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HIV in Cerebrospinal Fluid and Central Nervous System

Amar R Pazare

Introduction

It is believed that HIV in humans originated in Congo basin in 1920 when it crossed from chimpanzees to humans. In 1981 first few cases of AIDS were reported from New York and California with presentation of PCP pneumonia and Kaposi sarcoma. Since then patients presented with all sort of signs and symptoms and amongst them neurological clinical features dominate. It includes HIV-associated neurocognitive disorders (HANDs), and HIV-sensory neuropathy (HIVSN). These patients are also prone for various CNS infections like tuberculosis, cryptococcal meningitis, cytomegalovirus infection and primary CNS lymphoma.

Transmission

HIV-1 traverses the blood brain barrier (BBB) within few days of primary infection, and it replicates within macrophages, perivascular microglia and astrocytes. One study reported CNS invasion in 18 patients by HIV as early as 8 days after infection with mean duration of transmission of 14 days. HIV particles present in the CSF can have different origins: they can drain from perivascular spaces or infected cells of the meninges or they can originate in the plasma and pass through the choroid plexus during CSF production, particularly in the case of inflammation of the choroid plexus. Although HIV does not directly invade neurons, it can be affected indirectly through HIV-infected macrophage and microglia cells with release of pro inflammatory cytokines. Basal ganglia, frontal cortices, and subcortical white matter are the main injury sites of HIV. Furthermore, CNS suffers volume loss despite the use of ART, suggesting irreparable damage or ongoing injury. This CNS damage occurs irrespective of immunosuppression.

The BBB is composed of endothelial cells that selectively restrict the transport of cell components and macromolecules from the systemic circulation to the CNS. CNS cells do not have proteins with immunological properties such as MHC class I and II. And it lacks a lymphatic system.

ART and Neurocognitive Function

Determining the HIV viral load in the CSF is important for monitoring the therapeutic effects of ARV treatment and for identifying patients with CNS escape (compartmentalization). With the introduction of ART, there is decreased CNS-related morbidity and mortality but neurologic disease still remains a persistent burden for many patients. In one large study from Alberta, Canada, 24.5% of 1653 HIV positive patients had neurologic impairment, despite the good virologic suppression. Few infections like neurosyphilis increases the HIV viral load in the peripheral blood and CSF.

Compartmentalization

Blood-brain barrier (BBB), rapid mutation, recombination of HIV, and poor ARV drugs penetration in CNS contribute to the compartmentalization of HIV. CNS penetration-effectiveness (CPE) score is different for different ART regime and the drug with higher CPE scores are associated with good HIV-1 viral suppression in CSF and improved neuropsychological performance. CNS is an immunologically privileged site and it serves as an important reservoir for HIV. Other than CNS, genital tract, and gastrointestinal lymphoid tissue are also site for HIV viral reservoirs that allow HIV to persist despite good and active ART regime which may eliminates the virus from the peripheral blood. Despite the effective suppression of viremia with ART, HIV can still replicate...
in the CNS, with the development of resistant strains in the CNS with or without neurological manifestations. CSF Viral load of >200 copies/mL and plasma viral load is <50 copies/mL in a same patient is accepted as compartmentalization.

**Mutations**

The neurological symptoms of HIV changed with the introduction of highly active ART. The main objective of ART is to suppress HIV replication in all cells and tissues. Incomplete suppression of the virus in the CNS is mainly due to poor penetration of ART drugs in the CNS and it promotes resistance to ARV drugs. Both these mechanisms allow the resistant virus to redistribute to CNS and non-CNS tissues. Mutation with high error rate (0.2–2 mutations per genome per cycle) and recombination are the factors responsible for genetic diversity of HIV and the HIV-1 pandemic.

Article published in this issue by A.D. Mathur and, Devesh S. also suggest that neuropsychological manifestations are associated with high CSF viral load.

**References**


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A Comparative Study of CSF Viral RNA Loads between HIV Positive Patients with Neurological Manifestations and Neurologically Asymptomatic HIV Patients

AD Mathur¹, S Devesh²

Abstract

Introduction: There are conflicting reports in literature about correlation of CSF viral RNA levels with neurological manifestations in HIV positive patients. Many studies in animals and human subjects have shown that CSF HIV-1 RNA can be useful as a specific marker of HIV induced neuropathology. To the contrary there are studies which show that neurological disease states can occur in absence of significant increase of CSF HIV RNA.

Materials and Methods: This was a prospective study conducted at Base hospital Delhi Cantt, New Delhi, a tertiary care hospitals for HIV patients. The study period was from 16 May 2006 to 16 Jun 2011. The current study included forty (40) patients (Twenty HIV positive patients with neurological manifestations and twenty HIV positive patients clinically without any neurological manifestation). All potential study subjects and controls were explained the nature of this study and enrolled thereafter with written consent.

Results: In our study all the cases (HIV/AIDS patients with Neuro AIDS) and controls (HIV/AIDS patients without Neuro manifestations) were males only. 45% of the cases and 60% of controls were in the age group of 25 to 35 yrs and 35% of cases and 40% of controls were in age group of 36 to 45 yrs. Among cases (HIV patients with neurological manifestations), The neurological manifestations in our 20 patients included; dementia-5, cryptococcal meningitis-4, Tubercular meningitis-4, CVA-3, Headache-3, (without CSF abnormality), 1 case each of pyogenic meningitis, Candida meningitis, Tremors and Herpes Zoster. Among the 20 cases fourteen patients had abnormal CSF (70%) whereas only one patient among the controls showed CSF abnormality (5%). Out of 20 cases, radio-imaging (CT Scan/ MRI) of brain was done in 18 cases. Twelve cases (66.66) had some abnormality on CT/ MRI. Various abnormalities seen were as under Calcified granuloma-1, Infarcts-5, Hydrocephalus-2, TBM (meningeal enhancement)-2, Candidiasis (Focal hypodensities in subcortical white matter of cerebral hemispheres)-1, Cryptococcoma-1, Cerebral atrophy-1, Focal enhancing lesions-2. In our study, mean CSF viral load in cases was 5236.3 copies/ml and in controls 502.4 copies/ml. Viral load in CSF among cases was significantly higher than viral load in CSF among controls.

Conclusion: CSF HIV-1 RNA viral load estimation can be a useful tool for clinicians in confirming neurological involvement in HIV infected

Editorial Viewpoint

There is no study which clearly correlates neurological disease and CSF viral load in HIV/ AIDS.

This study indicates increased CSF viral load in neuroAIDS and its probable role in prognostication.

Introduction

There are conflicting reports in literature about correlation of CSF viral RNA levels with neurological manifestations in HIV positive patients. Many studies in animals and human subjects have shown that CSF HIV-1 RNA can be useful as a specific marker of HIV induced neuropathology. To the contrary there are studies which show that neurological disease states can occur in absence of significant increase of CSF HIV RNA. While utility of plasma viral load estimation in management of HIV patients is proven it is not yet clear if CSF viral RNA loads can be clinically utilized as a marker of CNS involvement in HIV positive patients. In this

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patients. Hence, in HIV positive patients suspected to have neurological involvement, CSF viral load studies should be done. Serial estimations of CSF HIV-1 RNA levels can be of prognostic significance. Estimation of CSF HIV-1 RNA level before and serially during administration of HAART can be useful to judge the efficacy of HAART.

prospective observational study we have tried to address this issue and observed that even though Viral RNA loads can also be high in CSF of neurologically asymptomatic HIV positive patients, these are significantly elevated in HIV patients with varied neurological involvement.

Material and Methods

This was a prospective study conducted at Base hospital Delhi Cantt, New Delhi, a tertiary care hospitals for HIV patients. The study period was from 16 May 2006 to 16 Jun 2011. The current study included forty (40) patients (Twenty HIV positive patients with neurological manifestations and twenty HIV positive patients clinically without any neurological manifestation). All potential study subjects and controls were explained the nature of this study and enrolled thereafter with written consent. All patients underwent a detailed clinical examination with emphasis on neurological examination. Routine investigations of HIV patients including CD4 counts were carried out. In patient with neurological manifestations, CT Scan Head was carried out where indicated. MRI was done whenever feasible. Thereafter lumbar puncture was done and CSF examination was carried out in all forty patients (HIV patients with and without neurological manifestation). CSF was subjected to cytological, biochemical and bacteriological analysis and HIV viral load estimation. Simultaneously blood samples were collected in all cases for plasma viral load estimation. HIV viral loads were estimated by Amplicor HIV-1 Monitor test version 1.5 manufactured by ROCHE, which is a nucleic acid amplification test for the quantification of HIV-1 RNA in human plasma. Amplicor HIV-1 monitor has high levels of sensitivity for an accurate measurement of viral suppression in patients on anti-retroviral therapy (99.85% specificity) and can do quantification of HIV-1 RNA over the range of 50 to 750,000 copies/ml. Test results less than 400 are below the lower limit of quantitation of standard test and was reported as “HIV-1 RNA detected less than 400 copies / ml”. For quantitative results below 400 copies/ml ultrasensitive specimen preparation is required which was not done in this study.

Results

All patients were males. Age group of patients with and without neurological manifestations was as shown in Table 1. Table 2 shows the neurological manifestations in 20 patients. Table 3 shows CSF viral load in cases and controls with and without neurological manifestations. Table 4 shows CSF abnormalities in HIV / AIDS cases with neurological manifestations. Table 5 shows comparison of viral load in plasma and CSF in patients with and without neuroAIDS. Table 6 enlists various radioimaging findings in cases with neuroAIDS.

Discussion

A high percentage of variety of neurological disorders is observed in HIV infected patients. Neurological disorders may occur

Table 1: Age distribution of patients with neurological manifestations and controls

<table>
<thead>
<tr>
<th>Age group (yrs.)</th>
<th>No. of cases (%</th>
<th>Controls (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-25 yrs.</td>
<td>2 (10)</td>
<td>0</td>
</tr>
<tr>
<td>26-35 yrs.</td>
<td>9 (45)</td>
<td>12 (60)</td>
</tr>
<tr>
<td>36-45 yrs.</td>
<td>7 (35)</td>
<td>8 (40)</td>
</tr>
<tr>
<td>46-55 yrs.</td>
<td>2 (10)</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 2: Neurological manifestations

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>No. of cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryptococcal meningitis</td>
<td>4 (20)</td>
</tr>
<tr>
<td>Tubercular meningitis</td>
<td>4 (20)</td>
</tr>
<tr>
<td>Pyogenic meningitis</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Candida meningitis</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Dementia</td>
<td>5 (25)</td>
</tr>
<tr>
<td>CVA</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Seizures</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Headache (with normal CSF and CT scan head)</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Tremors</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>1 (5)</td>
</tr>
</tbody>
</table>

Table 3: CSF viral load in patients and controls

<table>
<thead>
<tr>
<th>CSF viral load</th>
<th>Cases (HIV/AIDS patients with neuro AIDS)</th>
<th>Controls (HIV/AIDS patients without neuro AIDS)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CSF abnormal</td>
<td>CSF normal</td>
</tr>
<tr>
<td>0-400</td>
<td>6 (42.85)</td>
<td>1 (16.66)</td>
</tr>
<tr>
<td>&gt;400</td>
<td>8 (57.15)</td>
<td>5 (83.33)</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>6</td>
</tr>
</tbody>
</table>

Table 4: CSF abnormalities in patients

<table>
<thead>
<tr>
<th>CSF abnormality</th>
<th>No. of cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raised proteins</td>
<td>10 (50)</td>
</tr>
<tr>
<td>Pleocytosis</td>
<td>11 (55)</td>
</tr>
<tr>
<td>Decreased sugar</td>
<td>5 (25)</td>
</tr>
<tr>
<td>Candida growth on culture</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Positive India ink preparation</td>
<td>4 (20)</td>
</tr>
<tr>
<td>Pneumococci grown</td>
<td>1 (5)</td>
</tr>
</tbody>
</table>

Table 5: Viral loads in plasma and CSF of patients and p value

<table>
<thead>
<tr>
<th>Mean viral load (copies / ml)</th>
<th>20 cases (HIV/AIDS patients with neuro AIDS)</th>
<th>20 controls (HIV/AIDS patients without neuro AIDS)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>In plasma</td>
<td>109428.75</td>
<td>110025.75</td>
<td>0.9935125</td>
</tr>
<tr>
<td>In CSF</td>
<td>5236.3</td>
<td>502.4</td>
<td>0.042659</td>
</tr>
</tbody>
</table>
Table 6: Radiological abnormalities on CT/MRI – 18 patients

<table>
<thead>
<tr>
<th>Radio-imaging findings (n=18)</th>
<th>No. of cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcified granuloma</td>
<td>1 (5.5)</td>
</tr>
<tr>
<td>Infarcts</td>
<td>5 (22.2)</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>2 (11.1)</td>
</tr>
<tr>
<td>TBM (Meningeal enhancement)</td>
<td>2 (11.1)</td>
</tr>
<tr>
<td>Candidiasis</td>
<td>1 (5.5)</td>
</tr>
<tr>
<td>Cryptococcoma</td>
<td>1 (5.5)</td>
</tr>
<tr>
<td>Cerebral atrophy</td>
<td>1 (5.5)</td>
</tr>
<tr>
<td>Focal enhancing lesions</td>
<td>2 (11.1)</td>
</tr>
<tr>
<td>Normal study</td>
<td>6 (33.3)</td>
</tr>
</tbody>
</table>

Due to opportunistic infections, neoplasms, direct effect of HIV and its products and undesirable treatment related effects. HIV associated neurological syndromes and effects of treatment are often undiagnosed and untreated. While HIV associated dementia is the result of HIV infection of CNS, peripheral neuropathy result from HIV infection of peripheral nervous system. Vacuolar myelopathy and increased risk of seizures are other HIV induced neurological disorders.

In human subjects many studies have observed strong association of high CSF HIV-1 RNA levels with cognitive impairment and have suggested that CSF HIV-1 RNA load can be useful as a specific marker of HIV induced neuropathology and cognitive dysfunction.

To the contrary there are many reports in literature which show that neurological disease states can occur in absence of CSF HIV RNA. We have tried to address this issue in the present study by estimating CSF and plasma viral loads in 20 HIV infected patients with wide ranging neurological manifestations and compared this data with CSF viral loads in 20 HIV infected patients without any clinically apparent neurological illness. Basic aim of this study was to determine if HIV infected patients with neurological manifestations have higher CSF RNA viral loads which can be utilized as a marker of neurological disease in clinical practice. Presently, Indian data on this subject is scant.

Mean CSF viral load in HIV infected patients with neurological manifestations was 5236.3 copies/ml while the controls had mean CSF viral load of 502.4 copies/ml, thereby showing significantly higher viral load values in HIV infected patients with clinically apparent neurological involvement as compared to HIV patients without any clinical neurological manifestations (P value = 0.042659).

Conclusion

CSF HIV-1 RNA viral load estimation can be a useful tool for clinicians in confirming neurological involvement in HIV infected patients. Hence, in HIV positive patients suspected to have neurological involvement, CSF viral load studies should be done.

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Use of Freestyle Libre Pro™ Flash Glucose Monitoring System in Different Clinical Situations at a Diabetes Centre

Bangalore Srinivasan Ratna¹, Radhakrishnan Subashini², Ranjit Unnikrishnan³, Viswanathan Mohan⁴

Abstract
Flash Glucose Monitoring (FGM) is a newly introduced Glucose Monitoring system. FGM provides both graphical representation of qualitative and quantitative changes in glucose levels occurring over 14-day period collapsed into single modal day graph as well as day by day graphs. In this report, we present our experience with FGM in different clinical situations. In our experience FGM is an extremely useful clinical tool for detection of glucose variability, hyperglycemia and hypoglycemia. It can also be used as an effective educational tool when the data from FGM is shared with the patient. This helps in motivating the patient in achieving better glycemic control.

Introduction
Adequate control of blood glucose levels largely depends upon frequent monitoring of control both at the clinic as well as at home by the patient. Self monitoring of blood glucose (SMBG), introduced in the 1980s, is the most widely used method of all the glucose monitoring techniques. It is most useful in patients on multiple insulin doses or on continuous subcutaneous insulin pump. It may also be helpful for treatment or self management for patients using less frequent insulin injections or on non-insulin therapies.¹ SMBG however only gives point of test blood glucose measurements without predicting the direction or rate of change of blood glucose or a continuous monitoring. Moreover, the need for frequent painful finger pricks, issues with calibration and accuracy of the glucose meter as well as the cost of strips contribute to poor patient compliance. As the concept of glycemic variability and its importance evolved, techniques to measure glycemic variability have simultaneously been developed.²³ An example is the Continuous Glucose Monitoring System (CGMS) that has been in use for several years.⁴ We have earlier reported on our initial experience with CGMS at our centre.⁵ The limitations of the currently available CGMS devices include the need for multiple finger stick calibrations, pain at sensor insertion site, expense and the relatively short life of the sensor (up to 7 days only).⁶

Flash Glucose Monitoring (FGM) is a newly introduced method of flash glucose monitoring. It combines inputs from multiple days of glucose data and collapses them into a 24-hour modal day period. It allows quick analysis of poor glycemic control and glycemic variability and can be used as a patient education tool. It consists of three parts: a disposable sensor, a hand-held reader and a proprietary software. The sensor is placed on the back of upper arm with the help of an applicator (Figure 1). The sensor has a small, flexible 4mm-long tip inserted just under the skin; it can be worn up to 14 days. Its amperometric electrochemical sensor measures glucose readings in the 40 to 500 mg/dl range every 15 minutes during the entire wear period and stores them. Using near field communication technology, the sensor data is downloaded into the reader. While the sensor is

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single-use only, the reader can be used to collect data from multiple sensors. The report is generated by connecting the reader to a computer in which the software has been installed. The graphical data provided by FGM includes mean of glucose values at different point of day, a median curve representing the 50th percentile and also the 75th percentile and 25th percentile curves defining the Inter Quartile Range (IQR). The width of the band between the 10th and 90th percentile curve is an index of the glucose excursion (variability). The glycemic trends for individual days can also be obtained in a graphical way. For the purpose of this paper, we have also manually calculated the Mean Amplitude of Glycemic Expression (MAGE) as the arithmetic mean of differences between consecutive peaks and nadirs of the glucose readings. The MAGE was calculated by taking 24-hour glucose values of Day 2 and we compared this with 24-hour glucose readings of Day 13, Days 1 and 14 were not considered, as they usually have only incomplete readings depending on time of application and removal.

The aim of this paper is to show the use of FGM in a few clinical situations. Specifically, we report on cases illustrating the use of FGM in different types of diabetes.

Case 1 (FGM in a Normal Person)

This was a 61 year old person with normal glucose tolerance in whom FGM was applied for a few days to see the normal glycemic variability. His fasting plasma glucose (FPG) was 96 mg/dl, post prandial plasma glucose (PPPG) 128 mg/dl and HbA1c, 5.6%. The MAGE on Day 2 was 37 mg/dl with the lowest recorded glucose reading of 74 mg/dl and highest of 151 mg/dl during the days when he wore the FGM (Figures 2A and 2B).

Case 2 (Type 2 diabetes of short duration)

This was a 44 year old male patient with type 2 diabetes of 3 years duration, on Tab. Glimepiride 2 mg two times a day. His FPG was 162 mg/dl, PPPG 296 mg/dl and
HbA1c, 8.2%. He was started on Inj. Glargine 10 units at bedtime along with tab Glimepiride 2 mg + Metformin 500 mg two times a day in view of high blood glucose levels. His AGP (Figure 3A) shows high blood glucose levels during the first week, which improved during second week with no hypoglycemic episodes. The MAGE was 150 mg/dl on Day 2 which improved to 74 mg/dl on Day 13 (Figure 3B and 3C). The dose of glargine was later reduced and eventually withdrawn. In this case AGP helped us to analyse the glycemic control after initiation of insulin and also helped to document improvement in glycemic variability.

**Case 3 (Type 2 diabetes of long duration)**

This was a 55 year old male patient with type 2 diabetes of 20 years’ duration with diabetic retinopathy, diabetic nephropathy, systemic hypertension, ischaemic heart disease, dyslipidemia and hypothyroidism. His FPG was 227 mg/dl, PPPG 236 mg/dl and HbA1c, 8.6%. He was on Inj Aspart 16U-8U-4U plus inj Glargine 28U at bedtime, along with Tab Gliclazide 30mg once a day and Tab Linagliptin 5 mg once a day. FGM was initiated for achieving a better glycemic control in view of the comorbidities especially organ related complications. FGM (Figure 4A) showed uncontrolled diabetes at several points of the day during the two week period. On Day 2 (Figure 4B) MAGE was 120 mg/dl. On Day 13 (Figure 4C) MAGE was still 158 mg/dl. Further adjustments were made in insulin doses based on sensor readings. The lab reports post treatment change were FPG 122 mg/dl, PPPG 150mg/dl and HbA1c of 7.7%. A second FGM report (Figure 4D) shows much better control with less glycemic variability shown by reduction in MAGE to 83 mg/dl on Day 2 (Figure 4E) to 86 mg/dl on Day 13 (Figure 4F). In this patient, AGP, along with adjustment of dosage of drugs enabled us to achieve better glycemic control with a reduction in HbA1c level by 0.9%.

**Case 4 (Gestational Diabetes Mellitus)**

This was a 26 year primigravida diagnosed with gestational diabetes mellitus (GDM) in the second trimester of pregnancy. Her FPG was 125 mg/dl, PPPG-229 mg/dl and HbA1c, 5.8 mg/dl. She was started on Inj Biphasic insulin Aspart 8U-0-6U. FGM was initiated to monitor glycemic control during pregnancy. FGM showed (Figure 5A) high postprandial blood glucose during the day time, with few low blood glucose levels early morning during initial first week.
period. During the second week of sensor use, there was significant improvement in the post prandial blood glucose levels with a few hypoglycaemic episodes persisting during early morning hours. The MAGE of 108 mg/dl on Day 2 (Figure 5B), decreased to 59 mg/dl on Day 13 (Figure 5C). The morning dose of insulin was increased to 10 U for further control of postprandial spikes, with reduction in the night dose in view of early morning hypoglycemia. Thus FGM enabled us to achieve strict glycemic control in pregnancy and detect the asymptomatic hypoglycemia which helped in insulin dose adjustment.

**Case 5 (Type 1 Diabetes)**

This was a 10 year old boy with Type 1 DM of 5 months duration. His blood glucose values were FPG 162 mg/dl, PPPG 174 mg/dl and HbA1c of 9.7%. He was on Inj Aspart 3U-3U-3U along with Inj Glargine 8U at bedtime. FGM was initiated to see why his HbA1c was so high, in spite of relatively acceptable fasting and postprandial glucose levels. His FGM (Figure 6A) showed high blood sugar levels at several points during the day with occasional hypoglycemic episodes. The MAGE on Day 2 was 88 mg/dl (Figure 6B) and 284 mg/dl on Day 13 (Figure 6C). This type of profile is characteristic of type 1 diabetes. The dose of insulin was adjusted to Inj Aspart 3U-2U-2U and Inj. Glargine 10 U. In this case, the FGM enabled us to detect wide fluctuations in the blood glucose levels and to improve the diabetes control by adjusting the insulin doses.

**Case 6 (Fibrocalculous Pancreatic Diabetes)**

This was a 55 year patient with fibrocalculous pancreatic diabetes of 18 years’ duration. His current medications were Inj Biphasic Isophane insulin 22U-0-8U. His FPG was 99 mg/dl, PPPG 252 mg/dl and HbA1c, 7%. FGM was initiated to study the blood sugar fluctuations. FGM showed high blood glucose levels during postprandial periods, with a few hypoglycemic episodes during early morning hours (Figure 7A). Even though HbA1c was 7%, AGP showed high glycemic variability with MAGE of 120 mg/dl on Day 2 (Figure 7B) and 93 mg/dl on Day 13 (Figure 7C). In this case, the FGM enabled us to visualize the day to day variability of blood glucose even when the patient’s HbA1c was apparently under control and helped us to make adjustments in the dosage of insulin.

**Discussion**

In this paper we have presented 5 different clinical types of diabetes in which FGM was initiated and also 1 normal individual. The first case shows a normal glucose tolerant subject where there is
but also by the oxidative stress
generated by glycemic variability. The FGM provides an easy visual
analysis of presence of glycemic variability. Glycemic variability is said to present when glucose values are widely spread, for example, when the IQR and 10th and 90th percentile curves cover a wider area. Asymptomatic hypoglycemia can be also detected.

In this report, we calculated the intraday glycemic variability by manually calculating the MAGE. By comparing MAGE on Day 2 with that on Day 13 we could analyse the effect of the treatment prescribed over the 2 week duration and make adjustments to the prescription given at the clinic 2 weeks earlier.

In our experience, FGM helps us to easily visualize whether patient blood glucose level is within the target range. When FGM report is communicated to the patient, they can understand the glucose levels better and become more involved in diabetes management. This ultimately helps to reduce the practically very little fluctuation of glucose levels. The second case shows how, in a recent onset T2DM patient, after starting treatment, the MAGE dramatically decreased and the control of diabetes improved. Till such technology became available, physicians would only get a snapshot of the improvement based on occasional SMBG’s that are done. Case 3 illustrates greater fluctuations in a T2DM patient with longer duration of diabetes. Case 5 shows the marked fluctuations in a case of type 1 diabetes illustrating the 'brittle diabetes' in this patient. In contrast, Case 4, a patient with GDM shows how mild the diabetes is, and how quickly GDM responds to treatment. The case with FCPD demonstrates more fluctuations in glucose levels like the type 1 patient.

The FGM is a very useful tool to learn about the glycemic status of the patient over a 14 day period after initiating or altering a patient’s antidiabetic drug regimen. As it provides day to day information about blood glucose levels for 2 weeks after a clinic visit, this is most useful to adjust dosage of drugs. It also helps us to educate and motivate the patients to achieve good glycemic control.

Mazze et al first introduced Universal Software report (Ambulatory Glucose Profile for systematic presentation of SMBG data) and this was further developed by the same group. An expert panel of diabetes specialists has given recommendations for standardizing glucose reporting and analysis of FGM to optimize clinical decision making. A study by European diabetologists supports the use of FGM for glucose data analysis and to take treatment decisions. FGM is considered as a valuable tool in the case of patients with type 1 diabetes and type 2 diabetes who are on insulin to identify poor glycemic control, to detect hypoglycemia and to study glycemic variability.

It is now believed that the risk of complications of diabetes is not solely determined by exposure to sustained chronic hyperglycemia but also by the oxidative stress generated by glycemic variability. The FGM provides an easy visual analysis of presence of glycemic variability. Glycemic variability is said to present when glucose values are widely spread, for example, when the IQR and 10th and 90th percentile curves cover a wider area. Asymptomatic hypoglycemia can be also detected.

In this report, we calculated the intraday glycemic variability by manually calculating the MAGE. By comparing MAGE on Day 2 with that on Day 13 we could analyse the effect of the treatment prescribed over the 2 week duration and make adjustments to the prescription given at the clinic 2 weeks earlier.

In our experience, FGM helps us to easily visualize whether patient blood glucose level is within the target range. When FGM report is communicated to the patient, they can understand the glucose levels better and become more involved in diabetes management. This ultimately helps to reduce the
fluctuations of glucose readings and to improve HbA1c values. We therefore feel that the FGM is an excellent new tool in the physician’s armamentarium to assess response to therapy. This paper is an illustration of different scenarios where the Freestyle Libre Pro™ FGM system can be used in clinical practice.

References

Rickettsial Infections in Goa—Not Just Scrub Typhus!

Kedareshwar Narvencar¹, Gurleen Kaur², Savio Rodrigues³

Abstract

Background and Objectives: Rickettsial infections are an important cause of undifferentiated febrile illness in tropics. While scrub typhus was reported from Goa, other rickettsial infections have not been reported earlier. The present study was planned to identify pattern of rickettsial infections in Goa.

Materials and Methods: All patients presenting with undiagnosed acute febrile illness were recruited over a two-year period. Other causes of febrile illness were ruled out by appropriate tests. Sera of the patients were subjected to Weil Felix testing. Patients were labelled as probable rickettsial infection if the titres to any one antigen was >1:80 as per DHR-ICMR guidelines. Clinical details were obtained retrospectively from case records.

Results: Sixty-one patients met inclusion criteria, of which six were excluded because of alternative diagnosis. Out of remaining patients, 32 were positive by Weil Felix test (positivity rate 58.18%). Eighteen were males; there was no age predilection. Twenty-one patients were positive for OXK (scrub typhus); of these, 13 were positive for other antigens also. Of the remaining, 6 were positive for OX2 alone, 2 were positive for OX 19 alone, one patient was positive for both OX2 and OX19 and 2 were positive for all three antigens. Most patients had non-specific clinical presentation. Two patients in scrub typhus group and one in spotted fever group died (mortality rate =9.5% and 11.1 %).

Interpretation and Conclusion: Our study shows that rickettsial infections other than scrub typhus are also prevalent in Goa. Weil Felix test is useful in diagnosis; however, there is cross reactivity between various antigens of the test, hence differentiation into various groups of rickettsiosis should not be done based on Weil Felix test alone.

Editorial Viewpoint

- Rickettsial disease should feature in differential diagnosis of acute febrile illness in India.
- Though Weil Felix test is used for diagnosis, there can be cross-reactivity to different antigens of the test.
- Specific IgM Elisa or DNA PCR are preferred tests.

Introduction

Rickettsiosis is an under recognised cause of acute febrile illness in the tropics, owing to non-specific clinical features as well as due to lack of access to diagnostic modalities.¹ However, in last few years, there have been multiple reports of occurrence of the disease from different parts of the country.²⁻⁸ Though the prevalence of scrub typhus was reported earlier from Goa,⁹ data on other rickettsial diseases was not available from this part of the country.

The present work was undertaken to study the prevalence of rickettsial infections amongst patients presenting with undiagnosed fever to our Institution. The primary aim was to ascertain the pattern of rickettsial infections in Goa. We also aimed to study the utility of Weil Felix test in diagnosis of the disease.

Materials and Methods

This study was conducted at a tertiary care institution in the state of Goa. All patients who had presented to our institution with an undiagnosed acute febrile illness over a two year period were included in the study. Other causes of acute febrile illness such as malaria, leptospirosis, dengue, chikungunya, bacterial sepsis, etc were ruled out by appropriate investigations. The sera of patients who remained undiagnosed were collected after informed consent and stored at -70°C. These samples were subjected for Weil Felix test.
Table 1: Pattern of positivity for antigens of Weil Felix

<table>
<thead>
<tr>
<th>Case</th>
<th>OX19</th>
<th>OKX</th>
<th>OX2</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Neg</td>
<td>Neg</td>
<td>1:320</td>
<td>SFG</td>
</tr>
<tr>
<td>2</td>
<td>1:320</td>
<td>Neg</td>
<td>1:320</td>
<td>SFG</td>
</tr>
<tr>
<td>3</td>
<td>Neg</td>
<td>1:320</td>
<td>Neg</td>
<td>Scrub typhus</td>
</tr>
<tr>
<td>4</td>
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</tr>
<tr>
<td>6</td>
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<td>Typhus group</td>
</tr>
<tr>
<td>7</td>
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<td>1:320</td>
<td>1:80</td>
<td>Scrub typhus</td>
</tr>
<tr>
<td>8</td>
<td>Neg</td>
<td>1:320</td>
<td>Neg</td>
<td>Scrub typhus</td>
</tr>
<tr>
<td>9</td>
<td>Neg</td>
<td>1:80</td>
<td>Neg</td>
<td>SFG</td>
</tr>
<tr>
<td>10</td>
<td>Neg</td>
<td>Neg</td>
<td>1:160</td>
<td>SFG</td>
</tr>
<tr>
<td>11</td>
<td>Neg</td>
<td>1:160</td>
<td>Neg</td>
<td>Scrub typhus</td>
</tr>
<tr>
<td>12</td>
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<td>Neg</td>
<td>1:320</td>
<td>SFG</td>
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<tr>
<td>13</td>
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<td>1:320</td>
<td>1:320</td>
<td>Scrub typhus</td>
</tr>
<tr>
<td>14</td>
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<td>1:320</td>
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<tr>
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<td>1:320</td>
<td>Scrub typhus</td>
</tr>
<tr>
<td>16</td>
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<td>1:640</td>
<td>1:640</td>
<td>SFG</td>
</tr>
<tr>
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<td>1:1280</td>
<td>1:640</td>
<td>1:320</td>
<td>SFG</td>
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<tr>
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<td>1:640</td>
<td>Scrub typhus</td>
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<td>Scrub typhus</td>
</tr>
<tr>
<td>23</td>
<td>1:320</td>
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<td>Neg</td>
<td>Typhus group</td>
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<tr>
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</tr>
<tr>
<td>26</td>
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<td>Scrub typhus</td>
</tr>
<tr>
<td>27</td>
<td>1:320</td>
<td>1:320</td>
<td>Neg</td>
<td>Scrub typhus</td>
</tr>
<tr>
<td>28</td>
<td>Neg</td>
<td>1:320</td>
<td>1:320</td>
<td>Scrub typhus</td>
</tr>
<tr>
<td>29</td>
<td>Neg</td>
<td>1:640</td>
<td>1:160</td>
<td>Scrub typhus</td>
</tr>
<tr>
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<td>Neg</td>
<td>Neg</td>
<td>1:160</td>
<td>SFG</td>
</tr>
<tr>
<td>31</td>
<td>Neg</td>
<td>Neg</td>
<td>1:160</td>
<td>SFG</td>
</tr>
<tr>
<td>32</td>
<td>Neg</td>
<td>1:80</td>
<td>Neg</td>
<td>Scrub typhus</td>
</tr>
</tbody>
</table>

The study was approved by institutional Ethics Committee.

Results

Sixty-one patients met the inclusion criteria and were screened for the present study; out of which 6 patients were excluded as they had an alternative diagnosis. The remaining 55 patients were tested for rickettsial diseases with Weil-Felix test. Thirty-two patients were found to be positive (positivity rate = 58.18%). Of this, 18 patients were males; there being no specific predisposition for any age group. The youngest patient was 13 years while the oldest was 61 years of age. Twenty one patients were positive for OXK suggesting scrub typhus, of which, 8 were positive for OXK alone while remaining 13 were positive for other antigens also. Out of the remaining 11 patients, 6 were tested positive for OX2 alone, 2 were positive for OX 19 alone, and one patient was positive for both OX2 and OX19 suggesting that all these patients had rickettsial diseases other than scrub typhus. Remaining 2 patients had positivity for all three antigens, however both of them had high titres of OX19 and OX2 and had petechial rash, hence they were also labelled as spotted fever group (SFG) rickettsiosis.

The pattern of positivity for different antigens of Weil-Felix is given in Table 1.

All 32 patients tested positive by Weil Felix had fever, additionally 7 patients in scrub typhus group, 4 patients in spotted fever group and 1 patient in typhus group also had rash. Eschar was seen in 4 patients of scrub typhus, none of the cases of other rickettsial infections had eschar. Hepatitis and acute kidney injury were the most common complications. Two patients in scrub typhus group and one patient in spotted fever group succumbed to the illness, giving a mortality rate of 9.5% and 11.1% respectively.

