediterranean. They have prominent face stripes which led to the common name fox faces. The majority of fishes of the family have bright and unique colour patterns with large, dark eyes and small rabbit-like mouths. These species have uniform feature with pelvic fins, which are formed from two spines, with three soft rays between them dorsal fin bears 13 spines with 10 rays behind, while the anal fin has seven spines and nine rays behind; the fin spines are equipped with well-developed venom glands. Care must be taken during aquarium maintenance and cleaning, as rabbit fishes are often easily frightened and will use their venomous spines in defense. Their venom is not life-threatening to adult humans, but causes immediate, local, intense pain, soft tissue edema and a variable extent of bleeding. The crude venom of rabbit fish possesses hemolytic activity on chicken, sheep, goat and human blood. There are few case reports of secondary infections following rabbit fish sting, gas gangrene caused by Gemella morbillorum and a case of necrotizing fasciitis due to vibrio dambel. Both these cases responded well with appropriate antibiotic therapy and
wound management.\textsuperscript{36,37}

\textbf{Spotted Scat}

The Spotted Scat (Scatophagus Argus) has a large distribution; they are commonly found throughout the Indo-Pacific region and in India. Most seen for sale are usually collected near Thailand. This fish is commonly known as Argus Fish, Leopard scat, Red Scat, Spotted Butter Fish, Ruby Scat, Green Scat, Common scat, and Spadefish.\textsuperscript{38} Scats have a quadrangular and laterally compressed body. They are greenish brown in colour with white belly and black dots of varying sizes all over the body. The average length of S. Argus is about 200 mm, and they can grow up to a length of 350 mm.\textsuperscript{39} The beautifully spotted rhombic body makes it preferable as an attractive aquarium fish, while the taste and quality ranks it as a good edible fish. Scats are venomous fishes and the venom apparatus comprises of 11 dorsal spines, 4 anal spines and a pair of ventral spine, elongated venom glands and an integumentary sheath enveloping all. The spines are very sharp and pointed, accommodating a pair of venom glands in each spine.\textsuperscript{40} Scats are not aggressive and they don’t try to inflict a wound actively. However the fishermen and aquarists get stung accidentally and more frequently while handling them. The envenomation appears within 5-10 minutes as excruciating local pain disproportionate to the size of the injury, swelling, redness and throbbing sensation that extend to the limbs followed by dizziness.\textsuperscript{41} The severity of the presentation varies depending on the amount of venom injected, and the size of the fish. Larger, the fish, more amount of venom can be injected.\textsuperscript{42} The biochemical nature of the venom of S. Argus has been found to cause hemolysis in human erythrocytes. In addition, when tested on mice, the venom appears to be “cytolytic, oedematous, nociceptive, myotoxic and proteolytic leading to tissue damage and pain.”\textsuperscript{43}

\textbf{Catfish}

Catfish (order Siluriformes) are a diverse group of ray-finned fish with prominent barbells, resembling that of a cat’s whiskers. Catfish range in size and behavior from the heaviest and longest, the Mekong giant catfish from Southeast Asia and the second longest, the wels catfish of Eurasia, to a tiny parasitic species commonly called the candiru, Vandellia cirrhosa. Many of the smaller species, particularly the freshwater genus Corydoras, are important in the aquarium.\textsuperscript{44} Catfish species live inland or in coastal waters of every continent except Antarctica. Catfish are most diverse in tropical South America, Asia, Africa and Europe. More than half of all catfish species live in the Americas. They are found in freshwater environments, though most inhabit shallow, running water.\textsuperscript{45} The stinging catfish \textit{Heteropneustes fossilis} has become a popular aquarium fish and is available in almost every pet shop. A great number of species of marine catfish, including \textit{Plotosus lineatus} (the oriental catfish) and \textit{Galeichthys felis} (the common sea catfish) and several other species of freshwater catfish are capable of human envenomation.\textsuperscript{46} Venom is delivered through a single dorsal spine and two pectoral spines. Clinically, a catfish sting is comparable to that of a stingray. The marine catfish envenomation is generally more severe than those of their freshwater counterparts. Venomous catfish have a sharp and stout sting immediately in front of the soft-rayed portion of dorsal and pectoral fins. Stings are derived from fin rays and are covered by a thin integumentary sheath. There is no external sign of the venom glands, which are located in a series of sharp recurring teeth capable of cutting into a victim’s flesh, helping the venom to be absorbed and often seeding serious infections. The stings of the catfish are very dangerous once they have been erected.\textsuperscript{47} In catfish, the pectoral fins aid the fish in its defense mechanism against predators. The ability of catfish to inflict extremely painful wounds with their pectoral and dorsal stings has been well known for many decades. The venom in the spines remains active for days, so discarded spines and even refrigerated specimens should be treated with caution.

Catfish sting envenomation is a frequent cause of morbidity among anglers, fishermen, food processors, and aquarists.\textsuperscript{48-50} Catfish have two toxicity mechanisms: the first is linked to sting penetration and rupture of the venom glandular tissue surrounding the sting, whereas the second, called ichthyocrinotoxicity is associated with the production of toxins in the entire fish skin.\textsuperscript{51} The venom of catfish is a complex composition of hemolytic, dermonecrotic, oedema-producing, and vasospastic factors and contains several amino acids, SHT, 5-nucleotidase, and phosphodiesterase. Although these stings are often innocuous, significant morbidity may result from stings, including severe pain, retained foreign bodies, infection, respiratory compromise, arterial hypotension, and cardiac dysrhythmias. There are few case reports on freshwater catfish stings by immersion of hand into the catfish.
Properties of Fish Venoms

The chemical nature of piscine venoms is poorly understood. The loss of toxicity seen when these venoms are subjected to common denaturing agents suggests that proteins constitute the major toxic component of these secretions. Fish venoms are usually mixtures of heat-labile high molecular weight proteins with systemic toxic effect and low molecular weight amines which cause inflammatory reactions. Although there is a complex balance between different components of the venom response, similarities exist between the responses to the venoms of all species of fish. The most potent effects of piscine venoms are on the cardiovascular system. All piscine venoms produce profound cardiovascular changes, both in vitro and in vivo. These include changes in blood pressure and endothelium dependent smooth muscle relaxation, as well as inotropic and chronotropic responses.

Envenomation symptoms such as paralysis, muscles spasms, and prolonged weakness clearly demonstrate that fish venoms also targets the neuromuscular system. Mice injected with *P. volitans* venom in experimental conditions showed skeletal muscular weakness indicative of neuromuscular activity. Based on the convulsions and paralysis observed in experimental conditions on exposure to *S. Argus* venom, explained the neurotoxic nature of the venom. Intense pain and severe edema are the major symptoms common to the vast majority of fish Envenomation. Various substances were postulated for this property including kinin like substance, substance recruiting inflammatory mediators but still studies are needed to the understand the nociceptive properties of fish venoms. Studies have confirmed that piscine venom has myotoxicity, as indicated by an increase in serum creatine kinase in mouse models following injection of the crude venom. Hemolysis caused by fish venom exhibits species sensitivity, like that of other animal venoms. Venom from the catfish *Arius maculatus* is approximately four times potent hemolytic to chicken blood than to blood from sheep and humans. In addition to their hemolytic activity, fish venoms also possess the ability to lyse other cell types. *S. Argus* venom has been found to cause the lysis of HeLa cells and platelets. In fish venoms, it has even been suggested that proteolytic enzymes could be partially responsible for the extreme lability of the venom components and they have been confirmed. Fish venoms have also been shown to contain a number of enzymes other than proteases. *S. Argus* venom has both alkaline and acid phosphatase activity, as well as phosphodiesterase activity.

Hyaluronidase is a common venom enzyme and facilitates the distribution of toxic components by breaking down the structurally important hyaluronan around the envenomation site. Hyaluronidase activity has been found in several different fish venoms. These include stonefish, soldier fish, lionfish, weever fish, and stingrays. As previously stated, no fish venoms have been found to exhibit phospholipase A2 activity. However, *S. Argus* was recently shown to possess phospholipase C activity which is suggested as a haemolytic agent. Piscine venoms have shown lability with regards to heat, pH, lyophilisation, storage, and repeated freezing and thawing.

Clinical Features

Despite their wide taxonomic range, the venom apparatus and pharmacology are similar throughout most venomous fish species. Envenomation incurs a large range of symptoms that have occasionally been shown to cause fatalities. The most notable symptom is extreme pain disproportionate to the size of the injury. The pain, in addition to being severe, may also radiate up the affected limb to the regional lymphatic vessels. Edema and erythema are also relatively common and in some cases vesicles may form around the wound. Systemic symptoms resulting from fish stings include ischemia, muscle spasms, tissue necrosis, prolonged weakness, and nausea, as well as paralysis of the affected limb, hallucinations, loss of perception, hypotension, tachycardia, and respiratory distress. Slow healing and necrosis have been observed following envenomation.

Death is rare even though, if it occurs it will do so within the first several hours following contact. The extent of the damage from envenomation can vary according to the species, number and depth of envenomation sites, and individual reaction to the venom components. Secondary infections are also known to occur, leading to addition damage.

Pre Hospital Care

Pre hospital personnel who come in contact with such injuries should be properly educated on marine envenomation. In case of an underwater accident, victims must be brought ashore as quickly as possible, because panicking as a result of severe pain and the systemic effects of venom increases the risk of drowning. Access to marine aquaria, puncture wounds and extreme pain should always arouse suspicion of a potential marine envenomation. Identification or description of potential marine species responsible for the envenomation should be obtained. Irrigation of the wound with clean water and transport the victim to the nearest medical facility should be done early as possible. They should recognize serious systemic symptoms and establish intravenous access in the unaffected extremity, administer oxygen, institute Cardio-pulmonary resuscitation (CPR) and treatment for anaphylaxis, if required.