Discussion

Rickettsial infections are one of the common causes of undiagnosed febrile illness in the tropics. These diseases have a high mortality if the diagnosis and treatment are delayed. Rickettsial infections are diagnosed mainly by serological assays or DNA-PCR, which are expensive and unavailable in most parts of our country. As a result, these infections remain grossly under diagnosed and underreported. In the last 2 decades, the outbreaks of rickettsial diseases have been reported from various parts of India. The prevalence of scrub typhus in Goa was reported earlier; however, the presence of other rickettsial diseases was not documented from our State. This study was therefore aimed to identify the presence of various rickettsial diseases in Goa.

A confirmed case of rickettsial disease is diagnosed by the presence of either rickettsial DNA on PCR or raising antibody titres on indirect immune fluorescence assay (IFA). Weil Felix test is a cheap alternative in resource poor settings and is mostly used for the diagnosis in our country. Though the test lacks sensitivity, it is relatively specific. In the present study, Weil Felix test was used for the diagnosis. A titre of 1:80 or above for any of the three antigens was considered as a probable case of rickettsial infection.

Based on pattern of positivity to the various antigens on Weil Felix testing, the patients can be classified into three categories. OX19 reacts strongly with serum from patients of typhus fever group (also Rocky Mountain Spotted Fever), OX2 reacts with serum from patients having spotted fever group rickettsiosis (except Rocky Mountain Spotted Fever) and OKX reacts with serum from scrub typhus patients. We have also used the same pattern for classifying our patients. However, as can be seen from Table 1, majority of our patients had positive titres for more than one antigen. Further, though scrub typhus was believed to give positive reaction for OXK alone, in our study many of the probable scrub typhus patients (13 out of 21) had positivity to other antigens. This shows that there can be a cross reactivity to the different antigens.
of Weil Felix test. However, as we have not done specific IgM ELISA or DNA-PCR tests for scrub typhus, we will have to interpret this finding with caution. Such cross reactivity has been reported in many other studies, which suggests that differentiation of rickettsial infections into various groups such as scrub typhus, spotted fever group and typhus group based on pattern of agglutination in Weil Felix test is not specific.

The other reason for the positivity to different antigens could be the possibility of mixed infections with scrub typhus and other rickettsiosis; however, this again needs to be confirmed by specific tests.

As Weil Felix test uses antigens from Proteus species, the test may give false positivity. Hence, the test is not confirmatory for rickettsial diseases. The specificity of the test could be increased by repeating it in convalescent sera. In our study, we could not obtain convalescent sera. We have not used any other gold standard tests for confirmation. However, most of our patients have shown positivity to higher dilutions; some even to 1:640 or 1:1280, which rules out false positivity. Positivity rate of 56% in undiagnosed febrile illness shows that rickettsial infections are prevalent in Goa and should be considered in the differential diagnosis of any acute febrile illness. Further, there is cross reactivity to various antigens in a positive case; hence, categorisation into various groups based on Weil Felix testing alone may not be specific.

Limitations of the Study

We have not used any of the Gold standard tests to confirm the diagnosis of rickettsial disease, thus all patients were categorised as “probable” cases as per DHR-ICMR guidelines. The small sample size is also a major limitation of the study.

Conclusion

In conclusion, our study shows that not only scrub typhus but also other types of rickettsial infections are prevalent in Goa and should be considered in the differential diagnosis of any acute febrile illness. Further, there is cross reactivity to various antigens in a positive case; hence, categorisation into various groups based on Weil Felix testing alone may not be specific.

References


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Name, Years of experience, Current designation and Affiliations, Area of interest, List of publications, e-mail id and Mobile number.

Kindly send above information at the earliest to: **onlinejapi@gmail.com**

Prof. Milind Y. Nadkar

*Editor-in-Chief, JAPI*
Clinical Profile of Patients Presenting with Malignant Pleural Effusion to a Tertiary Health Care Centre

Nitin Gadewad¹, Kunal Deokar², Shivhari Ghorpade³

Abstract

Background: Malignant pleural effusions are one of the leading causes of exudative pleural effusions. We studied the clinical profile of patients presenting with malignant pleural effusion, their cytological and histopathological features and the efficacy of pleurodesis in preventing recurrence.

Materials and Methods: 100 patients who were positive for malignant cells in pleural fluid cytology or pleural biopsy were recruited. After history and clinical examination, Chest radiographs, Computed tomography of chest were performed. After diagnostic thoracocentesis and Pleural biopsy, Tube thoracostomy was done. Pleurodesis was performed in 40 patients.

Results: Most of the patients (65%) were in the age group of 61 to 70 years with a male to female ratio of 1.5:1. Most common presenting symptoms were breathlessness (86%) and cough (86%). All (100%) of the malignant pleural effusions were exudative. Pleural fluid cytology was positive in 86% while pleural biopsy was positive only in 44%. Pleural biopsy was positive only in 17% of patients with negative cytology. Adenocarcinoma (59%) was the most common type of cytological diagnosis. Pleurodesis was performed in 40 patients of which 30% had recurrence.

Conclusion: In our tertiary health care centre, malignant pleural effusions presented as large pleural effusions. Most common presenting symptoms were breathlessness and cough. They were exudative, lymphocytic predominant with low ADA levels. Thoracocentesis and cytologic study should be the initial diagnostic approach to malignant pleural effusions. Adenocarcinoma of the lung was the most common cause of malignant pleural effusion. Pleurodesis with oxytetracycline was successful in majority of cases.

Introduction

Malignant pleural effusions are one of the leading causes of exudative pleural effusions. They are a common medical problem associated with 50% of the cases of primary and metastatic pleural malignancies.¹² They are commonly associated with carcinomas of the lung, breast, lymphoma and leukaemia.³⁴ The diagnosis of malignant pleural effusions requires thorough history, complete clinical examination, radiographs

Editorial Viewpoint

- Malignant pleural effusions present as large effusions causing breathlessness.
- Thoracocentesis and cytology should be included in evaluation of pleural effusions.
- In this study pleurodesis with oxytetracycline was successful.

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catheters, pleuroperitoneal shunt or pleurectomy. Pleurodesis is a treatment that aims to obliterate the pleural space by instillation of a sclerosing agent into the pleural space or by mechanically abrading the pleura. The aim of pleurodesis in patients with malignant pleural effusions is to prevent the re-accumulation of the effusion and thereby development of symptoms, and avoid the need for repeated hospitalization for thoracocentesis.

We studied the clinical profile of patients presenting with malignant pleural effusion, their cytological and histopathological features and the efficacy of pleurodesis in preventing recurrence of malignant pleural effusions.

**Materials and Methods**

It was a hospital based descriptive study which was carried out in the period from April 2012 to October 2013. The patients suspected of malignant pleural effusion were selected from outpatient departments of the Department of Medicine, Department of Pulmonary Medicine and Department of Oncology of the same institute. The study was carried out after approval from the institutional ethics committee and with fully informed written consent from the subjects. Patients included were those positive for malignant cells in pleural fluid cytology or those who were negative for malignant cells in pleural fluid cytology but positive on pleural biopsy. 100 consecutive patients were included in the study.

At first meticulous history with detailed clinical examination was done by filling a written questionnaire. Chest radiographs PA and lateral views in erect position were obtained. On chest radiograph, the pleural effusion was quantified as follows:  

- **a.** Minimal, free-flowing effusion (<10 mm on lateral decubitus).
- **b.** Moderate free-flowing effusion (>10 mm and < ½ hemithorax).
- **c.** Large, free-flowing effusion (> ½ hemithorax), loculated effusion, or effusion with thickened parietal pleura.

**Computed tomography of thorax** was performed to look for presence of pleural nodularity, lung masses, nodules, infiltrates, mediastinal adenopathy, chest wall involvement, lymphangitis carcinomatosa.

Diagnostic thoracocentesis used to be undertaken as outlined in Pleural procedures and thoracic ultrasound: British Thoracic Society pleural disease guideline 2010. The pleural fluid was immediately sent for following investigations

- **i.** pH – 1 ml of pleural fluid drawn in a heparinized syringe immediately after aspiration and immediately capped to avoid exposure to air.
- **ii.** Protein and LDH – 5 ml of pleural fluid in a plain container.
- **iii.** Sugar – 3 ml in a bulb containing fluoride oxalate.
- **iv.** Cytological examination and differential cell count – 40 ml of pleural fluid in a plain container.

Pleural biopsy was carried out under strict aseptic conditions and after fully informed written consent from the patient. Using Abrams pleural biopsy needle, four to six biopsy specimens were taken and sent for histopathological examination.

Tube thoracostomy used to be undertaken as outlined in Pleural procedures and thoracic ultrasound: British Thoracic Society pleural disease guideline 2010.

**Pleurodesis**

**Selection of patients for pleurodesis**

1. Those willing for pleurodesis
2. Lung fully expanded on chest radiograph
3. No bubbling in the drainage bag

Pleurodesis was done using 35 ml/kg of oxytetracycline. The patients in whom pleurodesis was done were followed up at 1 month, 3 months and 6 months post procedure. Chest radiograph PA view was done at each visit to look for recurrence of effusion.

Data was entered in Microsoft excel 2007 and analyzed using Epi Info 2000. The proportions of study variables were calculated and expressed in terms of percentages.

**Results**

Most of the cases 65(65%) were in age group of 61 to 70 years with a mean age of 61.48 ± 9.5 years. Most of the cases were male 60(60 %) and 40(40%) were female with a male to female ratio of 1.5:1.

It was observed that most common presenting symptoms were breathlessness 86(86%), cough 86 (86%) followed by loss of appetite 78 (78%) chest pain 75 (75%), hemoptysis 19 (19%), fever 35 (35%). Common physical signs on admission were Lymphadenopathy 38(38%) followed by finger clubbing 30(30%) and SVC obstruction 13(13%).

92 patients (92%) had large pleural effusion and 8 patients (8%) had moderate effusion. The abnormalities which were noted on computed tomography of thorax were lung masses, nodules or infiltrates (57%), mediastinal adenopathy (51%), pleural nodularity (43%), lymphangitic carcinomatosa (11%), chest wall involvement (6%).

52 % subjects had blood stained fluid while 48 % had straw coloured fluid. All (100%) of the malignant pleural effusions were exudative. 82(82%) patients were exudative by protein criteria and 18 (18%) of the patients were exudative by LDH criteria. Mean pleural fluid pH was 7.39(± 0.17). Mean pleural fluid protein level was 4.71(± 0.72) g/dl, mean serum protein level was 6.42(±0.62) g/dl and pleural fluid to serum protein ratio was 0.73 (±0.12), mean pleural fluid LDH level was 623.98 (± 81.14) U/L, mean serum LDH level were 630.85
Table 1: Biochemical data of serum and pleural fluid of patients with malignant pleural effusion

<table>
<thead>
<tr>
<th>Biochemical levels</th>
<th>No. of patients 'n'</th>
<th>Mean</th>
<th>SD</th>
<th>Maximum</th>
<th>Minimum</th>
</tr>
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<tbody>
<tr>
<td>Pleural fluid ADA (U/L)</td>
<td>100</td>
<td>23.50</td>
<td>3.93</td>
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<td>11.10</td>
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<tr>
<td>Pleural fluid (PF) Protein (g/dl)</td>
<td>100</td>
<td>4.71</td>
<td>0.72</td>
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<tr>
<td>Serum (S) Protein(g/dl)</td>
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<td>6.42</td>
<td>0.62</td>
<td>6.84</td>
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<tr>
<td>(PF:S) Protein</td>
<td>100</td>
<td>0.73</td>
<td>0.12</td>
<td>0.64</td>
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<td>Pleural fluid(PF) LDH (U/L)</td>
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<td>623.98</td>
<td>81.14</td>
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<tr>
<td>Serum (S) LDH (U/L)</td>
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<td>630.85</td>
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<td>626</td>
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<td>(PF:S) LDH</td>
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<td>0.98</td>
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<tr>
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<td>39</td>
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<tr>
<td>Pleural fluid PH</td>
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<td>0.17</td>
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<tr>
<td>Pleural fluid leucocyte subsets (%Total WBC)</td>
<td>100</td>
<td>1307</td>
<td>478.89</td>
<td>3000</td>
<td>500</td>
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Majority of the patients (92%) presented with large pleural effusion. Computed tomography findings noted were lung masses, nodules or infiltrates (57%), mediastinal adenopathy (51%), pleural nodularity (43%), lymphangitic carcinomatosa (11%), chest wall involvement (6%). Yilmaz et al. reviewed the CT scans in 146 patients with malignant pleural effusion and abnormalities reported were mediastinal adenopathy, 43%; chest wall involvement 11%; lymphangitic carcinoma 7% and suspicious lung masses, nodules, or infiltrates, 56%.

52 % subjects had blood stained fluid while 48 % had straw coloured fluid. All (100%) of the malignant pleural effusions were exudative. 82(82%) patients were exudative by protein criteria and 18 (18%) of the patients were exudative by LDH criteria. Mean pleural fluid pH was 7.39 (± 0.07). Mean ADA activity was 23.50 (±3.93) U/L.

In the present study out of total 100 patients of malignant pleural effusion it was found that 83 (83%) patients were positive for malignant cells by pleural fluid cytology. Zay Soe et al. observed that out of 73 patients of malignant pleural effusion 47(64.4%) had positive pleural fluid cytology for malignant cells. Bhattacharya et al. observed that out of total 66 cases. It has been reported that the diagnostic yield of pleural fluid cytology for malignant cells ranges from 62%-90%. Several factors influence the yield of pleural fluid cytology including mechanism of effusion, type of primary tumour, nature of specimens, number of specimens and the skill of the cytopathologists.

In our study, closed needle biopsy of the pleura was positive only in 44(44%) of the patients. The sensitivity of closed pleural biopsy is less than pleural fluid cytology in malignant effusions. The diagnostic yield of closed pleural biopsy ranges between 40 to 75%. Factors which influence the yield of closed pleural biopsy include metastatic tumor areas not reached during blind biopsy, minimal pleural involvement and the skill of the person performing the procedure.

We observed that closed needle pleural biopsy was positive in 17(17%) of the patients with negative cytology. Studies have shown that closed needle pleural biopsy is positive in 7 to 12% of the patients with negative cytology.

In present study we observed that adenocarcinoma (59 (59%)) was the most common type of cytological diagnosis in malignant pleural effusion, followed by small cell carcinoma (08 (08%)), lymphoma (66%), squamous cell carcinoma (4 (4%)), large cell carcinoma (4 (4%)). In 19 (19%) patients exact histological type could not be determined. Bhattacharya et al. observed similar findings, with adenocarcinoma being the most common type of malignancy (65%) on the basis of analysis of histopathological examination of pleural biopsy sample while other histological types were squamous cell carcinoma (3%), small cell carcinoma (6%), large cell

Discussion

In our study, malignant pleural effusions were most common in the age group of 61-70 years. It was more common in males as compared to females. Most common presenting symptoms were breathlessness and cough. All the above findings are in concordance with previous studies.
carcinoma (3%), and indeterminate (23%).

We observed that the most common primary site in patients with malignant pleural effusion was lung (59(59%)) followed by breast (25(25%)), lymphoma 6(6%) female genital tract 1(1%) and in 09 (09%) patients primary site could not be determined. Similar findings were observed by Spriggs and Boddington et al.\textsuperscript{15} who found that most common primary site was lung (43%), followed by breast (25%), lymphoma (08%), female genital tract (06%), gastrointestinal tract (05%), malignant melanoma (02%) and primary could not be determined in 10%.

We performed pleurodesis in 40 patients and followed them at 1, 3 and 6 months after pleurodesis. It was observed that 12(30%) patients had recurrence of pleural effusion. In a review of 11 reports\textsuperscript{16} involving 359 patients, the success rate with tetracycline was 67% which is consistent with present study.

Conclusions

In our tertiary health care centre, malignant pleural effusions presented as large pleural effusions. Most common presenting symptoms were breathlessness and cough. They were exudative, lymphocytic predominant with low ADA levels. Pleural fluid cytology plays an important role in diagnosis. Thoracentesis and cytologic study should be the initial diagnostic approach to malignant pleural effusions. Adenocarcinoma of the lung was the most common cause of malignant pleural effusion. Pleurodesis with ox-tetracycline was successful in majority of cases.

References

Clinical Profile of Dysphagia in Patients with Parkinson’s Disease, Progressive Supranuclear Palsy and Multiple System Atrophy

Sulena1, Dipti Gupta2, Anjani Kumar Sharma3, Baltej Singh4

Abstract

Background: Swallowing changes are commonly observed in Parkinson’s and Parkinsonism plus syndromes. Expeditious identification is necessary to provide early intervention in this population to avoid risk of aspiration and swallowing complications.

Objectives: To investigate swallowing problems using detailed case history and swallowing speed on 3 ounce water test in three groups i.e. PD, MSA and PSP groups and further, to compare it with control group.

Subjects and Methods: Cross sectional study design. A total of 73 patients were classified in MSA, PSP and PD for testing aged between 38 yrs and 70 yrs according to respective diagnostic criteria. A simple bedside water swallowing test was performed using 90 cc of water. Detailed assessment was done to check swallowing function.

Results: The mean age of both experimental group and control group was 62.4±8.37 yrs. and 61.05±7.07 yrs. Males were affected more in every pathological group compared to females. The dysphagia presented earlier in PSP and MSA groups as compared to PD groups. The water swallowing speed was found to be significantly less than 10ml/sec amongst three neurological groups compared to control group. The patients were found to have significant difficulty in parameters like repetitive swallowing, transferring food bolus through mouth, and food sticking in throat after swallowing.

Conclusion: This is the first study comparing clinical profile of dysphagia in patients with PD, MSA, and PSP. Although there is no specific pattern of dysphagia for each of these disorders, the presence of some findings may provide clue to the diagnosis and necessary intervention.

Editorial Viewpoint

- This is a cross-sectional study done in tertiary care center for comparing dysphagia in patients with movement disorder.
- Simple bedside water swallowing test was used to assess dysphagia.
- Identifying dysphagia is important to prevent aspiration.

Introduction

Parkinson’s disease (PD) is a syndrome characterized by a combination of tremor-at-rest, rigidity, bradykinesia, loss of postural reflexes, flexed posture, and freezing. The second most common group of parkinsonism is Parkinsonism-plus syndromes depending on associated signs and symptoms. The spectrum of motor features in the Parkinson’s disease and Parkinsonism-plus syndromes – Progressive Supranuclear Palsy (PSP), Multiple System Atrophy (MSA) is broad and often missed in clinical practice. PSP was first described by Steele, Richardson, and Olszewski in 1964 and characterized by supranuclear ophthalmoparesis and parkinsonism. Despite greater awareness in recent years, many patients with PSP remain undiagnosed or misdiagnosed for much of their disease duration. Multiple system atrophy is described as a syndrome characterized clinically by parkinsonism and dysautonomia. The dysphagia is one of the important symptom in these diseases and was long ignored in clinical practice. The integrity of swallowing mechanism is affected in Parkinson and Parkinsonism-plus syndromes with risk of neurogenic dysphagia. Dysphagia may lead to malnutrition, difficulty in taking medication, inadequate drinking, silent aspiration and inability to eat. Dysphagia in less common...
neurologic diseases such as PSP and MSA has not been consistently evaluated with clinical and, in particular, objective swallowing examinations. The rationale for the study is to evaluate dysphagia in these three groups and compare them (PD, MSA and PSP).

**Methodology**

This was a cross-sectional study conducted in a tertiary care center in Rajasthan (North West India). The study was done in a time span of one year. Routine admissions were monitored to neurology ward and patients of PSP, PD and MSA were enrolled. We enrolled patients with clinical diagnosis of Parkinson’s disease according to UKPD diagnostic criteria, PSP using NINDS – SPSP criteria and MSA using Consensus diagnostic criteria. We assessed dysphagia by 3 ounce water swallow test. One-to-one interview in the local dialect was conducted with open-ended questions, and detailed neurological examination was done and the medical records were reviewed. Detailed examination for swallowing was done which included assessment that is 3 ounce water swallow test. A total of 26 subjects of PD, 22 of MSA and 25 of PSP were classified for testing. The inclusion criteria for the study was every patient should have adequate cognitive abilities and oromotor functioning. The exclusion criteria included inability of subjects to remain alert for testing or presence of any feeding tube /Ryle’s tube or tracheostomy. The control group consisted of healthy age and gender matched individuals. A total of 20 participants were taken as control.

The aims for the study were to evaluate dysphagia and related swallowing problems in these three groups and compare them (PD, MSA and PSP). The other aim was to investigate swallowing speed in these three groups i.e. fast (>10ml/sec) and slow (<10ml/sec) and to compare it with control individuals depending on 3 ounce water swallowing test.

**Description of a 3-ounce water swallowing test:** It was used to assess neurogenic dysphagia in these subjects. For performing this test, the subject was instructed to sit comfortably in an upright position suitably at a chair. A glass of cold water of 90 ml (measured) was applied to calculate the swallowing speed (ml/sec). During testing, it was made cautionary that we did not perform this test in those subjects who were at risk of aspiration.

**Statistical Analysis:** The descriptive statistics has been used to show the frequency, percentage, mean and standard deviation of variables. Chi square test was applied to find the association between attribute of variables.

| Table 1: Gender distribution in experimental group (three sub groups) and Control group |
|---------------------------------|---------|---------|---------|
| Diagnosis group | Females | Males | Total no. of patients |
| MSA | 6 | 16 | 22 |
| PD | 8 | 18 | 26 |
| PSP | 6 | 19 | 25 |
| Control group | 8 | 12 | 20 |

| Table 2: Demographics of patients with parkinson's disease, multiple system atrophy, and progressive supranuclear palsy |
|---------------------------------|---------|---------|---------|
| **Factors** | **Variables** | **Experimental group (n)** | **Control Group(n)** |
| | MSA | PD | PSP | | MSA | PD | PSP |
| Sex | Males | 16 | 18 | 19 | 12 | 8 | 6 |
| | Females | 6 | 8 | 6 | 8 |
| Education | Literates | 17 | 12 | 9 | 13 |
| | Illiterates | 9 | 14 | 16 | 7 |
| Duration of disease | 22±8.2 | 26±18.1 | 25±8.3 |

**Results**

A total of 73 patients were enrolled in pathological group and 20 patients were enrolled in control group. The mean age of both experimental group and control group was 62.4±8.37 yrs. and 61.05±7.07 yrs respectively. The gender distribution for three sub-groups (diagnosis group) and control group was given in Table 1. It was observed that males were more in every experimental group compared to females though not clinically significant within and across the groups. The demographics are shown in Table 2 (p value<0.05).

When compared within sub groups (MSA, PD and PSP) it was seen disease duration was significantly different within the groups. Presentation of dysphagia was earliest in PSP (25 ± 8.3 months) and MSA (22 ± 8.2 months) as compared to PD (26 ± 18.1 months) as shown in Table 2. The symptoms of dysphagia within sub groups were compared using chi square test for p value as shown in Table 3. The proportion of dysphagia (difficulty initiating swallowing) in all the 3 patients groups were ranging from 15.3% (n=4) in PD cases, 41% (n=9) in MSA cases and 36% (n=9) in PSP cases which was significantly different when compared with control group (p=.005).

Four of PD patients, four of PSP patients and eight of MSA patients were found to have delayed swallowing which was significantly different from control group (p=0.01). Ten of PSP cases and nine of MSA cases were found
Table 3: Clinical characteristics of patients with parkinson’s disease, multiple system atrophy, and progressive supranuclear palsy

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>MSA</th>
<th>PD</th>
<th>PSP</th>
<th>Chi square correlation (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (n)</td>
<td>22</td>
<td>26</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Assessment of dysphagia (liquid)</td>
<td>22</td>
<td>26</td>
<td>25</td>
<td></td>
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<tr>
<td>Difficulty initiating swallowing</td>
<td>9</td>
<td>13</td>
<td>4</td>
<td>22</td>
</tr>
<tr>
<td>Delayed swallowing</td>
<td>8</td>
<td>14</td>
<td>4</td>
<td>22</td>
</tr>
<tr>
<td>Repetitive swallowing</td>
<td>9</td>
<td>13</td>
<td>2</td>
<td>24</td>
</tr>
<tr>
<td>Maneuvers relieving difficulty</td>
<td>1</td>
<td>21</td>
<td>2</td>
<td>24</td>
</tr>
<tr>
<td>Painful</td>
<td>0</td>
<td>22</td>
<td>0</td>
<td>26</td>
</tr>
<tr>
<td>Difficulty transferring food through mouth</td>
<td>9</td>
<td>13</td>
<td>2</td>
<td>24</td>
</tr>
<tr>
<td>Food sticking in throat after swallowing</td>
<td>1</td>
<td>21</td>
<td>1</td>
<td>25</td>
</tr>
<tr>
<td>Coughing while swallowing</td>
<td>1</td>
<td>21</td>
<td>2</td>
<td>24</td>
</tr>
<tr>
<td>Choking sensation</td>
<td>0</td>
<td>22</td>
<td>1</td>
<td>25</td>
</tr>
<tr>
<td>Nasal regurgitation</td>
<td>1</td>
<td>21</td>
<td>1</td>
<td>25</td>
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<tr>
<td>Lingual tremors</td>
<td>0</td>
<td>22</td>
<td>4</td>
<td>22</td>
</tr>
<tr>
<td>Drooling of saliva</td>
<td>8</td>
<td>14</td>
<td>4</td>
<td>22</td>
</tr>
<tr>
<td>3 ounce water swallowing test</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Water swallow&lt;10 ml/sec</td>
<td>17</td>
<td>5</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Water swallow&gt;10 ml/sec</td>
<td>4</td>
<td>18</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>Coughing during or after swallowing</td>
<td>1</td>
<td>21</td>
<td>6</td>
<td>20</td>
</tr>
</tbody>
</table>

To have repetitive swallowing problem while only two of PD patients have repetitive swallowing which was clinically significant across the experimental and control group (p= 0.06) and within sub groups (p= 0.013).

None of the patients were presented with pain sensation during swallowing. Ten of PSP cases, nine of MSA and two of PD patients were found to have difficulty transferring food through mouth which was clinically significant within sub-group. Food sticking in throat after swallowing was seen in 8 patients of PSP which is significantly different from PD (n=1 patient) and MSA (n=1 patient) cases. Four PD cases, one PSP case, and zero MSA case were presented with lingual tremors which was clinically significant within sub-groups but not across the groups. Drooling of saliva was found in majority of patients with PSP (n=9 patients), then in MSA (n=8 patients) and lastly in PD (n=4 patients) cases, but was not clinically significant.

Results of 3 ounce water test: The other aim of the study was to assess patients on 3 ounce water test. 17 of MSA cases, 10 of PSP cases and 13 of PD cases were found to have water swallowing speed less than 10ml/sec which differed significantly (chi square= 6.938, p=0.03) among the three neurological disorders (Table 3). None of the subjects from the control group had swallowing speed less than 10 ml/sec for 3 ounce water swallowing test. The presence of coughing symptom during or after 3 ounce water swallowing test was found to be significantly different amongst 3 experimental groups.

Discussion

Dysphagia can manifest in the form of drooling of saliva, poor bolus formation, slowed oral transitory time, repetitive tongue movements to propel the bolus, abnormal food residual collection in the vallecula or in pyriform sinus, delayed initiation of pharyngeal swallow reflex and narrowing of lumen of upper esophageal sphincter.13 Dysphagia in Parkinson and Parkinsonism plus syndromes can result in complications like aspiration pneumonia, malnutrition, dehydration and increased mortality. The reported prevalence of dysphagia in Parkinson’s disease ranges between 40% to 95%.8,10 The Prevalence of dysphagia in PSP is 16% initially to 83% in later stages.11 The prevalence of dysphagia in MSA ranges from 44%-73%.12,14

Males were affected more than females in all three groups as seen in other study.15 In our study, dysphagia was not the initial manifestation of neurological illness in any of the three affected groups. It was found that patients in PSP (25 ± 8.3) months and MSA (22 ± 8.2) months group have presented earlier with dysphagia than PD (26 ± 18.1 months). Kalf et al16 suggested that dysphagia is seen early in PSP and MSA patients as compared to PD patients.

In the present study, difficulty initiating swallowing was seen in 30.1% of Parkinson and Parkinsonism plus syndromes which was significant as compared to control group. The overall reduced mandible and tongue movement leads to difficulty initiating swallowing.17

The present study observed that patients have statistically significant difficulty in these parameters- repetitive swallowing, difficulty transferring food through mouth, food sticking in throat after swallowing and decreased swallowing speed (<10 ml/sec) when compared across three groups (PD, MSA, PSP). However, no significant differences were seen for other parameters amongst the experimental group.

In the present study, Ten of PSP cases and 9 of MSA cases were found to have repetitive swallowing problem while only 2 of PD patients have repetitive swallowing which was clinically significant across the experimental and control group (p=0.06) and within sub groups (p= 0.013). Logemann suggested the recurring “rocking and rolling” festinating-type motion of the tongue during oral transfer is frequently seen in patients with PD.18 In dysphagic
PD patients, the number of swallow movements are increased but the swallowing volume capacity is significantly decreased as compared to non-dysphagic PD subjects.\(^{19}\)

As the typical parkinsonian gait is slow with small regular steps, the same type of rhythmicity is also observed with the tongue movements. It has been demonstrated that in PD, the tongue muscles lose manoeuvrability and the movement pattern tends to become rhythmic.\(^{17,20}\) It has been suggested that PD and PSP may be differentiated by lingual tremors, which may be evident in PD but generally not in PSP.\(^{21}\) In our study, we observed that lingual tremors were seen more in PD(4) as compared to PSP(1) and none in MSA.

Difficulty in transferring food through mouth was seen in all three groups and was statistically significant. In a Japanese study, comparing PD with PSP using videofluorography demonstrated food pooling on the tongue, difficulty in bolus formation, and bolus falling into pharynx before swallow.\(^{22}\) In this study, food sticking in throat after swallowing was seen in 8 patients of PSP which is significantly different from PD (n=1) and MSA (n=1) cases. The cause of delayed bolus transit from oral to pharyngeal stage may be attributed to bradykinesia or disturbed tongue movement in MSA.\(^{23}\) The brainstem swallowing network includes a dorsal and a ventral swallowing group located within the nucleus of the tractus solitarius and the reticular formation adjacent to the nucleus ambiguus which is affected in neurodegenerative diseases.\(^{24}\)

Drooling of saliva was found in majority of patients with PSP, then in MSA and lastly in PD cases, but was not clinically significant. This is attributed to reduction in frequency of spontaneous swallows and anteriorly flexed neck position and not to increased production of saliva. However, xerostomia has been reported in 55 % of cases of PD in response to high levodopa dosage.\(^{25}\)

Delayed swallowing was seen in all three groups. The maximum delay in swallowing was seen in MSA without significant difference across study groups but significantly more than controls. In one study, on measurement of swallowing time periods, no significant differences between the PD and PSP groups was noted but significantly longer periods during many swallowing phases were seen when compared to those in the control group. The variation in dysphagia characteristics between the two diseases arises from the difference in pathology of PSP, which include the cerebral cortex, cerebellum, pons and medulla tegmentum in addition to the basal ganglia.\(^{22}\)

In the present study we found significantly reduced swallowing speed on 3 ounce water swallow test in three groups (PD, MSA and PSP). 17 (77%) MSA patients, 13 (50%) PD cases and 10 (40%) PSP patients were found to have water swallowing speed <10 ml/sec. The reduced swallowing speed in these three groups is considered along with other symptoms for e.g. difficulty in initiating swallowing, choking or coughing sensation, drooling during water swallowing test. Dysphagia and frequent coughing can occur in all stages of PD.\(^{26}\)

Patients who pass on this test can be safely recommended to take an oral diet. The advantage of early assessment is to provide timely identification and necessary intervention in the form of food thickeners, semisolids, use of straws and percutaneous endoscopic gastrostomy. This is used as a screening tool by Speech Language pathologist or Neurologist in daily clinical examination of neurological population.\(^{8}\) The differences in the dysphagia profile of these three diseases can help in differentiating amongst them. With this present study, this information may be helpful in guiding physician, patients and their families in planning for long-term care.

The limitation of study was small number of patients and lack of objective test in the form of videofluoroscopy or endoscopy.

**Conclusion**

This is the first study comparing dysphagia in PD, MSA, and PSP. Although there is no specific pattern of dysphagia for each of these disorders, the presence of some findings may provide clue to the diagnosis. Further studies should aim to correlate the findings in larger group of population and correlation with objective tests.

**References**

8. Nester DM, Leder SB. Clinical utility of the


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Comparison of Two Creatinine Based Equations for Routine Estimation of GFR in a Speciality Clinic for Diabetes

Satyavani Kumpatla¹, Anju Soni², Vijay Viswanathan³

Abstract

Objectives: To compare the bias, absolute bias, precision and accuracies between the equations, viz., CKD-EPI (Scr), CKD-EPI (Scys) and MDRD in Indian patients with type 2 diabetes.

Methods: 198 patients who underwent 24 h urinary collection for assessing kidney function between November 2014-January 2015 were included. Cohen’s κ coefficient, Bland-Altman plot were calculated between estimated kidney function equations, and bias, precision, accuracies was calculated between the formulae.

Results: The mean eGFR based on MDRD, CKD-EPI (Scr) and CKD-EPI (Scys) equations were 64.5±21.9, 70.2±25.1 and 74.7±31.0 ml/min/1.73 m² respectively. The overall mean absolute bias was smallest for MDRD vs CKD EPI (Scr). The precision was also least for MDRD vs CKD EPI (Scr) indicating that the agreement between these equations is consistent for the range of values. MDRD vs CKD EPI (Scr) had the highest accuracy in comparison to other compared formula. The performance between MDRD versus CKD EPI (Scys) was different. There was a good agreement between MDRD and CKD EPI (Scr).in both stage 3 and stage 4 CKD. The MDRD vs CKD EPI (Scr) classified 72.2% of the patients correctly.

Conclusion: In conclusion, there was a good agreement between CKD-EPI (Scr) and MDRD equations. CKD-EPI equation based on creatinine estimation is widely accepted method and clinicians may use this equation in routine clinical practice to assess kidney function among patients with type 2 diabetes.

Introduction

Life-threatening complications of diabetes are also on the rise due to the epidemic rise in the prevalence of type 2 diabetes. Among these, diabetic nephropathy (DN) predisposes to excess morbidity and mortality resulting from renal failure and cardiovascular disease. A recent study from India reported that the expenditure on hospital admissions for chronic kidney disease (CKD) was considerably higher than for those without any diabetic complications.

The diagnosis of CKD is made in terms of kidney damage or glomerular filtration rate (GFR) of less than 60 ml/min/1.73 m² for 3 or more months, irrespective of the cause. Accurate measurement of GFR can be done by inulin clearance or radionuclide-labeled markers, but it is quite impractical, expensive and cumbersome to perform on a large number of patients. However, in routine clinical practice kidney function is estimated rather than measured. GFR can be estimated from serum creatinine or cystatin C concentrations, demographic variables, such as age, sex, ethnicity, and body size. The most frequently used formulae are the Cockcroft–Gault (CG), Modification of Diet in Renal Disease (MDRD), and the recently developed formula of Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations.