Treatment

Hot Water Immersion- Primary Treatment

The primary treatment of venomous fish sting is to inactivate the heat-labile venom by immersing the injured body parts in hot water for 30-90 minutes. Two theories have been proposed to support this management. First theory showed that at temperatures over 43°C, venom lost its lethality more rapidly and as longer the exposure time. However, no significant loss of lethality was seen after exposure to temperatures less than 39°C. An alternative theory is that hot water immersion causes modulation of pain receptors in the nervous system leading to a reduction in pain. Established pain hypotheses such as the gate control theory and the diffuse noxious inhibitory control theory have also been proposed as possible mechanisms of...
action for hot water immersion. This treatment modality appears to be safe. It is an inexpensive, and there is only a single recorded case of significant thermal burn from over 200 cases of the use of hot water immersion. The most commonly referenced methods of application are thermal packs, basins of hot water, and hot showers. The choice depends on the availability of the methods. Application of hot, but not scalding, water (42-45°C) for 30–90 minutes or until the pain resolves, seems to be standard advice, but some patients may find such temperatures difficult to tolerate. The best method is to use the highest temperature that can be applied safely and that is tolerable. Lau et al. found that thermal insulators (standard coolers) were able to maintain water temperature effectively for a full 30 min alleviating the difficulty of maintaining hot-water at an appropriate temperature on site otherwise. Other methods, include the use of reusable hot packs instead of water, continual hot-water input (such as from a shower).

**Supportive Measures**

Victims of marine envenomation require supportive care and sometimes the administration of anti-venom in certain situations. Cardio-pulmonary resuscitation (CPR) and other resuscitation measures are rarely required. Initial history should include a description of the marine species responsible for the envenomation, coexisting medical conditions, and drug and horse serum allergies. Gentle removal of visible spines, the application of direct pressure to control bleeding and the administration of analgesia may also be indicated. The site of envenomation should be examined for the presence and number of puncture wounds, retained spines, edema, erythema, and ecchymosis. Puncture wounds surrounded by a ring of cyanotic tissue, vesicle formation, rapid tissue sloughing and hypesthesia have been associated with Scorpaenida envenomation. Early excision of blisters has been advocated based on the notion that blisters may contain residual active venom effecting on-going dermal necrosis. Limb elevation, to reduce edema, and early mobilization, to mitigate joint stiffness, has been recommended. The use of pressure immobilization technique is not recommended. No specific laboratory tests are recommended for the management of marine envenomation.

Whenever possible, a local nerve block with an anaesthetic is most effective. Regional anesthesia with a long acting agent such as bupivacaine offers reliable, prompt, and prolonged anesthesia. Regional anesthesia also reduces the risk of accidental thermal burn from heat immersion and facilitates procedures such as spine removal, irrigation and wound debridement and exploration. Parental analgesics may be indicated when wound location prohibits regional analgesia or for persistent pain. Opiate analgesics may be required. Cryotherapy is contraindicated. Severe hypotension may respond to adrenaline (epinephrine), bradycardia to atropine. Antibiotic treatment should be considered for serious wounds and for envenomation in immune-compromised hosts. The initial antibiotics should cover Staphylococcus and Streptococcus organisms. The most common marine pathogens involved are facultative anaerobic Gram-negative bacteria such as Vibrio vulnificus. Bacteremia resulting from wound infection with Aeromonas or Vibrio is more likely in patients with diabetes, cirrhosis, or the immune-compromised. Ciprofloxacin can be preferred as it covers Vibrio and Aeromonas. Aeromonas is common in freshwater environments. A marine animal injury is an indication for tetanus prophylaxis and should be considered based on patient’s immunization history.

Plain radiographs of the injured site due to fish sting are required for suspected embedded foreign bodies. In cases of cartilaginous fish such as stingray and catfish, ultrasound and even magnetic resonance imaging may be indicated to detect the cartilaginous parts. Complete blood picture, ECG, culture of wounds, with special request for marine micro-organisms for infected wounds may be required in some cases. Mechanical injury, remaining fragments of spines, and tissue damage caused by injected venom may require surgery. Anti-venom is available for stonefish sting. It is a horse antistonefish toxin immunoglobulin-G with clearly established efficacy for analgesia and diminution of tissue damage due to stonefish toxin. It is indicated for envenomation by stonefish with significant local pain or presence of systemic symptoms. The use of the stonefish antivenin is not routinely recommended because of potential adverse effects and the limited toxicity of these stings. The dose depends on the number of stings and is the same for adult and children. It is given intramuscularly and can be repeated when necessary. In general, one ampule (2000U) Stonefish Antivenom is given IM for puncture wounds from one or two spines. For three to four spine envenomation two vials are administered. Known allergy to horse serum remains a contraindication for stonefish anti-venom. In case of severe systemic envenomation, it can be diluted and infused intravenously. There is no anti-venom for other fish stings however; in vitro studies have shown stonefish (Synanceia spp.) antivenin cross reacts with components of lionfish venom.

**Prevention**

Inexperienced fishermen should take care when handling venomous fish and use thick, sturdy gloves. When preparing venemous fish for cooking, the fins should be carefully removed; the venom continues to be active even after the fish has been killed. It is better to swim in shallow water rather than wade. In addition, shoes with sturdy soles should be worn. A diving mask allows clear visibility under water. Other advice to divers is not to swim or dive in murky water or in stormy weather, not to touch venomous or unknown fish, especially if it is brightly coloured or has sharp or pointed spine; or has sharp teeth. Never reach for submerged rocks with bare hands or feet and to seek immediate medical care if stung by venomous fish. In aquariums, precautions should be aimed at minimizing exposure to dangerous marine specimens while cleaning tanks. Avoidance of toxic species in homes and offices frequented by young children, chronically ill, or compromised individuals should be strongly considered. Marine aquarium enthusiasts should purchase marine animals from a well-informed dealer and inquire about the potential toxicity of animals prior to purchase. Contact the local Poison Control Center in case of queries regarding venomous fishes.
or its sting.

Conclusion

Toxicology centers forecast a great growth in the number of cases of such exposure in the coming years due to the exploding fashion to keep tropical fish in home aquariums. Fish envenomation in aquariums mostly cause minor injuries, but offer the potential for lethal sequelae. Most often this involves acutely painful fish stings that respond well to hot water immersion, analgesics and appropriate wound care. Effective educational activities on this subject among professional fishermen, divers and in aquarium users are necessary to reduce sufferings. Many serious incidents can be avoided through an increase in public education and awareness. It is therefore important to identify and assess the hazards posed by various aquatic organisms in a given region and bring the results to public attention. In order to assess the extent of the phenomenon of injuries by marine organisms objectively, there is a need to maintain an organized database.

References

Head and Neck Infections in Diabetic Patients

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Abstract

 Globally, the burden of diabetes is increasing very rapidly as is the diabetic related complications. Infections in diabetes mellitus are relatively more common and serious. Diabetic patients run the risk of acute metabolic decomposition during infections, and conversely patients with metabolic decomposition are at higher risk of certain invasive infections. Infections in diabetic patients result in extended hospital stays and additional financial burden. Medicine in modern world has seen tremendous advancements like newer generation of anti-diabetic drugs, modern insulin therapy, better intensive care facilities and more potent antibiotics. Despite all these advancements, infection still remains one of the major cause for increasing morbidity and mortality in diabetic patients. This article focuses on the common diabetes related infections in the Head and Neck region of the body. Some of the life threatening infections like malignant otitis externa and rhino-cerebral mucormycosis affect this region of body.

Introduction

Patients with diabetes mellitus are more prone for infections. Infection can affect any region of the body and some of the common infections in the head and neck region include furunculosis involving the skin of ear canal and nasal vestibule, cellulitis, necroting fasciitis, malignant otitis externa, rhino-cerebral mucormycosis, parotid abscess and parapharyngeal abscess. Among these infections malignant otitis externa is almost always seen in diabetics only. Some of these infections are very difficult to treat and have a greater mortality rate. Treatment of all these diabetes associated head and neck infections is quite challenging and many a times patient need long term hospitalisation for anti-microbial therapy and better glycemic control. Such long term hospitalisation incurs greater treatment cost and increased absence from work place which in turn causes huge financial burden to the family. Nevertheless if a prompt diagnosis of a major life threatening infection is made at an earlier stage, one can avoid the onset of major complication which in turn can reduce overall morbidity and mortality. Thus the aim of this article is to give an overview of common diabetic infections in head and neck region, their management and prevention strategies.

Pathophysiology

There are certain pathogenic mechanisms that make diabetic patients more susceptible to infection. It includes hyperglycemic environment increasing the virulence of some pathogens; lower production of interleukins in response to infection; reduced chemotaxis and...
phagocytic activity; immobilization of polymorphonuclear leukocytes; glycosuria; gastrointestinal and urinary dysmotility.1 In short all these effects are caused by hyperglycemia. Hyperglycemia causes protein glycation and formation of AGEs, which can have a diverse impact on host cell function. It can cause impairment of host proteins involved in complement activation, bacterial uptake, phagocytic killing, and scavenging of biolimiting nutrients and change the binding of host surface receptors for pathogens.6

In addition hyperglycemic environment also blocks the antimicrobial function by inhibiting glucose-6-phosphate dehydrogenase (G6PD), thereby increasing apoptosis of polymorphonuclear leukocytes, and reducing polymorphonuclear leukocyte transmigration through the endothelium.5 Glycation of immunoglobulin occurs in patients with diabetes in proportion with the increase in HbA1c, and this may harm the biological function of the antibodies.5 Some studies have also demonstrated that when the glycated hemoglobin (HbA1c) is <8.0%, the proliferative function of CD4 T lymphocytes and their response to antigens is not impaired,3 thereby stressing the importance of long term glycemic control.

**Effect of infection on Diabetes**

Stress and infections in diabetic patients can lead to hyperglycemia and diabetic ketoacidosis. Hyperglycemia is due to augmented gluconeogenesis, increased glycogenolysis and poor utilization of glucose in the tissues.6 Diminished insulin levels, increased concentrations of cortisol, catecholamines and glucagon contribute to both hyperglycemia and ketoacidosis.6 Uncontrolled glucose level makes the disease more aggressive and as the disease becomes aggressive glycemic control becomes more challenging and it forms a vicious cycle.