Michels et al. reported that CKD-EPI gives the best estimation of GFR, although its accuracy is almost the same as that of MDRD. A few studies from India have also tried to validate the accuracy of these prediction equations for assessing kidney function but these equations may need to...
be validated before they can be applied for accurately estimating kidney function in the Indian population. Nevertheless, there is a lack of information on this aspect, especially in relation to patients with diabetic kidney disease in India. Therefore, the present study was planned to compare the bias, absolute bias, precision and accuracies between the equations, viz., CKD-EPI (Scr), CKD-EPI (Scys) and MDRD in Indian patients with type 2 diabetes attending a tertiary care centre for diabetes in south India.

Subjects and Methods

Subjects with type 2 diabetes who underwent 24 h urinary collection for kidney function test from November 2014 to January 2015 in a tertiary care hospital for diabetes were included in this study. A total of 198 patients were selected for this analysis and all the patients were on treatment with oral hypoglycemic agents and known hypertensives were on antihypertensive medication. The study and the consent procedure was approved by the Ethics Committee of M. Viswanathan Diabetes Research Centre.

Age, sex, weight and height and body surface area were recorded. Written informed consent was obtained from the patients. The 24h urine collection was started from morning for assessing kidney function. Serum or urine creatinine was assayed with a kinetic test without deproteinization according to the Jaffe method. The creatinine assay was traceable to a standard NIST SRM967. Urinary protein was determined by immunoturbidimetric procedure. Serum Cystatin C was measured by particle enhanced immunoturbidimetric assay calibrated with reference material traceable to the ERM-DA 471/IFCC.

Patients were classified into stages of CKD on the basis of the estimates of the MDRD, and CKD-EPI (Scr) and CKD-EPI (Scys) equations where Scr is serum creatinine and Scys is serum cystatin C. Stratification of kidney disease was based on the GFR stages as per KDOQI guidelines: stage 1 (≥ 90 ml/min/1.73 m²), stage 2 (60–89 ml/min/1.73 m²), stage 3 (30–59 ml/min/1.73 m²) and stage 4 (<30 ml/min/1.73 m²).

GFR prediction equations

In the GFR prediction equations, creatinine is expressed in mg/dl.

1. The abbreviated MDRD estimate of kidney function was calculated as eGFR = 186 × (Scr) (mg/dl)−1.154 × Age−0.203 (× 0.742 if female) (× 1.21 if black).

2. The CKD-EPI (Scr) equation expressed as a single equation as: eGFR = 141 × min (Scr /k, 1)α × max (Scr /k, 1)−1.209 × 0.993Age × (1.018, if female) × (1.159, if black), k is 0.7 for females and 0.9 for males, α is –0.329 for females and –0.411 for males, min indicates the minimum of Scr /k or 1, and max indicates the maximum of Scr /k or 1.

3. Serum Cystatin C 2012 Equation (Age and Sex) Consider, 133 × min (Scys/ 0.8, 1)−0.499 × max (Scys/0.8, 1)−1.329 × 0.996Age ×(×0.932 if female), where min indicates the minimum of Scys/k or 1 and max indicates the maximum of Scys/k or 1.

Statistical analysis

All statistical analyses were performed using SPSS 20.0 version. To evaluate the performance of the equations, bias, mean absolute bias, precision, and 15% (P15), 30% (P30) and 50% (P50) accuracies were calculated.

The bias was defined as the mean difference between the equations. Precision was expressed as S.D of the mean difference and accuracy was calculated as the percentage of subjects who had a difference between the equations within 15% (P15), 30% (P30) and 50% (P50) limits. Differences in bias, absolute bias and accuracy between formulae were tested with paired t-test and Mc Nemar test, respectively.

Agreement between the equations in the classification of patients into CKD stages was assessed by calculating Kappa coefficient. Bland-Altman plots were applied to assess the bias as well as the limits of agreement. The difference between the equations of renal function is plotted against the average of equations of renal function, therefore the positive difference suggests an overestimation by the formula, whereas a negative difference suggests an underestimation. The center line represents the mean difference between the equations; the two lines opposite to center lines represents the lines of agreement, calculated as the mean difference between plus or minus two times the SD of this difference. P value less than 0.05 was considered as statistically significant.

Results

A total of 198 GFR measurements were performed on patients with type 2 diabetes. Among the total study subjects, 140 (71%) were males, mean age of total subjects was 55.3±9.8 years. Mean creatinine level was 1.26±0.6 mg/dl and the mean cystatin C level was 1.22±0.6 mg/l. The mean eGFR based on MDRD, CKD-EPI (Scr) and CKD-EPI (Scys) equations were 64.5±21.9, 70.2±25.1 and 74.7±31.0 ml/min/1.73m² respectively.

Table 1 shows the comparison of mean bias, precision, absolute bias and accuracies between the formulae. The overall mean absolute bias was smallest for MDRD vs CKD EPI (Scr) (Figure 1, Panel A). The precision was also least for MDRD vs CKD EPI (Scr) indicating that the agreement between these equations is consistent for the range of values. MDRD vs CKD EPI (Scr) had the highest accuracy in comparison to other compared formula. The performance between MDRD versus CKD EPI (Scys) was different (Figure 1, Panel B).
There was a good agreement between MDRD and CKD EPI (Scr) in both stage 3 and stage 4 CKD (Figure 2, Panel A). Agreement between MDRD and CKD EPI (Scys) was better only in stage 4 CKD (Figure 2, Panel B).

Classification of type 2 diabetic patients in stages of chronic kidney disease according to estimated GFR by equations is presented in Table 2.

The MDRD equation compared with CKD EPI (Scys) classified 53% of the patients correctly, in 9.1% of the patients the kidney function was underestimated, and in 37.9% it overestimated (kappa κ=0.36). The MDRD vs CKD EPI (Scr) classified 72.2% of the patients correctly. It underestimated kidney function in 1% and overestimated in 26.8% of the patients (kappa κ=0.60).

### Table 1: Comparison of the mean bias, precision, absolute bias and accuracies between the formulae

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean bias</th>
<th>Precision</th>
<th>Mean absolute bias</th>
<th>Accuracy within</th>
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</thead>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>15(%) 30(%) 50(%)</td>
</tr>
<tr>
<td>MDRD vs CKD-EPI (Scys)</td>
<td>10.03</td>
<td>17.24</td>
<td>15.64</td>
<td>37.9 79.8 97.5</td>
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<tr>
<td>MDRD vs CKD-EPI (Scr)</td>
<td>5.70*</td>
<td>5.25</td>
<td>6.20*</td>
<td>92* 97.5* 100</td>
</tr>
</tbody>
</table>

Note: The values in the table for accuracy are percentages. Abbreviations: CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; MDRD: Modification of Diet in Renal Disease; Scr: Serum creatinine; Scys: Serum cystatin C. *P<0.0001, MDRD vs CKD-EPI (Scys) versus MDRD vs CKD-EPI (Scr).

**Discussion**

This study investigated the performance of GFR estimated using Cystatin C and creatinine based equations among patients with type 2 diabetes in a tertiary care centre. The comparison was done between MDRD equation and CKD-EPI (Scys) and CKD-EPI (Scr). The overall mean absolute bias was smallest for MDRD vs CKD-EPI (Scr) which suggest the highest precision of these two

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**Fig. 1**: Bland-Altman plots of the estimated equations. Panel A comparison is between MDRD versus CKD EPI (Scr). Panel B comparison is between MDRD versus CKD EPI (Scys). The two lines opposite to center line represent the lines of agreement, calculated as the mean difference between plus or minus two times the SD of this difference.

**Fig. 2**: Comparison of the agreement between estimated equations in stages of CKD. Panel A comparison is between MDRD versus CKD EPI (Scr). Panel B comparison is between MDRD versus CKD EPI (Scys).
Table 2: Comparison of classification of type 2 diabetic patients in stages of chronic kidney disease according to estimated GFR equations

<table>
<thead>
<tr>
<th>Stages of GFR (ml/min/1.73 m²)</th>
<th>Total</th>
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<tr>
<td>&lt;30</td>
<td>12</td>
</tr>
<tr>
<td>30 to 59</td>
<td>62</td>
</tr>
<tr>
<td>60 to 89</td>
<td>46</td>
</tr>
<tr>
<td>≥90</td>
<td>14</td>
</tr>
</tbody>
</table>

The bold numbers indicate the number of patients classified to the same chronic kidney disease stage according to both compared equations. Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; Scr: Serum creatinine; Scys: Serum cystatin C.

equations. Precision was also least for MDRD vs CKD-EPI (Scr) which shows that agreement was consistent for the range of values. A higher percentage of patients were classified correctly by CKD-EPI (Scys) and MDRD equations. The accuracies within 15%, 30%, and 50% was highest for MDRD vs CKD EPI (Scr). The agreement remained the best for MDRD vs CKD EPI (Scys) equations. It was previously reported that performance was similar between CKD-EPI and MDRD in CKD patients of Asian population.12

There was a good agreement between MDRD and CKD-EPI (Scr) in both stage 3 and stage 4 CKD. The agreement between MDRD and CKD EPI (Scys) was better only in stage 4 CKD. The possible reason could be that these equations were developed primarily based on western populations; hence the performance will vary among Asian Indians because of the significant anthropometric difference. This implies that these formulae might need to be modified and validated in specific ethnic groups.

The strength of this study is that a large diverse South Indian population with type 2 diabetes with and without kidney disease were included. However, the study has few limitation, firstly the study doesn’t use the gold standard method for measuring true GFR, secondly the study used relatively limited number of patients.

Conclusions

The study concludes that there is a good agreement between CKD-EPI (Scys) and MDRD equations. Perhaps it still remains unclear whether CKD EPI (Scys) is superior to CKD-EPI (Scr) in assessing true kidney function in this population and it requires additional studies. GFR using CKD-EPI based on creatinine estimation is widely accepted method and clinicians may use CKD-EPI (Scr) for routine clinical practice. Further the findings have to be confirmed by comparing the eGFR equations with the gold standard methods.

Acknowledgement

We acknowledge help rendered by Mr Sriram Ramchandran, biostatistician in doing statistical analysis.

Authors Contribution

SK interpreted the results and wrote the manuscript and reviewed the discussion, AS involved in the collection of data and helped in the preparation of manuscript, VV designed the study and reviewed the discussion.

References

Comparison of Rifaximin Plus Lactulose with the Lactulose Alone for the Treatment of Hepatic Encephalopathy

Kiran Ahire¹, Archana Sonawale²

Abstract
Hepatic encephalopathy is challenging complication of liver dysfunction. Therapeutic treatment options for hepatic encephalopathy are currently limited and have appreciable risks and benefits associated with their use. Rifaximin is a novel anti microbiological agent with wide spectrum of activity that has shown promise as an alternative option for hepatic encephalopathy.

Aims and Objectives: The present study was undertaken to compare the effectiveness of Rifaximin and Lactulose as a combination vs Lactulose alone, to compare the adverse effects and to study the rapidity of therapeutic effects of Rifaximin and Lactulose.

Methods: It was a prospective observational study. 60 patients suffering from hepatic encephalopathy (HE) were studied. Patients were investigated and treated as per treating physician’s decision. At the time of analysis, patients were divided into 2 groups, Rifaximin group who received Rifaximin+Lactulose (R+L) and Lactulose group(L), who received Lactulose only. Parameters such as mental status grade, Asterixis grade, Serum Ammonia grade, Number Connection Test grade (NCT grade), Hepatic Encephalopathy Index (HE index) were evaluated and compared in both groups. Clinical efficacy was determined using HE index improvement. Primary end points were decrease in HE index and reversal of HE grades. Secondary end points were mortality from HE or any other cause, decrease in mental status grade, asterixis grade, serum Ammonia grade, NCT grade.

Results: Out of 60 patients, 32 received Rifaximin+Lactulose combination and 28 patients received Lactulose alone. Mean Child-Turcotte-Pugh score (CTP score) was 10.6 in R+L group and 10.32 in L group. There was statistically significant improvement in mental status grade, Asterixis grade, Serum Ammonia grade, NCT grade, Hepatic encephalopathy index in both groups, p value <0.05 but no statistically significant difference between improvement in mental status grade, Asterixis grade, Serum Ammonia grade, NCT grade, HE index between the two groups. Rifaximin + Lactulose combination was effective in 31 out of 32 i.e.96.87% and Lactulose alone in 24 out of 28 patients, i.e. in 85.71%, which is not statistically different, p=0.3251.

Discussion: Rifaximin+ Lactulose combination is not superior to Lactulose alone in treatment of refractory hepatic encephalopathy. Addition of Rifaximin may help in the treatment of refractory hepatic encephalopathy.

Editorial Viewpoint

- Rifaximin as shown a promise in the management of hepatic encephalopathy.
- However, this study reveals that addition of rifaximin may help only in cases with refractory hepatic encephalopathy.

Introduction
Hepatic encephalopathy is a syndrome observed in patients with cirrhosis. Hepatic encephalopathy is defined as a spectrum of neuropsychiatric abnormalities in patients with liver dysfunction after exclusion of other known brain diseases and characterized by personality changes, intellectual impairment, and a depressed level of consciousness, in severe form can lead to coma and death. Ammonia has been implicated as a key molecule in the disease pathogenesis, due to its frequent elevation in patients with cirrhosis and known cellular toxicity. The clinical diagnosis of overt hepatic encephalopathy is based on two concurrent types of symptoms: impaired mental status, as defined by the Conn score (also called West Haven criteria) (on a scale from 0

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to 4, with higher scores indicating more severe impairment), and impaired neuromotor function.\(^2\)\(^3\) Most therapies for hepatic encephalopathy focus on treating episodes as they occur and are directed at treatment of precipitating factors, reducing the nitrogenous load in the gut. In general, the oral antibiotics neomycin, paromomycin, vancomycin, and metronidazole have been effectively used, with or without lactulose, to reduce ammonia-producing enteric bacteria in patients with hepatic encephalopathy.

Treatment with nonabsorbable disaccharides lactitol or lactulose is the current standard of care for patients with hepatic encephalopathy, which decreases the absorption of ammonia through cathartic effects and by altering colonic pH. Gastrointestinal acidification ultimately inhibits the production of ammonia by coliform bacteria. An analysis of Cochrane Hepato-Biliary Group data demonstrated efficacy of lactulose over placebo, but showed no benefit in survival.\(^5\)

Rifaximin is a semisynthetic, nonsystemic antibiotic that is almost exclusively and completely excreted in the feces as unchanged drug. It was approved in late March 2010 by the FDA for the treatment of overt hepatic encephalopathy. It is believed that by altering the flora in the gastrointestinal tract, rifaximin decreases intestinal production and absorption of ammonia. Rifaximin has a broad spectrum of antibacterial activity and thus may be an appropriate agent for eliminating both the anaerobic and aerobic colonic bacteria that are capable of producing ammonia but with low risk of inducing bacterial resistance.\(^6\) Rifaximin is well tolerated in nearly all patient populations, including young children. No dosage adjustment is needed in patients with hepatic encephalopathy or renal insufficiency.\(^6\)\(^11\)\(^13\) With minimal systemic bioavailability, rifaximin may be more conducive to long-term use than other, more bioavailable antibiotics with detrimental side effects. It has been proven to prevent the episode of HE and decrease the risk of hospitalization.\(^7\) In randomized studies, rifaximin was more effective than nonabsorbable disaccharides and had efficacy that was equivalent to or greater than that of other antibiotics used in the treatment of acute HE.\(^8\)\(^16\) In recent meta-analysis of 12 randomized controlled trials, Eltawil et al.\(^17\) reported that rifaximin is as effective as other conventional oral agents for the treatment of HE with a better safety profile. But studies comparing the efficacy of combination of Rifaximin and Lactulose are limited. Hence current study is undertaken to compare the efficacy and safety profile of combination of Rifaximin and Lactulose vs Lactulose alone in treatment of HE.

**Methods**

This was a prospective observational nonrandomized study conducted from January 2011 to July 2012 at tertiary care institute. After obtaining Ethics committee permission from institution, 60 patients suffering from overt HE, fulfilling inclusion and exclusion criteria were enrolled. All patients were investigated and treated as per treating physician. Duration of treatment varied from 7-15 days till discharge from the hospital or death. Any adverse event was recorded specifying the time of onset, duration and severity.

**Conclusion:** Rifaximin + Lactulose combination is effective, but not superior to Lactulose alone in treatment of hepatic encephalopathy.

**Study Design**

The severity of HE was graded according to West Haven criteria. Severity of cirrhosis was graded by CHILD-PUGH-TURCOTTE (CPT) score. Detailed history, clinical, neurological examination was carried out in every patient. Routine investigations like complete blood count, liver function test, renal function test, serum electrolytes, blood sugar, Prothrombin time and International normalized ratio were recorded. Details of special investigations like USG Abdomen, Sr. Ammonia, CT brain, CXR, viral markers, ascitic fluid analysis, hepatoportal Doppler were recorded. The blood investigations were done on the day of admission (Day-1) and were subsequently repeated serially from the day of admission till the final outcome. At the time of analysis patients were divided into two groups:

Rifaximin+Lactulose, (R+L) group who received Rifaximin 1200 mg / day in 3 divided doses and Lactulose, 30–60 ml/three times a day, so that patient passes two to three semisoft stools in a day. Lactulose Group (L) in which patients who received lactulose 30–60 ml/three times a day so that patient passes two to three semisoft stools in a day.

**Parameters like mental status grade, Asterixis grade, Sr. Ammonia grade, number connection grade (NCT grade), hepatic encephalopathy index (HE index) were estimated on Day 1, Day 3, and Day (5-8) in both groups.**

**Grade of Mental State**

This was examined semi-quantitatively using Conn’s modification of the Parsons-Smith classification. Grade 0: no abnormality; Grade 1: trivial loss of awareness, euphoria or anxiety, shortened attention span, impairment of addition or subtraction performance; Grade 2: lethargy, disorientation with respect to time, obvious personality...
Table 1: Baseline characteristics of study patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A (n-32)</th>
<th>Group B (n-28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>49.5 ± 9.7</td>
<td>53.9 ± 10.2</td>
</tr>
<tr>
<td>Male/ female</td>
<td>28/5</td>
<td>26/2</td>
</tr>
<tr>
<td>Etiology HBV/ HCV/ Alcohol</td>
<td>5/4/23</td>
<td>5/4/15</td>
</tr>
<tr>
<td>CTP score (A/B/C)</td>
<td>1/6/25</td>
<td>1/9/18</td>
</tr>
<tr>
<td>HE grade 1/2/3/4</td>
<td>0/10/18/4</td>
<td>0/13/11/4</td>
</tr>
<tr>
<td>Mental status grade 1/2/3/4</td>
<td>0/10/18/4</td>
<td>0/10/15/3</td>
</tr>
<tr>
<td>HE index</td>
<td>13.31</td>
<td>12.96</td>
</tr>
<tr>
<td>T. bilirubin mg/dl</td>
<td>5.6</td>
<td>5.67</td>
</tr>
<tr>
<td>Albumin mg/dl</td>
<td>2.39</td>
<td>2.6</td>
</tr>
<tr>
<td>Creatinine mg/dl</td>
<td>1.46</td>
<td>1.39</td>
</tr>
<tr>
<td>INR</td>
<td>2.02</td>
<td>1.95</td>
</tr>
<tr>
<td>S. ammonia</td>
<td>172 ± 46.1</td>
<td>191.7 ± 60.4</td>
</tr>
</tbody>
</table>

Blood ammonia. Requirement of renal replacement therapy and inotropic support, Upper GI scopy, Fresh Frozen Plasma support was also looked for in both groups. Patient outcome and response to treatment was assessed using these parameters, with respect to demographic factors, which drug they received, and adverse effects if any. Efficacy was graded as improved, unchanged or worsened. A decrease in HE index by at least 1 point was defined as improved and increment of HE index by one point or more was defined as worsened. The treatment duration was 7-15 days depending on the course and outcome.

Primary end points were decrease in HE index and reversal of HE grades. Secondary end points were mortality from HE or any other cause, decrease in mental status grade, asterixis grade, serum ammonia grade and NCT grade.

The Severity of Flapping Tremor

Severity was determined by extending the patients’ arms and forearms with the wrists dorsiflexed for at least 30 seconds. We adopted a simplified grading system to minimize inter-observer variance. Grade 0: no flapping motion; Grade 1: infrequent flapping motion; Grade 2: continual flapping motion; and Grade 3: unable to test.

Number Connection Test (NCT)

The time taken to connect 25 progressive numbers, i.e. part A of the number connection test. Grade 0: < 30 sec (normal); Grade 1: 31-50 sec; Grade 2: 51-80 sec; Grade 3: 81-120 sec; and Grade 4: > 120 sec.

Blood Ammonia Levels

Blood ammonia was measured before and after the treatment using Cobas Integra 800 (Roche, Basel, Switzerland). Grade 0: < 75 µM/L; Grade 1: 76-150 µM/L; Grade 2: 151-200 µM/L; Grade 3: 201-250 µM/L; and Grade 4: > 251 µM/L.

HE Index

HE index was calculated by (Grade of mental state) X 3 + Grade of Number connection test + Grade of Flapping tremor + Grade of blood ammonia. Requirement of renal replacement therapy and inotropic support, Upper GI scopy, Fresh Frozen Plasma support was also looked for in both groups. Patient outcome and response to treatment was assessed using these parameters, with respect to demographic factors, which drug they received, and adverse effects if any. Efficacy was graded as improved, unchanged or worsened. A decrease in HE index by at least 1 point was defined as improved and increment of HE index by one point or more was defined as worsened. The treatment duration was 7-15 days depending on the course and outcome.

Primary end points were decrease in HE index and reversal of HE grades. Secondary end points were mortality from HE or any other cause, decrease in mental status grade, asterixis grade, serum ammonia grade and NCT grade.

Statistical Analysis

Mean of mental status grades, Serum ammonia grades, NCT grade, flapping tremor grades, HE grade and HE index were calculated. To compare the change in grades post treatment, independent paired T test was used. To compare the change in mental status grade, Serum Ammonia grades, NCT grade, flapping tremor grades, HE index post-treatment in both the groups, multivariate analysis of variance test was applied. Fisher exact test was used to know the improvement in HE grades and HE index.

Results

A total of 74 patients, suffering from cirrhosis of liver and hepatic encephalopathy (HE) were screened. Of these 14 were excluded not fulfilling inclusion criteria. 60 patients were included.

Mean age was 50.8 yrs and S.D of 10.07. Male to female ratio was 6:5:1.

32 (53.33 %) patients received Rifaximin + Lactulose (R+L) group, and 28 (46.66%) patients received Lactulose only (L) group. Etiology of cirrhosis were, Alcoholic 60%, Alcoholic with hepatocellular carcinoma 1.7%, Alcoholic+HCV infection 1.7%, Cryptogenic 6.7%, HBV infection related cirrhosis 16.7%, HCV infection related cirrhosis 13.3% of patients. Out of 60 patients, 23 (38.33%) were in grade 2 hepatic encephalopathy, 29 (48.33%) were in grade 3 and 8 (13.33%) in grade 4 hepatic encephalopathy. Out of 60 patients, 46 had 1 st episode of hepatic encephalopathy and 14 had recurrent episodes. Out of 60 patients, 2 had child score grade A, 15 patients B, 43 patients C (Table 1).

6 (10%) patients needed inotropic support and 54 (90%) did not. In patients who needed inotropic support, 2 received Rifaximin + Lactulose combination and 4 patients received Lactulose only. 12 (20%) patients needed Fresh Frozen Plasma support and 48 (80%) did not require the same. In patients who received Fresh Frozen Plasma, 7 patients received Rifaximin + Lactulose and 5 patients received Lactulose. In Rifaximin + Lactulose group, 3 had loose motions, 2 had pain in abdomen. In Lactulose group 1 patient had pain in abdomen, 4 had loose motions.

Baseline hemogram, liver function test, renal function test, serum electrolytes, arterial ammonia were comparable in both groups.

Recovery of HE

HE grades improved in 31 out of 32 i.e. 96.87% in R+L group. In Lactulose group, it improved in 24 out of 28 patients, i.e. in 85.71%, p value 0.3251, which is (Table 3) not statistically significant. In our study, mental status grade improved from 1.81 to 0.22 (p=0.05) in R+L group and from 1.57 to 0.43 (p=0.05) in L group (Table 2); using independent paired T test. Asterixis grade improved from (Table 2) 2.13 to 0.16 (p=<0.05) in R+L group and
Table 2: Changes in HE index and related parameters post-treatment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rifaximin + Lactulose</th>
<th>Lactulose</th>
<th>P value</th>
<th>Rifaximin + Lactulose</th>
<th>Lactulose</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1</td>
<td>Day 3</td>
<td>Day 5 - 8</td>
<td></td>
<td>Day 1</td>
<td>Day 3</td>
</tr>
<tr>
<td>Blood ammonia level (mmol/L)</td>
<td>172.53</td>
<td>-</td>
<td>130.97</td>
<td>&lt;0.05</td>
<td>191.75</td>
<td>-</td>
</tr>
<tr>
<td>Ammonia grade</td>
<td>2.0</td>
<td>1.59</td>
<td>0.81</td>
<td>&lt;0.05</td>
<td>2.36</td>
<td>2</td>
</tr>
<tr>
<td>Mental status grade</td>
<td>1.81±0.64</td>
<td>0.91</td>
<td>0.22±0.6</td>
<td>&lt;0.05</td>
<td>1.57±0.69</td>
<td>0.82</td>
</tr>
<tr>
<td>Grade of flapping tremor</td>
<td>2.12</td>
<td>1.06</td>
<td>0.16</td>
<td>&lt;0.05</td>
<td>2.18</td>
<td>1.04</td>
</tr>
<tr>
<td>Grade of NCT</td>
<td>3.84</td>
<td>3.44</td>
<td>1.75</td>
<td>&lt;0.05</td>
<td>3.75</td>
<td>3.36</td>
</tr>
<tr>
<td>HE index</td>
<td>13.31</td>
<td>8.78</td>
<td>3.56</td>
<td>&lt;0.05</td>
<td>12.96</td>
<td>8.79</td>
</tr>
</tbody>
</table>

Table 3: Changes in HE index and HE grade

<table>
<thead>
<tr>
<th>Improvement in HE grades</th>
<th>Rifaximin + Lactulose</th>
<th>Lactulose</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement</td>
<td>31</td>
<td>24</td>
<td>0.325</td>
</tr>
<tr>
<td>HE index</td>
<td>31</td>
<td>24</td>
<td>0.325</td>
</tr>
<tr>
<td>Improved</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Unchanged</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Worsened</td>
<td>1</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

from 2.18 to 0.39 (p=<0.05) in L group after treatment. In our study, after applying independent t test, it showed that; NCT grade improved from 3.84 to 1.75 (p=<0.05) in R+L group and from 3.75 to 2.07 (p=<0.05) (Table 2) in L group after treatment. Serum Ammonia grade improved from 2 to 0.81 (p=<0.05) in R+L group and from 2.36 to 1.11 (p=<0.05) in L (Table 2) group after treatment. In our study, after applying independent t test, it showed that; HE index pretreatment was 13.31 and 12.96 in R+L group and L group, respectively. After treatment, HE index improved to 3.56 in R+L group and 4.86 in L group. P value being <0.05 in both cases (Table 2).

Improvement in HE Index After Treatment

In our study, hepatic encephalopathy index improved in 31 out of 32 i.e.96.87% in R+L group. In Lactulose group, it improved in 24 out of 28 patients, i.e. in 85.71%. After applying fisher exact test, it showed that there was no statistically significant difference in improvement of HE index in both groups after treatment, P value (2-tail) 0.3251 (Table 3). 6 patients expired and 54 patients survived. 2 deaths occurred in Rifaximin+ Lactulose group and 4 in Lactulose group.

Major causes of deaths were progressive hepatic encephalopathy, acute renal failure, hepatorenal syndrome, shock. Progressive hepatic encephalopathy accounted for 2 (33.33%) of deaths, hepatic encephalopathy +acute renal failure accounted for 1 (16.66%), hepatic encephalopathy +hepatorenal syndrome accounted for 2 (33.33%) of deaths, hepatic encephalopathy +shock due to hematemesis accounted for 1(16.66%) of deaths.

Adverse Effects

In Rifaximin + Lactulose combination group, loose motions occurred in 3(9.3%) patients, pain in abdomen in 2(6.2) patients. No serious adverse effects occurred in Rifaximin +Lactulose group. 27(84.5%) patients were free of any side effects. In Lactulose alone group, loose motions occurred in 4 (14.3%) patients, pain in abdomen in 1(3.6%) patient. No serious adverse effects occurred in this group. 23(82.1%) patients were free of any side effects. No patient withdrawn from the study due to an undue adverse effect. Frequency of adverse effects was same in both the groups.

Discussion

Rifaximin is an effective treatment of reversing HE. Several randomized controlled trails found Rifaximin to be at least as effective as current first line therapy in improving HE grades at a dose of 400 mg tds. A meta-analysis by Karim M Eltawil,17 published in World J Gastroenterol 2012, performed a systematic review and random effects meta-analysis of all eligible trials identified through electronic and manual searches. 7 studies that investigated the efficacy of rifaximin (n = 184) vs non-absorbable disaccharides (n = 165) revealed that both groups experienced either full resolution of HE or clinical improvement that was considered significant by the primary investigators without reaching statistical significance (OR = 1.92, 95% CI: 0.79-4.68, P = 0.15). Bucci et al9 also showed equal efficacy of rifaximin and lactulose, with better tolerability and lack of side effects with rifaximin. Paik et al10 reported that both rifaximin and lactulose were effective in the majority of patients (84.4% and 95.4%, respectively) with significant improvement in blood NH3, flapping tremor, mental status, and psychometric test. In a randomized trial by sharma et al.18 Comparing Rifaximin Plus Lactulose vs Lactulose Alone in treatment of Overt Hepatic Encephalopathy, 48 (76%) patients in group Rifaximin plus Lactulose compared with 25 (44%) patients in group who received Lactulose alone had complete reversal of HE (P=0.004) within 10 days. There was a significant decrease in mortality in the lactulose plus rifaximin group (15 (24%)) vs. lactulose alone (28 (49.1%), P<0.05).

In our study, mental status grade improved from 1.81 to 0.22 (p=<0.05) in R+L group and from 1.57 to 0.43 (p=<0.05) in L group; using independent paired t test (Table 2). But after applying multivariate analysis of variance test to compare the mental status grade between...
two groups on day 1, 3, 5-8, we found that the difference in the improvement in mental status in the two groups was not statistically significant; (p=0.191). In our study, Asterixis grade improved from 3.84 to 1.75 (p=0.05) in R+L group and from 3.75 to 2.07 (p=0.05) in L group after treatment. But after applying (Table 2) multivariate analysis of variance test to compare the Asterixis grade between two groups on day 1, 3, 5-8, we found that the difference in the improvement in Asterixis grade in the two groups was not statistically significant; (p=0.465). In our study, after applying independent t test, it showed that; NCT grade improved from 2.13 to 0.16 (p=0.05) in R+L group and from 2.18 to 0.39 (p<0.05) in L group after treatment. But after applying multivariate analysis of variance test to compare the Asterixis grade between two groups on day 1, 3, 5-8, we found that the difference in the improvement in Asterixis grade in the two groups was not statistically significant; (p=0.361). It showed that both the drug groups are equally effective in improving NCT grade after treatment. The combination of Rifaximin+Lactulose is not superior to Lactulose alone in improving NCT grade in patients of hepatic encephalopathy. In our study, after applying independent t test, it showed that; Serum Ammonia grade improved from 2 to 0.81 (p<0.05) in R+L group and from 2.36 to 1.11 (p<0.05) in L group after treatment (Table 2). But after applying multivariate analysis of variance test to compare the Serum Ammonia grade between two groups on day 1, 3, 5-8, we found that the difference in the improvement in Serum Ammonia grade in the two groups was not statistically significant; (p=0.417). After applying multivariate analysis of variance test to compare the HE index between two groups on day 1, 3, 5-8, we found that the difference in the improvement in HE index in the two groups was not statistically significant; (p=0.523). In our study, hepatic encephalopathy grade improved in 31 out of 32 i.e. 96.87% in R+L group. In Lactulose group, it improved in 24 out of 28 patients, i.e. in 85.71%. After applying Fisher exact test, it showed that there was no statistically significant difference in improvement of HE grade in both groups after treatment. P value (2 tail) 0.3251 Clinical efficacy was determined using HE index improvement (Table 3).

Rifaximin + Lactulose combination is effective in 31 out of 32 i.e.96.87% and Lactulose alone in 24 out of 28 patients, i.e. in 85.71%, which is not statistically different, p=0.3251.

So, we can conclude from the study that, Rifaximin + Lactulose combination is effective, but not superior to Lactulose alone in treatment of hepatic encephalopathy.

Conclusion

The drug groups, Rifaximin+ Lactulose combination and Lactulose are equally effective in treatment of hepatic encephalopathy. But the combination of Rifaximin+Lactulose is not superior to Lactulose in improving HE grades, HE index, Serum Ammonia and in treatment of hepatic encephalopathy. Adverse effects included pain in abdomen, diarrhea in few patients. Limitations of study are its non-randomized study, small sample size. Further such studies are required in future.

References

2. Gastroenterology and Hepatology Volume 7, Issue 4 April 2011 R. Todd Frederick, MD
Scrub Typhus - The Most Common Cause of Febrile Jaundice in a Tertiary Care Hospital of Himalayan State

Jatinter Mokta¹, Rahul Yadav², Kiran Mokta³, Prashant Panda⁴, Asha Ranjan⁵

Abstract

Background: Most common cause of jaundice in south east Asia is of infective etiology. Combination of fever with jaundice can cause diagnostic problem as this duo is present in many infective diseases. Timely diagnosis by simple laboratory investigations can save a lot of time and prevent morbidity and mortality. Our main aim was to determine the most common etiology of infectious jaundice in a tertiary care hospital of Himalayan state and to study their clinical profile.

Methodology: This was a prospective observational study done in one year. All the patients more than 18 years of age presenting with jaundice with bilirubin > 1.5mg/dl were taken. The clinical profile was observed and investigations for etiology were done.

Results: Total number of patients studied were 170. Maximum number of patients were 50 (39.4%) in age group less than 30 years and females outnumbered males with 1.8:1 ratio (64.7% v/s 35.3%). Fever was the most common presenting complaint in 127 (74.7%) patients and most common etiology was scrub typhus with 103 patients (60.6%) followed by hepatitis E in 36 patients (21.2%) and leptospirosis in 9 patients (5.3%).

Conclusion: scrub typhus is the commonest cause of febrile jaundice in Himachal Pradesh. The general physicians should be sensitized for the early diagnosis to reduce mortality.

Introduction

In southeast Asia region the common causes of jaundice of infective origin are Hepatitis A, B, C, E, dengue, leptospirosis and scrub typhus.¹ Timely diagnosis and treatment of these diseases become important by the fact that they are easily amenable to appropriate use of antibiotics, thus causing significant reduction in morbidity and mortality. Besides that, combination of fever and jaundice may cause diagnostic problems, especially in tropics where viral hepatitis, malaria and dengue are very common. Timely diagnosis by simple laboratory investigations can save a lot of time, which is important in this part of world as vast majority of people seek medical attention late in the course of disease.

Our main aim was to determine the most common etiology of infectious jaundice in a tertiary care hospital of Himalayan state and to study their clinical profile.