**High risk patients**

Compared to patients without diabetes, people with type-1 diabetes were 7.2 times more at risk of S. aureus infection whereas people with type-2 diabetes were 2.7 times more at risk. Also more at risk were those suffering from other complications such as heart/circulation problems and diabetic ulcers. Kidney problems associated with diabetes were one of the highest risk factors, with a 4.2 times increased risk. The risk of infection also increases with the number of years a patient has had diabetes; those who had suffered for 10 years or more were 3.8 times more at risk. The extent to which patients had control over their diabetes is also important, those with poor management of their diabetes (HbA1c > 7%) show a greater risk for infections.7

**Furunculosis of ear canal and nasal vestibule**

Furunculosis refers to staphylococcal infection of the hair follicle. Furunculosis is common in diabetics. Many a times, initial diagnosis of diabetes is usually made during the workup for recurrent furunculosis. In the Head and Neck region furunculosis commonly involves skin of external auditory canal and nasal vestibule. Furunculosis in mid facial region around external nostril (Nasal vestibulitis) is quite dangerous as they have tendency to cause cavernous sinus thrombosis due to the extensive communication between the valve less veins of orbit and face.

Regarding the furunculosis of ear canal, when the infection involves anterior wall of ear canal, patient usually presents with pain on chewing of food rather than ear pain. This is due to proximity of anterior canal wall to temporo-mandibular joint. Such presentation can cause a delay in diagnosis and treatment. Ear canal furunculosis if left untreated can easily develop into rapidly spreading cellulitis and osteomyelitis. Thus furunculosis in these two sensitive regions of Head and Neck must be treated aggressively. Patients must be advised not to do repeat scratching or rubbing over the lesion as it can enhance the spread of lesion. Localized furunculosis should ideally be treated with oral antibiotics. However intra venous antibiotic therapy is required when there is cellulitis with evidence of local spread. Infection with MRSA strain should be considered when there is history of recurrent furunculosis, or nosocomial infection or with a positive nasal swab and antibiotic therapy must be tailored accordingly. Topical mupirocin or fuscidic acid cream can be applied locally for a period of 2 weeks to prevent bacterial colonization especially when there is MRSA infection.

**Malignant otitis externa**

It refers to the infection of the ear canal which has tendency for rapid spread into bone of entire temporal bone and hence into other bones of skull base. Hence it is also known as skull base osteomyelitis. Such an extensive skull base involvement causes greater morbidity and mortality due to excruciating pain and lower cranial palsy. The disease has aggressive clinical course, with poor treatment outcome and relatively increased mortality rate. Such features mimic that of a malignancy and hence the name malignant otitis externa. Malignant otitis externa is almost always seen in diabetic individuals only hence it is one of the diabetes defining infections.

**Infection is usually caused by pseudomonas aeruginosa in 98% of cases.** Occasionally other bacteria like staphylococcus, MRSA, E-coli and Protues species have also been isolated. Initial clinical symptoms include severe ear pain with purulent ear discharge. Ear pain is usually unbearable, it worsens at night and they spend sleepless nights. Ear discharge is yellowish in colour and it is persistent. It is associated with diffuse swelling of the pinna and ear canal. Sometimes patients ignore the initial symptoms and seek treatment only when they develop facial palsy and also when the pain becomes unmanageable anymore.

When a diabetic patient presents with such severe pain and ear discharge, a diagnosis of malignant otitis externa should be suspected and an urgent referral to an Otorhinolaryngologist must be made. ENT examination usually will reveal diffuse edema of pinna and ear canal with purulent discharge. Evaluation of ear under microscopy will reveal granulations in ear canal and biopsy of the same must be done to rule out any malignancy. Depending upon the extent of disease spread, clinical examination may also reveal facial palsy, conductive/sensory neural hearing loss, nystagmus. Features of lower cranial nerve palsy like palatal weakness, absent gag reflex with nasal regurgitation, vocal cord palsy with aspiration, tongue muscle weakness with reduced mobility is seen when the disease has spread beyond...
jugular foramen. Such an advance stage of disease at presentation carries poor prognosis.

To confirm the diagnosis and to assess the disease progress a series of investigations needs to be done. It includes culture and sensitivity of ear discharge, biopsy of granulations from ear canal and audiometry to assess the type and degree of hearing loss. Imaging usually includes high resolution CT scan of the temporal bone and technetium Tc 99/ Gallium 67 bone scan. MRI of brain and temporal region is done when any intra cranial complication is suspected. Haematological investigations will usually reveal a very high ESR level (above 80mm/hr) at presentation and ESR level usually begin to settle during the course of treatment.

Treatment includes strict glycemic control, long term intra-venous antibiotics for a minimum period of 6 weeks and oral antibiotic for another 6 weeks. Anti-pseudomonal antibiotics like ciprofloxacin, piperazillin-tazobctum, netilmicyn, ceftazidine are the antibiotics of choice. Ideally one pencillin group of antibiotic must be combined with either fluoroquinolone or aminoglycoside for optimal outcome. Many a time’s patients usually cannot tolerate such a higher dose of antibiotics on long term due to associated renal or hepatic derangement. Nevertheless such aggressive treatment is crucial because the infection has involved the bone of skull base which has poor perfusion due to diabetic microangiopathy and pseudomonas induced vasculitis. Medications with ciprofloxacin and acetic acid combination is used a topical ear drops.

While the patient is on long term iv antibiotics, charting of pain score, weekly monitoring of ESR and regular monitoring of renal profile is done. Declining trend of ESR and improved pain score indicates good response to treatment. Bone scan especially Gallium 67 scan (if available) should be done at the end of treatment to look for complete resolution of inflammation.

**Rhino-cerebral Mucormycosis**

Mucormycosis is a rare opportunistic invasive fungal infection caused by fungi of the following genus namely Rhizopus, Mucor or Cunninghamella. Mucormycosis in diabetic patients commonly involves nose and para nasal sinuses and from there it can spread into orbit and cranial cavity via angio and perineural invasion, hence the name rhino-cerebral mucormycosis. The classical triad is characterized by paranasal sinusitis, ophthalmoplegia with blindness and unilateral proptosis with cellulitis. The disease is highly fatal with a survival rate of 38-50% only and death can occur in one or two days if treatment is not initiated immediately.

Fungus causing mucormycosis is a saprophytic fungi and it is commonly found in decaying vegetable matter, bread mold and soil. They are easily susceptible to phagocytic activity of macrophages in healthy individuals and hence they rarely cause infection in immune-competent individuals. They thrive well in conditions with acidic PH, hyperglycemia and reduced phagocytic activity. All these factors make persons with diabetic ketoacidosis more prone for mucormycosis. The fungus has the tendency to invade blood vessels and cause thrombosis and tissue necrosis. Aggressive clinical course of this infection is mainly due to angio-invasion, which provides a channel for rapid spread of infection along the vessels into orbit, cavernous sinus and intra cranial cavity. Also the ensuring tissue necrosis provides a viable medium for fungus to growth where penetration of anti-fungal drugs is poor due to loss of tissue perfusion.

Initial symptoms usually include headache, facial and periorbital pain mimicking that of acute sinusitis. Sometimes patients or even physicians tend to ignore these initial symptoms. Once the fungus has started spreading beyond the sinuses, patients will start getting facial swelling with discoloration, ophthalmoplegia, loss of vision, palatal discoloration. Facial and palatal discoloration is caused by ischemic necrosis. To begin with the discoloration is of pale white in color and then the color changes into white, grey hue and finally black (gangrene). The necrotic area is often well demarcated, appear black in color and such features can be seen easily in hard palate, periorbital region of face and nasal septum. Presence of ophthalmoplegia and vision loss usually indicates cavernous sinus involvement. The disease shows a very rapid clinical progression and the progressive tissue discoloration due to ischemia happens within few minutes. So treatment must be initiated soon after a diagnosis of mucormycosis is suspected. CT-scan and MRI of Paranasal sinuses and Brain is done to assess the disease extent and to guide for debridement.

Treatment must be very aggressive as is the disease. Soon after admission, sample of necrotic tissue must be sent for fungal- KOH study and culture. In case of mucormycosis, KOH study usually reveals aseptate fungal hyphae with right angled branching. Anti-fungal therapy with Amphotericin-B must be initiated soon after admission along with other measures to control hyperglycemia and ketoacidosis. Urgent surgical debridement of the necrotic tissue is also crucial for disease control as fungus in necrosis will evade anti-fungal treatment due to absent tissue perfusion in these areas. Thus urgent anti-fungal therapy, glycemic control and surgical debridement form the main triad of treatment.

Most of the times, it is very difficult to stabilise the patients for a major debridement surgery. In such situations, debridement under local anaesthesia must be considered as the necrotic tissue is pain free and does not bleed much. Necrotic tissue involving nasal cavity, para nasal sinuses, palate can be debrided easily using endoscope. Orbital involvement usually necessitates orbital exentration. Craniotomy and debridement is required when there is significant intra cranial spread. Anti-fungal therapy must be initiated soon after establishing a diagnosis of mucormycosis. Amphotericin B is given at a dose of 1 to 1.5 g/kg body weight/day. Total cumulative dose of 2 to 3 mg is ideal. Given the potential nephrotoxic effect of this drug, periodic monitoring of electrolytes and renal profile is done during the entire course of treatment. Liposomal amphotericin B is considered in patients with deranged renal function. Currently amphotericin B is the only anti-fungal drug which is showing potential activity against mucormycosis infections. However in certain refractory cases other antifungal agents like posaconazole, caspofungins can be considered as adjuvant therapy along with amphotericin B.
Parotid Abscess

Parotid abscess is one of the common infections in diabetic patients. Infective agent is a mixed flora of gram positive and anaerobic organisms as they usually ascend from oral cavity via parotid duct. Clinical presentation includes fever, pain and swelling in the parotid region. Infection is usually aggressive in diabetics and many a time’s patients do present with severe trismus, discoloration of overlying skin, facial palsy while using cotton swabs to clean the ear canal to water with a high risk of bacteremia: a population-based case–control study. Eur J Endocrinol 2016; 174:631-639.