Editorial Viewpoint

• Infective jaundice is very common in Indian subcontinent.
• This study from Himachal Pradesh finds 60% of infective jaundice to be due to scrub typhus.

Material and Methods

This was a prospective study of one year (1st June 2012 to 31st May 2013) done in patients >18 years of age in Indira Gandhi Medical College, Shimla, Himachal Pradesh. All patients admitted with jaundice and had serum total bilirubin > 1.5 mg/dl were included. A detailed history of patients including working in field, exposure to domestic animals and exposure to scrub bush were noted. Their presenting complaints, age, sex, duration of fever, headache, nausea, vomiting, diarrhea, myalgia, dyspnea, travel history, sexual exposure, blood transfusion were noted. Routine biochemistry tests including RFTs, LFTs, blood sugar and complete hemogram were done. IgM ELISA was used for scrub typhus and leptospirosis. Rapid card tests

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Received: 11.08.2015; Accepted: 31.05.2017
Irritation
Meningeal
Pallor 4 (2.4) 0 4 (3.6)
SBP <90 15 (8.8) 3 (5) 12 (10.9)
Eschar 32 (18.8) 4 (6.7) 28 (25.5)
rate ≥20
Abdominal
Loose stool 16 (9.4) 1 (1.7) 15 (13.6)
Icterus 134 (78.8) 49 (81.7) 85 (77.3)
Examination
sensorium
Altered
Seizure 3 (1.8) 0 3 (2.7)
Nausea/
Dyspnea 52 (30.6) 8 (13.3) 44 (40)
Myalgia 85 (50) 21 (33.3) 64 (58.2)
>3 days 92 (54.1) 25 (41.7) 67 (60.9)
0-3 days 78 (45.9) 35 (58.3) 43 (39.1)
Fever
Urban 26 (15.3) 19 (31.7) 7 (6.4)
Rural 144 (84.7) 41 (68.3) 103 (93.6)
Background
Others 45 (26.5) 39 (65) 6 (5.5)
Farmer 28 (16.5) 20 (33.3) 8 (7.3)
Housewife 97 (57.1) 0 97 (87.3)
Occupation
Hepatitis B 3 (1.8) 3 (5) 0
Hepatitis A 7 (4.1) 3 (5) 4 (3.6)
Hepatitis C 0 0 0
Hepatitis E 36 (21.2) 25 (41.7) 11 (10)
Hepatitis B and C and for hepatitis A
and E standard immunoassay were
applied. For malaria, examination
of peripheral smear and rapid card
test based on P-LDH and HRP-2
antigen were done. Examination
and laboratory findings were
recorded and analyzed using Epi
info software.

Results

Total number of patients studied
were 170. In our study mean age was
38.76 ± 12.89 years with range from
18 to 75 years (Table 1). Maximum
number of patients were 50 (39.4%) in
age group less than 30 years, followed
by 45(26.5%) in age group
40-49 years. Females outnumbered
males with 1.8:1 ratio (64.7% v/s
40-49 years. Females outnumbered
40.9 ± 10.34
13.45

Table 1: Baseline characteristic of patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>All cases (n=170)</th>
<th>Men (n=60)</th>
<th>Women (n=110)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yrs.)</td>
<td>38.76 ± 12.89</td>
<td>38.5 ± 12.69</td>
<td>40.9 ± 10.34</td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Housewife</td>
<td>97 (57.1)</td>
<td>0</td>
<td>97 (87.3)</td>
</tr>
<tr>
<td>Farmer</td>
<td>28 (16.5)</td>
<td>20 (33.3)</td>
<td>8 (7.3)</td>
</tr>
<tr>
<td>Others</td>
<td>45 (26.5)</td>
<td>39 (65)</td>
<td>6 (5.5)</td>
</tr>
<tr>
<td>Background</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>144 (84.7)</td>
<td>41 (68.3)</td>
<td>103 (93.6)</td>
</tr>
<tr>
<td>Urban</td>
<td>26 (15.3)</td>
<td>19 (31.7)</td>
<td>7 (6.4)</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-3 days</td>
<td>78 (45.9)</td>
<td>35 (58.3)</td>
<td>43 (39.1)</td>
</tr>
<tr>
<td>&gt;3 days</td>
<td>92 (54.1)</td>
<td>25 (41.7)</td>
<td>67 (60.9)</td>
</tr>
<tr>
<td>Headache</td>
<td>72 (42.4)</td>
<td>14 (23.3)</td>
<td>58 (52.7)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>85 (50)</td>
<td>21 (35)</td>
<td>64 (58.2)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>52 (30.6)</td>
<td>8 (13.3)</td>
<td>44 (40)</td>
</tr>
<tr>
<td>Nausea/ Vomiting</td>
<td>72 (42.4)</td>
<td>24 (41.7)</td>
<td>47 (42.7)</td>
</tr>
<tr>
<td>Loose stool</td>
<td>16 (9.4)</td>
<td>1 (1.7)</td>
<td>15 (13.6)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>43 (25.3)</td>
<td>5 (8.3)</td>
<td>38 (34.6)</td>
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<tr>
<td>Seizure</td>
<td>3 (1.8)</td>
<td>0</td>
<td>3 (2.7)</td>
</tr>
<tr>
<td>Altered sensorium</td>
<td>24 (14.1)</td>
<td>5 (8.3)</td>
<td>19 (17.3)</td>
</tr>
<tr>
<td>Examination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Icterus</td>
<td>134 (78.8)</td>
<td>49 (81.7)</td>
<td>85 (77.3)</td>
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<tr>
<td>Respiratory rate ≥20</td>
<td>79 (46.5)</td>
<td>13 (21.7)</td>
<td>66 (60)</td>
</tr>
<tr>
<td>Eschar</td>
<td>32 (18.8)</td>
<td>4 (6.7)</td>
<td>28 (25.5)</td>
</tr>
<tr>
<td>SBP ≥90</td>
<td>15 (8.8)</td>
<td>3 (5)</td>
<td>12 (10.9)</td>
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<tr>
<td>Pallor</td>
<td>4 (2.4)</td>
<td>0</td>
<td>4 (3.6)</td>
</tr>
<tr>
<td>Meningeal irritation</td>
<td>3 (1.8)</td>
<td>0</td>
<td>3 (2.7)</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>7 (4.1)</td>
<td>5 (8.3)</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>23 (13.5)</td>
<td>1 (1.7)</td>
<td>22 (20)</td>
</tr>
<tr>
<td>Hepatomegaly + Splenomegaly</td>
<td>5 (2.9)</td>
<td>0</td>
<td>5 (4.5)</td>
</tr>
<tr>
<td>Ascitis</td>
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Table 2: Etiological agents

<table>
<thead>
<tr>
<th>Variable</th>
<th>All cases (n=170)</th>
<th>Men (n=60)</th>
<th>Women (n=110)</th>
</tr>
</thead>
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<tr>
<td>Hepatitis A</td>
<td>7 (4.1)</td>
<td>3 (5)</td>
<td>4 (3.6)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>3 (1.8)</td>
<td>3 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>0 0 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis E</td>
<td>36 (21.2)</td>
<td>25 (41.7)</td>
<td>11 (10)</td>
</tr>
<tr>
<td>Scrub typhus</td>
<td>103 (60.6)</td>
<td>16 (26.7)</td>
<td>87 (79.1)</td>
</tr>
<tr>
<td>Leptospirosis</td>
<td>9 (5.3)</td>
<td>4 (6.7)</td>
<td>5 (4.6)</td>
</tr>
<tr>
<td>Dengue</td>
<td>4 (2.4)</td>
<td>3 (5)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Malaria</td>
<td>8 (4.7)</td>
<td>6 (10)</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Enteric fever</td>
<td>0 0 0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
|                   | using immunochromatographic technique were used to detect Hepatitis B and C and for hepatitis A and E standard immunoassay were

Table 3: Organ dysfunction in patients with MODS

<table>
<thead>
<tr>
<th>Variable</th>
<th>All cases (n=170)</th>
<th>Men (n=60)</th>
<th>Women (n=110)</th>
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</thead>
<tbody>
<tr>
<td>ARDS + shock</td>
<td>17 (10)</td>
<td>2 (3.3)</td>
<td>15 (13.6)</td>
</tr>
<tr>
<td>ARDS + hepatic dysfunction</td>
<td>1 (0.6)</td>
<td>0</td>
<td>1 (0.9)</td>
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<tr>
<td>ARDS + renal dysfunction</td>
<td>1 (0.6)</td>
<td>1 (1.7)</td>
<td>0</td>
</tr>
<tr>
<td>ARDS + hepatic + renal dysfunction</td>
<td>1 (0.6)</td>
<td>0</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>ARDS + meningencephalitis</td>
<td>1 (0.6)</td>
<td>0</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>ARDS + shock + meningencephalitis</td>
<td>2 (1.17)</td>
<td>0</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Hepatic dysfunction + renal dysfunction</td>
<td>2 (1.17)</td>
<td>0</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Hepatic + renal dysfunction + shock</td>
<td>1 (0.6)</td>
<td>0</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>ARDS + shock + hepatic dysfunction</td>
<td>1 (0.6)</td>
<td>0</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>ARDS + shock + renal</td>
<td>2 (1.17)</td>
<td>1 (1.6)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>ARDS + shock + renal + hepatic dysfunction</td>
<td>1 (0.6)</td>
<td>0</td>
<td>1 (0.9)</td>
</tr>
</tbody>
</table>

Among patients of scrub typhus, most common presenting complaint was fever in 101 patients (98.0%), followed by headache 60 (58.2%), myalgia 58 (56.3%), shortness of breath 53 (51.4%) and abdominal pain in 40 (38.8%). On examination, icterus was found in 79 patients (76.6%), tachypnea 78 (75.7%), eschar in 32 (31.0%), hypotension in 31 (30.0%) and meningeal irritation in 3 patients (2.9%). Among 36 patients of Hepatitis E noted in our study, most common presenting complaint was nausea and vomiting in 22 patients (61.1%), followed by myalgias 9 (25%), and fever in 2 (5%) of patients. In general physical examination, icterus was present in 34 (94.4%) patients, while 7 (19.4%) patients had hepatomegaly. Among 9 patients of leptospirosis in our study, most common
presenting complaint was fever 9 (100%), followed by headache and myalgia 8 (88.8%), nausea and vomiting 4 (44.4%), altered sensorium 3 (33.3%) and shortness of breath 1 (11.1%) of patients. On examination, icterus, tachypnea and bilateral crackles were present in 2 (22.2%) patients each. ARDS was present in 2 (22.2%) patients. Among patients of scrub typhus, mean total bilirubin was 5.75 ± 4.37 mg% and mean conjugated bilirubin was 3.58 ± 3.13 mg%. Mean SGOT was 316.66 ± 660.97 IU/L and raised SGOT (>40 IU) was present in 102 (99%) patients. Mean SGPT was 212.64 ± 427.96 IU/L and raised SGPT was present in 97 (94.1%) patients. Mean ALP was 518.65 ± 458.18 IU/L. Hypoalbuminemia (<3 gm%) was present in 78 (75.7%) patients. Total 21 (12.4%) patients died out of which 18 were females and 3 males. Maximum mortality was in patients with scrub typhus.

**Discussion**

In our study mean age was 38.76 ± 12.89 years. Maximum number of patients were 50 (39.4%) in age group less than 30 years and only 10 patients in age group 60 and above (5.9%). The lower incidence of jaundice among elderly patients probably relates to the fact that they are not engaged in high risk behaviour like sexual exposure, alcoholism, travel and farming activities and moreover they are ignored in society. Incidence was more among females because females are more engaged in farming activities. Similar observations have been made in a Korean study done by Kweon et al.² Our study has shown a great seasonal pattern of distribution of cases which coincided with the distribution of cases of Scrub typhus. Among 103 cases of Scrub typhus, maximum were in the month of September 54 (52.1%), and October 41 (39.8%). 95.1% of cases of Scrub typhus had occurred in peak three months of rainy season.³⁴ Next important cause of infectious jaundice in our study was Hepatitis E. Maximum number of cases were noted in the month of November 13, followed by December 10 and October 4. This was probably due to outbreak of Hepatitis E noted around Shimla city during these months. Out of 9 cases of leptospirosis noted, 8 cases were during months of August, September and October. Thus, coinciding with monsoon and post monsoon season.³ Out of 8 cases of malaria, 5 were during July, August and September again, mainly during monsoon season. In our study fever was the most common presenting complaint in 127 (74.7%) patients, followed by myalgia 85 (50%), headache 72 (42.4%), nausea and vomiting 72 (42.4%), dyspnea 52 (30.6%), abdominal pain 43 (25.3%), altered sensorium 24 (14.1%), loose stool 16 (9.4%) and seizures in 3 (1.8%) patients respectively. These findings are comparable to most of the other studies on scrub typhus as most cases in our study comprises of those.⁶⁷ Among 36 patients of Hepatitis E noted in our study, most common presenting complaint was nausea and vomiting in 22 patients (61.1%), followed by myalgias 9 (25%), and fever in 2 (5%) of patients. In our study most common finding in general physical examination was icterus 134 (78.8%), tachypnea 79 (46.5%), eschar 32 (18.8%), hypotension 15 (8.8%), pallor 4 (2.4%) and meningeal irritation in 3 (1.8%) of patients. Among patients of scrub typhus, icterus was found in 79 patients (76.6%), tachypnea 78 (75.7%), eschar in 32 (31.0%), hypotension in 31 (30.0%) and meningeal irritation in 3 patients (2.9%). In a study conducted by Aung-Thau et al in Thailand,⁸ icterus was present in 35% of patients of scrub typhus. The mechanism of hepatic impairment is unknown so far. It might be direct invasion of Orientia tsutsugamushi and cellular immunity may be attributed to pathogenesis of hepatic injury.⁹ The higher incidence of icterus in our study is due to the fact that study population in our study included only patients having jaundice. In our study, only positive finding in general physical examination in viral hepatitis group was icterus. Splenomegaly was present in 1 patient of malaria. In our study 7 patients had isolated hepatomegaly, all of them were Hepatitis E positive. Among patients of scrub typhus, the mean total bilirubin was 7.12 ± 5.49 mg% and mean conjugated bilirubin was 4.92 ± 7.52 mg%. Raised SGOT (>40IU) was present in 102 (99.0%) of patients, with mean of 455.91 ± 790.69 IU/L. Raised SGPT (>40IU) was present in 97 (94.1%) of patients, with mean of 493.12± 811.39 IU/L. Hypoalbuminemia (<3 gm%) was present in 61 (59.2%) of patients. Mahajan et al¹⁰ has observed raised transaminase levels in 66.67% of patients. Hu M L et al¹¹ also reported similar finding in their study with increased AST levels in 81%, ALT 79% of patients. Most common cause of jaundice in our study was Scrub typhus 103 (60.6%), followed by Hepatitis E 36 (21.2%), Leptospirosis 9 (5.3%), Malaria 8 (4.7%), Hepatitis A 7 (4.1%), Dengue 4 (2.4%) and Hepatitis B 3 (1.8%). There were no cases of Enteric fever and Hepatitis C in our study.Highest number of cases of scrub typhus in our study relates to the endemicity of this disease in the state. Himachal Pradesh is a mountainous state in northern India, with the altitude of 350-7000 meters above mean sea level. During the rainy seasons, areas at lower altitudes experience average temperature between 20 to 35°C which is also suitable for the spread of arthropod vector. Unlike most of the other studies, in which Hepatitis E²¹,¹² was the predominant cause of jaundice, in our study it is the second most common cause after scrub typhus. This may not reflect the true pattern in community as it is a hospital based study and more admissions of patients of scrub typhus due to
Himachal Pradesh comes in non-endemic region for malaria due to its geographical conditions. Malaria is rare above height of 1800 metres from sea level. 4 cases of dengue were noted in our study, indicating low prevalence of dengue in the state. Unlike plains, rain water does not stagnate here, causing unfavourable conditions for the vector. There were 9 cases of leptospirosis, 7 cases of Hepatitis A and 3 cases of acute Hepatitis B in our study. There were no cases of Hepatitis C and enteric fever in our study. Studies have also described Hepatitis C viremia as a rare cause of sporadic acute viral hepatitis. 

Hepatitis C and enteric fever in our study. Conclusions in non-endemic region for malaria due to its geographical conditions. Malaria is rare above height of 1800 metres from sea level. 4 cases of dengue were noted in our study, indicating low prevalence of dengue in the state. Unlike plains, rain water does not stagnate here, causing unfavourable conditions for the vector. There were 9 cases of leptospirosis, 7 cases of Hepatitis A and 3 cases of acute Hepatitis B in our study. There were no cases of Hepatitis C and enteric fever in our study. Studies have also described Hepatitis C viremia as a rare cause of sporadic acute viral hepatitis. 10. Mahajan SK, Rolain Jean-Marc, Kashyap R, Bakshi D, Sharma V, Prasher BS, et al. Scrub typhus in Himalayas. Emerging Infectious Diseases 2010; 12:63-65.

References
Guiding Principles for the use of Fluroquinolones in Out-patient Community Settings of India: Panel Consensus

Agam Vora¹, K Krishnaprasad²

Abstract
Introduction: Respiratory tract infections have been an important cause of morbidity and mortality worldwide that is looming large especially in context of antibiotic resistance that is confronted both by a pulmonologist as well as a general practitioner. A reflection to this trend has been the rising phenomenon of MICs as shown the respiratory pathogens towards conventional antibiotics including macrolides or β lactam/β lactamase inhibitor combinations. Respiratory fluoroquinolones offer broad yet potent cover of respiratory pathogens leading to their obvious choice for empirical therapy for clinical persisters or high risk cases with prior history of antibiotics not-withstanding the clinical concerns in tropical countries.

Aim: To further assess the clinical role of respiratory quinolones in outpatient settings of India especially in line with the known endemicity of chronic infections or tuberculosis.

Method: Cross-sectional, national survey questionnaire survey to explore the clinical perceptions, attitude and insights on the clinical use of respiratory fluoroquinolones was rolled out amongst pulmonologists and consultant physicians practicing respiratory medicine in India. Descriptive statistics was utilized to describe the numerical and categorical data.

Results: Nationwide representative sample of fourteen pulmonologists provided response and clinical insight on the current management strategies for community acquired pneumonia (CAP) with ‘respiratory’ fluoroquinolones. Each of the doctor in the panel agreed that the ideal antibiotic for the treatment in CAP or lower respiratory tract infection (LRTI) should be highly effective with lesser side effects and broader spectrum covering atypical bacteria. Doctors agreed that most the fixed dose combination (FDC) has gone into disrepute probably because of pharmacokinetic incompatibility that could have further fuelled the epidemic of antibiotic resistance. 9 (64%) doctors suggested that there is omnipresence if not overwhelming presence of patient poor response to beta-lactam or fluoroquinolones in clinical practice. It was agreed that fluoroquinolones would be the rightful choice for patients with prior history of antibiotic use with or without comorbidities. Amongst the newer fluoroquinolones available, Garenoxacin offers broad and potent action against resistant strains for CAP. Despite the overwhelming concern of tropical infection in Indian context, Garenoxacin could be considered for mono- or add-on therapy in moderate to severe yet stable cases of CAP. Short course therapy of 5 to 10 days should offer no complimentary masking of anti-mycobacterial activity since the relevant minimum inhibitory concentration (MIC₉₀) are high that are beyond the comprehension of suggested therapeutic dose of 400 mg tablets.

Conclusion: The growing incidence of Macrolide resistance suggests the clinical role of new generation fluoroquinolones including Garenoxacin as a clinically useful therapeutic strategy for moderate to severe CAP as monotherapy or in combination.

Introduction
Respiratory tract infections have been an important cause of morbidity and mortality worldwide that is looming large especially in context of antibiotic resistance. A reflection to this trend has been the rising phenomenon of MICs as shown by the respiratory pathogens towards conventional antibiotics including macrolides or β lactam/β lactamase inhibitor combinations. Again despite the availability of

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above agents, community acquired pneumonia (CAP) continues to remain as a leading cause of death.\(^1\) The mortality rate of the pneumonia patient in outpatient setting is low, in the range of 1-5%, but amongst patient who require admission to intensive care unit (ICU) it approaches 25%.\(^2\) Streptococcus pneumonia (S. pneumonia) is the common pathogen causing CAP and is associated with the greatest morbidity and mortality.\(^3\) Similarly, the high rates of macrolide-resistant \(M.\) pneumoniae reported in China (>90%) and Japan (87.1%) has limited the available therapeutic options while managing CAP empirically.\(^4\)

The successive generation of Quinolones introduced after 1962 have offered improved coverage of gram-positive and atypical pathogens. The fluoroquinolones for treatment of respiratory diseases, including gatifloxacin, moxifloxacin, and levofloxacin, have been the representative examples in this direction. The rate of fluoroquinolone-resistant \(pneumococcus\) infection is < 3% in most countries.\(^5,6\) As a result, the fluoroquinolones for treatment of respiratory diseases have been recommended and are increasingly being used as preferred or alternative therapy for the treatment of CAP.\(^7\) Amongst the new generation fluoroquinolones, Moxifloxacin and Garenoxacin offer broad and potent coverage of gram +ve, gram –ve, atypical and anerobic pathogens offering relevant therapeutic action in community acquired RTIs. Unlike other conventional fluoroquinolones, Garenoxacin shows negligible incidence of gastrointestinal, central nervous system and cardiovascular complications including QTc prolongation or Torsades pointes.\(^8,9\)

**Method**

A nationwide representative sample of fourteen pulmonologists provided responses to a standardized questionnaire with relevant insights and insights on the current management strategies of CAP with respiratory fluoroquinolones. The responses related to following items on the questionnaire, including:

a. Clinical challenges in the management in Community acquired pneumonia.

b. Likely risk factors or contributing mechanism for antibiotic resistances: FDC and rising resistance.

c. Feature of ideal Antibiotic in treating CAP.

d. Clinical perceptions on fluoroquinolones in RTI.

e. Role of respiratory fluoroquinolones in CAP.

**Results**

**What was the clinical challenges in the management in Community acquired pneumonia (CAP)?**

**Panel Consensus:** Despite substantial progress in therapeutic options, CAP remains a significant cause of morbidity and death. There exists a major controversy concerning the antimicrobial management of this infection.\(^10\) The mixed etiology and the changing susceptibility of pathogens causing CAP particularly with that of Streptococcus pneumoniae has created a circumstantial challenge to clinicians regarding appropriate therapeutic approaches in terms of optimal patient outcome.\(^11\) Normally empirical antimicrobial therapy is initiated before bacterial cause is determined which may continue due to lack of reliable microbiological data. An understanding of the possible pathogens and resistance patterns is helpful in guiding antibiotic choice. A detailed knowledge of the local susceptibility of the potential pathogens ensures an appropriate selection of the antimicrobial agent to be used. The panel agreed that managing CAP is a difficult task as doctor has to consider the severity of the disease, bacterial resistance to antibiotic and the cost of the therapy. The panel suggested that owing to the increased incidence of \(Streptococcus Pneumoniae\) resistance to macrolides, treating patients without laboratory finding is a big gamble towards developing antibiotic resistance.

**Which are the likely risk or contributing factors for mechanism for Antibiotic resistances?**

**Panel Consensus:** Of the respiratory pathogens, penicillin-resistant \(Streptococcus Pneumoniae\) (PRSP) has attracted the greatest interest. PRSP is a widespread problem, with rates of resistance ranging from 5% to 80% in various parts of the world.\(^12\) Panel discussed the probable mechanism for antibiotic resistance. The principal mechanism of penicillin resistance to beta-lactams in \(Streptococcus Pneumoniae\) is the production of altered penicillin-binding proteins (PBPs). Two main discussed mechanisms of macrolide resistance in \(Streptococcus Pneumoniae\) were ribosomal methylase, referred to as an MLSB-type resistance mechanism, and a macrolide efflux pump. The development of reduced susceptibility to fluoroquinolones in \(Streptococcus Pneumoniae\) due to presence of \(parC\) and \(gyrA\) mutations, especially in combination, was found to be a major contributing factor for high-level resistance. Efflux probably plays a lesser role in reduced susceptibility to some newer fluoroquinolones. Panel also discussed the risk factors for infection with PRSP strains include young age, day-care center attendance, prior administration of antimicrobial agents, and severe underlying diseases. As the use of nonpenicillin antimicrobials has increased, so has the development of resistance to these agents among \(Streptococcus Pneumoniae\). Worldwide rate of macrolide resistance has risen dramatically in recent years. The prevalence of resistance is highly variable between countries, range
starting from 70%.\textsuperscript{13,14} Emergence of Streptococcus Pneumoniae with reduced susceptibility to quinolones has also been reported in England and US.\textsuperscript{15} However, the worldwide incidence of quinolone resistance is currently low (<1%).\textsuperscript{16} Panel discussed that due to irrational antibiotic use in recent years, stringent actions were taken to restrict FDC use that led to restricted resources available to doctors for treating CAP. Due to rising antibiotic resistance and limited resources of classical FDC, there was a major concern to select appropriate antibiotic without risking development of antibiotic resistance.

**What would be an ideal feature of an Antibiotic in treating Community acquired pneumonia?**

Panel Consensus: Panel debated a study conducted in India which showed 4% total resistance to penicillin and 10% intermediate resistance, suggesting the increase in emergence of resistance strains of S. pneumonia in India.\textsuperscript{17} Panel also discussed a three-year surveillance study\textsuperscript{18} for penicillin resistance from Vellore that revealed 4.6% of intermediate resistance to penicillin, whereas, a study conducted in north India\textsuperscript{19} reported 15.2% (26/170) intermediate resistance and 2.3% (4/170) penicillin resistance. The difference in the resistance pattern of S. pneumoniae as observed in South and North Indian studies has been explained by Lalitha et al,\textsuperscript{20} on the basis of the high genetic diversity that exists among strains isolated from different geographical areas within India making it difficult to choose appropriate antibiotic for the treatment of CAP and recent stringent action taken against fixed dose combination due to pharmacokinetic incompatibility that could have further fuelled the epidemic of antibiotic resistances making it more difficult for the doctors to treat CAP. Panel suggested that treating CAP would be a big challenge and they would look out for an ideal antibiotic which will be highly effective with lesser side effect with broader spectrum covering atypical bacteria without causing antibiotic resistance.

**What is clinical perceptions on fluoroquinolones in RTI?**

Panel Consensus: Panel suggested that there is a good pharmacological and clinical evidence to support the use of respiratory fluoroquinolones in CAP. Their favorable pharmacokinetic and pharmacodynamic profiles result in good penetration of respiratory tissues. The broad antibacterial activity of respiratory fluoroquinolones provides excellent coverage of the major CAP-causing pathogens, including penicillin- and macrolide-resistant S. pneumoniae. A meta-analysis of 23 clinical trials showed that pneumonia was cured or improved in significantly more patients treated with fluoroquinolones than those treated with macrolide or beta-lactam antibiotics.\textsuperscript{21} Fluoroquinolones were also more effective than macrolides with or without beta-lactams for patients with severe pneumonia, those who were hospitalized and those who required intravenous therapy.\textsuperscript{22}

Panel discussed that fluoroquinolones are generally recommended in different management guidelines for use in CAP, i.e., pneumonia in immunocompetent subjects arising outside of the hospital such as The Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS) consensus guidelines. The European Respiratory Society (ERS) and European Society for Clinical Microbiology and Infectious Diseases (ESCMID) guidelines recommend that a fluoroquinolone is as effective as macrolide/beta-lactam combination particularly for patients with comorbid conditions or repeated infections in the last three months.\textsuperscript{23} Importantly, non-adherence to CAP treatment guidelines is a significant risk factor for treatment failure and mortality.\textsuperscript{24}

**Is there a role of Respiratory fluoroquinolones in community acquired pneumonia?**

Panel Consensus: Literature review suggests evolving documentation of antibiotic resistance amongst gm+ve pathogens exposed to fluoroquinolones. A prospective study\textsuperscript{25} of eleven Asian countries from 2000-01 cited Ciprofloxacin resistances in 6% of isolates; whereas fluoroquinolones resistances was highest in Hong Kong (11.8% to Ciprofloxacin and 8% to Levofloxacin) which concluded that there is resistance getting developed for Ciprofloxacin and Levofloxacin. Whereas in China 6.8% of 192 pneumococcal isolates were resistant to Levofloxacin and 4.2% were resistant to Moxifloxacin. Panel concluded that factors influencing fluoroquinolones are complex and frequency of resistance depends on the type of mutation and preferential binding site of the fluoroquinolones driving the transformation. Fluoroquinolones like Levofloxacin and Moxifloxacin preferentially bind with either topoisomerase IV or DNA gyrase respectively. Panel agreed that there is need of newer agents that would resist resistance development.

Despite the availability of fluoroquinolones i.e Levofloxacin and Moxifloxacin, their clinical use has been limited due to the considerations of tuberculosis in tropical countries including India. There is therefore a need of newer quinolones to be considered in the treatment of CAP. Panel suggested that Garenoxacin should be consider due to its unique structure compare to other fluoroquinolones and it should be called as des-fluoroquinolones. Panel agreed that Garenoxacin unique structure which offers an add-on advantage when compared with other fluoroquinolones such as lower MIC\textsuperscript{90} and higher AUC/MIC\textsuperscript{90} ratio governing higher potency and
killing power, lower susceptibility to efflux, and resistance mechanisms against prevailing respiratory Gram-positive/negative and atypical pathogens including Streptococcus pneumoniae. In a study conducted by Takagi H. et al.20 showed that Garenoxacin bacteriological eradication rates for S. pneumonia was effective for most of the resistant strains including quinolone resistant strain. Regarding the concern of Garenoxacin in mycobacterium tuberculosis about the in vitro susceptibility to mycobacterium tuberculosis being on the higher side and MIC 90 being 4 µg/ml along with lower sputum concentration as compared to plasma,21 the panel agreed that the lower penetration of Garenoxacin in sputum coupled with lower kill ratio or Cmax/MIC against mycobacterium tuberculosis would on the contrary, not mask the diagnosis or subjudice the therapeutic response by selection pressure for mutants.

The panel concluded that the treatment of CAP is incomplete without des fluoroquinolone (Garenoxacin) as a monotherapy or as add on therapy. Garenoxacin can be given as an oral therapy in Mild to severe CAP. Garenoxacin can be used in OPD to hospital settings. It can be prescribed across age group (young adult to geriatric) with or without comorbidities. Garenoxacin therefore overcomes the limitations for classical or traditional FDC combination and can be suggested as a useful therapeutic strategy for moderate to severe CAP as monotherapy or in combination.

Acknowledgements

CLASS Panel - Dr. Agam Vora, Dr. B.M. Prasad, Dr. Ketan Mehta, Dr. V.K. Singh, Dr. Tejinder Pal Singh, Dr. R. Paul, Dr. Ramesh Sahoo, Dr. Bijay Satapathy, Dr. Shashank Gupta, Dr. Raghu Janardhan, Dr. Rajesh Atal, Dr. Manoj Sharma, Dr. N. Balaji, Dr. V. Valayudhan, Dr. Krishnaprasad K. The authors would also like to acknowledge Dr. Ameet Rathod, Dr. Pramod Katke, Ms. Nilofer Allarakha and Mr. Akshay Mahaputra for the logistic support in collation and analyses of the results.

References

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- **2 mg**
  - Metformin HCl 500 mg SR + Glimperide 2 mg + Voglibose 0.2 mg

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**Glycomet® Trio Forte**
- **2 mg**
  - Metformin HCl 1000 mg SR + Glimperide 2 mg + Voglibose 0.2 mg

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References:

For the avoidance of doubt, the advice given is that of the Hospital Laboratory.

1. **Flunarizine 5/10mg**

2. **Flunarizine 5/10mg**

3. **Flunarizine 5/10mg**

4. **Flunarizine 5/10mg**

5. **Flunarizine 5/10mg**
Epidemiology of Depression and its Relationship to Diabetes in India

Subramani Poongothai1, Ranjit Mohan Anjana2, Shankar Radha3, Balasundaram Bhavani Sundari4, Coimbatore Subramanyam Shanthi Rani5, Viswanathan Mohan6

Abstract
Depression is one of the most common chronic mental illnesses globally and in India. It has been reported that depression is twice as common in individuals with type 2 diabetes. The prevalence of both depression and type 2 diabetes are rapidly increasing. This article reviews the prevalence of depression in the general population as well as in patients with type 2 diabetes and its complications with special reference to recent data from India. It also makes a case for screening for depression in diabetes clinics and integrating depression treatment with diabetes care in order to make the treatment more holistic.

Introduction
The World Health Organization (WHO) ranked depression as the fourth most common disease in 1990, after lower respiratory tract infections, diarrheal diseases and perinatal infections.1 Depression is expected to be the second most common disease by 2020 and to account for 15 percent of the disease burden in the world. Depression is currently estimated to affect 340 million people globally.1 Depression is also a leading cause of disability, workplace absenteeism, decreased productivity and high suicide rates.2

The rising burden of non-communicable diseases (NCDs) like diabetes, hypertension, obesity, cardiovascular disease, cancer and mental illness, especially depression have been amongst the major health transitions that has been witnessed in the second half of the twentieth century. Depression is a mood disorder diagnosed by depressed mood, guilt feeling, decrease in appetite, thinking about death and suicide, insomnia, fatigue and loss of energy, considerable weight loss and loss of function.3

India is home to the second largest number of adults with diabetes worldwide, after China.4 It also has a large number of people with depression. In this article, we try to look at the prevalence of depression in the general population and in people with type 2 diabetes with and without diabetes related complications. Finally we make a case for integrating depression with diabetes care in specialized diabetes centers in India.

Prevalence of Depression
International studies
The occurrence of depression is associated with factors such as age, marital status, social class, and social conditions.5 Depression is one of the most prevalent psychiatric conditions in later life.6 In the Mini Finland Health Survey7 the association between the prevalence of depression and age was clearly more significant in women than in men. In this study, marital status was associated with the occurrence of depression; the prevalence of depression was higher among widowed and divorced persons and the prevalence of depression increased with decreasing social class. The prevalence of depression was higher among women and this may be attributed to a type of depression associated with somatic symptoms such as changes in appetite, sleep disturbances and fatigue accompanied by pain and anxiety.8 In the developed countries, depression is the most common psychiatric disorder, ranging from 10 to 37.7% as reported in various studies. Table 1 compares the prevalence of depression globally. In developing countries, 10–44% are reported to suffer from depression and anxiety disorders and an

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Table 1: Studies on prevalence of depression in population based studies – International studies

<table>
<thead>
<tr>
<th>Author / Year</th>
<th>Place</th>
<th>Total subjects</th>
<th>Age (years)</th>
<th>Diagnostic criteria</th>
<th>Population</th>
<th>Method of survey</th>
<th>Prevalence of depression (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovuga et al, 2005</td>
<td>Adjumani and Bugiri [Uganda]</td>
<td>939</td>
<td>18</td>
<td>13 item Beck Depression Inventory (BDI)</td>
<td>Rural population</td>
<td>Structured interview</td>
<td>17.4</td>
</tr>
<tr>
<td>Vasiliadis et al, 2007</td>
<td>Canada and USA</td>
<td>3,505</td>
<td>&gt;18</td>
<td>Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)</td>
<td>In and out patient population</td>
<td>Telephone survey</td>
<td>8.2</td>
</tr>
<tr>
<td>DM Ndetri, et al, 2009</td>
<td>Kenya</td>
<td>2770</td>
<td>&gt;18</td>
<td>BDI</td>
<td>Out patient population</td>
<td>Interviews</td>
<td>41%</td>
</tr>
<tr>
<td>Pouwer et al, 2010</td>
<td>Netherlands</td>
<td>772</td>
<td>29-74</td>
<td>CIDI and CESD-16</td>
<td>Out patient population</td>
<td>Self-report measures of depression and a diagnostic interview</td>
<td>32.9%</td>
</tr>
<tr>
<td>Dirmaier et al, 2010</td>
<td>Germany</td>
<td>866</td>
<td>57-77</td>
<td>DSQ score</td>
<td>Primary care center</td>
<td>Standardized assessment, including questionnaires for patients and the physician and diagnostic screening measures</td>
<td>MDE-11.8% Minor-20.7%</td>
</tr>
<tr>
<td>Agbir et al, 2010</td>
<td>Nigeria</td>
<td>160</td>
<td>20-99</td>
<td>Structured Clinical Interview for DSM-IV axis I disorder (SCID) Hamilton Rating Scale for Depression (HDRS)</td>
<td>Out patient population</td>
<td>Interview by psychiatrist</td>
<td>19.4%</td>
</tr>
<tr>
<td>Yu et al, 2010</td>
<td>China</td>
<td>100</td>
<td>49±11</td>
<td>Self-Rating Depression Scale (SDS)</td>
<td>Out patient population</td>
<td>Self-reported</td>
<td>28%</td>
</tr>
<tr>
<td>Trento et al, 2011</td>
<td>Italy</td>
<td>459</td>
<td>40-80</td>
<td>Zung self-rating depression scale</td>
<td>Out patient population</td>
<td>Self-reported Questionnaire</td>
<td>14.1%</td>
</tr>
<tr>
<td>Tovilla – Zarate et al, 2012</td>
<td>Mexico</td>
<td>458</td>
<td>18-80</td>
<td>Hamilton Rating Scale of depression (HAM-D)</td>
<td>Out patient population</td>
<td>Interview by psychologist / nurse</td>
<td>48.3%</td>
</tr>
</tbody>
</table>

estimated 50.8 million people suffer from major depression. The prevalence of depression is steadily increasing and is expected to move to the 1st place with reference to global burden of disease by 2030 as predicted by World Health Organization.

Indian studies

The prevalence of depression is high, both in urban and rural India. In a cross-cultural study conducted by WHO at 14 sites, the most common diagnosis in primary care settings was depression. Earlier Indian studies have reported prevalence of depression varying from 21-83% in primary care settings. However as these are all clinic based studies, they are subject to various degrees of referral bias.

A study conducted in Goa on postnatal depression in India has shown that the prevalence of depression was 23%, economic deprivation and poor marital relationships were the important risk factors for the occurrence and chronic nature of depression. The prevalence of depression in Dharwad district, Karnataka was reported to be high at 29.3%, while in a rural population of Ahmednagar, Maharashtra, it was even higher - 31.4%. The prevalence of depression was high (39.0%) among the elderly in Surat city and it was observed that several important socio-demographic variables had shown a significant association with depression in the elderly. A large population-based study which involved 26,001 subjects in urban South Indians called the “Chennai Urban Rural Epidemiology Study (CURES)” also looked at the prevalence of depression in Chennai city in South India. The study showed that the overall prevalence of depression in Chennai was 15.1%. Female gender, age, low socio-economic status, lack of education and marital factors were associated with depression in this population. Studies done in an elderly community in Vellore, South India reported that the prevalence of depression was 12.7%. Such wide variations in prevalence of depression could be attributed to the different methods of assessing depression and the different populations studied.

There are many studies which have looked at the association of depression with the socio-economic status. A study by Shidhaye done on 5703 women with mental disorders showed that socio-economic factors were independently associated with common mental disorders.

Nair et al studied the prevalence of depression aiming geriatric subjects in Raichur and found that prevalence of depression was very high. Moreover it was associated with substance abuse, unemployment, disrupted mental status, illiteracy and lower
Table 2: Studies on prevalence of depression in population based studies – National studies

<table>
<thead>
<tr>
<th>Author / Year</th>
<th>Place</th>
<th>Total subjects</th>
<th>Age (yrs)</th>
<th>Diagnostic Criteria</th>
<th>Population</th>
<th>Method of Survey</th>
<th>Prevalence of depression (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biswas et al, 2009</td>
<td>Vellore</td>
<td>204</td>
<td>&gt; 60</td>
<td>(CIS-R), a Revised Clinical</td>
<td>Elderly population</td>
<td>Door to door survey</td>
<td>31.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Interview Schedule</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poongothai et al, 2009</td>
<td>Chennai</td>
<td>25,455</td>
<td>&gt; 20</td>
<td>Modified Patient Health</td>
<td>Representative sample of chennai city</td>
<td>Interview – Door to Door survey</td>
<td>15.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Questionnaire (PHQ-12 item)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joseph et al, 2013</td>
<td>Karnataka</td>
<td>230</td>
<td></td>
<td>PHQ – 9</td>
<td>Clinic population</td>
<td>Interview based</td>
<td>45.2</td>
</tr>
<tr>
<td>Jain et al, 2015</td>
<td>Jaipur</td>
<td>100/100</td>
<td>18-70</td>
<td>PHQ – 9</td>
<td>Clinic population</td>
<td>Self-reported</td>
<td>53</td>
</tr>
<tr>
<td>Kulikarni et al, 2014</td>
<td>Karnataka</td>
<td>100</td>
<td>25-65</td>
<td>PHQ – 9</td>
<td>Clinic population</td>
<td>Interview based</td>
<td>29.1</td>
</tr>
<tr>
<td>Poongothai et al, 2015</td>
<td>Punjab</td>
<td>290</td>
<td>60&gt;80</td>
<td>Geriatric Depression Scale</td>
<td>Cross sectional study</td>
<td>Interview method - semi-structured questionnaire</td>
<td>Urban –10.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(GDS short version)</td>
<td></td>
<td></td>
<td>Rural –7.3</td>
</tr>
</tbody>
</table>

Table 3: Studies on prevalence of depression in special population in India

<table>
<thead>
<tr>
<th>Author / Year</th>
<th>Population</th>
<th>Set up</th>
<th>Location</th>
<th>Prevalence of depression (%)</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patel et al</td>
<td>Women</td>
<td>Clinic population</td>
<td>Goa</td>
<td>23</td>
<td>2002</td>
</tr>
<tr>
<td>Pillai et al</td>
<td>Adolescents</td>
<td>Rural population (school children)</td>
<td>Goa</td>
<td>0.5</td>
<td>2008</td>
</tr>
<tr>
<td>Nair et al</td>
<td>Adolescents</td>
<td>Rural population (school children)</td>
<td>Kerala</td>
<td>11.2 (school dropouts) 3 (school going)</td>
<td>2009</td>
</tr>
<tr>
<td>Barua et al</td>
<td>Elderly</td>
<td>Rural population (medical students)</td>
<td>Karnataka</td>
<td>21.7</td>
<td>2010</td>
</tr>
<tr>
<td>David et al</td>
<td>Adolescents</td>
<td>Clinic population</td>
<td>Hyderabad</td>
<td>11.7</td>
<td>2012</td>
</tr>
</tbody>
</table>

A study done in Kolkata by Neelanjana Paul found the depressed subjects were significantly older, had less education, belonged to lower socioeconomic status, and had greater cognitive impairment and disability. Education was found to have a protective role.

Table 2 compares the prevalence of depression obtained from India. It can be seen that the estimates on prevalence of depression vary widely in different populations. This could be attributed to different ethnicity and demography of the study populations and/or different diagnostic criteria and study instruments employed.

Table 3 shows the prevalence of depression in special populations i.e. elderly, adolescence and women in India. It is interesting to note that the prevalence of depression in elderly in Chennai is higher in both urban and rural compared to Kerala and Punjab. Also it is found that the prevalence is higher in rural areas compared to urban areas of Tamil Nadu.

Prevalence of Depression and Diabetes

The connection between depression and type 2 diabetes was recognized as early as in the 17th century. Today, depression and type 2 diabetes have become a great global challenge. Several studies have shown that depression is associated with type 2 diabetes; however, the direction of the relationship is unclear. In addition to depression being a consequence of type 2 diabetes, depression may also be a risk factor, or a triggering factor, for the onset of type 2 diabetes. Thus there appears to be a bidirectional relationship between type 2 diabetes and depression. This was confirmed by a recent study by Golden and colleagues, in which they found that diabetic individuals without depressive symptoms at baseline had higher odds of developing depressive symptoms during the follow-up period.

Conversely, even during routine screening, those with depression seem to have a higher prevalence of undiagnosed diabetes and pre-diabetes where the depression was clearly not produced by their glucose intolerance status as they are totally asymptomatic. 65% of the increased risk of diabetes mellitus is attributed to be due to depression in some studies.

It is found that only less than one third of the patients received depression screening to assess the depressive symptoms in a case control study. People with depression and diabetes should be adequately treated counseled as this can potentially result in improvement of psychological and medical outcomes. This would be the first step towards improved treatment of depression in people with diabetes. It is therefore heartening that recent diabetes guidelines recommended routine screening for depression in people with diabetes.

People with diabetes and depression are at greater risk of disability, reduced work productivity and lower quality of life. They are also at greater risk of death, as shown in a study that found the coexistence of diabetes and depression is associated with significantly higher risk of death, beyond that due to having either diabetes or depression alone.

International studies

An Ethiopian study demonstrated that depression is a common health problem in type 2 diabetic...
outpatients with a prevalence rate of 13%. In Jamaica, Wilks et al found that diabetes mellitus was more prevalent among those with symptoms of depression. A Trinidad study reported a prevalence of 17.9% among subjects with type 2 diabetes. In a study done in Nigeria, the prevalence of depression among T2DM was 30% while in Bangladesh, a prevalence of 34% was reported.

It was reported by the World Health Study, the prevalence of depression in diabetes was 2% in adults aged 18 years and above, in 60 different countries over the period of one year. Studies by de Groot et al showed that depression was significantly associated with a wide range of diabetes complications. The overall prevalence of depression in diabetes was reported to vary from 8.5% to 27.3%.

**Indian studies**

Madhu et al reported the prevalence of depression to be 49% amongst subjects with diabetes in Trivandrum, India. The predictors of depression were found to be female gender, elevated fasting blood sugar level, physical disability and lack of physician’s advice regarding lifestyle modifications.

Ranjan Das et al showed that in West Bengal, the prevalence of depression was 46.2% and reported that the presence of depression in type 2 diabetes further deteriorates the quality of life of the patients. Therefore, it is reasonable to assume that treating depression would have a beneficial effect on the quality of life. Naseer Ali et al found the prevalence of depression was 27.0% amongst diabetic subjects and 11.1% amongst healthy controls, in New Delhi.

Siddiqui et al found that there is a higher prevalence of depression in patients with type 2 diabetes was almost twice as high compared to those without diabetes (35.4% vs 20%; p=0.006) in Delhi and suggested that assessment of depression should be performed as part of the routine practice in India as persons with type 2 diabetes are at higher risk of developing depression.

In the CURES study, 25,286 subjects in whom fasting capillary glucose estimation was available were assessed for depression, using a self-reported and previously validated instrument. Depression was studied in relation to the different stages of glucose intolerance. It can be seen that the prevalence of depression was highest among known diabetic subjects (30.2%) followed by the newly diagnosed diabetes (19.7%), impaired fasting glucose (15.5%) and lowest among normal fasting glucose subjects (13.8%) and the trend was significant (p<0.001) (Figure 1). Thus it is clear that the prevalence of depression increases with greater degrees of glucose intolerance.

According to the National Institute of Mental Health, depression has a more serious progression in persons with diabetes, is linked to a higher rate of depression relapse, is associated with more diabetes-related medical complications, and engenders higher healthcare costs than depression in persons without diabetes. Earlier studies have examined the association of depression with micro- and macro vascular complications of diabetes and there is evidence to suggest that the long-term complications of diabetes are associated with depressive symptoms.

The majority of studies on the association between depression and diabetic complications have been cross sectional. However, prospective studies have shown that depression is associated with a higher and more rapid incidence of diabetic complications.

The prevalence of depression was significantly higher among diabetic subjects with DR (35.0% vs 21.1%, p<0.001), neuropathy (28.4% vs 15.9%, p=0.023), nephropathy (35.6% vs 24.5%, p=0.04) and PVD (48.0% vs 27.4%, p<0.001) as compared to subjects without these complications. The CURES study demonstrated that all the microvascular complications and macrovascular complications are associated with the depression even after adjusting for confounding factors.

The CURES study also found that the risk of depression was significantly higher in those on insulin (OR: 1.9, p=0.037) compared to diet only group while the odds
ratio for depression in subjects treated with OHA was 1.3 (p=0.210) compared to those who were on diet only regimen (Figure 2). This is understandable as taking insulin is associated with depression in some people. Alternatively, those treated with insulin or OHA may be more symptomatic because of more severe disease or may have one or more complications because of which, many physicians put them on insulin in the first place.

Studies have shown a significant relationship between depression and poor adherence to self-management guidelines, which is confirmed by the higher rate of diabetes complications among those who have depression. People with diabetes therefore need to successfully manage their disease to avoid complications.

Epidemiologic evidence of an association between atherosclerosis and depression in the general population is lacking and most earlier studies have been performed in patients with preexisting vascular. These studies show high risk of comorbid depression on survival after a cardiovascular event. There are only few studies which have looked at the association of depressive disorders and atherosclerosis. The CURES Study looked at the relationship between two measures of atherosclerosis, structural (intima-media thickness) and functional (augmentation index) and depressive disorders in an urban south Indian population. The prevalence of depression in subjects with normal IMT (<1.0 mm) was 16.2% compared to 30.4% in subjects with increased IMT (≥ 1.0 mm, p=0.013). This study shows that depression is associated with IMT, an early atherosclerotic marker in Asian Indians, a population with a high prevalence of premature CAD.

Figure 3 shows the association of depression and type 2 diabetes. Depression and diabetes are both chronic and complex disorders. Hence there is a need to find solutions step towards clinical- and self-care for these conditions. Both behavioral activation and motivation are critical for adherence to management plans in both conditions. Unfortunately this is hampered by major barriers like stigma at the patient level, as well as clinical inertia to intensify treatment by the provider. Patients and care providers should interact with each other to address the co-existing depression and diabetes, which is the need of the hour.

Integrating Depression with Diabetes Care

As diabetes and depression are both common conditions, it is important to assess depression in patients with diabetes and associated complications because they are particularly vulnerable to further deterioration.

Vikram Patel et al suggested evidence-based treatments such as antidepressants along with psychotherapy are effective in managing depression. The delivery of these treatments should ideally be carried out through an
The integration of depression programs into existing health services or community settings with task-shifting to non-specialist health workers to deliver front-line care and a supervisory framework of appropriately skilled mental health workers. This was well demonstrated by the chronic care model developed by Katon et al. called as TEAM care. Significant improvement in depression and glycemic control was observed in the group where intervention was provided by non-specialists compared to the usual care. There is currently a study ongoing in India at 4 centres called as the “INDEPENDENT Study” which is looking at intervention in subjects with depressive symptoms, seen at 4 diabetes centers in India. A study by Lydia et al. demonstrated the feasibility of implementing a collaborative care program for poorly-controlled type 2 diabetes and complex behavioral health disorders in an urban primary care clinic. They showed that integration of behavioral healthcare into chronic care management of patients with diabetes is a promising strategy to improve outcomes among the high risk population. The study showed that there was a mean decrease in HbA1c of 0.9 (10.6 to 9.4) among those referred to the collaborative care team, compared to a mean decrease of 0.2 (9.4 to 9.2) among those not referred. This was a significantly greater percent change in HbA1c (p=0.008).

The demand for chronic care for both diabetes and depression is high as their interactions produce biological, social, and economic confluence among populations. Adapting syndemic framework in recognizing, evaluating and implementing integrated health programmes appears to be the way forward as emphasized in a recent Lancet review.

The rationale for integrating treatment for depression and diabetes is that people with diabetes will comply with their treatment plan better if the depressive symptoms are treated. Treatment of depression could be a pre-requisite for good diabetes self-management. Hence it is important that physicians dealing with diabetes are also trained for recognition and treatment of depressive disorders.

References


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Awarded the ease-of-use commendation from the Arthritis Foundation

The text below appears to be a series of charts or images related to medical information, possibly from a health or pharmaceutical context. However, the text is not legible enough to transcribe accurately.
Thyroid emergencies are major life-threatening endocrine conditions associated with life-threatening disorders resulting from either severe deficiency or excess of thyroid hormones. Deficiency of thyroid hormones may present as myxedema coma whereas excessive hormone production can present as life threatening thyrotoxic storm. The diagnosis of both requires a high index of clinical suspicion. Thyroid storm, in spite of accurate diagnosis, continues to have high fatality, whereas myxedema management has markedly improved with advancement in intensive care facility. The key to successful management of these emergencies is timely diagnosis and management by experienced physician in an intensive care setting. This article discusses the basic differences of both entities with an attempt to appropriate recognition and awareness of clinical signs and symptoms, highlight the salient diagnostic points and delineate the rational approach, which can lead to appropriate treatment at the earliest and reduce mortality.

**Introduction**

Emergencies in thyroidology can present as relatively uncommon conditions which can be life threatening, but at the same time potentially reversible clinical entities, if picked up at the right moment. They are the natural outcome of either severe deficiency or excess of thyroid hormones. The deficiency of thyroid hormones may present as myxedema coma whereas decompensated thyrotoxicosis with the markedly raised thyroxine (T4) and triiodothyronine (T3) exceeding metabolic demands of the organism may present as fatal thyrotoxic storm. The basic understanding the differences of two entities (Thyroid storm Vs myxedema) and appropriate recognition and awareness of clinical sign and symptoms will lead to early diagnosis and better management ultimately leading to better outcome in these fatal disorders.

**Thyroid Storm**

Thyroid storm is a rare, life-threatening condition characterized by severe clinical manifestations of thyrotoxicosis. First described in 1926, still remains a diagnostic and therapeutic challenge for clinician. The incidence of thyroid storm has shown a steady decline in the recent past, perhaps due to better awareness, early diagnosis and treatment of the primary condition leading to thyrotoxicosis thereby precluding its progression to the stage of acute crisis. Nevertheless, it may occur in 1% to 2% of hospital admissions for thyrotoxicosis.

Thyroid storm usually develops in a setting of a specific precipitating event such as surgery, infection, sepsis, trauma, cerebrovascular accident, drugs, an acute iodine load, or parturition. Thyroid storm may be the initial presentation of thyrotoxicosis in undiagnosed children especially in neonates. Clinical presentation includes hyperthermia, tachycardia, hypotension, severe agitation and altered mental status. It is commonly seen in Graves’ disease but can also occur in other thyrotoxicosis conditions like toxic multi nodular goiter. Thyroid storm is almost invariably fatal if left untreated, hence rapid diagnosis and aggressive treatment is of paramount importance. No laboratory abnormality is specific to thyroid storm and the available scoring system is based on clinical criteria. The exact mechanisms of thyroid storm are poorly understood. A heightened response along with the increased availability of free hormones has been postulated. In addition to specific therapy directed against the thyroid, supportive therapy in an intensive care unit (ICU) and recognition and treatment of any precipitating factors is essential, since the mortality rate of thyroid storm is substantial.
Risk factors and pathogenesis of Thyroid storm

Thyroid storm is commonly seen in patients with long-standing untreated hyperthyroidism (Graves’ disease, toxic multinodular goiter, solitary toxic adenoma). Rarely thyroid storm may develop secondary to sub acute thyroiditis or factitious thyrotoxicosis caused by excessive thyroxine intake. It is usually precipitated by an acute event such as thyroid or non-thyroidal surgery, trauma, infection, extreme weather, metabolic disturbances, drugs or an acute iodine load, or parturition.

The precise pathogenesis of thyroid storm has not been defined but it has been hypothesized that a rapid rate of increase in serum thyroid hormone levels, increased responsiveness to catecholamines, or enhanced cellular responses to thyroid hormone are the main contributing factors. Thyroid hormones levels are found to be elevated in myriad of patients during storm, but a value does not differ significantly from those with uncomplicated thyrotoxicosis. An increase in free thyroid hormone levels has been proposed as causative of storm. But storm has occurred even in the absence of elevated free thyroid hormones levels.

Adrenergic hyperactivity due to altered interaction between thyroid hormones and catecholamines has also been suggested, but the exact role of catecholamines in storm awaits further study.

Clinical features

Earliest signs include fever, tachycardia, diaphoresis, increased CNS activity and emotional lability. If left untreated a hyperkinetic toxic state ensues in which symptoms are intensified. Progression to congestive heart failure, refractory pulmonary edema, circulatory collapse, coma and death may occur within 72 hours.

Central nervous system disturbances occur in 90% of patients. As the storm evolves and intensifies the CNS dysfunction may stimulate as encephalopathy, which may progress to include increasing agitation, emotional lability, confusion, paranoia, psychosis and ultimately coma. There has been case reports of patients of thyroid storm presenting as status epilepticus, stroke and even bilateral basal ganglia infarction. Cerebral sinus thrombosis has been reported more frequently in severe hyperthyroidism and therefore physicians treating thyroid storm should keep high index of suspicion in patients of thyroid disease presenting with neurological symptoms. Paralysis in a patient with thyroid storm can occur secondary to either stroke or rarely due to thyrotoxic periodic paralysis with hypokalemia, more frequently seen in Asian populations.

Cardiovascular abnormalities are seen in 50% of patients regardless of underlying heart disease. The most common manifestation includes rhythm disturbances, which may include tachyarrhythmia’s (sinus tachycardia, atrial fibrillations, supra-ventricular tachycardia or ventricular tachycardia), which may occur even in previously normal heart. Death in young patients with normal heart due to cardiovascular collapse from congestive heart failure (CHF) and hypotension has also been reported. Congestive heart failure or a reversible dilated cardiomyopathy also may be present even in young or middle-aged patients without known antecedent cardiac disease. A high-output state develops in thyrotoxicosis due to fluid overload attributable to excessive activation of the renin-angiotensin-aldosterone axis and also reduced afterload due to direct smooth muscle relaxing effect on vessels, leading to clinical presentation of systolic hypertension with widened pulse pressure. The characteristic feature of the hyperthyroid heart is its high myocardial oxygen demand, which may lead to acute coronary syndrome even in young patients.

Gastrointestinal Manifestations commonly presents as diarrhea and vomiting, which can aggravate volume depletion, postural hypotension, and shock with vascular collapse. The diffuse abdominal pain due to neurohormonal dysregulation or delayed gastric emptying may present as acute abdomen but sometime surgical obstruction can be a presentation in thyrotoxicosis. Rarely patient may present with liver dysfunction, jaundice and hepatic failure. Increased levels of serum alkaline phosphatase are also observed, predominantly because of increased osteoblastic bone activity in response to the augmentation of bone resorption. The jaundice in thyrotoxicosis is a poor prognostic marker and needs to be managed with immediate and vigorous treatment of the primary condition. As carbimazole as well as propylthiouracil, both are hepatotoxic drugs therefore treating these patients with hepatic dysfunction needs experience and critical judgment. Lithium, iodine therapy, cholestyramine or plasmapheresis may be life saving in these patient’s with acute hepatic failure.

Laboratory and Hematological finding

Elevated T4 (thyroxine) and T3 (triiodothyronine) levels and low TSH levels, are the common finding even in young or middle-aged patients without known antecedent cardiac disease. As carbimazole is often rapidly absorbed, the increased TSH levels need to be managed with immediate and vigorous treatment of the primary condition. As carbimazole as well as propylthiouracil, both are hepatotoxic drugs therefore treating these patients with hepatic dysfunction needs experience and critical judgment. Lithium, iodine therapy, cholestyramine or plasmapheresis may be life saving in these patient’s with acute hepatic failure.

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Bilirubin, lactate dehydrogenase, and serum enzymes, transaminase, serum results in elevated levels of liver dysfunction in thyroid storm and the laboratory findings of is predominantly a clinical one Diagnosis

Other laboratory abnormalities may include a modest hyperglycemia without previous diabetes, probably as a result of augmented glycolysis and catecholamine-mediated inhibition of insulin release, as well as increased insulin clearance and insulin resistance. In prolong thyrotoxicosis cases the glycogen deposits in liver gets totally depleted leading to hypoglycemia in elderly, malnourished and acute abdomen patients who present with vomiting, abdominal pain and poor intake. Hepatic dysfunction in thyroid storm results in elevated levels of liver enzymes, transaminase, serum lactate dehydrogenase, and serum bilirubin.

Diagnosis

The diagnosis of thyroid storm is predominantly a clinical one and the laboratory findings of raised T3 and T4 may not be much different than those observed in uncomplicated hyperthyroidism. In few cases, even serum total T3 levels may be within normal limits, as in these patients T4 to T3 conversion is reduced due to some underlying conditions or illness as seen in sick euthyroid syndrome. Therefore, there are no universally accepted criteria or validated clinical tools for diagnosing thyroid storm. In 1993, Burch and Wartofsky et al. introduced a scoring system (Table 1) using precise clinical criteria for the identification of thyroid storm. A score of 45 or more is highly suggestive of thyroid storm, whereas a score below 25 makes thyroid storm unlikely. A score of 25 to 44 is suggestive of impending storm. This scoring system lacks specificity. The decision to initiate treatment is based on clinical judgment.

Treatment

Formulating a prompt and appropriate treatment strategy to overcome this emergency can be a real challenge. A multipronged management approach is recommended which is based on usage of different drugs acting through different pathways and by different mechanisms. The foremost target of treatment should be with specific antithyroid drugs to reduce the increased thyroid hormone production and reduce serum T4 and T3 hormone levels. The second line of action should be to control or block effects of excessive circulating thyroid hormones (free T4 and T3) in blood. This should be followed by a third component, which involves treatment of any systemic de-compensation, for example, congestive heart failure, and shock. And finally the fourth component should look for any underlying precipitating illness such as infection or ketoacidosis.

1. Therapy directed to the thyroid gland: Thyroid hormone synthesis is inhibited by the administration of thionamide anti-thyroid drugs, such as carbimazole, methimazole, and propylthiouracil. These drugs need to be given by nasogastric tube or per rectum as enema/ suppositories in comatose or uncooperative patient. Thionamides block new thyroid hormone synthesis within 60-120 minutes of administration but do not have any effect on the already released thyroid hormone or preformed hormone in blood. According to the recently published guidelines by the American Thyroid Association and the American Association of Clinical Endocrinologists, propylthiouracil (PTU) can be started with a loading dose of 500mg-1000mg followed by 250 mg every 4 hours, and methimazole should be administered 20 mg orally every four to six hours. Propylthiouracil may also block peripheral conversion of T4 to T3, and there is some evidence that over the first few hours after

### Table 1: Burch and Wartofsky diagnostic criteria for thyroid storm

<table>
<thead>
<tr>
<th>Thermoregulatory dysfunction</th>
<th>Scoring points</th>
<th>Cardiovascular dysfunction</th>
<th>Scoring points</th>
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</thead>
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<tr>
<td>Temperature (°F)</td>
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<td>Tachycardia</td>
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</tr>
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<td>99-99.9</td>
<td>5</td>
<td>99-109</td>
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</tr>
<tr>
<td>100-100.9</td>
<td>10</td>
<td>110-119</td>
<td>10</td>
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<tr>
<td>101-101.9</td>
<td>15</td>
<td>120-129</td>
<td>15</td>
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<tr>
<td>102-102.9</td>
<td>20</td>
<td>130-139</td>
<td>20</td>
</tr>
<tr>
<td>103-103.9</td>
<td>25</td>
<td>&gt;140</td>
<td>25</td>
</tr>
<tr>
<td>&gt; 104</td>
<td>30</td>
<td>Atrial fibrillation</td>
<td>10</td>
</tr>
</tbody>
</table>

CNS effects

- Mild: 10
- Agitation: 20
- Moderate: Pedal edema
- Delirium: B/L basilar rales
- Psychosis: Severe
- Extreme lethargy: 30
- Seizure: Severe
- Coma: Pulmonary edema

Gastrointestinal-hepatic dysfunction

- Moderate: 10
- Diarrhea: Nausea/vomiting
- Abdominal pain: Severe
- Unexplained jaundice: 20
administration, PTU reduces serum T₃ concentrations more rapidly than methimazole, whereas methimazole has some immunosuppressive effects also and is less hepatotoxic. Albeit there are no data showing that patients do better clinically with one thionamide over another, PTU is preferred for acute treatment of thyroid storm.

Iodine therapy complements the effects of thionamide therapy by blocking the release of stored hormone, a phenomenon called as Wolff-Chaikoff effect. The administration of iodine should be delayed for at least one hour after thionamide administration to prevent the iodine from being used as substrate for new hormone synthesis. Available iodine formulations like Lugol’s iodide, SSKI can be used (5 drops orally every 6-8 hourly). Iodinated radiocontrast agents- Iopanoic acid and other iodinated radiocontrast agents block T₄ to T₃ conversion and inhibit thyroid hormone binding on cellular receptor. They have been extremely useful in treating severe hyperthyroidism and in preparing hyperthyroid patients for urgent surgery, and can be used at a dose of 0.5-1 g once daily.

2. Therapy to block Thyroid hormone action: When serum levels of T₃ and T₄ are very high in severe thyroid storm the anti-thyroid drugs may be inadequate. In these circumstances urgent plasmapheresis, therapeutic plasma exchange and peritoneal dialysis can be life saving, as they can reduce T₄ and T₃ levels within 36 hours. Intravenous albumin and fresh frozen plasma solution given during therapeutic plasma exchange provide new binding sites to reduce circulating levels of free thyroid hormones. Although the effect of plasma exchange is transient, it should always be supported by definitive therapy with anti-thyroid drugs or any other measures like early thyroidectomy. Surgical thyroidectomy has also been reported to reduce the mortality rate from about 20-40% under standard treatment to less than 10%. Beta-blocker’s are very effective in ameliorating the peripheral action of thyroid hormones and have immediate effect. Propranolol is frequently used for initial therapy because it can be given intravenously. However, it should be given under strict hemodynamic monitoring. Initial dose is 0.5 to 1 mg over 10 minutes followed by 1 to 2 mg over 10 minutes every few hours, can also be given orally or via nasogastric tube to achieve adequate control of heart rate, typically 60 to 80 mg orally every four to six hours.

An alternative to propranolol therapy is a short acting beta-blocker esmolol, specially preferred in a critically ill patient in compensated shock or borderline blood pressure. A loading dose of 250 to 500 mcg/kg is given, followed by an infusion at 50 to 100 mcg/kg per minute. This regimen permits rapid titration of the dose of the drug to achieve adequate beta blockade while minimizing adverse effects. If there is a contraindication to use of beta-blocker, diltiazem can be used at 60-90 mg orally every 6-8 hours.

Glucocorticoids are another important medications characterized by a high therapeutic potency and modest ability to inhibit peripheral conversion of T₄ to T₃. Drugs such as hydrocortisone also exert immunosuppressive effect. Hydrocortisone, 300 mg initially followed by 100 mg intravenously every eight hours is routinely used in thyroid storm. The additional rationale behind the routine use of glucocorticoids is perhaps theoretical and unproven, but relates to possible relative adrenal insufficiency secondary to increased metabolic demands and more rapid turnover of cortisol.

3. Therapy directed at systemic decompensation: Fluid replacement should be done in time as thyrotoxic patient’s are fluid depleted due to fever, diaphoresis, as well as by vomiting and or diarrhea and any delay may lead to vascular collapse. Judicious replacement of fluids is necessary in elderly patients with CHF or tachyarrhythmias. Intravenous fluids administration with 10% dextrose and appropriate electrolyte according to individual case scenario will help in better restoration of depleted hepatic glycogen store. Vitamin supplementation may also help in correction of any deficiency. Hypotension not readily reversed by adequate hydration may temporarily require inotropes and/or glucocorticoid therapy.

Supportive therapy includes cooling measures, antipyretics, fluid and electrolyte correction. Avoid using salicylates as they can exacerbate thyrotoxic
4. Therapy directed at the precipitating illness: A search for precipitating cause should be made in all cases of thyroid storm and immediate treatment is indicated for that underlying illness. If the cause is too obvious, like trauma, surgery, labor, or premature withdrawal of anti-thyroid drugs etc., there may not be requirement for any additional measures, as they are known causes of precipitating thyroid storm. But in case no apparent cause is found, then infectious cause should be suspected and evaluated accordingly with urine, blood cultures, and cultures from other sites as well on the basis of clinical grounds. Broad-spectrum antibiotic coverage on an empiric basis may be required initially while awaiting culture results. In an obtunded patient, conditions like ketoacidosis, stroke or pulmonary embolism may be masked and therefore should be clinically suspected and treated vigorously if found.

### Myxedema Coma

Myxedema coma is a severe life threatening form of decompensated hypothyroidism with a high mortality rate commonly seen in elderly hospitalized females with untreated hypothyroidism, although it may occur in young as well as pregnant females too. Infections and noncompliance with thyroid supplements are the major precipitating factors. Fortunately, it is now a rare presentation of hypothyroidism, probably due to early diagnosis. Careful history and examination can reveal important clues regarding hypothyroidism and precipitating events in a poorly responsive patient. Early recognition and treatment are consequential. Timely intervention in a hypothyroid patient developing sepsis and other precipitating factors may reduce morbidity and mortality associated with myxedema coma. Treatment should be started on the basis of clinical suspicion without waiting for laboratory results.

#### Etiopathogenesis of Myxedema Coma

Myxedema coma is 4 to 8 times more common among women. It can result from any of the usual causes of hypothyroidism, particularly chronic autoimmune thyroiditis, usually precipitated by an acute event such as infection, myocardial infarction, cold exposure, or the administration of diuretics and sedative drugs, especially opioids. In a study by Dutta et al they have shown that nearly half of their patients had been treated with diuretic for edema.\(^3\)

Chu and Seltzer reported a case of myxedema crisis precipitated by consumption of raw bok choy (Chinese white cabbage), which contains glucosinolates, which reduces thyroid hormone levels by inhibiting iodine uptake.\(^3\) A commonly ignored background factor in myxedema crisis is the discontinuation of thyroid supplements in critically ill patients. It has been also reported in patients with secondary hypothyroidism, in some series 5%-15% of cases have been found to be due to hypothalamic or pituitary disease.\(^4\) There are also few case reports of its occurrence in patients with lithium or amiodarone induced hypothyroidism.

Markedly reduced intracellular \(T_3\) due to hypothyroidism is the basic underlying pathology in myxedema coma, which causes hypothermia and suppression of cardiac activity. Decreased central nervous system sensitivity to hypoxia and hypercapnia leads to respiratory failure.\(^5\) Pleural effusion and generalized swelling may occur due to altered vascular permeability. Markedly reduced thyroid hormone may lead to reduced glomerular filtration rate (GFR), decreased water and solute delivery to distal nephron as well as secondary to increased vasopressin secretion.\(^6\)

#### Clinical presentation

While dealing with myxedema coma a detailed history focusing on precipitating factors like infection, drug intake, discontinuation of thyroxine medication, thyroid surgery and radioactive iodine ablation are paramount. The term myxedema coma is a misnomer, as quite a few patients are obtunded, rather than frankly comatosed.