Deep Neck Space Infections / Abscess

Deep neck space abscess refers to the collection of pus between the fascial planes of Head and Neck region. Of all the deep neck space infections, parapharyngeal abscess is seen more commonly in diabetics. Majority of the lymphnodes and major vein of Head and Neck lie in the parapharyngeal space. So any odontogenic or upper respiratory infection, easily spreads into this space via the draining nodes. Most common infective agents include Streptococcus. Strptococcus, Staphylococcus, Klebsiella and anaerobic Bacteroides. Clinical presentations includes fever, neck swelling with pain, dysphagia, reduced mouth opening. Respiratory difficulty is seen when there is significant airway obstruction due to swelling. Imaging studies like contrast enhanced CT scan and MRI are done to see the disease extent and for treatment planning. Treatment includes control of hyperglycemia, intra venous antibiotics and aspiration of pus. Localised pus collection is easily managed by image guided aspiration. However surgical drainage is required when there is poor response to antibiotic therapy, multi-loculated collection and in refractory cases.

Prevention

In view of the significant morbidity and mortality associated with these infections, it becomes essential to educate patients about various precautionary measures. To reduce the chance of getting ear infection, susceptible patients should be educated to avoid manipulation of the ear canal (i.e.,) they should not cause ear trauma while using cotton swabs to clean their ears and to minimize exposure of the ear canal to water with a high chloride concentration. Patients must be advised to seek medical care at the earliest possible time when they develop symptoms like severe ear pain, nodule with swelling near external nostril, peri-orbital swelling, diplopia, neck swelling and difficulty in mouth opening. When patients seek medical care, a prompt diagnosis should be made and efforts must be made to avoid any significant treatment delay. Also anticipating serious complications of common infections in patients with diabetes is as important as appreciating rare disease entities that affect these patients disproportionately. Finally, one must not forget the importance of regular exercise, strict dietary control and good compliance with diabetic medication.

References

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Thrombosis of Bioprosthetic Mitral Valve

Rajeev Bhardwaj¹, Munish Dev²

Fig. 1: Evidence of thrombus over the mitral bioprosthetic valve

A 5 years female, had undergone mitral valve replacement for severe MR, with bioprosthetic valve, two and half months back. She was on Warfarin, 4 mg once a day. She presented with breathlessness for three day. She also had paroxysmal nocturnal dyspnoea. On examination her BP was 100/70 mm Hg, heart rate 124/min, respiratory rate 24/min. On cardiovascular examination, she had long mid diastolic murmur at apex. Echocardiography showed evidence of thrombus over the prosthetic mitral valve (Figure 1). Peak gradient across mitral valve was 19mm Hg and mean gradient was 6 mm Hg. Her INR was 1.3. She was thrombolized with streptokinase and improved.

The incidence of thrombosis of mechanical prosthetic valves ranges from 0.5 to 6 percent (in the aortic- and mitral-valve positions) to 20 percent (in the tricuspid-valve position) per patient-year. For bioprostheses, the overall average rate of thrombotic stenosis is 0.03 percent per year.¹ Heart-valve thrombosis may present insidiously, and recognition of it may be difficult. Guidelines differ in their recommendations regarding the choice of treatment for prosthetic valve thrombosis. For example, although the Society for Heart Valve Disease (SHVD) recommends fibrinolytic therapy (FT) for all patients,² the European Society of Cardiology (ESC) recommends FT only if the risk of surgery is prohibitive or in the event that it is not available and the patient cannot be transferred.³

References

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**Storage:** 本品应存放在2°C至8°C的冰箱中。

**References:**
2. NovoMix™ summary of product characteristics.
7. Nissen et al.
Kaposi Sarcoma in Non-immunocompromised Adult

Atul Bhasin¹, RK Singal², Amit Agarwal³, Suhail Qureshi⁴, Gagan Anand⁵, Chandragouda D⁶, Seema Sachan⁷

A 27 year old female patient, with no known co-morbidities or drug allergies presented to us with complaints of painful swelling and redness over both peri-orbital regions, of insidious onset, gradually progressive for past 6 months. Initially, unilateral it progressed to other side with associated peri-orbital redness and swelling.

There were no associated eye discharge, epiphora or bleeding suggestive of nasolacrimal obstruction. However, vision was compromised later on as a result of severe peri-orbital swelling (Figure 1).

She was administered antibiotics, local application and systemic steroids, and other Intra-lesional injections which were largely unsuccessful. As the symptoms of peri-orbital swelling increased, pain and color of lesion changed to black, and skin dryness with scaling appeared and increased progressively, she was brought to our hospital.

Evaluation for Hepatitis B, C and HIV was negative. Cultures of the blood, urine and swab culture from the wound were sterile. Swabs taken from the skin lesions around the eyes were unproductive for any infective pathology on Gram stain and fungal stain. MRI of the face revealed diffuse and extensive skin, subcutaneous and soft tissue thickening and edema involving the scalp and soft tissues of face and neck and features consistent with angioedema. Globes and intra-orbital structures were normal. Work-up for vasculitis was negative. A skin biopsy was planned to ascertain the diagnosis. Skin biopsy was consistent with a diagnosis of atypical vascular proliferative lesion, low to intermediate grade, most likely Kaposi sarcoma (KS).

KS is a multifocal, vascular lesion of low-grade malignant potential that presents most frequently in mucocutaneous sites and commonly involves lymph nodes and visceral organs. The musculoskeletal system, central and peripheral nervous system, larynx, eye, major salivary glands, endocrine organs, heart, thoracic duct, urinary system and breast represent unusual locations for the development of KS. Peri-orbital edema may occur with KS of the face.²⁻³ KS of the conjunctiva and ocular adnexa has been reported in association with Classic and AIDS-related KS.⁴⁻⁷

In view of the diagnosis Oncology opinion was requested and due obvious cosmetic disfigurement and widespread facial disease, our patient was planned for treatment with Pegylated Liposomal Doxorubicin (PLD). She received 6 cycles of PLD over a period of 6 weeks and responded very well to the treatment. Her lesions subsided substantially and vision also improved with treatment (Figure 2).

This case represents an unusual location for the development of KS in an immune competent host. It also stresses on the value of suspecting KS at atypical sites and also the importance of systemic therapy for KS when site and extent of the disease involvement make local treatments rather less attractive options.

References

Paradoxical Response in Cerebral Nocardiosis in a Renal Transplant Recipient

Rajeev Soman¹, Vidyullata Koparkar², Alan Almeida³, Anjali Shetty⁴, Camilla Rodrigues⁴

Abstract
Paradoxical response (PR) in patients on anti-tuberculosis drugs and immune reconstitution inflammatory syndrome (IRIS) in patients started on antiretroviral therapy are well known phenomenon. We encountered a case of a paradoxical response in cerebral nocardiosis in a renal transplant recipient. To our knowledge this phenomenon in cerebral nocardiosis has not been reported earlier in literature.

Introduction
Paradoxical response is worsening of an existing infection or disease process or appearance of a new infection/disease process after starting effective therapy and preceded by initial improvement. The immunopathogenesis of this syndrome is unclear and seems to be the result of unbalanced reconstitution of effector and regulatory T-cells, leading to exuberant inflammatory response in patients. PR is associated with infections like Mycobacterium tuberculosis, especially Tuberculous lymphadenopathy and meningitis, Mycobacterium avium complex infection, PCP infection and Cryptococcal meningitis.¹,²,³

Case Report
A 55 year old lady underwent live related kidney transplant surgery (LRKTR) in September 2011. Induction immunosuppression was with Methylprednisolone. Maintenance immunosuppression was with Tacrolimus, Mycophenolate mofetil and Deflazacort. She received TMP-SMX and VGCV prophylaxis till 6 months after transplant. She maintained stable renal function with creatinine clearance around 30%. In September 2015, she presented with a subacute onset of dry cough for 3 weeks followed by intermittent high grade fever. There was an erythematous, non tender skin nodule in the right axillary region. The cough then turned productive and headache developed. Xray chest (Figure 3) and CT chest showed consolidative lesions with signs of early breakdown. Patient’s sputum examination with modified acid fast stain confirmed the diagnosis of nocardiosis. MRI brain (Figure 1) revealed multiple small cerebral abscesses with perilesional edema located in cerebral parenchyma, posterior right basal ganglia and cerebellum. The initial treatment regimen included, TMP-SMX, Ceftriaxone, and Linezolid. This was later modified as per DST reports to TMP-SMX, Linezolid and Moxifloxacin. TMP-SMX was given in modified dose as per creatinine clearance.

One month later, she presented with two episodes of generalized tonic clonic convulsions, drowsiness and right sided monoparesis. MRI (Figure 2) brain confirmed increase in size of old lesions with increase in perilesional edema, and there were no new lesions. Chest X-ray (Figure 4) showed marked resolution of previous right upper zone lesion.

The treatment of nocardiosis in this patient was as per DST and drugs chosen had a good CNS (central nervous system) penetration, and the pulmonary lesion had shown clear improvement. Thus the clinical and radiological worsening could not be explained by failure of treatment and therefore a likelihood of paradoxical response of cerebral nocardiosis was considered. Review of doses of immunosuppression showed that an eight fold reduction of the dose of tacrolimus was done as the measured levels were too high. This change in dosage had been done three weeks prior to clinical and radiological deterioration thus showing temporal association with the neurologic manifestation.

20/9/2015: Diagnosed as disseminated nocardiosis and initiated on treatment. Tac dose – 2 mg/day, MMF – 1 gm/day Deflazacort 6 mg/day
10/10/2015: Tac levels – 40 ng/ml, hence dose reduced to 0.25 mg/day (1/8th of previous dose) Same doses of MMF and Deflazacort continued.
17/10/15: Tac levels - 4.83, tacrolimus dose kept at 0.25 mg/day. Same doses of MMF and Deflazacort continued.
8/11/15: Patient presented with seizures and altered sensorium, the Tac level was 0.27 ng/ml (A 18 fold decrease in level of immunosuppression). Treatment was as per DST, drugs used had good CNS penetration and were dosed as per creatinine clearance. The lung lesion showed resolution. Thus this can be a paradoxical response in CNS.