The two hallmark features of myxedema coma are decreased mental and profound hypothermia, but hypotension, bradycardia, hypotension, hypoglycemia, and hypoventilations are often present as well. Physical examination findings like dry skin, sparse hair, a hoarse voice, hypothermia, delayed tendon reflexes, macroglossia, non-pitting edema, goiter may be present.

The hypoxemia is a frequent development in myxedema coma. It’s primarily due to hypoventilation secondary to depressed hypoxic respiratory drive and a depressed ventilatory response to hypercapnia. Other contributing factors are obstruction of the upper airway caused by edematous tongue and vocal cords, as well as due to plural effusion and ascites, which are commonly associated with this condition.\(^7\)

Confusion with lethargy and obtundation are the prominent neurological features, focal or generalized seizures may occur, due to concomitant hyponatremia, and status epilepticus has also been reported.\(^8\) Patients with severe hypothyroidism are at higher risk of developing shock and fatal arrhythmias. Cardiovascular involvement with bradycardia, decreased myocardial contractility, a low cardiac output, pericardial effusion and hypotension are other common features. Sinus
bradycardia, low voltage complexes, bundle branch blocks, complete heart blocks, and nonspecific ST-T changes are the prominent ECG findings. Patient may have normocytic or macrocytic anemia along with bleeding manifestations with elevated PT and APTT. Acquired Von-Willebrand disease has also been reported.  

**Diagnosis**  
Diagnosis is based on history, examination and exclusion of other causes of coma. Patient with altered sensorium with hypothermia, with clinical and biochemical features of hypothyroidism in the setting of a precipitating factor, should be identified with a high index of suspicion and replacement therapy should be started as soon as possible. A diagnostic scoring system for myxedema has been proposed based on patient risk of myxedema coma, but its usefulness is limited by the fact that it has been derived from a study involving very small number of patients.

Physical examination in a suspected case may include bradycardia, macroglossia, hoarseness of voice, delayed reflexes, dry skin, general cachexia, hypoventilation, and hypothermia, commonly without shivering. Laboratory evaluation may indicate hypoxemia, raised 

2. Thyroid hormone therapy: Thyroid hormone replacement therapy is one of the most controversial aspects of myxedema management, due to paucity of good control trials of comparing the efficacy of various regimens and obvious difficulty in doing proper trials. There is still no consensus on oral versus intravenous T4/T3 and how to give it (dose, bolus, nasogastric or intravenous preparation).

The optimum therapy should balance the need for quickly attaining physiologically effective thyroid hormone levels in the serum against the risk of precipitating a fatal tachyarrhythmia or acute coronary syndrome. T4 provides a steady, smooth, and slow onset of action with relatively few adverse events but is given intravenously in a loading dose of 200 to 400 mcg followed by a daily dose of 1.6 mcg/kg thereafter.

Oral administration of T4 through nasogastric tube has proved to be equally effective, with a drawback that gastric atony may prevent absorption and put the patient at risk for aspiration. However, T3 is the active hormone in the body, and in a setting of severe illness there may be a decreased conversion of T4 to T3. Simultaneous T3 is administered in a dose of 5 to 20 mcg, followed by 2.5 to 10 mcg every eight hours for 1 or 2 days, and continued till the time the patient is alert enough to continue therapy through oral route. The single intravenous bolus of T4 was popularized by reports suggesting that replacement of the entire estimated pool of extra thyroidal T4 (usually 300–600 mcg) was desirable to restore near-normal hormonal status. This initial loading dose is followed by the maintenance dose of 50 to 100 mcg given daily (either intravenously or by mouth if the patient is adequately alert). Advantage of treatment with higher doses of T4 is still unproven and probably it may be more dangerous. Instead there are reports of improved outcomes with even lower doses of T4.

The T4 to T3 conversion rate is somewhat reduced in systemic diseases (sick euthyroid syndrome or low T3 syndrome), hence T3 generation may be reduced in myxedema coma as a consequence of any associated illness (sick hypothyroid
The negative side of neuropsychological symptoms in patients suffering from may have more positive effects as compared to T4 therefore blood brain barrier more rapidly be advantageous as it crosses therapy. The use of T3 may also 8-14 hours after intravenous T4 the same changes may take upto of intravenous T3 while the seen within 2-3 hours of use oxygen consumption may be T4 hormone, the rise in body onset of action compared to T4 hormone, the rise in body temperature and increase in oxygen consumption may be seen within 2-3 hours of use of intravenous T3 while the same changes may take upto 8-14 hours after intravenous T4 therapy. The use of T3 may also be advantageous as it crosses blood brain barrier more rapidly as compared to T4 therefore may have more positive effects in patients suffering from neuropsychological symptoms and coma during myxedema.

The negative side of intravenous T3 treatment is its large unpredictable fluctuation in its serum levels and also higher serum levels which may lead to fatal outcomes, especially cardiac mortalities.

Considering various risk and benefit of only T4 vs only T3 hormone treatment regimen, there lies an intermediate or combined (T4+T3) regimen pathway. The rational behind this combined therapy approach is to provide combination of T4 and T3. In this regimen the intravenous T4 dose of 4mcg/kg lean body weight (or approximately 200-300 mcg) is given with a bolus dose of 10 mcg of intravenous T3. After this an additional single intravenous dose of 100 mcg T4 is given on day two with 20-30 mcg of intravenous T3 in divided doses. The T3 should be continued at the same dose of 10 mcg twice or thrice a day till patient regains consciousness and start accepting orally, while the T4 should be continued at maintenance dose of 50 mcg per day by intravenous or oral depending on the consciousness and oral acceptance.

3. Hypothermia management: The body temperature can be restored with treatment with thyroid hormone replacement. Simultaneous use of warming measures, such as warm blankets and increasing the room temperature with heater can be used as additional interventions to keep the patient warm until the thyroid hormone effect is achieved. Too aggressive warming should be avoided, as it may be deleterious to patient’s health secondary to peripheral vasodilation, leading to hypotension and shock.

4. Hyponatremia management: Patient with hyponatremia are prone to develop seizures and coma even in euthyroid state, in myxedema crisis this hyponatremia may further contribute to comatose state. The mortality of severe hyponatremia (105-120 mmol/L) is manifold higher in myxedema patients. The appropriate management of severe hyponatremia is slightly tricky in these patient and need close monitoring of serum sodium after correction with hypertonic saline followed by rapid diuresis with loop diuretics. This often require administration of 50–100 mL of 3% sodium chloride, initially to increase serum sodium concentration by about 2 mmol/L early in the course of treatment, followed by an intravenous bolus furosemide (40 to 120 mg) to promote a water diuresis. A small, quick increase in the serum sodium concentration by 2–4 mmol/L in severe hyponatrexemic patient may be effective in improving sensorium because even a slight reduction in brain swelling results in a substantial decrease in intracerebral pressure (ICT). On the other hand, too rapid correction of hyponatremia can cause a dangerous complication, the osmotic demyelination in the form of central pontine myelination.

In patients with chronic hyponatremia, the serum sodium correction should be <10 to 12 mmol/L in 24 hours and less than 18 mmol/L in 48 h. After achieving a serum sodium level of >120mmol/L restriction of fluids may be good enough to correct hyponatremia. But patient with cardiovascular disease may need close monitoring of volume status with central venous pressure monitoring. The intravenous vasopressin antagonist, conivaptan can be effective medicine in treating hyponatremia in hypothyroid patients as high vasopressin levels has been documented in Myxedema coma patients. The Conivaptan is approved by US FDA and the recommended dose is 20 mg of loading dose, to be infused over 30 minutes followed by 20 mg/day of continuous infusion for up to 4 days. Unfortunately, at present no data are available on the use of conivaptan in severe hyponatremia (<115 mEq/L) in hypothyroidpatients.

5. Hypotension: Hypotensive myxedema patients may require additional volume-repletion therapy in spite of corrected...
T3/ T4 replacement to correct volume status. Fluids maybe administered cautiously as 5% to 10% dextrose in N/2 sodium chloride if hypoglycemia is present, or as isotonic normal saline if hypotenatremia is present. An agent such as dopamine might be used to maintain coronary blood flow, but patients should be weaned off the vasopressor as soon as possible because of the risk of an inotropes induced iatrogenic ischemic event. Hypocortisolemia may be due to primary or secondary adrenal insufficiency. Thyroid hormone replacement may increase cortisol clearance and may aggravate cortisol deficiency. Patient must be treated with glucocorticoids in stress doses (e.g., hydrocortisone given intravenously, 100 mg every eight hours).

Summary
Thyroid storm and myxedema coma are two major life-threatening thyroid emergencies encountered in endocrinology clinical practice. The diagnosis of both requires high index of clinical suspicion and early appropriate treatment can markedly reduce mortality. In thyroid storm in spite of accurate diagnosis and high fatality has been documented in literature. While Myxedema fatality has markedly decreased with advances in intensive care management. The key to successful management of these emergencies is timely diagnosis and management by experienced physician in an intensive care setting.

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THE POWERFUL ONE

Novel des-fluoroquinolone for bacterial respiratory tract infections.*

Increased activity against organisms causing typical and atypical pneumonia and respiratory tract infections.*

Structure activity relationship suggestive of increased spectrum and decreased chances of development of resistance.*

Venomous Snake Bite in India - Why do 50,000 Indians Die Every Year?

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Abstract
Snakebite is an occupational hazard causing considerable morbidity and mortality worldwide, particularly so in tropical countries like India. An estimated 50,000 Indians die due to venomous snakebite every year, seventy percent of whom are males between the ages of 20 to 50 years. Along with the associated morbidity and mortality, snakebite leads to a significant financial burden on the victim, both by way of hospital bills and labour hours lost. Snakebite is also a cause for considerable psychological stress among survivors. Most snakebites are eminently treatable and curable. Given a concerted thrust from all concerned, this menace could surely be curtailed considerably over the next few years.

Background
Snakebite is a predominantly rural agrarian problem rampant in the tropics and subtropics. Snakebite is an occupational, environmental and domestic health hazard with a significant economic fallout on the individual and the family. The estimated number of snakebites worldwide has been put as 5.4 million resulting in 2.5 million envenomations and 125,000 deaths.² It is estimated that there are over 1,000,000 snakebites in India alone leading to between 45,000 and 50,000 deaths annually. Of the estimated deaths due to venomous snakebite worldwide, half occur in India (Alirol et al., 2010). Seventy percent of bites are in males between 20 and 50 years of age (Alirol et al., 2010). What this basically means is that bites are most common in the active, productive bread winners of the family. The economic implication is tremendous as in most villages males are the sole earning member on whom depend the rest of the family.

Venomous snakebite has a significant global and national impact, in spite of which it has remained a low priority for governmental health policy makers, pharmaceutical industry, health providers and public health advocacy groups. There is a paucity of data regarding snakebite prevalence, treatment, course in hospital and outcomes in India as elsewhere in the tropics. Venomous snakebite was listed as a NTD-“Neglected Tropical Disease”, by the WHO in 2009. What this implies is that snakebite is in a group of diseases that prevail in tropical and subtropical conditions in 149 countries affecting more than a billion people, costing developing economies billions of dollars of loss every year. NTDs mainly affect populations living in poverty. Effective control against NTDs can be achieved when public health approaches are combined. In the case of snakebite, interventions are therefore guided by local epidemiology and availability of appropriate detection, prevention and treatment measures that can be delivered locally.¹

The Australian continent has many more species of venomous snakes but in contrast to India the number of deaths due to venomous snakebite is less than 10 per year. Similarly the United States too does not lack in number of venomous snake species, but there too, the number of deaths due to venomous snakebite is less than 10 per year.

Why this stark difference in numbers?

The reasons for the alarming statistics from India are many, and include:

Socio demographic factors
• Ever increasing population leading to greater encroachment thereby increasing the chances of human reptile contact and bites
• inadequate infrastructure in villages, including lighting, sewerage systems, roads, in house water supply etc all of which co-contribute to bites specially at night
• improper sanitation which in turn increases the rat population and thereby...
increases the likelihood of
snake presence
• poor transport facilities in the
rural hinterland leading to an
enormous and at times fatal
delay in the shift of patients
to a secondary or tertiary care
centre
Socio-Cultural
• the fact that most village
dwellers do not use protective
foot wear (70% of bites are on
the lower limbs)
• habit of sleeping on the floor/
ground
• presence of livestock near the
house which in turn attracts
rats
• defecating in open fields, often
after dark
• increasing alcoholism, a
significant number of male
victims being under the
influence of alcohol when
bitten
Medical
• lack of awareness among
victims of the immediate
measures to be followed when
bitten
• Alternate forms of treatment
practised in villages wherein
the victim is first taken to a
faith healer (quack), precious
time being lost therein
• Improper first aid measures
immediately after the bite
which increases the chances of
systemic envenomation and
additional complications
• unavailability of the standard
treatment, anti-snake venom
(ASV) in rural centres,
• reluctance on the part of
the primary caretaker at
the village centre to admit
and treat snakebites fearing
complications and reactions to
ASV
Legislative / Governmental
• High cost of horse serum based
ASV
• absence of a centralized quality
control on the process of
manufacture of ASV as also its
standardization
• absence of regional or zonal
pools of snake venom. The
venom used for the manufacture
of ASV for the entire country is
from one or two sources limited
to a small geographical area.
Venom researchers have shown
regional variation in venom
constituents and chemical
properties, intra-species, which
is why it is mandatory that
regional/zonal venom centres
come up with the facilities to
manufacture ASV for a
particular region or zone
• delay in initiation of ASV due to
non-availability of kits for the
early diagnosis of venomous
snakebite
• absence of a national protocol
for the diagnosis and effective
treatment of venomous
snakebite
• step motherly treatment meted
out to the subject of snake bite
in the medical curriculum as
also in the governmental health
policies
A few of these points need
further discussion. Presently the
Irula Co-operative Society, near
Chennai, is the only authorised
supplier of venom for manufacture
of Anti-Snake Venom (ASV). The
Society supplies venom to the major
manufacturers of ASV, namely
VINS Bioproducts, Bharath Serum
and Premium Serums. Which
means that ASV manufactured for
the entire country is from venom
procured from a small geographical
area. Basic scientists have shown
that the venom of the Naja naja
(Spectacled Cobra) or the Daboiae
russellii (Russel’s Viper) from South
India is different in its physico-
chemical properties and thereby
toxicity profile from that of the East,
though of the same species, namely
Daboiae or Naja. They also proved
through further experiments that
there is a significant difference in
the neutralising capacity of ASV
to venom from different zones. What
this boils down to is that
the standard ASV available in
India may not be ideal for treating
venomous snakebite in the East,
West and Northern parts of our
country.

The standard ASV neutralises
the venom of the Big 4 namely
Daboiae russellii, Naja naja, Echis
carinatus (Saw-scaled Viper) and
Bungarus caeruleus (Common Krait).
There are a significant number of
bites reported from Hypnale
hypnale (Hump nosed Pit Viper),
Trimeresurus malabaricus (Malabar
Pit Viper), Trimeresurus gramineus
(Bamboo Pit Viper), Echis carinatus
sochureki (Sochurek’s Saw-scaled
Viper) and Naja kaouthia (Monocled
Cobra) in areas where these snakes
abound. There are other species
like Bungarus fasciatus (Banded
Krait), Bungarus sindanus (Sind
Krait) and Ophiophagus hannah
(King Cobra), bites of which have
been reported, but rarely. The
venom of the snakes mentioned
above is not neutralised by the
standard ASV available in India.
It is believed that there would be
some degree of para-specificity
to venom of similar species for
example Echis carinatus sochureki
with Echis carinatus carinatus and
Naja naja with Naja kaouthia. We
do not have any robust data on
the degree of neutralisation and it
may well be that the venoms of the
above mentioned species are not
neutralised to the desired degree.
This may also be a reason for the
extravagant use of ASV in certain
parts of the country when standard
doses of ASV do not bring about a
clinico-biochemical improvement
in status of the bitten patient.

Unfortunately, patients in
many parts of the country depend
more on traditional medicine men
(OJhas, Visha chikitsa, kavirajs
etc.), precious time being lost
therein. It has to be stressed that the
only scientifically proven treatment
for venomous snakebite is ASV.

In the medical curriculum
venomous snakebite is covered in
the textbook of Forensic Medicine and Toxicology. Identification of venomous species and symptomology is covered from a forensic angle, which is to say for the dead. It is compulsory that venomous snakebite and scorpion sting be taught as part of Internal Medicine, where it belongs. This and other tropical diseases are what a fresh MBBS graduate from any of the medical colleges is likely to face in his day to day practice. The focus of medical education we believe should shift from the knowledge based approach as taught in most of our medical colleges, from Western texts to a more practical one based on the disease conditions medical graduates are likely to encounter in their practice.

Most Peripheral Health Centres in the country lack the manpower and the equipment necessary to manage venomous snakebite. This is particularly pertinent to areas where neurotoxic snakebites are aplenty. A person in respiratory distress secondary to a neurotoxic snakebite (especially krait bite) is unlikely to survive a 1 hour journey to a tertiary care centre without ventilatory support. Doctors in PHCs especially in areas where neurotoxic bites are common should be trained in endotracheal intubation or ‘Bag and Mask Ventilation’, which would be enough to maintain oxygen saturations till definitive treatment is given.

Venom analysis is severely hampered by the excessive cost of snake venom and also by the fact that the Big 4, being protected species, requires permission from the Forest Department of states for milking. Availability of venom has been a major stumbling block for Ph.D scholars in Mysore, Tezpur and MGR Universities who along with the Kolkata group have been at the forefront of venom research for two to three decades now. The necessary permissions for venom and genetic material from snakes are hard to get, which is why fewer and fewer of young researchers venture into this area.

Manufacture of ASV is now almost solely by private companies, the two State producers, Haffkine Institute and King Institute having stopped production years back. Standardisation of ASV is done in situ in the companies itself without governmental verification or standardisation.

Cost of ASV is ever on the increase; in 2016 one vial of ASV cost as much as Rs950.

**Mitigation of Snakebite in South Asia -- Some Suggestions for a Way Forward**

1. **Improvement of venom production protocol to the WHO standard by the Irula Snake-catchers Co-operative, India’s primary venom producer for anti-venom production.**
2. **Production of venom from different geographic regions in India to solve the problem of geographic variation by amalgamating the Irula Co-operative into a Multi-State Co-operative.**
3. **Improvement of Indian anti-venoms by raising the titre to the levels of anti-venom produced in the 1950s.**
4. **Standardizing and translating into local languages an accepted protocol for snakebite FIRST-AID AND TREATMENT with attention and discussion given to the more controversial and much debated subjects such as anti-venom dosages, use of neostigmine and a long list of other things regularly argued about by clinicians and others.**
5. **Guaranteed stocking of anti-venom where it is needed, at Primary Health Centres in areas with high incidence of snakebite, with adequate training in its administration.**
6. **And perhaps one of the most important measures to be taken: Development of well-publicized, all-India snakebite hotlines, with appropriate regional/language representations by doctors willing to receive calls at all hours to give instant advice on snakebite.**
7. **Bringing ASV into the list of essential medicines in states thereby helping reduce the cost. The Government must provide anti-venom free of charge to rural India.**
8. **Development of a national protocol for the treatment of venomous snakebite.**

**10. Make snakebite a notifiable disease and carry out epidemiological studies in states where venomous snakebite is a significant problem so as to be able to arrive at an accurate mortality and morbidity figure.**

9. **Venom to be made available to research laboratories to foster snake venom and genetic research on snake species.**
10. **To analyse the LD50 of regional variants of the Big 4, namely Naja kouthish, Echis sochureki etc, study their toxicity profile.**
11. **Fostering snake venom and genetic research on snake species.**
12. **Improvement of Indian anti-venoms by using methods developed at the Instituto Clodomiro Picado in Costa Rica using caprylic acid fractionation of plasma.**
and degree of neutralisation (ED50) by the standard ASV now available.

13. To include treatment of venomous snakebite in the subject of Internal Medicine in the medical curriculum, and encourage research and conferences on this much neglected subject.

Snakebite in India has remained a much neglected subject in spite of the significant mortality and morbidity it causes. If diagnosis and treatment be given in a timely fashion the victim can go back to a productive life. Given the fact that most (70%) of bitten are males and the bread winners of the family adds an extra dimension to this problem. Snakebite was and still remains a problem that can easily be tackled given a sustained effort towards that goal involving all concerned, namely herpetologists, clinicians, basic scientists, industry and most importantly, the government. A number of state governments pay Rs.100,000 to the family in case of death due to snakebite. If 50,000 families of victims were to claim the same, it would drain the exchequer of Rs 500 crores annually. We believe that a small fraction of the above mentioned amount would be enough to mitigate the problem in India, to a large extent, once and for all. We are sure that with the advances that India has made on all fronts here too we can be successful in bringing down the annual death rate to a fraction of what it is in the coming years.

References

1. WHO Neglected Tropical Diseases, www.who.int/neglected_diseases/en
Creating Posters for Effective Scientific Communication

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Abstract
A scientific poster is a summary of one’s research that is presented in a visually engaging manner. Posters are presented as a means of short and quick scientific communications at conferences and scientific meetings. Presenting posters has advantages for the presenters and for conference attendees and organizers. It also plays a part in dissemination of research findings and furthering science. An effective poster is the one that focuses on a single message and conveys it through a concise and artistically attractive manner. This communication intends to provide tips on creating an effective poster to young scientists.

Introduction

Scientific poster exhibitions are an integral part of medical conferences and scientific meetings. Although considered as poor cousins of published papers,¹ scientific posters do serve important functions for the presenters, viewers and conference organizers (Table 1). They are a good medium to disseminate salient findings of a recently-completed research project expeditiously. They allow the conference delegates to have a ‘snap shot’ of the findings² and know what is current research focusing on. The findings are presented in a relaxed environment with greater opportunities for exchange of ideas.³ Through feedbacks and discussions, the presenters gain greater understanding of appropriate methodology, analysis and interpretation. This helps them in writing a better research paper for publication. They are able to practice and improve upon their public speaking skills and their abilities of defending their work. Planning a poster, executing the design, and presenting it to the viewers require managerial, coordinating and organizational skills. Poster presentations provide opportunities to hone these skills. Through interactions with conference attendees, the presenters can network with experts in the field, which in turn, can provide openings for advancement of career and for research collaborations in future. They also improve one’s curriculum vitae (CV) and help develop national reputation.⁴

The poster exhibitions are organized in many different ways:

i. The presenters are requested to put up the posters at a pre-designated place or room. The organizers encourage the attendees to visit the exhibition to view the posters at their convenience.⁵ They also urge presenters to make themselves available near their poster at least during ‘breaks’ to interact with the delegates.

ii. Some organizers arrange a formal session assigning 4-6 minutes for every poster to be presented in a conference room in presence of a moderator.

iii. A team of (two or three) experts visits the exhibition and interacts with the poster presenters at a pre-designated time. Many other delegates present there interact with the presenter.

Making of an Effective Poster: The Basics

Once your research project is complete, you should plan to present it at a conference for the obvious advantages discussed earlier. However, making an effective poster is not akin to sticking any research paper on a board. An effective poster is a source of information, a summary and advertisement of your work and a conversation starter. It is focused on conveying a single message in a simple language with textual elements, figures and charts arranged in a sequential and aesthetically pleasing manner.⁶ This requires planning, coordination and discipline. The following description can help the newly-initiated scientists on how to create and present an effective poster:

Step 1: Identify the key message in your research

The first step is to identify one key or core message that you would

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Table 1: Advantages of poster presentation

General
- An opportunity for early dissemination of research observations to the scientific community. Enhancement of understanding and furthering science.

For the presenters
- As compared to a research publication in a peer-reviewed journal, lesser details of results and discussion are expected. Shorter preparation time.
- Selection and acceptance criteria not as rigorous as for a research publication: Easy access to showcase your research.
- Enhancement of cognition: Interpretation of results, critical thinking, organization of thoughts and arguments.
- Enhancement of skills: Writing abstract, editing content, presentation skills and public speaking.
- Interactions during presentation can inform the presenter about the flaws in methodology, errors in results and gaps in arguments.

For the viewers and readers
- Get to know “what research is going on” in one’s field of interest.
- Get novel ideas for future research.
- An opportunity to clarify doubts through face-to-face interaction.
- Interact and network with researchers working in the area of interest.

For the conference organizers and scientific community
- An added attraction for the young scientists to register for the Conference.

Step 2: Select the right conference

The choice of conference should primarily be decided on the basis of who the message is for (generalists, specialists, super-specialists), whether the research is of regional, national or international import and the time period between the completion of interpretation of results and the conference dates. If these are too close, you may not be able to do justice as the time available may not be sufficient for creating an effective poster. If the conference is several months away, there is a danger of the findings getting outdated or some other researcher presenting findings of a similar research project in the intervening period. In addition, to these factors, logistical factors such as your commitments and expenses likely to be incurred (registration fees, travel and lodging) among others may influence the decision.

Step 3: Visit the Conference website and contact the organizers

The next step is to get all the details pertaining to poster presentation from the conference website or from conference brochure. You would definitely want to know about the last date of submission and expected format of the abstract, layout (landscape or portrait) and dimensions of the poster, whether formal presentation would be allowed, criteria for ranking posters, what assistance (in terms of material and services) would be available at the poster exhibition, etc. If sufficient information is not available regarding any aspect, do not hesitate to contact the conference organizers for clarifications and additional information.

Step 4: Define milestones and specify time lines

You should be aware of the different tasks involved in converting an idea into a concrete and effective poster. It is always better to define and list these tasks or milestones and specify the time that you would assign for each of these milestones. While assigning timelines, you should be reasonably sure that it will be feasible to attain the milestone in the time period provided. It is better to work backwards. A suggested “time table” is provided in Table 2, which can be suitably modified. If the poster is authored by many, additional time will be required for coordinating with other authors.

Step 5: Prepare and finalize Abstract

The importance of a good abstract cannot be over-emphasized. The poster is accepted for presentation on the basis of abstract submitted. Abstracts are published in the conference proceedings booklet or book of abstracts. Several delegates decide which posters to view after reading the abstracts published. Abstracts are also posted on the conference website. These can be picked up through search engines enabling others to know the work that you are doing. Similar to abstracts of published research papers, poster abstracts should be an honest, accurate, succinct and complete summary of the research presented in the poster. Abstracts can be unstructured or structured (with sub-headings such as background or rationale, objectives, Methodology, Results
Table 2: An example of a working “time table” for preparing and presenting a poster

<table>
<thead>
<tr>
<th>Week Preparation</th>
<th></th>
</tr>
</thead>
</table>
| -5 | Prepare a draft abstract  
|     | Identify the core message |
| -4 | Plan out poster  
|     | Finalize and post the abstract  
|     | Seek suggestions and guidance from mentor and discuss with peers |
| -3 | Distribute poster to peers inviting comments and suggestions (Round 1)  
|     | Edit draft of the poster thoroughly and ruthlessly  
|     | Create a draft poster |
| -2 | Distribute pre-final version of the poster to peers for comments (Round 2)  
|     | Formulate answers to possible questions and share with peers  
|     | Prepare a draft for presentation of poster and share with peers  
|     | Make changes suggested by peers (Round 1) |
| -1 | Final print  
|     | Finalize answers to probable questions  
|     | Finalize Presentation (what you would speak)  
|     | Make changes suggested by peers (Round 2) |
| 0  | Present Poster  
|     | Practice Presentation  
|     | Practice answers to questions |

...and Conclusions). You will have to submit the abstract as per the instructions provided. However, it is logical to prepare initial drafts of the abstract on the basis of sub-headings stated. While submitting the Abstract, do pen a covering letter to the conference organizers describing the relevance and importance of the research, in brief. You may also use the letter to inform the organizers if the same poster was presented earlier at another conference or if paper based on the same research has already been published. Your declaration conforms to the highest levels of transparency and ethical behavior. Most organizers will allow you to present the poster again.

**Step 6: Plan out, prepare a draft and create a Poster on the Computer**

Poster is a visual medium and hence it should be designed in an attractive and aesthetically pleasing manner. At the same time, it is a form of scientific communication and hence the content is of vital importance, too.

**Content**

The most important aspect of the content is the core message. You should state the main purpose and the core message of the poster in a lucid, plain and comprehensible manner. The information provided in the poster should be significantly novel and valuable for those attending the conference. Due to limited space available, you should include only the vital and essential information and dispense with unnecessary details. You will have to edit the successive drafts ruthlessly to ensure that only critically important material finds place in the poster. You should present the information in a clear and concise manner by using vocabulary that delegates would understand easily. It is preferable to use bulleted short sentences or phrases rather than complete sentences. The content is divided into various sections not very dissimilar to a research manuscript. The sections include Banner, Introduction (or Background or rationale), Aims and Objectives (or Research Questions or Hypothesis), Material and Methods (or Methodology), Results (or Observations), Discussion, Conclusions and Lessons learnt and optional contents (References, Acknowledgments and contact details).

The banner includes the title, names of authors and their institutional affiliations. Many researchers in addition, put institutional logo in the banner. The title is important as is the only thing that the delegates see. It should make them want to come and read. The title can pose a key question, define the scope of the research study or suggest a new finding, but it should be drafted in a way to effectively and succinctly communicate the topic and significance of the research project. Use of two-part titles with colon between the two parts are quite common. This is done to provide additional details or add humor. However, it makes the title a bit long and this runs contrary to the common advice that the title should be short, sharp and compelling like newspaper headlines.

The content of the poster must conform to the norms of sound scientific reporting: clarity, precision of expression and economy of words. The total word count of a poster (excluding banner, references and legends) should not exceed 600-1000 words. Use figures, graphs or charts to explain complex methodology and intricate data and not just to impress viewers with complex artistry. They also help reduce the amount of text material (word count). The poster looks better with the right mix of textual matter and figures.

“Introduction” (or Background or rationale) should inform the viewers about gaps in knowledge and justify the need to conduct the study. State the objectives with greatest clarity under the heading titled Aims and Objectives (or Objectives or research questions or hypothesis). Describe the population studied, recruitment procedure, the study design, the interventions, parameters studied, outcome measures and statistical plan under the section of Methodology (or Material and Methods). You may not be able to present all the details of methodology for want of space. Describe observations under the section entitled “Results” (or observations). This section may have the highest number of graphs and tables. Use the “Discussion” section, to compare results with those obtained in earlier studies and describe the strengths and limitations of the study. Use the “Conclusions (or Lessons learnt)” section for stating the impact and significance of the study and future plans on further research. Many a times, the sections entitled “Discussion”...
and “Conclusions” are merged into one. Most organizers do not ask for an “abstract” or a “summary” to be included in the poster, as a poster itself is an abstract of the research done. The other sections are optional: It is always a good practice to acknowledge the assistance provided by funding sources and gratefully acknowledge the contributions of individuals who provided guidance or technical assistance in the section entitled “Acknowledgment”. Since, networking is one of the primary aims of presenting posters; it is worthwhile providing your “Contact Information” (email and telephone numbers). The delegates can use this for seeking clarifications or additional information about your research or for inviting you for a collaborative research project or a guest lecture. The list of references referred to in the poster can be cited. For want of space, you may just cite the name of the first author and journal details. One may also include the title of the cited article if space is available. Some researchers prefer to position institutional logo in the lowermost section of the poster (where its size can be adjusted) than to include it in the banner (where a large-sized logo needs to be put up for ensuring balance with large-sized letters in the banner). It becomes almost imperative to include logos in the lower portion if multiple logos are to be depicted.

Design and Layout

Whether the poster layout is portrait or landscape, the banner runs across poster’s full-length, just below the top margin. It should stand out and be large enough (10-12 inches in height) to be easily read from a distance of 12-20 feet. The rest of the content needs to be divided into columns. This facilitates reading.

Alignment, balance and spacing are crucial aspects of designing a poster. Align headings, columns, graphs, figures and diagrams. The text should be left-aligned. Distribute the text and figures in a balanced manner so that the poster is aesthetically pleasing. Use only one or two font styles. One can use serif (for example, Times New Roman, Cambria) or non-serif/ sans serif (for example, Arial, Calibri, Tahoma, etc.) fonts for the title. You should, however, use a serif font for the main body of the poster; as serif fonts are easier to read when the font is smaller than usual. Do stay away from fonts that are too distinctive, clichéd or hackneyed. Print title, section headings and sub-headings in boldface; but not the whole poster content. Underlining the content for emphasis makes the poster look cluttered. Instead, use boldface or italics or a combination of both. But use this sparingly. Avoid using ‘all capitals’ (all letters in upper case) even for the title, as they are difficult to read. Ensure enough ‘white space’, use a margin of about an inch along all sides of the poster and employ adequate line-spacing. These will make the poster look neat and organized. White space (also called negative space) is an area that is not covered by any design element such as a word or a picture. Its importance cannot be over-emphasized. It guides the eye and ensures that other elements stand out. Too little white space makes the poster look jumbled and too much white space makes the poster look empty and viewers’ eyes start to wander. Consistency in use of font and in dimensions of illustrations, diagrams and figures provides a better look to the poster. Patterns or complex images should not be used in the background for scientific posters, as they tend to distract viewers. A colored poster definitely looks better than a ‘black and white’ or ‘grey’ poster. Colors help create contrast between the text and background and this should be considered while choosing colors. Use a light color for the background and dark color for text. Overly bright colors help attract attention, but then wear out viewers’ eyes. Restrict to two or four colors, usually white, black red, blue and green. Text printed in yellow usually is not seen well. Overuse of colors mars the visual appeal and is distracting and annoying. In addition, it does not comply with the sobriety expected of a scientific communication. Viewers, by force of habit, tend to read from left to right and from top to bottom. Use arrows, numbers or headings to assist the readers’ direction of reading.