The patient was treated with tapering doses of dexamethasone (12 mg to 1mg and then continued on 6 mg of deflazacort). She responded well to the treatment. At 6 month follow up she is doing well, and follow up MRI brain (Figure 5) and CXR shows good resolution of all previous lesions.

Discussion
The exact pathophysiology of the PR phenomenon is not known. It has

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been proposed that PR occurs as a result of shift in the dominant T helper responses that restrain inflammation (T reg and Th2) towards generation of proinflammatory T cells (Th17 and Th1). Nocardia, like mycobacteria have mycolic acid polymers in their cell walls which are implicated in the development of an immunosuppressive microenvironment. Hence an effective treatment by itself could result in a heightened pro-inflammatory response.

Tacrolimus (Tac) is a calcineurin inhibitor (CNI) which leads to inhibition of cytokine genes concerned with T cell activation and proliferation. In our patient the eight fold reduction of tacrolimus dosage, caused 18 fold reduction in tacrolimus levels, which could have led to a rebound in T-cell activation leading to an enhanced inflammatory response. It is not common in clinical practice to have such a drastic (18 fold) reduction in the level of Tac and the consequent rebound in the inflammatory response. This may be the possible reason why PR in cerebral nocardiosis has not been reported before. A PR is well described with cryptococcal brain lesions in transplant recipients. A case of paradoxical response in a case of Nocardia transvalensis osteomyelitis and cerebral abscess is described. In this case, however the brain lesions had improved with concomitant unresolving osteomyelitis. This is totally different from what we encountered.

Diagnosis of PR requires exclusion of resistance and hence drug susceptibility testing (DST) is essential. Disseminated nocardiosis with CNS involvement in immunocompromised needs two, preferably three drugs. Amikacin, trimethoprim-sulfamethoxazole, linezolid display minimal or no resistance as found on isolates at our institution. However, amikacin is less preferred in renal transplant recipients and hence betalactams, and fluoroquinolones are needed, but these drugs can be used only is susceptibility is shown.
Toluene Poisoning Presenting as Bilateral Basal Ganglia Haemorrhage

Sunil Mahavar1, Ashutosh Chaturvedi2, Aradhna Singh1, Ramesh Kumar3, Sher Singh Dariya4, Raman Sharma5

Abstract

Toluene is an aromatic hydrocarbon that is often used as a solvent in paints, paint thinners, glues, disinfectants and as an industrial solvent for the manufacturing of pharmaceuticals, paints and chemicals. Metabolic acidosis is a recognized complication of toluene poisoning. However, we here report an unusual case of toluene poisoning presenting with bilateral intracerebral haemorrhage.

Introduction

Toluene (Structural formula: C6H5CH3) is also known as toluol, phenylmethane, methylbenzol, methyl-benzene, monomethyl benzene, and methacide. Several studies have examined the absorption of toluene and other organic solvents following oral ingestion, toluene accumulates in the liver, while after inhalation, it accumulates in the brain. Acute intoxication affects the central nervous system (CNS), leading to euphoria, confusion, depression, headache, vertigo, hallucinations, seizures, ataxia, and finally, stupor and coma.

Toluene has been known to cause increased anion gap acidosis and hypokalemia. But we hereby report an unusual case of toluene ingestion presenting with severe metabolic acidosis and bilateral basal ganglia bleed which has never been reported.

Case Report

A young 25 year old male, working in the glass industry, was referred to our emergency department with alleged history of accidental ingestion of approximately 100 ml of paint thinner two days back, following which the patient became drowsy and complained of headache, vertigo, hallucinations, seizures, ataxia, and finally, unconsciousness. The patient was non-responsive and in painful stimulus and had decreased deep tendon reflexes bilaterally. Suddenly after two days of ingestion, patient developed shortness of breath and loss of consciousness when he was brought to the emergency department. There was no history of any fever, trauma or seizure preceding the loss of consciousness. The patient was non-hypertensive, non-diabetic.

At the time of presentation to the emergency department, the patient was gasping and was immediately intubated and ventilatory support initiated. His ABG showed severe metabolic acidosis.

A thorough examination done after stabilising the patient revealed a blood pressure of 120/80 mmHg; pulse rate of 90/minute; a normal Cardiac examination. There were crepitations bilaterally suggesting aspiration pneumonitis. The pupils were sluggishly reactive and the patient was unconscious (E1M1V1) with plantar reflex mute bilaterally.

Basic laboratory studies revealed an haemoglobin level of 15.0gm%; TLC of 9100/cumm with 84% neutrophils, 10% lymphocytes, 4% monocytes and 2% eosinophils; platelet count of 1,52,000/cumm; PCV of 49%; S. Sodium 140 mEq/L; S. Potassium 7.2 mEq/L; Blood urea 30 mg/dl; Serum creatinine 1.1mg/dl; Serum uric acid 8.9mg/dl; Serum calcium 9.8 mg/dl; Serum phosphorus 2.8mg/dl; Serum magnesium 2.4 mg/dl; PT INR of 1.1; random blood sugar of 103mg/dl; serum bilirubin 0.4mg/dl; SGPT 52 U/L; SGPT 26 U/L; Alkaline phosphatase of 183 U/L; serum LDH 1152 IU/L (Normal 240 to 480IU/L); Serum CPK 1291 IU/L (normal 25 – 190 IU/L); serum protein 6.6 gm/dl; serum albumin 4.2gm/dl; serum globulin 2.4gm/dl. ECG done at time of admission showed tall T waves suggestive of hyperkalemia for which appropriate treatment was started immediately. A chest radiograph revealed bilateral infiltrates.

ABG revealed an high anion gap metabolic acidosis with Ph of 7.06, HCO3 of 6.1mmol/l; S. Sodium 140 meq/L; S. Chloride 106 meq/L. NCCT head showed bilateral basal ganglia bleed (Figure 1).

The patient was managed for intracranial bleed, aspiration pneumonitis and metabolic acidosis with a tracheostomy, ventilator support, intravenous fluids, cerebral decongestive therapy, broad spectrum antibiotics, steroids and bicarbonate infusions with daily monitoring of metabolic parameters. However despite treatment, the patient suffered a cardiac arrest and despite best efforts at resuscitation, the patent expired.

Fig. 1: NCCT Head showing bilateral basal ganglia haemorrhage

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Discussion

Toluene is one of the main compounds of glue, gasoline, acrylic paints, varnishes, lacquer, paint thinners, adhesives, and so forth. Toxicity can occur either from accidental or deliberate inhalation or direct absorption through the skin, but the most frequent and widespread cause of intoxication is glue sniffing.

Distribution in Body

Toluene that is absorbed into the blood is distributed throughout the body. Ameno et al. reported that in a 51-year-old man who died from accidental oral overdose, the highest toluene concentrations (per gram tissue) were in the liver, followed by the corpus callosum, with the lowest in the caudate-putamen.

Thus, the available human data suggest that more toluene accumulates in the brain than in the liver following inhalation exposure, whereas following oral exposure, the liver contains the greatest concentrations of toluene.

Our patient during the course of his occupation had probably been exposed to fumes containing toluene and had also had an acute exposure following oral ingestion.

Acute toluene exposure can provoke disorientation, euphoria, exhilaration, and tinnitus. Higher levels cause disinhibition, decreased level of consciousness, hallucinations, nausea, and fatigue. Electrolyte and acid/base abnormalities after toluene exposure have been reported.

Clinical Manifestations of Toluene Poisoning

Toluene intoxication leads to metabolic acidosis either with a normal anion gap or an increased anion gap. It is metabolized to hippuric acid by way of benzoic acid, both of which are found in the serum of patients who abuse toluene. If renal elimination of hippuric acid is impaired or hippuric acid production is high relative to renal elimination, the molecule accumulates and produces an elevated anion gap metabolic acidosis.

Hypokalemia has been reported in patients of toluene poisoning possibly because of increased urinary excretion due to the presence of poorly reabsorbed anions and low urinary chloride concentration as seen with urinary excretion of hippurate and benzoic acid accompanied by volume contraction. However, in our patient the serum potassium levels were high and ECG showed tall T waves. This could be due to renal failure and rhabdomyolysis.

Cardiovascular side effects in acute toluene poisoning appear as a result of direct negative effects on cardiac automaticity and conduction or oversensitization of the heart to endogenous catecholamines, which itself can lead to sudden cardiac death. Other cardiac abnormalities, which have been reported in association with toluene toxicity are recurrent myocardial infarction, dilated cardiomyopathy, and coronary vasospasm.

The central nervous system abnormalities described in toluene poisoning patients include ataxia, tremors, temporal lobe epilepsy, decreased intelligence quotient, paranoid psychosis, hallucinations, nystagmus, cerebral atrophy, abnormal EEG record and impaired speech, hearing, and vision.

Organic solvents readily cross the blood-brain barrier following inhalation and produce CNS effects similar to those of alcohol and benzodiazepines. Positron Emission Tomography (PET) studies have indicated that solvents have rapid entry into the brain, short half-lives, and high rates of metabolism and clearance.

Little is known about the mechanisms by which toluene produces acute effects but it is reasonable to assume that its toxic effects are due, at least in part, to its general characteristics as a solvent. Because of its lipophilic character, toluene has a serious impact in the brain and in other parts of the nervous system. It acts as a central nervous system depressant and this is the most common cause of death in toluene ingestion. The presence of solvent molecules in cholesterol-filled interstices between phospholipids and sphingolipids changes membrane fluidity, thereby altering intercellular communication and normal ion movements. The lipid solubility, volatility, and route of exposure of the compound enhances its toxicity.

References

Methemoglobinemia – The Cryptic Cause of Dyspnoea

Kavita Krishna1, Baldeep Singh2, Vivek Nikam2, Rohit Jakhodia2, Vrushabh Phade2

Abstract

Methemoglobinemia is a life threatening condition that can be difficult to diagnose. It can be congenital or, more often an adverse drug effect. A good, detailed history taking and thorough knowledge of drugs and toxins is the secret to early diagnosis. We present two interesting cases of methemoglobinemia. First was phenol poisoning with G6PD deficiency leading to hemolysis and methemoglobinemia and second was phenol induced methemoglobinemia. Here we discuss the diagnosis and management of a patient with acquired methemoglobinemia.

Introduction

The majority of cases of acquired methemoglobinemia described in literature have resulted from exposure to exogenous oxidizing agents like nitrites used as preservatives in food or as a deliberate poison1 amyl nitrate used as a recreational agent, abuse of paint thinner by addicts, intake of nitrate containing vegetables use of EMLA cream and Dapsone intake.

Phenols like dinitrophenol and pentachlorophenol are very toxic substances. They have significant inhibitory effect on various enzymes; such as G6PD. G6PD deficiency can lead to hemolytic crisis, favism, and chronic nonspherocytic hemolytic anemia.

Dapsone (4,4’-diaminodiphenyl sulfone) is a sulfone antibiotic and potent anti-inflammatory that inhibits folate synthesis.2 It is metabolised in liver via the cytochrome P450 pathway to potent oxidants that are responsible for its adverse hematological effects – hemolytic anemia and methemoglobinemia.

Here, we report 2 cases of methemoglobinemia following ingestion of phenol and dapsone respectively.

Case Report 1

A 28 year old male, computer engineer by profession, admitted with alleged history of consumption of 300 ml phenol 6 hrs back, with complaints of oral and posterior pharyngeal wall ulceration, odynophagia, mild dyspnoea and abdominal pain.

His blood pressure was 120/80 mm of Hg with SpO2- 85%. On investigating, his laboratory parameters revealed: Haemoglobin – 13.0 g/dl; WBC – 15600 /cummm; Platelet count 2.20 lakhs/cumm, Serum bilirubin (T)-1.4, (I)- 1.0 mg/dl, Arterial blood gas showed pH-7.4, PO2- 92 mmHg; SpO2- 90%, rest WNL and Chest Xray and ECG were normal.

Patient started passing dark brown urine for which we repeated laboratory parameters after 6 hrs, which were suggestive of haemolytic picture s/o Hb - 11.5g/dl (↓), bilirubin (T)- 6.75 mg/dl (↑), (I)- 6.58 mg/dl (↑), Serum LDH- 1024 U/L (↑), G6PD levels were- 2.75 (4.6-13.6) U/gm of hemoglobin, Methemoglobin-14.54 (0-1.5%) of total Hb, Renal functions WNL, Urine routine- albumin- 3+, RBC-8-10/hpf

Plenty of oral and IV fluids were given. Urine output, haemogram and liver function tests were monitored. Because of G6PD deficiency methylene blue was not given. Patient was given Ascorbic acid 1 gram daily for 2 weeks. Over next 1 week his liver functions improved and he was discharged.

Case Report 2

48 yrs male known case of leukocytoclastic vasculitis (diagnosed on biopsy in 2012), with palpable purpura over the legs had been on varied immunosuppressive medications (Dapsone, Azoran and Mycophenolate mofetil) and steroids, to which he responded well. Patient was on irregular treatment and had omitted all medications since 6 months except for steroids (Tablet Methylprednisolone 2mg OD).

This time, he had complaints of increased rash over the legs since 2 weeks, for which he was started on tablet Dapsone 100 mg BD 7 days before. There was no history of fever, joint pain, hematuria. On admission, patient also had complaints of shortness of breath and tingling sensation over the head since 5 days.

Blood pressure was 120/80 mm of Hg, Pulse was 86/min, SpO2- 85 %. On investigating, his investigations were as follows:

Chest X-ray was normal, HRCT chest was suggestive of early interstitial lung disease and PFT’s showed mild restrictive disease.

Pulmonologist advised to increase methyl prednisolone to 8mg, to continue dapsone, and added formoterol + budesonide inhalation. Later on taking detailed history, patient gave history of shortness of breath and similar symptoms 2 years ago after starting dapsone.

ABG s/o pO2- 88 mmHg, pCO2- 38, SpO2 – 90%.

Blood was reddish brown colour, Methemoglobin levels were 5.2% and G6PD level were normal.

Patient was advised to stop Dapsone. Since methemoglobin levels were not very high, he was given iv ascorbic acid and Methylene blue was not given. Over the next 5 days patient’s dyspnoea improved, Spo2 was 96-97% off o2 and was discharged on day 5.

Meth Hb after 15 days was 2% and normal after 2 months. On follow up, patient was asymptomatic on 4 mg methyl prednisolone, with no other symptoms and counselled to start Azoran/mycophenolate mofetil.

Discussion

In the first case, patient presented with haemolytic anaemia with mild hepatic injury, due to toxic injury with...
phenol was postulated. Acute toxicity causes intense burning sensation in mouth, throat, and stomach. Phenol is rapidly absorbed in the blood and there may be hyper or hypothermia, tachycardia, tachypnoea, generalised weakness, dizziness, nausea and shock leading to death. The average fatal dose is 2 grams and the half life is rapidly absorbed in the blood and there may be hyper or hypothermia, tachycardia, tachypnoea, generalised weakness, dizziness, nausea and shock leading to death. The average fatal dose is 2 grams and the half life is 72-83 hours. It is excreted chiefly in the urine and also by the liver, lungs and skin. Derivatives of phenol like dinitrophenol, pentachlorophenol interfere with oxidative phosphorylation in cells. Storage of energy in the form of adenosine triphosphate is prevented, thereby leading to a compensatory increase in the basal metabolic rate which is responsible for most of the principle clinical features of toxicity of this substance.

The main source of energy in red blood cells is anaerobic glycolysis. Due to shortage of energy, red blood cells cannot continue to perform their vital functions like preventing the osmotic equilibrium across the cell membranes, the cation pump and cell deform ability. This metabolic handicap may lead to premature lysis of the cells causing hemolysis. Also phenol may produce Heinz bodies and contribute to hemolysis. The mechanism that protects the red cells against oxidants include G6PD, the entry enzyme to the hexose monophosphate shunt that generates NADPH and the related enzymes that maintain GSH in the reduced form and protect haemoglobin from irreversible oxidation. Heinz body anaemias are found in individuals with defects in these protective mechanism when they are exposed to oxidants in the form of chemicals or drug that normally are not haemolytic. Low G6PD level explains the moderate haemolysis that develops after phenol poisoning as in our patient. Anaemia will be first noted as asymptomatic drop in spO2 and the appearance of bluish discoloration is an immediate clue to the presence of methemoglobinemia which is produced from oxidation of ferrous to ferric ions which cannot carry oxygen.

In second case, after detailed history, methemoglobinemia secondary to dapsone was suspected and methemoglobin levels were sent. Dapsone is a drug that is used in the treatment of leprosy, dermatologic conditions like acne vulgaris, pyoderma gangrenosum and dermatitis herpetiformis, and various rheumatological disorders like systemic lupus erythematosus, Giant cell arteritis, vasculitis, relapsing polychondritis etc owing to its immunsuppressive effects. Long-term administration of dapsone at standard doses (100 mg/day) results in methemoglobinemia in about 15% of patients. The peak plasma concentrations of Dapsone are reached within 2-8 hours after ingestion. The mean elimination half-life varies from 10 up to 80 hours in overdose situations. In healthy erythrocytes, cellular enzymes rapidly reduce any naturally occurring methHb. An exposure to oxidative medications can overcome these reducing enzymes thus causing an accumulation of methaemoglobin. The role of nitric oxide (NO) in the pathophysiology of methemoglobinemia is also being studied. Our patient became symptomatic within 1 week of starting Dapsone. Methemoglobinemia after short duration of therapy is uncommon.

ABG is the appropriate diagnostic test and brown colour of arterial blood is another useful clue to the presence of methemoglobinemia but co-oximetry is the gold standard. Methylene blue and ascorbic acid is given to reduce the methemoglobinemia. IV methylene blue will exacerbate NADPH deficiency in such patients resulting in increased free radicals and a hemolytic crisis. In such cases, ascorbic acid, a potent antioxidant and reducing agent is used.

## Conclusion

- Diagnosis of methemoglobinemia requires a high index of suspicion.
- A good, detailed history taking and thorough knowledge of drugs and toxins is the secret to early diagnosis.
- In patients with G6PD deficiency, phenol can cause methemoglobinemia and significant hemolysis.
- Methemoglobinemia should be considered of possibility if a patient on Dapsone complain of shortness of breath.
- Methylene blue should not be administered in asymptomatic cases and until after G6PD levels are shown to normal and ascorbic acid should be given instead.

### References

Granulomatous Hepatitis with Miliary Mottling: A Rare Cause

Vinod Joshi, Shubhra Jain, Vinod Sharma, Narendra Khippal, Ashutosh Chaturvedi

Abstract
Miliary mottling is most commonly seen in tuberculosis. Clinical features of tuberculosis mimic many other lung diseases. Here we report a 40 yr old male with clinical features suggestive of tuberculosis, miliary mottling on skiagram chest and granulomatous hepatitis on histopathology. Case was finally diagnosed as sarcoidosis on liver biopsy and improved on oral corticosteroid.

Introduction
The typical differential diagnosis for miliary opacities of the lung includes tuberculosis, metastatic lesions, and pneumoconiosis. Miliary shadows are atypical feature in sarcoidosis. There is paucity of literature on hepatic involvement in sarcoidosis. It rarely causes symptoms and may remain undiagnosed. Common causes of liver granuloma are sarcoidosis, AIDS, drugs, primary biliary cirrhosis. We report a case of a young male with miliary shadows on skiagram chest and hypodense lesion in liver. Patient was on antitubercular treatment but no relief. Final diagnosis was confirmed after histopathology of liver lesion.