Illustrations

Diagrams are used for showing complex methodological details and for explaining concepts, structures, processes and procedures. Charts or graphs are used for depiction of observations. The type of data determines the type of graph used. For example, frequency of different categories is depicted by a bar chart, while changes in levels of a parameter over a period of time are best shown using line diagrams. Providing a grey background to charts consumes costly ink and looks unsightly. Including gridlines in graphs is meaningless because the viewers are not interested in knowing exact values, anyway and they make the graph look “too busy”. The novelty of once popular 3-D charts has waned over a period of time. Avoid using 3-D charts, as they decrease the clarity and are viewed by most as a mere “gimmick”. Make sure that the graphics are simple, consistent in scale, properly labeled and large enough in size to be easily viewed from a distance of about four feet. Photographs are not commonly included in research posters, but are more commonly included in posters describing novel cases (Case Reports). Use photographs only if they contribute in explaining or emphasizing the message. Label every diagram, photograph and graph. Refer to every figure in the text for providing context. The illustrations should be clear.
Table 3: Making an Effective Poster\textsuperscript{7,9-11,17}

Content
- State the purpose of the poster in a clear manner taking into consideration the needs and general level of understanding of the conference delegates
- Include information only if it is novel and of value to the delegates
- Desist from providing unimportant or non-essential details
- Ensure that your central or core message is not tucked in margins or in an insignificant place. Put it in a central place so that viewers do not miss it
- Use active voice
- Avoid jargon. Use words, terms and expressions that the conference attendees would understand with ease
- Keep text elements fewer than 10 lines long. Do not exceed the 50-word limit
- Avoid use of complete sentences. Use phrases as bullet points. Reduce sentence complexity
- Present the information in a clear and ‘short and snappy’ way

Design
- Banner: Includes title (with large font size), author names and institutional affiliation. Should be large enough to be readable from a distance of 12-20 feet. The title should be 4-5 cm in height
- Columns: Breaking the text into columns increases the ease of reading
- Alignment: Align Headings, columns and graphs and figures. For example, the tops of columns should be aligned and the sections should be left aligned
- Make efforts to align the graphs, diagrams and figures (e.g. top edge of a figure in one column may be aligned with the bottom edge of a graph in another column)
- Balance and Spacing: Distribute text, images and diagrams in a balanced manner
- Ensure uncluttered look: Use margin along poster edges, adequate line spacing, enough white space
- Create a logical visual flow: Use headings, arrows or numbers to direct the viewer where to look next
- Other Aspects:
  - Font sizes: Title 72-120 pt.; Names and Affiliations: 48-60 pt.; Headings: 32-48 pt.; Text: at least 24 pt
  - Most prefer a serif font for the main text. Title can be written with serif or sans serif font
  - Title and headings should be bold. Text should not be bold
  - Text: Left justify, preferably bulleted. No bullets for headings
  - Color: Use of one or two colors enhances visual appearance and appeal
  - Use charts and diagrams, whenever necessary. They help make the poster less text-heavy and more visually appealing
  - Use photographs only if they are relevant to the purpose and help explain the message. Photographs, when used should be aesthetically pleasing, have proper exposure, focus, contrast and resolution
  - Be consistent in font (type and color), dimensions of diagrams and figures and color design

and properly proportioned. Avoid using images downloaded from the internet. Images that look good on computer screen, do not necessarily look good in a poster and may look excessively pixilated.\textsuperscript{9} They may also raise copyright infringement issues. High resolution images (200 dpi or higher) should be used; TIFF (tagged image file format) or GIF (graphics interchange format) images are the best. It is important to note that using drop-and drag method for adjusting the image size can result in a distorted image.\textsuperscript{10}

Many software programs can be used for creating posters: Microsoft PowerPoint, Adobe design programs such as Illustrator, In Design and Photoshop, Impress and LaTeX.\textsuperscript{10,16} Having decided on the content and software program, create the poster on the computer. Make sure that your page size is the same as the final print size.\textsuperscript{17} Take print outs of the draft and edit it thoroughly and ruthlessly to cut the jargon, reduce sentence complexity, and get rid of non-essential details.\textsuperscript{7} The salient issues are reiterated in Table 3.

Step 7: Seek feedback from peers regarding all aspects of the poster

Once you are satisfied with the draft share its printouts with your peers and request for feedback, comments and suggestions regarding the content of the poster as well as design.\textsuperscript{14} Share the printouts even with non-experts, whose suggestions regarding the designing aspects (free space, color combinations, clarity, ease of reading, etc.) can be helpful in improving the poster. Multiple checklists are available.\textsuperscript{7,9,11,12,18} You can use any one of them or prepare a composite checklist. Share it with your “assessors”, so that you get a more objective and structured feedback. Mount the draft poster and let your colleagues have a look at it. This may elicit a more honest critique.\textsuperscript{12} Study the comments received and implement the sensible suggestions. Ensure that the revised version meets the criteria set earlier for an effective poster. Take printout and repeat the process once more before you finalize the poster. Use spellchecker and proofread the material before the final printout. Complete the entire poster on a single platform. Switching from PC to Mac or vice versa invites disaster in the form of lost image files, changes in layout, alterations in font and garbled graph axes.\textsuperscript{11,12} To guard oneself from formatting trouble when transferring to another computer or platform is inevitable, convert your poster file into pdf or portable document format before transferring to the computer from which you will print.\textsuperscript{11}

Step 8: Prepare and finalize the presentation talk. Plan on how to encourage interaction

While the poster content is being finalized you need to simultaneously work on how you are going to present your poster to the attendees. You know a lot on the subject and especially about your own research project.
However, remember you are not preparing for a 30-minute talk on the subject. The time available for you to introduce your research to an attendee is going to be very short. It is better to prepare a two-minute speech (something akin to the “elevator talk”). To make it effective, you need to know the general profile of the attendees: would they be specialists in the field, generalists, specialists in another field, students or fellows. However, for most large meetings, the delegates would be a mix of different categories. You may, therefore have to prepare two-three levels of presentations (with different content and emphasis). You may prepare a one-minute talk (consisting of information about background delivered over 45 seconds and take-home messages given over 15 seconds) for those with general knowledge about the topic. Details should be provided only if explicitly asked for. Prepare a 3-5 minute presentation consisting mainly of methods and results for those with advanced knowledge about the subject. They are unlikely to require background information. Think about possible questions that the attendees may ask and formulate the answers. Show the script of the presentation-talk to colleagues and peers and invite their comments and suggestions. Practice the “talk” and “question-answer sessions” with your friends, family, colleagues and peers.

Devide a strategy for beginning the conversation when people visit your poster area.

**Step 9: Printing the poster**

Decide whether you will create poster yourself or outsource the work. Decide if you intend to print the poster on standard sheets of paper, matte finish bond paper, glossy paper or polyester fabric. Poster made of multiple sheets of paper is now outdated. Most scientific posters are now printed as large single glossy prints. Matte paper is water resistant in the sense that image won’t run, but the paper will become soggy in the rain. Glossy paper is the most commonly used material for printing scientific posters. It is water resistant and almost like photographic paper. Polyester fabric is wrinkle-resistant, fade-resistant, tear-resistant and waterproof. The text appears crystal clear and colors look more vibrant. The material can be folded and ironed. This is probably the best material for printing scientific papers, but is also quite expensive.

You will have to decide if you intend to take a printed “all-ready” poster to the meeting site or you wish to print it at the meeting site. The former option seems generally preferable. If you are not traveling far with your poster, it is sufficient to roll it up, secure it with a couple of rubber bands and take it to the conference venue. If you are traveling long-distance, it is better to put the rolled up poster in a cardboard or plastic tube. The plastic tubes are sturdier and come with straps that make them easy to carry. Another option is to ship the poster separately. Even when a ready-poster is being carried to the conference venue, it is prudent to carry a soft copy of the final version of the poster. The onsite printing option eliminates travel hassles, but is fraught with limited options and time for corrective actions, if any problems arise.

**Step 10: Putting up and discussing the poster**

In addition to your poster, it is better to carry other materials to ensure that you are not inconvenience while putting up the poster. Although, you may have prepared the poster as per the instructions provided, there can always be last minute challenges. Many presenters go an extra mile to try to make it foolproof, provide additional service to visitors and optimize the potential benefits (Table 4).

You should be wearing a professional attire. Your clothing and shoes should be comfortable, as you will be required to stand for a long period of time. When attendees come to view the poster have an eye contact and wish them. There are multiple ways of starting the conversation. You may start with introducing yourself and requesting for their names, starting the conversation. You may have an eye contact and wish them. There are multiple ways of starting the conversation. You may start with introducing yourself and requesting for their names, affiliation and field of interest. This will give you an idea about the nature of their expertise. Then offer to explain the salient features of the research study in a minute or two. Almost always, they would accept the offer rather than trying to figure out what has been depicted on the poster by themselves. If you are uncomfortable with this strategy or think that this is intrusive, you may allow them to read the poster and then offer to introduce your work

<table>
<thead>
<tr>
<th>Table 4: Items to carry for last minute challenges that may arise</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Poster</td>
</tr>
<tr>
<td>• Protective cardboard or plastic tube: Useful if you wish to save the poster for later use or repeat presentations</td>
</tr>
<tr>
<td>• Soft copy of the poster in pdf</td>
</tr>
<tr>
<td>• Poster holders: Clips, pins, push pins, heavy duty pins, velcro strips, single/ double-sided masking tapes, adhesive putty, tapes to attach, secure or stick the poster to the surface (cork boards, wooden boards, fiber boards, fuzzy fabric surfaces, glass surfaces, metal plates or wall) provided</td>
</tr>
<tr>
<td>• Pair of scissors</td>
</tr>
<tr>
<td>• A black pen and correction fluid for correcting the embarrassing typographical mistake discovered after putting up the poster</td>
</tr>
<tr>
<td>• A sign to hang on poster that reads “Will be back shortly” or “Will be back in 5 minutes”, when you are away</td>
</tr>
<tr>
<td>• A sign-up sheet for interested visitors for providing their email addresses for further interaction or receiving pdf of poster</td>
</tr>
<tr>
<td>• Printed copies of your Abstract and poster on A4-sized paper for distribution</td>
</tr>
<tr>
<td>• A note pad and pen: To jot down visitors’ unanswered questions, contact details of visitors worth contacting</td>
</tr>
<tr>
<td>• Business cards</td>
</tr>
<tr>
<td>• A clear cup full of candy</td>
</tr>
</tbody>
</table>
in 10 seconds and offer to answer questions.  

While speaking, make an eye contact with the visitors. Talk to them (without referring to the notes) and not to the poster.  

Point to important figures and charts on the poster. Intermittently, check if they have understood what you have said (especially regarding the technical aspects) and offer to answer questions. Work all the visitors at once, don’t leave visitors waiting for your attention.  

You know the most about your research and your subject. And your knowledge, passion and excitement should be evident. When the attendees ask questions, take time to understand them before beginning to answer. If you do not know the answer, just admit it and speculate with the person or ask what he might do. You may even take down the individual’s contact information and promise to get back to him. Remember, the visitors who ask questions are not checking your knowledge or challenging your expertise. So there is no need to be combative. They may be attempting to gain information or seeking clarifications. These interactions can provide you with new insights.  

During interactions, speak with confidence with a voice that is a bit high on volume. You need to be heard in a busy, crowded place. Speak at low speed (tendency to speak quickly is interpreted to indicate nervousness) without fillers (“um”, “uh”, “you know”, etc. which detract your message) and without vague or meaningless phrases. Do not chew tobacco or gum while explaining the poster. Many people find these habits repulsive.  

After the presentation ask for feedback. Based on the comments, make the changes for the next presentation. If there is a possibility of collaboration, hand over your business card and also ask for the visitor’s contact details. Hand over a copy of the printed abstract or printed poster to interested visitors. Thank everyone for their interest in your research work.  

**Step 11: Picking up the threads after the scientific meeting**  
Your work isn’t over once the poster is folded and brought back at the end of the meeting. Remember the objectives when you decided to present the poster. Go over the notes that you have taken while exhibiting the poster. Thank experts and others who viewed your poster and offered insightful comments. Write to people who asked for additional information or clarifications. Write to those, whose questions remained unanswered. Dissemination of research findings was one of the main aims of presenting the poster. With presentation, this aim has only partially been met. You now need to take steps to publish the paper in a reputed peer-reviewed scientific journal. Do not forget that published papers always carry a greater value as they undergo a much more thorough formal review process, are available as a permanent record and are widely read and distributed. Go over the feedback and suggestions that you received during presentation and implement those that will help you improve the manuscript. These actions will help build your reputation in the scientific community as a serious, sincere and committed scientist.  

**References**  
2. Rowe N, Illic D. What impact do posters have on academic knowledge transfer? A pilot survey on author attitudes and experiences. BMC Medical Education 2009; 9:71  
19. Campbell RS. How to present, summarize and defend your poster at the meeting. Respir Care 2004; 49:1217-21.  
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Number Needed to Treat

NJ Gogtay, UM Thatte

Introduction

When any patient is treated with a drug, device, vaccine, or undergoes surgery or even an investigation with a diagnostic test in a clinical research setting, two broad outcomes are possible - the patient gets better [benefit] or the patient gets worse [harmed]. An important aspect of research is to meaningfully summate data obtained in terms of measures of effect that can readily be understood and used by physicians and researchers alike. A measure that is a single number that can be used to compare both benefits and harms of two or more preventive, diagnostic, therapeutic, or rehabilitative approaches would be extremely useful. One such single number is the “Number Needed to Treat” (NNT) and is defined as the number of patients that need to be treated with an intervention [relative to another intervention] in order for it to have an impact [benefit or harm] on one patient.

Since the NNT applies in equal measure to both benefit (B) and harm (H), the terms NNT-B and NNT-H are used to indicate them. We have used this convention throughout this article. However, in literature, the reader may find that the term “NNT” is used synonymously for benefit (NNT-B) while the “Number Needed to Harm” (NNH) is used to indicate the NNT-H. We also discuss in this paper, a lesser-known metric, the Number Needed to Screen [NNS], one that is useful for policy makers for the use of screening tests in populations.

History and Origins of the Number Needed to Treat [NNT]

The concept of NNT was first introduced in 1988 by Laupacis et al., who defined it as “the number of patients a clinician should treat in order to prevent one adverse outcome”. Its original intended use was for benefit. The NNT concept is essentially one based on noting the frequency of occurrence of an outcome [benefit or harm] measured as a cumulative incidence of that outcome per number of patients followed up over a given time period of time. This will result in a proportion of patients with the outcome over time [out of the total number followed up], which we then write as a percentage.

Understanding NNT-B, how it is Calculated and its Clinical Applications

Simply put, NNT equals the reciprocal of the Absolute Risk Reduction [ARR]. Let us understand the calculation and application of NNT using the example of a paper by Boonen and colleagues. The authors evaluated the efficacy of intravenous Zolendronic acid vs. placebo in preventing fractures in a double-blind, randomized controlled trial. They randomized n = 1199 men with primary or hypogonadism-associated osteoporosis who were between 50 and 85 years of age to receive either 5 mg of intravenous Zolendronic acid or placebo at the beginning of the study and at 12 months. The endpoint of interest was the proportion of patients with one or more new morphometric fractures over a period of 24 months.

The results of the study were as follows – 28/574 [4.87%] men who received placebo developed fractures over 24 months compared to 09/553 [1.68%] men who received Zolendronic acid, with the difference being statistically significant [p = 0.002].

What the authors have done here is really evaluate the association between the use [or lack thereof] of Zolendronic acid and the reduction in number of fractures. From a previous article on Measures of Association, you would remember the 2 x 2 table that we use to present this type of binary [fracture/no fracture] data. We will use the same table now to calculate the NNT-B [Table 1] in three steps.

Step 1

We first calculate the Absolute Risk [AR] of getting fracture in both groups. We use AR1 to indicate the risk of fractures with placebo and AR2 for the risk with Zolendronic acid. This measure

<table>
<thead>
<tr>
<th></th>
<th>Number of men with fractures</th>
<th>Number of men without fractures</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>28</td>
<td>546</td>
<td>574</td>
</tr>
<tr>
<td>Zolendronic acid</td>
<td>09</td>
<td>544</td>
<td>553</td>
</tr>
</tbody>
</table>

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Received: 03.07.2017; Accepted: 07.07.2017
would be calculated as a proportion (or a percentage) of the number of patients who developed fractures with either treatment.

Thus, Absolute Risk [AR1] for getting fractures with placebo would be

\[
\frac{28}{574} = 0.0487 \text{ or } 4.87\% 
\]

And the Absolute Risk [AR2] for getting fractures with zolendronic acid would be

\[
\frac{9}{553} = 0.0168 \text{ or } 1.68\% 
\]

For the sake of simplicity, we round off these values to 5% and 2% respectively in the subsequent calculations.

**Step 2**

It is obvious from the data that the Zolendronic acid group has a significant protective effect as it has fewer fractures relative to placebo. Thus, there is a risk difference [RD] between the two groups and we calculate this next. The risk difference is simply the difference between the two absolute risks or AR1 - AR2, and is also called Absolute Risk Reduction [ARR]

Thus, the ARR would be 5% - 2% or 3% (i.e. 3/100 = 0.03)

**Step 3**

The final step is the actual calculation of NNT-B, which is given by the formula

\[
\text{NNT-B} = \frac{1}{\text{ARR}} 
\]

\[
\text{NNT-B} = \frac{1}{0.03} = 33 \text{ patients.} 
\]

How did we arrive at this formula and thus the number?

If Zolendronic acid were to be completely ineffective [which would be our null hypothesis], the fracture risk with both Zolendronic acid and placebo would be identical at 5%. The ARR would then be zero [5% - 5%]. Zolendronic acid is however effective and only 2% patients treated with it get fractures relative to the 5% treated with placebo. If we were to see the impact on 100 patients, 2/100 would get fractures with Zolendronic acid and 5/100 with placebo. Thus, every time that n = 100 patients are treated with Zolendronic acid [rather than placebo], 3 patients [5 minus 2] would be spared the adverse outcome [fractures in this case]. Thus, if 1 patient were to be spared the adverse outcome, how many patients would be needed to be treated with Zolendronic acid?

This would be

\[
\frac{100 \times 1}{3} 
\]

Or 33 patients.

You will realize that we have already arrived at this number using the formula 1/ARR

Thus, NNT-B is that single number which tells the practicing clinician about the number of patients he would need to treat with one intervention rather than another, to prevent one adverse outcome [for a defined period under defined conditions]. It can also be defined as the number of patients that would need to be treated with one intervention rather than another, to prevent one additional adverse outcome.

In our example, we can interpret the NNT-B as follows - A total of 33 patients need to be treated with Zolendronic acid [rather than placebo] to prevent one patient from getting african [or additional fracture] over a 24-month period.

A perfect NNT-B would really be 1! This means that every time one patient is treated, one patient is prevented from getting an adverse outcome. It is intuitive that as the NNT-B increases, fewer and fewer patients would be helped. As a general rule of thumb, lower the NNT-B, the better is the treatment. For example, Quetiapine monotherapy has an NNT - B of 6 and the combination of olanzapine and fluoxetine an NNT - B of 4, both single digit NNTs relative to their placebo comparators for the management of acute bipolar depression [approved by the US FDA].

On the other hand, Zolendronic acid [relative to placebo; the Pivotal Fracture Trial,] was approved for its anti-fracture use [also by the US FDA] for the management of postmenopausal osteoporosis with a NNT of 14 for new morphometric vertebral fractures and a NNT of 91 for hip fractures. A very low NNT thus may not always be possible or necessary to allow for marketing approval and would depend upon the disease, outcome and intervention being evaluated.

**Number Needed to Treat-harm [NNT-H]**

The number needed to treat that we have discussed above is for benefit. A similar metric is the number needed to treat to harm or NNT-H or NNH as it is frequently referred to in literature is defined as the number of patients who need to be treated with one intervention [rather than another] for one patient to be harmed or for one patient to have an adverse outcome. Let us understand this as well with a published example.

Monteleascot G and colleagues evaluated n=4033 patients with non-ST segment elevation [NSTEMI] acute coronary syndromes to assess the effect of the timing of administration of Prasugrel (a P2Y12 antagonist) à vis à vis the angiography, on major ischaemic events within 30 days (Table 2). The patients were divided in a 1:1 ratio into two groups- one that received 30mg of Prasugrel pre-angiography followed by 30 mg Prasugrel post angiography in the event that percutaneous intervention [PCI] was undertaken and the second group that received placebo initially followed by 60mg of Prasugrel in the event that percutaneous intervention [PCI] was needed. Safety was assessed according to the Thrombolysis in Myocardial Infarction [TIMI] criteria of major and minor bleeding episodes regardless of whether or not they were related to the PCI. The safety data of the two groups is described in Table 2. The group that received Placebo pre-treatment
followed by 60 mg of Prasugrel had fewer bleeding episodes and this difference was statistically significant [p = 0.003].

Similar to the NNT -B, we calculate the NNT -H or NNH in 3 steps.

**Step 1**

The absolute risk of bleeding with Prasugrel (30 mg) pre-angiography [AR1] followed by 30 mg post intervention is 52/2037 or 2.6%. The absolute risk of bleeding with Placebo pre-angiography followed by 60 mg Prasugrel post intervention is 52/1996 or 2.6%. The study was increased the rate of bleeding that pre-treatment with Prasugrel the authors of the paper concluded bleeding episode [harm]. The will experience a major or minor lesser likelihood of harm relative to [60 mg], one placebo followed by Prasugrel [30 mg], one additional patient will experience a major or minor bleeding episode [harm]. The authors of the paper concluded that pre – treatment with Prasugrel increased the rate of bleeding complications. The study was also stopped by the Data Safety Monitoring Committee for safety concerns.

Unlike the NNT-B, the NNT-H or NNH should be high as this indicates lesser likelihood of harm relative to the comparator. For example, the NNT- H of Valbenazine, a newly approved drug for the management of Tardive Dyskinesia is 76 [for discontinuation due to an adverse event] compared to a NNT - B of 4 [both NNT-B and NNT-H being relative to placebo comparator] over a six-week period.10

**Likelihood to be Helped or Harmed [LHH] – the Ratio of NNH to NNT**

Since interventions can produce both benefits and harm, any comparison of two interventions will produce two NNTs – one for benefit [NNT-B] and one for harm [NNT-H]. A lesser-used metric called the “Likelihood to be helped / harmed” [LHH] is calculated as the ratio of NNT-H to NNT-B since treatment decisions are almost always a trade-off between harm and benefit. Intuitively, the value of LHH should be greater than 1 and the further away from 1 that the value is, greater is the likelihood that the intervention produces more benefit than harm. Let us understand this with an example.

Srivastava and Ketter7 in their eloquent narrative review evaluated RCTs that studied quetiapine, olanzapine and lamotrigine among other drugs for the management of acute bipolar depression [all studies with placebo comparators]; a difficult to treat disorder. Quetiapine [a second-generation anti-psychotic] had a NNT-B of 6 and a NNT-H of 6 for sedation giving a LHH for efficacy: sedation LHH value of 3.5. The LHH values thus indicate superiority of Lamotrigin over quetiapine and quetiapine over olanzapine [in that order] in terms of risk vs. benefits, thus enabling the clinician to make an informed choice.

**The Number Needed to Screen [NNS]**

National strategies for disease screening to identify patients at risk of developing disease or with yet undetected disease [for example, use of the Prostate Specific Antigen (PSA) for the diagnosis of prostate cancer or mammography for the detection of breast cancer] require evidence that measures the value addition that any screening test provides. The Number Needed to Screen [NNS] is one such metric and was first developed by Rembold in 199811 as a metric to define the number of people that are needed to be screened to prevent one death or one adverse event or one life-year gained. While it is conceptually similar to the metrics of NNT-B and NNT-H, its calculation differs slightly.

We require the knowledge of two elements before beginning the calculation of NNS:

- The background risk or prevalence of the disease in the population
- Knowledge of mortality or an adverse outcome in screened and unscreened cases

Let us now understand the steps in the calculations of NNS with an example.

**Step 1** - Calculate the cumulative rate of deaths in the two groups

**Unscreened group** - The Cancer Intervention and Surveillance ModelingNetwork (CISNET) USA,
estimates that the mortality from breast cancer in the absence of any screening mammography would be 3% for a woman aged 40 years or older. Thus, the death rate without screening would be 3% or 30 per 1000 women screened.

Screening group- Let us assume that a screening technique X is developed that reduces mortality by 90%. Now the deaths will be 3 per 1000 women screened.

**Step 2 –Calculate the number of deaths prevented [lives saved] due to screening**

Because intervention X is 90% effective, 27 lives per 1000 women screened are saved [or deaths prevented]

**Step 3- Calculate the number needed to screen as the reciprocal of the absolute difference in cumulative mortality**

Since 27 deaths were prevented for 1000 women screened, for one death to be prevented, 1000/27 or 37 women would need to be screened [NNS = 37 for an intervention that reduces mortality by 90% from 30/1000 to 3/1000].

If intervention Y were to produce only a 10% reduction in morality, 0.1 x 30 = 3 lives per 1000 women screened would be saved

Thus, to save 1 life, 1000/3 or 333 women need to be screened [NNS = 333 for an intervention that produces a 10% reduction in mortality]

Logically therefore, the lower the NNS, the more useful is the screening test.

**Challenges Associated with the Use of NNTs**

Interpret with caution and with an understanding of the baseline risk

A risk is essentially the probability that something will happen. If we toss an unbiased coin once for instance, the “risk” of heads would be 50%. Similarly, we can define risks in medicine as well. Let us take a hypothetical example of a drug A reducing the risk of dying of myocardial infarction from 3% to 2%. The NNT would be 100. Drug B reduces the risk of dying from rabies from 100% to 99%. The NNT is again 100. These NNTs simply cannot be compared! The reason is that rabies is a disease with 100% mortality [baseline risk] and even a 1% reduction [giving a NNT of 100] will make a huge impact to the disease. In the MI example, while the NNT of 100 is the same, given that the baseline risk of death itself is low, the 1% reduction may or may not really be meaningful. Thus, any comparison of NNTs [benefits or harm] must be made with a clear understanding of the baseline risks that are involved.

When NNTs are needed to be calculated for “time to an event”

When we carry out survival analysis [time to an event analysis], the calculation of the number needed to treat can become difficult as patients will have varying follow up times and some of them may be censored as well. The calculation is thus significantly dependent upon time. In survival or time to an event study, we use the term NNT[t] and calculate more than one NNT[t] at several time points [which can be fixed in advance]. The calculation at each time point is based on the survival probability at that time point which is estimated either by the Kaplan-Meier method or Cox regression method. A time specific NNT[t] is defined as the average number of patients needed to be treated to observe one event-free patient more in the intervention group relative to the control group at a given time point t.

**Presenting NNTs in Research Papers – Key Points to be Remembered**

Though NNTs are now widely used, their reporting in literature is less than optimal. The following need to be remembered while presenting NNTs in publications.

**Confidence Intervals for the Number Needed**

Similar to other measures we estimate in statistics [for example risk ratio, odds ratio] where we give confidence intervals to help the reader gauge the margin of error or uncertainty that was seen with the study, the number needed to treat similarly needs to be accompanied by a confidence interval. Several methods exist for the calculation of CIs and the Wald method is a commonly used one.

**Stating the direction of effect**

Although the NNT was originally devised as a measure of benefit, as interventions can produce both harm and benefit, simply stating the NNT without giving the direction [benefit or harm] can become difficult for the reader. Thus, the terms NNT-B to indicate benefit and NNT-H are recommended for use while presenting this metric.

**The importance of stating the comparator**

Since the NNT makes use of Absolute risks in both groups, it is logical that both groups are alluded to when presenting the NNT. However, this does not happen routinely in literature. For instance, simply stating that Drug X has a NNT of 25 makes no sense, unless the comparator Drug Y is clearly stated.

**Stating the time frame of the study**

Randomized controlled trials [RCTS] are often conducted over a long period of time. Hence stating the time frame along with the presentation of the NNT becomes very important. Let us understand this with an example. Study 1 compares two treatments X and Y over a two-year period and yields a NNT-B of 25. Study 2 compares two treatments A and B over a 10-year period and gives a NNT-B of 25. Though the NNT – B for both studies are identical, it is a very different matter to produce benefit in 1 patient for every 25 patients treated over 2 years versus over 10
years! Thus, mentioning the time frame for the study is a crucial component for presenting the NNT. In the example of association of fractures with Zolendronic acid, the NNT of 33 is over a 24-month period.

**Criticisms of the NNT**

Katz N and colleagues in their eloquent narrative review have put together evidence on and summarized the challenges associated with the use of the NNT. These range from the NNT having an infinite value when the ARR is zero or close to zero [when the interventions tested have very similar effects], to the NNT being dependent upon the choice of the binary outcome or not translating into the same NNT value when the intervention is actually used in the real-world setting.

**NNT and the Cost and Reimbursements of Treatments**

Graziano and colleagues have suggested that the NNT can be used by policy makers for pricing negotiations with the pharmaceutical industry and have expounded on this using the example of NNT for regorafenib [salvage therapy for metastatic colorectal cancer, the CORRECT trial].

**Conclusions**

RCTs report results in a wide variety of ways that include relative risk, odds ratio, hazard ratio and the p value when two interventions are being compared. Many clinicians have difficulty in translating these findings into actual patient care as the answer to the question “which therapy between the two should I use in my patient?” is often not clear to them. The NNT offers clinicians a “yardstick” for measurements as it helps compare benefits and harms of treatment by converting them into a single number. It helps practicing clinicians make an informed choice when more than one intervention is available. The explanation and elaboration document of the CONSORT guidelines suggest that the NNT-B and NNT-H can be presented as metrics for binary data from Randomized Controlled Trials. Clinicians should learn how to derive and use NNT from results of RCTs as the reciprocal of the Absolute risk difference. However, since benefits and risks are two sides of the same coin, each intervention in a RCT would have both a NNT-B and a NNT-H and both need to be considered in tandem so as to make careful, individualized, patient-centric as also policy decisions.

**Acknowledgment**

The authors are grateful to Dr. Robin Fener from the West Midlands Centre for Adverse Reactions Monitoring, Birmingham, for his constructive inputs that helped refine the manuscript.

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¹ Indian Medical Gazette 2006: 72-75  ² Arq Pharmacother 2003 May;37(5):701-10

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A 35 year old female presented in the emergency room with history of focal seizures involving the right side of the face. There was also history of nystagmoid eye movements during the episode. There was history of similar episodes of seizures since childhood. There was no history of any comorbid illness. Patient had mild mental retardation since childhood. She was born of a non-consanguineous marriage with no family history of any seizure disorder. On examination, the patient was conscious, oriented, afebrile, no neurocutaneous markers were found. Intelligent Quotient (IQ) was 70. Pupil 3mm equally reacting to light on both sides. Fundus examination was normal. Mild ataxia was noted. There was no limb weakness. All deep tendon jerks were normal. Plantars were flexor. On investigating the patient, the hemogram, renal and liver function tests were normal. Random blood glucose was 120mg/dl. Ultrasonogram of abdomen and pelvis was normal. MRI Brain (T2 Axial) also showed Bat wing appearance of fourth ventricle (Figure 1). MRI Brain (T2 Axial) showed typical molar tooth sign (MTS) (Figure 2).

Joubert syndrome (JS) was originally described in 1968 in four siblings with agenesis of the cerebellar vermis presenting with episodic hyperpnoea, abnormal eye movements, ataxia and intellectual disability. Several years later, a pathognomonic midbrain-hindbrain malformation, the “molar tooth sign” (MTS), was detected first in JS, and then in several other conditions previously considered as distinct entities. The term “Joubert syndrome and Related Disorders” (JSRD) was then coined to group all conditions sharing a characteristic MR appearance of the MTS, and this neuroradiological sign now represents the mandatory criterion to diagnose JSRD. Molar tooth sign is a characteristic MR appearance of brainstem which results from cerebellar vermis hypoplasia, thick and maloriented superior cerebellar peduncles, and an abnormally deep interpeduncular fossa. The incidence of JSRD ranges between 1/80,000 to 1/100,000 livebirths. There is severe hypo-dysplasia of cerebellar vermis with eftling in midline, fragmentation of cerebellar nuclei and heterotopia of Purkinje-like neurons, along with dysplasia of pontine and medullary structures such as the basis pontis, reticular formation, inferior olivary, dorsal column and solitary tract nuclei. Moreover, typical findings are represented by the lack of decussation both of the superior cerebellar peduncles and of the corticospinal tracts at the medullary pyramids. 10 causative genes have been identified all of which encode for proteins of primary cilium, this means that JSRD can be included as a ciliopathy. The cardinal neurological features of JSRD are hypotonia evolving into ataxia and developmental delay, often associated with intellectual disability, altered respiratory pattern in the neonatal period and abnormal ocular movements. Less common clinical features include seizures, hemifacial spasms, polydactyly, colobomas, ptosis, renal cysts, soft tissue tumours of tongue and occipital meningocele. The diagnosis of JSRD is suspected in patients presenting with hypotonia, oculomotor apraxia, nystagmus and abnormalities of respiratory pattern. The management is essentially symptomatic with antiepileptics. This case highlights the rare association of Joubert syndrome with seizures presenting with a typical radiological sign on imaging study.

References
Hydropneumopericardium

Rajeev Bhardwaj¹, Vandana², Vivek Rana³, Brij Sharma⁴

A 61 years male presented with pain in epigastrium and cough for two weeks. He also had dyspnoea for same duration, which was more on lying down. On examination, his BP was 94/74 mm Hg, Pulse 92/min, with presence of pulsus paradoxus, respiratory rate was 28/min. His JVP was 10 cm above the sterna angle. Apex beat was not palpable. Heart sounds were feeble and there was presence of pericardial friction rub. ECG showed sinus tachycardia with heart rate of 100/min, regular, with normal voltage. He was subjected to X-ray of chest P/A view, which showed air fluid level within the cardiac shadow (Figure 1). Suspecting hydro-pneumo pericardium, he was subjected to X-ray of chest in lateral decubitus position. There was shifting of air fluid level (Figure 2). Echocardiography showed presence of pericardial effusion, and on shaking the patient, air bubble could be appreciated. CT scan of chest showed suggestion of communication of pericardial cavity with esophagus (Figure 3). Endoscopy showed suggestion of esophageal tear with regular margins. Pig tail drainage of pericardial cavity was done It showed proteins 3.5 gm%, no sugar, WBC 4800/cubic mm, mostly lymphocytes and adenosine deaminase level was 64 IU/L. Culture of fluid was sterile. The patient also subjected to esophageal covered stent implantation (Figure 4). No antibiotics were given. He was put on antitubercular treatment but died after around one week.

Spontaneous pneumopericardium is a rare event, several causes have been proposed. These include trauma, infectious secondary to gas-producing bacilli in the pericardial fluid, fistula formation-secondary to perforation of a neighbouring viscus such as oesophagus, stomach, liver abscess or bronchus and iatrogenic, secondary to pericardiectomy, and assisted positive pressure ventilation. Infection spreading to the pericardium following oesophageal perforation is usually devastating, with a survival rate of only 17 percent in one review of 60 such patients. Spontaneous pyopneumopericardium is reported following bacterial infection also.

The first report of an esophago-pericardial fistula was published in 1838 and in a recent review by Hamid et al less than 100 cases have been reported to date, most of them in adult patients. Mortality rate was very high in the past (83% as reported by Miller) and we think this is in accordance with diagnostic delay, development of purulent pericarditis, severe sepsis and previous general health deterioration.

Several factors can influence the choice of the surgical technique: size of the fistula, coexistence or not of purulent pericarditis, primary disease, esophageal impairment and technological resources availability in the setting. General support and broad-spectrum antimicrobial therapy complete the tripod upon which patient’s life is kept, but early diagnosis and treatment is still the key for survival. Thus a greater clinical awareness is needed.

References


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Received: 05-10-2016; Accepted: 30-03-2017
Glucose-6-Phosphate Dehydrogenase Deficiency Unveiled by Diabetic Ketoacidosis: A Dual Dilemma

Pankti Mehta¹, Vishal Srivastav¹, Priya Bhate², Vishal Gupta², Milind Y Nadkar³

Abstract
An 18 year old male, known case of Type 1 Diabetes Mellitus was admitted in view of diabetic ketoacidosis. With normalization of blood sugars patient developed gross reddish discoloration of urine. Urine routine microscopy did not reveal RBCs or RBC casts. Peripheral blood smear revealed bite cells, Heinz bodies and spherocytes. Thus a diagnosis of hemolytic anemia with hemoglobinuria was made. Patient’s glucose-6-phosphate dehydrogenase (G6PD) levels were below the normal range. G6PD, an enzyme of the HMP shunt, is the most common enzyme defect causing hemolytic anemia. G6PD deficiency related hemolytic crisis is most commonly precipitated by infection, drugs or fava beans. Its association with DKA has been seldom reported.