Case Report
A 40 year old male presented with complaints of fever and cough since 3 months. He also reported nausea, vomiting, generalized weakness and loss of appetite since last 20 days. There was no h/o hemoptysis, chest pain, dyspnea and joint pain. He was a known case of psoriasis (diagnosed 8 years back) and diabetes mellitus (diagnosed 18 month back). Patient was on antitubercular treatment since 1 month on the basis of clinical findings and miliary mottlings on skiagram chest but he had no relief. On examination macular, hypopigmented lesions were seen on forearm and legs. There was no pallor, icterus, clubbing and palpable lymphadenopathy. Bilateral few scattered crepts heard on auscultation. Complete blood count, Renal Function tests were Normal. His Liver Function tests (LFTs) STB/SGOT/SGPT/Alkaline Phosphatase were 2.6/133/200/500 respectively. MP and Widal were negative. HIV was Non Reactive. Sputum smear was negative for AFB. Mantoux test was negative and urine microscopic examination was Normal. Chest X – Ray PA view showed miliary shadows in bilateral mid and lower zones (Figure 1). USG abdomen showed Hepatosplenomegaly. CECT Chest showed Randomly distributed miliary nodules mainly in lower lobes and bilateral enlarged hilar lymph node with bilateral minimal pleural effusion (Figure 2). Skin biopsy revealed hyperkeratosis, parakeratosis, focal collection of perivascular lymphocytes. Bone marrow biopsy was normoblastic and there was no evidence of granuloma or malignancy. Patient underwent Fibre optic bronchoscopy which didn’t show endobronchial growth or ulcer. BAL for pyogenic culture was sterile and CBNAAT was negative for Mycobacterium tuberculosis and Trans bronchial lung biopsy revealed no evidence of granuloma or malignancy. His CECT Abdomen showed Hepatomegaly with small hypodense lesion seen in Seg. VII of liver showing peripheral discontinuous nodular enhancement (Figure 3). Subtle perportal hypodensity seen along intrahepatic right and left portal veins and subcentimeter lymphnodes seen in portal-periportal and peripancreatic regions. Subsequently Liver Biopsy (Figure 4) revealed Granulomatous Hepatitis with presence of non-caseating epithelioid cell granulomas along with occasional Langhans’s Giant cells both in portal tract as well as lobular parenchyma. Non caseating granuloma suggested the diagnosis of sarcoidosis. Patient had high serum ACE level (105.3 u/l) and elevated 24 hour urinary calcium (659.0 mg/24hr) which further supported the diagnosis of Sarcoidosis. Serum calcium (8.9 mg/dl) was within normal range. As this case had non-caseating epithelioid cell granulomas on liver biopsy and lung involvement in form of miliary shadows, it was diagnosed as stage III Sarcoidosis. Patient was
put on oral prednisolone 50 mg and Hydroxychloroquine 400 mg daily. The dose of oral prednisolone was slowly tapered to 10 mg/day in 3 months as patient improved clinically. Patient continued prednisolone for next 3 months. X-ray chest (Figure 5) and CT scan chest (Figure 6) after 6 month of follow up showed marked improvement.

**Discussion**

Sarcoidosis is likely to be as a result of an interplay of environmental and genetic factors as well as an external agent triggering a characteristic immune response in genetically susceptible individuals.

It targets primarily the lung and hilar lymph nodes. Liver, spleen, heart, bone marrow and less often eye, skin and salivary glands are extrapulmonary sites of disease manifestation. In pulmonary sarcoidosis, the typical findings include perilymphatic nodules, interlobular septal thickening, and bilateral perilobar opacities. In contrast, miliary opacities are rare and atypical. The typical differential diagnosis for miliary opacities of the lung includes tuberculosis, metastatic lesions, and pneumococcosis.

Liver enlargement is found on USG or CT scan in up to 50% of cases, often accompanied by splenomegaly and less often by abdominal lymph node enlargement. Hepatic granulomas are found on CT in only few cases (< 5% of patients). They are typically visualized as multiple, discrete, low attenuating, non-enhancing nodules of variable size (0.5 – 0.8 cm).

Treatment of hepatic sarcoidosis depends on clinical manifestation. No treatment is required when non-caseating granulomas are encountered without clinical or biochemical liver disease. In cases of liver function test abnormalities without evidence of systemic sarcoid involvement-treatment is still a controversial issue because, even untreated patients demonstrate “spontaneous” LFTs improvement. Since chronic use of corticosteroids is the mainstay of therapy in systemic sarcoidosis, it seems prudent to observe (with serial liver function test) those patients who are asymptomatic or have only mild disease that may spontaneously remit.

Chloroquine and Hydroxychloroquine are antimalarial drugs with immunomodulating properties, which have been used for cutaneous lesions, hypercalcemia, neurological sarcoidosis, and bone lesions.

The diagnosis of sarcoidosis is established when clinicoradiographic findings are supported by histologic evidence of non-caseating granulomatous inflammation and other causes of granulomas have been excluded. The diagnosis of sarcoidosis requires evidence of multisystem disease such that granulomatous inflammation is present in at least two organs. However, the diagnosis of sarcoidosis does not necessarily require histological confirmation in a second organ. An elevated serum ACE (normal value 8-53 U/L) has specificity of 90% and sensitivity 57%. Our case is unique as randomly distributed miliary nodules are unusual feature in sarcoidosis. Secondly hepatic sarcoidosis is infrequently associated with symptomatic liver disease. Thirdly patient had all clinical features mimicking tuberculosis.

**References**

History of Ultrasound in Medicine

Jayant Pai-Dhungat

Lazzaro Spallanzani (1729-1799), an Italian biologist, can be called the originator of Ultrasound. He determined that bats were using their ears and not their eyes to navigate in darkness to locate their prey. Only after 1920s it became known that bats emitted very high frequency sounds above the limit of human hearing, and the echoes determined precise location of objects (echolocation or “bio-sonar”). The real breakthrough in the evolution of high frequency echo sounding technique came when Pierre (1859-1906) and Jacques Curie observed that an electrical potential was produced when mechanical pressure was exerted on certain quartz crystals in 1880. The technique came to be known as Piezoelectric (pressure electricity) effect. Conversely if a rapidly changing electric potential is applied to such crystal, its face can be made to vibrate rapidly. In this way crystal can be used to set up beams of ultrasonic sounds waves with frequencies far too high to hear. Curie’s discovery gave birth to transducer used in ultrasonography for generating and receiving Ultrasound echoes. USG became an industrial tool and also found use in detecting objects beneath water and ocean surface. French physicist Paul Langevin (1872-1946) developed powerful high frequency ultrasonic echo sounding device, a ‘hydrophone’. It was extensively deployed in the surveillance of German submarines during WW-I. Langevin’s use of ultrasound to detect submarines led to great advance in SONAR (Sound Navigation and Ranging) during WW-II.

Ultrasound was used in medicine therapeutically long before it became a diagnostic tool. The destructive ability of high intensity ultrasound was recognized in 1920 when Langevin noted destruction of group of fishes in sea by high intensity ultrasound. It was used in Parkinsonism combined with craniotomy, to destroy parts of basal ganglia. 1940s saw exuberant claims of ultrasound effectiveness in many diseases without any scientific evidence.

First use of ultrasound in diagnostic medicine was made by Austrian neurologist Karl Dussik (1908-1968) and his brother in 1946. They attempted to locate brain tumors and cerebral ventricles by measuring transmission of ultrasound beam through the skull. However, first definitive use of ultrasound was shown by George Ludwig in USA (1949) when he visualized gall stones.

In today’s practice, sound waves are pulsed into the patient and returned as echoes from targeted structures by means of a transducer. Echo returns are converted to signals and recorded on a CRT monitor. The number of times the sound wave is repeated per second is measured in megahertz and is referred to as frequency. There are various display modes like A-mode referring to amplitude, B-mode to brightness, Dynamic M modes to motion in real time 2D and 3D modes. Ultrasound is used to visualize urinary tract (KUB), liver, gall bladder, heart, eyes, fetus or any other organ; it is very useful in USG guided procedures. Obstetrical imaging has become a routine in antenatal examinations for observing fetal development.

Ultrasound was employed in experimental cardiac investigations by Inge Edler and Hertz in Lund Sweden. They described use of ultrasound for assessing mitral valve disease in 1953. Clinical use of M mode echocardiography for assessment of mitral valve and left ventricular dimensions was standardized in the 1960s. The advent of 2D Echo (1970s), pulsed Doppler (1970s) and color Doppler (1980s) introduced new methods for routine assessment of cardiac anatomy and hemodynamics at bedside.
Are we Competent to Call a Patient “Immuno-competent”?

Avinash Sharma¹, Ajay Sharma²
¹Medical Officer, Assistant Professor, Dr. Rajendra Prasad Government Medical College, Tanda, Himachal Pradesh
²Sirs,

A propos of the recently published case report on Invasive *Aspergillus* in an immuno-competent Patient.¹ In the above report, the affected young girl has been reported to be “immune-competent”. It is important to know in this regard that Chronic Granulomatous Disease (CGD) is a primary immunodeficiency disorder which is a defect in phagocytic functions and *Aspergillus* is a signature organism causing infections in patients with CGD. So, whenever a patient with *Aspergillus* infection is encountered, it is necessary to rule out CGD. The investigations needed to diagnose CGD are Nitroblue Tetrizolium (NBT) dye test, Dihyro-rhodamine (DHR) test and finally genetic testing.²

We also wish to highlight that it is not necessary that patients with CGD will present only in childhood and they can be seen in adulthood as well.³ Ruling out Human Immunodeficiency Virus (HIV) infection and documenting normal levels of immunoglobulins G and A does not rule out underlying immune defects in these patients.

Primary immunodeficiency disorders are rarely reported and the reason is lack of awareness regarding these conditions.³ It is important to know that these conditions are not rare and they can present at any age.³ Evaluation for an underlying immune-defect is warranted whenever a patient presents with an unusual infection. However, these patients should not be termed as immuno-competent only because no obvious immunodeficiency could be demonstrated in them. At best, these patients may be called as “apparently immune-competent”.

References

ATT-induced Hepatotoxicity: Culprit Drug

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Sir,

*Tuberculosis* is an ancient disease, major global health problem and a leading cause of death, especially among economically productive age group. India accounts for the highest *tuberculosis* burden i.e. approximately 20% of the total global burden. According to the WHO Global report 2015, TB remains one of the deadliest communicable disease.¹ Physical and social factor plays important role among patients taking treatment for *tuberculosis*.² The outcomes of various anti tubercular therapies (ATT) varies from place to place, as Fosite stated that health outcomes are worst in slums from place to place, as Fotso stated that health outcomes are worst in slums from place to place.³ Emergence of anti- tubercular drug resistance due to non-compliance has further aggravated the public health problem.

*Tuberculosis* is a mycobacterial disease, treatable with anti tubercular therapy (ATT), commonly used drugs are, *Isoniazid*, *Rifampicin*, *Pyrazinamide* and Ethambutol as first line drugs.⁴ All these drugs are used in combination for few months (2 to 6 months).Common side / toxic effects of these drugs are; *Isoniazid* causes peripheral neuropathy and hepatotoxicity (elevated serum transaminases and serum bilirubin); *Rifampicin* causes immune-allergic reactions and hepatotoxicity (elevated serum transaminases, alkaline phosphates and serum bilirubin); *Pyrazinamide* causes joint pains (increased serum uric acid) and hepatotoxicity (elevated serum transaminases and serum bilirubin).⁵

These three drugs isoniazid, rifampicin and pyrazinamide are hepatotoxic and this toxicity manifests in the form of nausea, vomiting, weakness, tiredness and yellowish discoloration of eyes. These side effects can be due to one/ two or all of the three drugs and some of the patients are not able to tolerate these and as a result stop taking anti tubercular drugs.

Management of these side / toxic effects are by stopping all the 3 drugs till the patient become asymptomatic with symptomatic treatment and till his Liver function test (LFT) are within normal range. As for as the individual drug is concerned, it has been observed clinically that if symptoms of hepatotoxicity appears within first 10 days of initiation of ATT rifampicin is culprit, if symptoms arise after by the end of second week of initiation of ATT, there are more chances of isoniazid being the culprit and if the symptoms arise after three weeks most liable drug is pyrazinamide. Sometimes one, two or all the three drugs are responsible. These side effects are more common in alcoholics.

As soon as the patient is asymptomatic and LFT are within normal range, the drugs one by one should be restarted in small doses and gradually the dose should be increased till therapeutic dose is achieved and should withdraw immediately if there is any indication of recurrent liver involvement. Isoniazid is to be first reinitated followed by rifampicin and then pyrazinamide. Generally patient takes 1 to 2 weeks to tolerate one drug and after 2 weeks another drug is added and generally after 4 weeks third drug is added.

Monitoring the degree of ATT induced hepatic injury is difficult in these patients as fluctuations in the biochemical indicators of LFT relating to pre-existing disease act as confounding factor. Therefore sometime it is difficult to decide whether the derangement in LFT is due to ATT or is manifestations of already existing liver diseases. However to exclude this pre-existing...
liver disease, it is advisable to have base line LFT before starting ATT.\(^6\)

Due to long duration of therapy concurrent use of multiple drugs, adverse effects are most important clinical consideration in patient taking ATT. Hepatotoxicity is most serious one which not only leads to high morbidity and mortality, but also decreases anti TB treatment effectiveness, owing to non adherence and leading to multi drug resistance tuberculosis (MDR TB), therefore regular LFT monitoring is required.

### References


### CA 19-9 in Obstructive Jaundice: A Common Confounder

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Sir,

Carbohydrate antigen 19-9 (CA 19-9) is a blood biochemical marker that is used in medical oncology in treatment and follow up of many abdominal malignancies like pancreatic and periampullary cancer. However, some benign abdominal pathologies may also cause significant rise of this marker in blood.\(^1\) This high value may be misinterpreted and hence, may lead to unnecessary investigations.\(^2\)

A 67 year old man with chronic alcohol addiction presented to the clinic with chronic epigastric pain for one month. He was treated for gastritis earlier, with no relief of the pain. Also, an ultrasonography of the abdomen was done outside which showed coarse echotexture of liver with dilated common bile duct (CBD). The pancreas was normal. As a part of this investigation, a CA19-9 level was also done which came as 5685 IU/L (N<35). The patient himself consulted the internet for interpretation of this report and had the impression that he had developed cancer. He came to the clinic in a highly anxious state.

On examination, there was mild epigastric tenderness with 2 cm hepatomegaly. The patient was jaundiced and had scratch marks of pruritus all over the body. His liver function test revealed bilirubin of 6.7 mg/dl with direct fraction of 5.8 mg/dL. SGOT/SGPT/ALP were 117/84/448 IU/L respectively. A repeat ultrasonography was done as an emergency which showed dilated biliary radicals in liver with dilated proximal part of CBD. The distal part of CBD and pancreas could not be seen due to gas shadows. The patient was taken for MDCT abdomen which showed a calculus lodged in distal CBD; no other mass was present. The patient was taken up for ERCP with stenting.

The extraction of the CBD stone by ERCP was done without any complications. His bilirubin levels came down after the procedure. CA 19-9 level was 1200 IU/L, 7 days after the procedure and 16 IU/L, 21 days after the procedure. At three months’ follow up, he is asymptomatic now, with all blood tests in the normal range.

CA 19-9 is a tumour marker for pancreatic and biliary cancer. But its main utility is for follow up.\(^2\) The elevation of CA 19-9 in benign conditions reduces its sensitivity for diagnosis of cancer.\(^1\) However, after therapy of pancreatic cancer, CA 19-9 has high sensitivity and specificity in detecting recurrence.

Benign hepatobiliary diseases, as in our patient, is one, often neglected, cause of raised CA 19-9.\(^1\) CA 19-9 is a mucin glycoprotein that is present in miniscule quantities in the bile and pancreatic secretions of adults. Cholangitis and other causes of biliary obstruction rapidly raise the CA 19-9 levels.\(^1\) Usually, the degree of elevation is more for malignant pathologies than benign diseases. But sometimes, benign conditions can also cause dramatic elevations of the CA 19-9 blood levels. A case of choledocholithiasis was reported from Greece where the CA 19-9 level was almost 100000IU/L.\(^3\) However, after surgery, the levels fell by more than 99% within two weeks.\(^3\) Similar rapid decrease was also seen in our patient.

The exact reason for elevation of CA 19-9 levels in benign biliary diseases is not known. There are several postulated hypotheses like leakage of CA 19-9 from biliary tracts into blood and enhanced production of CA 19-9 in biliary epithelium due to local inflammatory cytokines.\(^3\)

We report this case in order to sensitize clinicians to the false positive result of CA 19-9 in the detection of pancreatic cancer. A recent study from China has also found that CA 19-9 was elevated in many benign hepatobiliary disorders and hence, its value as a marker for diagnosis of cancer was limited.\(^7\) The American society of clinical endocrinology also currently discourages the use of this tumour marker for screening.\(^4\)

Thus, in a suspected pancreato-biliary disease, tumour markers like CA 19-9 should not be tested initially. A false high value can confound the diagnostic pathway and lead to unnecessary anxiety, as in our patient.

### References


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**Refractory Ventricular Arrhythmia in Myocarditis**

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Sir,

A 46 year old female, without any comorbidities, was admitted to our hospital wards with history of fever and severe myalgia, associated with thrombocytopenia and treated symptomatically as a viral fever. On the 2\(^{nd}\) day after admission, she...
had a sudden cardiac arrest, was resuscitated, shifted to ICU and mechanically ventilated. The cardiac monitor showed repeated episodes of polymorphic ventricular tachycardia (VT), necessitating cardioversion nine times along with CPR for about 30 minutes. Cardiac evaluation revealed hyperlipidaemia but no other risk factors and no family history of deafness, sudden death or long QT syndrome. She was started on intravenous magnesium and amiodarone. Echocardiography showed a severely hypokinetic apical segment with ballooning and an ejection fraction of 25%, suggestive of possible stress cardiomyopathy. Coronary angiography was normal. The patient improved clinically and was extubated. About one hour later, she had an episode of ventricular fibrillation (VF), requiring cardioversion 5 times and and CPR for about 10 minutes. She was again put on amiodarone and magnesium sulphate infusions. Further cardiology evaluation opined it to be a case of Viral Myocarditis with recurrent VT/VF.

The clinical presentation of viral myocarditis is heterogeneous, ranging from clinically silent conditions, acute coronary syndrome-like conditions, new onset of heart failure (HF), cardiogenic shock, ventricular arrhythmias and sudden cardiac death. The mortality rate of acute myocarditis is 15%-20%. Primary management involves medical management with anti-arrhythmics and supportive therapy. Refractory cases have been treated with implantable cardioverter-defibrillator (ICD) placement.

Our patient continued to have several episodes of polymorphic VT requiring repeated cardioversions and continued mechanical ventilation. She did not respond to increasing doses of amiodarone or lignocaine infusions.

In view of this refractory VT/VF, she was taken up for left thoracoscopic cardiac sympathectomy at T1–T4, from the lower half of the stellate ganglion to T4. However, the same night, she had another episode of VF requiring cardioversion. Following this, she underwent implantation of an automatic implantable cardioverter-defibrillator (AICD). This was associated with a dramatic improvement in her symptoms and she was discharged shortly afterwards. On follow up, she showed continued improvement with a repeat echocardiogram showing resolving of the apical hypokinesia and a normal ejection fraction.

This case highlights the importance of having a high index of suspicion for acute myocarditis, in patients presenting with the routine symptoms of a viral fever and the need for close monitoring for ventricular arrhythmias. Left cervical thoracic sympathectomy following refractory VT is associated with treatment failure and an incidence of sudden death of 6%. AICD may be considered as a measure in refractory VT prior to sympathectomy.

References

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