Introduction
Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common enzymatic disorder of red blood cells. G6PD is an enzyme involved in the pentose monophosphate pathway in the production of NADPH and regeneration of reduced glutathione. G6PD deficiency causes uncontrolled reactive oxygen species mediated damage to the erythrocytes, which in turn causes hemolysis. It is an X-linked disorder with high prevalence in malaria endemic regions i.e. Africa, Mediterranean and South East Asia. G6PD deficiency related hemolytic crisis is most commonly precipitated by infections, drugs or fava beans. Hemolysis due to G6PD deficiency in patients with Type 1 Diabetes Mellitus (T1DM) is uncommon. This case report aims to draw attention to this lesser known yet important phenomenon.

Case
18 year old male, born of a non consanguineous marriage, no siblings, known case of Type 1 Diabetes Mellitus since 5 years taking regular subcutaneous insulin injections, with no other co-morbidities, presented to the emergency department of another hospital with history of 6-7 episodes of vomiting and watery loose stools associated with fever and abdominal pain. On examination, patient was conscious, oriented, afebrile, with a pulse rate of 108/min, thready, with shallow acidotic breathing with a respiratory rate of 36/min, no lymphadenopathy or organomegaly, chest clear. Random blood glucose value by hemoglucotest was 401 mg%. Investigations on admission are listed in Table 1.

On admission, hemoglobin, total bilirubin and reticulocyte count were within the normal range. Other investigations such as chest radiograph, electrocardiogram, Ultrasonography Abdomen, and 2D echocardiography were within normal limits.

Thus a diagnosis of Diabetic ketoacidosis precipitated by acute gastroenteritis was made and the patient was started on insulin drip, hydration and other supportive care.

Patient gradually improved, blood glucose levels declined to less than 250 mg%. However, on day 3 of admission, patient developed gross reddish discoloration of urine. Patient was referred to our hospital for further management. Repeat investigations showed a sudden drop in hemoglobin a with normal platelet count and normal coagulation parameters. However, no significant RBCs or RBC casts present on urine routine examination. Ultrasonography and Computed Tomography of the Kidneys and Urinary Bladder were carried out to rule out any local cause and were within the normal limits. Investigations on day 3 of admission are listed in Table 1.
Table 1: Investigations

<table>
<thead>
<tr>
<th>Investigations</th>
<th>Day 1</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>13 g/dL</td>
<td>9.5 g/dL</td>
</tr>
<tr>
<td>Reticulocyte count</td>
<td></td>
<td>15%</td>
</tr>
<tr>
<td>WBC</td>
<td>8700/cmm</td>
<td>9500/cmm</td>
</tr>
<tr>
<td>Platelet</td>
<td>1.4 L/cmm</td>
<td>2.52 L/cmm</td>
</tr>
<tr>
<td>Random blood glucose</td>
<td>372 mg/dL</td>
<td>233 mg/dL</td>
</tr>
<tr>
<td>BUN</td>
<td></td>
<td>11 mg/dL</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.69 mg/dL</td>
<td>2.5 mg/dL</td>
</tr>
<tr>
<td>AST/ALT</td>
<td>26/30 IU/L</td>
<td>123/16 IU/L</td>
</tr>
<tr>
<td>T. Bilirubin</td>
<td>1.72 mg/dL</td>
<td>4.9 mg/dL</td>
</tr>
<tr>
<td>D. Bilirubin</td>
<td>0.9 mg/dL</td>
<td>0.8 mg/dL</td>
</tr>
<tr>
<td>Na</td>
<td>127 mEq/L</td>
<td>132 mEq/L</td>
</tr>
<tr>
<td>K</td>
<td>3.3 mEq/L</td>
<td>3.6 mEq/L</td>
</tr>
<tr>
<td>pH</td>
<td>7.26</td>
<td></td>
</tr>
<tr>
<td>pCO₂</td>
<td>16.1 mmHg</td>
<td></td>
</tr>
<tr>
<td>pO₂</td>
<td>142.8 mmHg</td>
<td></td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>7.3 mmol/L</td>
<td></td>
</tr>
<tr>
<td>Saturation</td>
<td>98.9%</td>
<td></td>
</tr>
<tr>
<td>Serum ketone</td>
<td>10.1 mg/dL</td>
<td></td>
</tr>
<tr>
<td>HbA1c</td>
<td>5.5 gm%</td>
<td></td>
</tr>
<tr>
<td>Calcium</td>
<td>9 mg%</td>
<td></td>
</tr>
<tr>
<td>Phosphorus</td>
<td>3.6 mg%</td>
<td></td>
</tr>
<tr>
<td>Uric acid</td>
<td>5.1 mg%</td>
<td></td>
</tr>
<tr>
<td>Urine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteins</td>
<td>Absent</td>
<td></td>
</tr>
<tr>
<td>Sugars</td>
<td>Trace</td>
<td></td>
</tr>
<tr>
<td>Ketones</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>Occult blood</td>
<td>Absent</td>
<td></td>
</tr>
<tr>
<td>Pus cells</td>
<td>Nil</td>
<td></td>
</tr>
<tr>
<td>RBCs</td>
<td>1-2/HPF</td>
<td></td>
</tr>
</tbody>
</table>

Peripheral blood smear examination revealed microcytosis, macrocytosis, hypochromasia, occasional micspherocytes, Heinz bodies and bite cells as shown in Figure 1.

On further work up of the patient, LDH levels came to be 5,520 IU/L (80-300 IU/L), serum Haptoglobin levels < 7.19 mg/dl (30-200mg/dl). Thus a provisional diagnosis of intravascular hemolytic anemia with hemoglobinuria was made. A G6PD enzyme assay was sent which was suggestive of G6PD deficiency, levels of which were 1.86 IU/gHb (4-13 IU/g Hb).

Other causes of hemolysis were ruled out such as Hemolytic Uremic Syndrome (HUS), Hypophosphatemia, Infections, Drugs, Autoimmune Hemolytic Anemia (AIHA) and Paroxysmal Nocturnal Hemoglobinuria (PNH). HUS was suspected in view of acute gastroenteritis with hemolytic picture on peripheral blood smear with raised creatinine however platelet count was normal. Hypophosphatemia can cause hemolysis as DKA\(^2\) commonly causes low phosphorus levels but they were within the normal range. No hemolysis inducing drugs were used. Coombs test was negative hence ruling out AIHA. PNH profile, i.e. Flow cytometry for CD55 and CD59 was normal. Infections could not be ruled out completely as a precipitating factor as acute gastroenteritis could have caused hemolysis however blood and urine cultures were sterile.

Thus a Diagnosis of Type 1 Diabetes Mellitus with Diabetic Ketoacidosis with G-6-PD deficient hemolytic crisis with pigment hemoglobinuria and acute kidney injury was made.

During further course in ward, patient’s hemoglobin dropped to 5.5 g/dl and was transfused with two units of packed red blood cells. Insulin and intravenous hydration was continued. Blood sugars and urine ketones were monitored. With the control of blood sugars and resolution of ketoacidosis, hemoglobinuria and hemolysis subsided on its own. Repeat G6PD assay was planned for a later date to classify the severity of G6PD deficiency (Table 2).\(^3\) Patient was counseled regarding the nature of the disease, food and drugs to be avoided (Table 3)\(^3\) and discharged without any further complications.

**Discussion**

We hereby describe a case of type 1 DM with ketoacidosis. Common complications of ketoacidosis include hypokalemia, cerebral edema, vascular thrombosis, acute kidney injury, acute respiratory distress syndrome; however in this case depicts an unusual complication of DKA which is hemolysis. Blood tests revealed G6PD deficiency. This phenomenon of unknown G6PD deficiency manifesting as hemolysis in a patient of DKA has been rarely observed, acute stress being a common factor precipitating both DKA and hemolysis. The association of DKA and G6PD deficiency was first reported in 1984 (Shalev Et al)\(^4\) and sporadic cases describing this underrated phenomenon have been reported since then.

G6PD is a cellular housekeeping enzyme that catalyzes the first step in the hexose monophosphate shunt (HMP) wherein Glucose-6-phosphate is converted to Ribose-5-phosphate, the latter being a precursor for RNA, DNA, ATP, coenzyme A, Nicotinamide adenine dinucleotide (NAD) etc. Another function of the HMP shunt is to maintain a supply of NADPH which acts as a cofactor for GSH\(^1\). The flowchart (Figure 2) describes the pathway for the same.

Most cells have alternative enzymatic pathways that can generate NADPH however as the RBCs lack a nucleus, mitochondria and other necessary organelles, they are solely dependent on G6PD and HMP shunt for maintaining high levels of NADPH and GSH for protection against oxidative stress.\(^1\)

G6PD is encoded by a gene located on the telomeric region on long arm of X chromosome (Xq28) consisting of 13 exons and spanning 18 kb. Males express G6PD deficiency whereas female are
Glutathione metabolism

Fig. 2: Glutathione metabolism

Table 2: WHO classification of G6PD allelic variants

<table>
<thead>
<tr>
<th>Class</th>
<th>Level of deficiency</th>
<th>Enzyme activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Severe</td>
<td>&lt;10% enzyme activity, chronic non-spherocytic hemolytic anemia</td>
</tr>
<tr>
<td>II</td>
<td>Severe</td>
<td>&lt;10% enzyme activity, intermittent hemolysis.</td>
</tr>
<tr>
<td>III</td>
<td>Moderate</td>
<td>10-60% enzyme activity, hemolysis with stressors.</td>
</tr>
<tr>
<td>IV</td>
<td>Mild-None</td>
<td>60-150% enzyme activity, no clinical sequelae</td>
</tr>
<tr>
<td>V</td>
<td>None</td>
<td>&gt; 150% of normal, no clinical sequelae</td>
</tr>
</tbody>
</table>

G6PD deficiency was first recognized in early 1950s during the Korean War when approximately 10% of African American soldiers developed primaquine induced hemolytic anemia. 

G6PD deficiency is the most prevalent human enzyme deficiency, its geographic distribution coinciding with that of endemic malaria implicating a survival benefit. 

The most common allelic variants of G6PD are G6PD A which is prevalent in Africa and G6PD Mediterranean prevalent in countries surrounding the Mediterranean Sea, India, and the Middle East. The WHO classification of allelic variants is as given in Table 2.

Oxidant injury to RBCs leads to oxidation of sulfhydryl groups on hemoglobin leading to formation of disulfide bridges and in turn decreased hemoglobin solubility and precipitation of oxidized hemoglobin. Normally, oxidized hemoglobin is reduced by GSH, which itself gets oxidized in the process but is restored by NADPH whose levels are maintained by G6PD.

In G6PD deficient individuals, GSH is not restored adequately leading to building up of free radicals and oxidative stress and formation of insoluble hemoglobin precipitates visualized under the microscope as ‘Heinz’ bodies. Precipitated hemoglobin is disruptive to the structure and function of RBCs leading to intravascular hemolysis and resultant visualization of ‘Bite cells’ or hemiblister cells.

G6PD deficiency as a disease can manifest as:

1. Congenital Non spherocytic Hemolytic Anemia- in class 1 G6PD variants.
2. Neonatal Jaundice
3. Drug induced: Symptoms of acute hemolysis occur 2-4 days after drug ingestion and is associated with 2-4 g/dl drop in hemoglobin.
4. Fava beans: Develops within 5-24 hours of ingestion-Divicine and isouramil present in fava beans play a role in precipitating hemolysis.
5. Infection induced hemolysis
6. Chemicals- Naphthalene and anti fungal sprays
7. Diabetic Ketoacidosis

Type 1 Diabetes Mellitus is an autoimmune disease caused by a T cell mediated reaction against pancreatic β-cells. This reaction leads to insufficient to absent production of insulin. Type 1 Diabetes Mellitus is characterized by the presence of auto antibodies (anti- Insula and anti- GAD antibodies) that sometimes induce diabetes outset. The disease’s etiology is still not clear but it is known that there is an interaction between the environment and polygenic traits. Hemolysis in patients with diabetic ketoacidosis (DKA) has been related to bacterial infections, hemolytic drugs, hypophosphatemia, hypoglycemia, blood glucose normalization, and glucotoxicity.

The correlation between diabetes and G6PD deficiency is still a controversy. It could be due to correction blood glucose towards normal values during treatment of DKA which leads to a relative glucose deprivation for the energy dependent functions of the red blood cells causing premature
Intensive blood glucose control case of deficiency one should avoid in Type 1 diabetic patients and in G-6-PD levels should be assessed causing premature red blood cell destruction. The sulphydryl group availability to oxidative stress and a loss of cell destruction is an increased sensitivity of RBCs to oxidative stress and a direct effect of this phenomenon. Deficient cells in oxidants response peroxidation, which occur in G6PD dysfunction. This loss of NADPH to preserve all energy-dependent functions. This loss of NADPH enhances the rate of all factors such as methaemoglobin generation, Heinz body formation, and lipid peroxidation, which occur in G6PD deficient cells in oxidants response to reactive oxygen species. The direct effect of this phenomenon is an increased sensitivity of RBCs to oxidative stress and a loss of sulphydryl group availability causing premature red blood cell destruction. In conclusion, hemolysis may be attributed to relative hypoglycemia during blood glucose normalisation. G-6-PD levels should be assessed in type 1 diabetic patients and in case of deficiency one should avoid intensive blood glucose control which may cause hemolysis in these patients.

Ketoacidosis itself causes hemolysis in the African but not Mediterranean variant of G6PD. Oral Hypoglycemic Agents like Metformin⁸ or glibenclamide⁹ have been responsible in causing hemolysis in G6PD deficient subjects however our patient was only on insulin.

The sole feature common to all the cases of acute hemolysis reported in diabetic patients is that the hemolysis occurs after diabetes decompensation. This suggests that hyperglycemia may induce hemolysis. Experimental data show that hyperglycemia can reduce expression of the G6PD gene and activity of the enzyme. Therefore, A G6PD deficiency can not only be due to mutations in the gene coding for it but also due to defects in factors regulating the transcription and activity of the enzyme.

(1) hormones or growth factors, (2) oxidative stress, (3) and post-translational regulation. Hormones and growth factors such as insulin, estrogen, and epidermal growth factor (EGF) have been shown to induce the expression of G6PD, and vitamin D₃ may increase G6PD activity, deficiency of which can manifest as G6PD deficiency. In terms of oxidative stress, G6PD mediated NADPH production helps in maintaining a cellular redox state and preventing oxidative damage to cellular components. Mutations that predispose the cells to oxidative stress may result in decreased G6PD expression. Finally, in terms of post-translational regulation, a classic phosphorylation/dedephosphorylation mechanism may affect functional control of G6PD activity.¹¹

Conversely, it has been observed that defects in the G6PD gene correlate with diabetes and G6PD deficiency can promote oxidative stress and free radical mediated impairment of insulin secretion by beta cells thus contributing as a predisposition to Diabetes Mellitus.¹²

Also, it has been observed that patients with G6PD deficiency have lower HbA1c compared to the normal ones because the average life span of erythrocytes is reduced in G6PD deficient individuals.¹³

Thus in our case the precipitant of hemolysis could have been the energy deprivation of RBCs or the stress of infection that precipitated DKA. Drugs and chemicals to be avoided in G6PD deficient individuals are listed in Table 3.³,¹⁴

**Conclusion**

We have thus reported the case of a patient presenting with a diabetic crisis with ketoacidosis, which was complicated by hemolysis secondary to G6PD deficiency.

Key learning points in this case are:

In a G6PD deficient diabetic patient, hemolysis can be due to hypoglycemia,⁶ infection, hyperglycemia, drugs, ketoacidosis,⁸ hypophosphatemia,² blood glucose normalization.⁷

G6PD levels should be assessed in patients of Type 1 Diabetes Mellitus especially from Mediterranean origin and in case of deficiency one should be less aggressive in treating hyperglycemia.⁷

Levels of HbA1c are lower in diabetic patients with G6PD deficiency.¹³

There may be increased incidence of Type 2 Diabetes in G6PD deficient individuals due to oxidative stress.¹³¹²

**References**


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**Table 3: List of agents to be avoided in G6PD deficient individuals¹,²**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs</td>
<td>Antimalarials: Primaquine</td>
</tr>
<tr>
<td></td>
<td>Sulfonamides and</td>
</tr>
<tr>
<td></td>
<td>Sulfones: Cotrimoxazole, Dapsone</td>
</tr>
<tr>
<td></td>
<td>Nitrofurantoin</td>
</tr>
<tr>
<td></td>
<td>Antipyretics: Antipyrine</td>
</tr>
<tr>
<td></td>
<td>Analgesics: Phenacetin</td>
</tr>
<tr>
<td></td>
<td>Quinolone: Nalidixic Acid, Norfloxacin</td>
</tr>
<tr>
<td></td>
<td>Methylene blue</td>
</tr>
<tr>
<td>Herbal</td>
<td>Chinese herbal preparations</td>
</tr>
<tr>
<td>Medicine</td>
<td>Vaccines</td>
</tr>
<tr>
<td>Moth balls</td>
<td>Naphthalene</td>
</tr>
<tr>
<td>Insecticides and Fungicides</td>
<td></td>
</tr>
<tr>
<td>Fava/Broad beans</td>
<td>Aniline dyes</td>
</tr>
<tr>
<td>Food coloring agents</td>
<td>Chinese herbal preparations</td>
</tr>
</tbody>
</table>

red blood cell lysis. In normal red blood cells, G6PD provides a source of NADPH for maintaining sulphydryl groups (SH) and facilitating the detoxification of free radicals and peroxides. This process needs energy which is exclusively supplied by glucose that is present in a large quantity due to the hyperglycemia. During insulin infusion this excessive glucose availability progressively decreases thus aggravating the inability of the senescent red blood cells to generate NADPH, and thus to preserve all energy-dependent functions. This loss of NADPH is a classic phosphorylation/dedephosphorylation mechanism may affect functional control of G6PD activity.


Mirror Aneurysm with Right Frontal ICH in a Patient with Osteogenesis Imperfecta

Vijay Sardana¹, Sumit Kamble², Sunil K Sharma², Dilip Maheshwari³, Bharat Bhushan³

Abstract

Osteogenesis imperfecta (OI) is a heterogeneous group of inherited disorders that occur owing to the abnormalities in type 1 collagen, and is characterized by increased bone fragility and other extraskeletal manifestations. OI may be associated with vascular complications such as aortic and cervical artery dissection, carotid cavernous fistula, and coronary artery aneurysms but unlike other connective tissue diseases, the cerebrovascular system is less frequently involved. We report a rare case of a 50 year female patient who was diagnosed with OI following right frontal haemorrhage secondary to a ruptured middle cerebral artery mirror aneurysm.

Introduction

OI is an inherited connective tissue disorder, caused by abnormalities in type 1 collagen, and is characterized by bone fragility and other extraskeletal features, including hearing loss, blue sclera, dentinogenesis imperfecta and hyperlaxity of ligaments and skin. It may lead to a wide range of associated neurologic abnormalities, and may also be associated with cavernous fistulas and dissection of carotid artery, and cerebral aneurysms. It has been reported that the exon 28 polymorphism of collagen type 1 alpha-2 gene (COL1A2) may predispose patients to intracranial aneurysms (IA).¹ In our case, OI was diagnosed following right frontal haemorrhage secondary to a ruptured middle cerebral artery mirror aneurysm.

Case History

A 50 year old female was admitted with acute onset headache since 1 day followed by one episode of generalised tonic clonic convulsion and left hemiparesis. On general examination patient had blue sclera (Figure 1), and dentinogenesis imperfecta (Figure 2). Neurologic examination revealed...
Glasgow coma scale 15/15 and mild left hemiparesis, with fundoscopy suggestive of vitreous haemorrhage (Figure 4). Patient also had past history of multiple fractures (thrice) associated with minor trauma before puberty. Family history of blue sclera in daughter (Figure 3), sister and mother was obtained. Clinical diagnosis of OI type 1A was kept.

Patient’s biochemical investigation including coagulation profile and serum bone metabolism markers were normal. Patient CT head showed right frontal hematoma (Figure 5). MR angiography (Figure 6) and cerebral digital subtraction angiography (DSA) showed bilateral M1 MCA bifurcation saccular mirror aneurysms (Figure 7). A series of radiographs showed old healed fracture in right clavicle and diffuse osteopenia (Figure 8). Genomic DNA testing for mutations in \textit{COL1A1} and \textit{COL1A2} could not be done because of financial limitations.

Patient was managed conservatively and was discharged with advising regarding neurointervention for aneurysm.

**Discussion**

Osteogenesis imperfecta, with estimated incidence of approximately 1 per 20,000 births, is a genetic disorder affecting the bones, ears, eyes, skin and other structures that contain a substantial amount of type I collagen. Most patients with OI have an autosomal dominant mutation in \textit{COL1A1} (located at 17q21.31-q22) or \textit{COL1A2} (located at 7q22.1) that affects the structure of one of the two alpha chains of type I collagen; these genes account for approximately 80% of cases of OA. Eight clinico-pathogenetic types share the common feature of bone fragility of which OI type 1, the case we describe, is least severe and commonest variety of OI accounting for approximately 50% of cases. Other well-described clinical features of type 1 OI include blue sclera, conductive hearing loss, ligamentous laxity and rarely dentinogenesis imperfecta. Diagnosis is usually established on the basis of a strong family history of OI or recurrent fractures, fractures occurring in a setting of minimal trauma especially in children, and a prominent scleral bluish hue. There is no definitive, readily available lab test for OI. Sequence analysis of cDNA or genomic DNA testing of white blood cells for mutations in \textit{COL1A1} and \textit{COL1A2} can detect 90% or more of all collagen type I mutations. With strong positive family history, history of recurrent fractures and blue sclera it can be presumed that this patient is clinically OI, although tests for mutation in the \textit{COL1A1} or \textit{COL1A2} gene were not done.

A prominent pathologic feature of cerebral artery aneurysms is reduced collagen content. A key feature of vessel wall competence, which is breached in the aneurysm setting, is collagen cross-linking, which affords the vessel tensile strength. OI is commonly associated with mutations for type I collagen genes, possibly causing amount reduction or structural variation which may result in weakening of arterial wall resulting in aneurysm formation. Alternatively vascular dissection may be the dominant pathomechanism of OI-related vascular disease with resultant pseudoaneurysm formation.

Mirror aneurysm are presence of paired or “twin” unruptured intracranial aneurysms located in similar positions bilaterally on the parent arteries. There estimated range is < 5% of all patients with unruptured intracranial aneurysms. According to Casimiro et al, mirror aneurysm are more likely to be unaccompanied by conventional risk factors like hypertension or smokings. Degenerative changes at arterial junction caused by hemodynamic stress on prior weakened vessel wall due to OA may predispose patients to mirror aneurysm at arterial junction. Compared with extracranial arteries of similar size, the internal elastic lamina of intracranial arteries...
is slightly thicker, but the adventitia and media are thinner. The adventitia lacks an external elastic lamina, and the media is devoid of elastic fibers, which may be the cause of multiple aneurysm intracranially than elsewhere in the body. It is hypothesized that bifurcation of vessel which is weakened due to abnormal type 1 collagen in OI is more prone for adventitial injury due to hemodynamic stress leading to mirror aneurysm formation at arterial bifurcation bilaterally. To best of our knowledge Mirror aneurysms has not been reported till date in OI.6,7

To the best of our knowledge, IA in patients with OI has been reported in only seven cases, and there are no such case reports from India (Table 1).

**Conclusion**

There may be some causative relationship between OI and IA because there are several reported cases of cerebral aneurysm in patients with OA. We propose that it may be worthwhile to screen patients with OI for asymptomatic aneurysm in order to prevent complications of ruptured IA.

**Table 1: Case reports of IA with OA**

<table>
<thead>
<tr>
<th>Authors (year)</th>
<th>Age, Sex</th>
<th>Location</th>
<th>Shape</th>
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</thead>
<tbody>
<tr>
<td>Okamura T, et al. (1995)1</td>
<td>33 F</td>
<td>A-com A</td>
<td>Saccular</td>
</tr>
<tr>
<td>Petruzzellis M, et al. (2007)4</td>
<td>44 M</td>
<td>VA union</td>
<td>Saccular</td>
</tr>
<tr>
<td>Matouk CC, et al. (2011)5</td>
<td>49 M</td>
<td>SCA</td>
<td>Dissection</td>
</tr>
<tr>
<td>Kaliaperumal C, et al. (2011)6</td>
<td>53 M</td>
<td>VA</td>
<td>Saccular</td>
</tr>
<tr>
<td>Hirohata T et al. (2014)7</td>
<td>37 F</td>
<td>MCA</td>
<td>Saccular</td>
</tr>
<tr>
<td>Our case (2016)</td>
<td>50F</td>
<td>MCA</td>
<td>Saccular</td>
</tr>
</tbody>
</table>

Absence of infrarenal inferior vena cava presenting with varicose veins

Mithun Kumar Kola1, S Sandeep2, Sri Harish Vankayalapati3, M Srinivas Reddy

**Abstract**

Inferior vena cava (IVC) anomalies were rare and usually asymptomatic. Among these, anomalies absence of infra-renal IVC is the rarest anomaly. Absence of infra-renal IVC may present with symptoms of venous insufficiency and idiopathic deep vein thrombosis. Contrast enhanced CT and MRI abdomen play crucial role in diagnosing these anomalies. These patients can be managed conservatively or by venous bypass. Identification of these anomalies is important to avoid surgeries for varicose veins.

**Introduction**

Inferior vena cava (IVC) anomalies are etiologically either true embryonic anomalies or the result of perinatal thrombosis. These anomalies are left IVC, double IVC, absent infrarenal IVC, circumaortic left renal vein, retroaortic left renal vein, retrocaval ureter and interruption of IVC withazygos and hemiazygos continuation. Among these, the absence of infra renal IVC is the rarest. Absent infra renal IVC usually presents with venous insufficiency and idiopathic deep vein thrombosis. Contrast enhanced CT and MRI abdomen are diagnostic tools.

**Case Report**

A 70 yrs old female patient presented with complaints of dull aching pain in both legs. Physical examination shows lower limb varicose veins and abdominal wall collaterals. Duplex scan of lower limbs shows superficial varicose veins in both lower limbs with dilated great saphenous vein in right lower limb secondary to incompetent saphenofemoral junction; also dilated great saphenous vein in left leg secondary to mid calf perforator incompetence, dilated left short saphenous vein with incompetent saphenopopliteal junction and no evidence of deep vein thrombosis. In order to evaluate lower limb varicosities and abdominal wall collaterals contrast enhanced CT abdomen (Figures 1 and 2) was done, and it interestingly showed the absence of infra renal IVC and

**References**


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both common iliac veins with multiple collaterals in lower pelvis, para pelvic gutter and along para vertebral region draining into prominent azygous and hemiazygous veins. Another interesting finding in this case was relatively prominence of right gonadal vein along with pelvic collaterals draining into the right renal vein. Thus the final diagnosis of absent infra renal IVC causing lower limb varicosities and abdominal wall collaterals was made.

Discussion

In 1793, Abernethy first reported IVC anomalies. IVC is formed from three paired veins. These are posterior cardinal veins, supra cardinal veins and sub cardinal veins. IVC has four segments: hepatic, supra renal, renal and infra renal. Hepatic segment is derived from vitelline vein, supra renal segment from right sub cardinal vein, renal from supra cardinal and post sub cardinal anastomosis and infra renal segment from right supra cardinal vein.1

Classification of IVC anomalies is based on the embryonic vein from which it is derived. Left IVC, double IVC and absent infra renal IVC were anomalies of supra cardinal veins. Retro aortic left renal vein, circumaortic left renal vein were anomalies of aortic collar. Anomaly of posterior cardinal veins is retrocaval ureter. And the anomalies derived from sub cardinal veins is interruption of the IVC with azygos and hemiazygos continuation.2

Absence of infra renal IVC with preserved supra renal segment is a rare anomaly. And it is due to developmental failure of posterior cardinal veins and supra cardinal veins. Patient with absence of infra renal IVC may present with symptoms of lower limbs varices, collaterals and idiopathic deep vein thrombosis.3 In the present case also patient presented with lower limb varicose veins and abdominal wall collaterals.

Contrast enhanced CT and MRI abdomen with 3D reconstructions like maximum intensity projection, multi planar reconstruction and volume rendering will help in the diagnosis of IVC anomalies.3 These patients are usually managed conservatively. Anticoagulation is the standard treatment for patients with deep vein thrombosis. If conservative treatment fails, venous bypass graft may be considered.4

Conclusion

Absent infra renal IVC is manifested by symptoms of venous insufficiency and idiopathic deep vein thrombosis. So, it is important to be aware of such a condition in the patients presenting with lower limb varicose veins and abdominal wall collaterals for the selection of appropriate management strategies. Contrast enhanced CT or MRI abdomen are diagnostic imaging tools. These patients are usually managed conservatively or by venous bypass graft if conservative treatment fails. Identification of these anomalies is important to avoid unnecessary surgeries in varicose veins.

References

Giant Cell Arteritis Presenting as PUO

Sham Santhanam¹, Sampath Kumar Mani²

Abstract
Giant cell arteritis (GCA) is a primary granulomatous vasculitis affecting the large and medium sized arteries. We present here a case of GCA with pyrexia of unknown origin (PUO) as the presenting manifestation in the absence of other typical features. On evaluation, the patient had raised inflammatory markers with features of large vessel vasculitis on whole body PET-CT scan. The colour doppler ultrasonography (CDUS) of the temporal arteries showed bilateral halo sign. Since bilateral ‘halo sign’ is more specific for the diagnosis of GCA, temporal artery biopsy is not mandatory. If CDUS is not conclusive, then biopsy can be considered being an invasive procedure.

Introduction
Giant cell arteritis (GCA) is also referred to as ‘temporal arteritis’, is a primary granulomatous vasculitis affecting the large and medium sized arteries. It usually affects adults older than 50 years. The common symptoms are headache, fever, weight loss, jaw claudication and visual symptoms associated with elevated inflammatory markers. Here, we report a case of GCA with pyrexia of unknown origin (PUO) as the initial presenting manifestation and in the absence of other typical manifestations.

Case Report
A 61 year old male presented with high grade fever and chills of 1 month duration. He had no associated cough, dysuria, rashes, joint pain, abdominal pain, malena or altered bowel habits. He had no recent travel history. He had reduced appetite, but there was no significant weight loss. He had no comorbidities or history of tuberculosis in the past. He was a smoker and had stopped smoking since 1 year. On examination, he had bilateral axillary nodes of 2 X 2 cm size. Otherwise, all his system examinations were within normal limits. He had a hemoglobin of 10.3 g/dl, total leukocyte counts of 8820 cells/cu.mm, platelets of 2,12,000 cells/cu.mm and ESR of 54 mm/hour and CRP of 185.1 mg/L. His peripheral smear revealed normocytic normochromic anemia, but had no abnormal cells or parasites. His Chest X ray and urine routine was normal. All infectious disease work-up including culture, serologies were negative. Computed Tomography (CT) of the chest and abdomen were normal. Excision biopsy of axillary node was suggestive of reactive lymphoid hyperplasia. As a part of PUO workup, PET-CT scan of the whole body was done. On PET-CT scan there was symmetrical linear metabolic activity associated with peri-arterial fat stranding in bilateral axillary, subclavian, carotid, aortic arch, thoracic aorta, descending aorta and bilateral iliac arteries suggestive of a large vessel vasculitis (Figure 1). In view of his age, a diagnosis of giant cell arteritis was considered and colour doppler ultrasonography (CDUS) of both the superficial temporal arteries were done. The temporal arteries had an increased diameter with ‘halo sign’ (Figure 2) present on both sides (Maximum thickness of halo was 1.4 mm on the right and 0.9 mm on the left side). Hence, the diagnosis of GCA was confirmed. Since the presence of bilateral ‘halo signs’ is more specific for diagnosis of GCA, temporal artery biopsy was not done. The patient was started on oral prednisolone at a dose of 1 mg/kg with calcium and vitamin D supplements and patient improved symptomatically. To our knowledge, very few cases of GCA with PUO as the presenting manifestation has been reported in literature.²,³

Discussion
GCA is a chronic granulomatous vasculitis with a special predilection for extracranial branches of carotid arteries.¹ GCA is rare in Asian population, with only small case series and isolated case reports published from India.³,⁴ Most of the cases reported from India were in the age group of

Fig. 1: PET-CT scan of whole body shows increased uptake in the aorta (from arch of aorta to abdominal aorta) and its major branches (bilateral axillary, subclavian, carotid arteries and both iliac arteries)

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unilateral ‘halo sign' has a sensitivity of 82% and specificity of 91%. If it is present on both sides, then the specificity increases to 100%. Similarly in our patient, the demonstration of bilateral halo sign confirmed the diagnosis of GCA and hence there was no need for a temporal artery biopsy. We should remember that CDUS is an observer dependent test and involvement of temporal artery can also be found in other conditions like Behcet syndrome, polyarteritis nodosa, ANCA(Anti neutrophil cytoplasmic antibody) associated vasculitis,10,11

The typical findings of large vessel vasculitis in a MRI are wall thickening and increased mural gadolinium contrast enhancement. It has a sensitivity of 81% and specificity of 97%. PET-CT scan of whole body can be considered in patients with fever and inflammation of unknown origin. It can be considered in patients with suspected large vessel vasculitis with negative biopsy, absent halo sign on CDUS and absent wall thickening on MRI, as it can detect early inflammation. In atherosclerosis there will be an increased uptake, but it will be patchy and of less intensity in comparison to the diffuse and high intensity uptake in LVV. PET-CT also helps in the detection of features suggestive of an associated Polymyalgia rheumatica.12

The gold standard test for diagnosis of GCA is temporal artery biopsy. It is an invasive procedure and it can be false negative due to the presence of skip lesions. In patients with palpable abnormalities of the vessel, smaller segment (1-2 cms) may be excised. But in others, a larger section (4-6 cms) of the vessel has to be excised and multiple sections need to be studied by the histopathologist.1

The initial treatment is oral steroids at a dose of 1mg/kg/day for a period of 4 weeks. Then, the steroid dose has to be gradually tapered every week or every 2 weeks by 10% till a dose of 20 mg and after that even slowly.1 Intravenous methylprednisolone can be given as a pulse therapy in patients with visual complications. On a long term, drugs like methotrexate, tocilizumab, abatacept, ustekinumab may be considered as steroid sparing agents. Since patients might be on long term steroids, measures to prevent side effects like osteoporosis must be initiated early.13

Conclusion

In the algorithm for diagnosis of GCA, clinical examination and inflammatory markers can be followed by CDUS of both the temporal arteries. It is a simple non invasive tool compared to the invasive temporal artery biopsy. If CDUS demonstrates ‘halo sign’ in bilateral temporal arteries, then the diagnosis is confirmed without need for a biopsy. If CDUS is not conclusive, then temporal artery biopsy can be done. If the biopsy is also negative, then PET-CT of whole body can be done on the background of a strong clinical suspicion.10

References

Ataxia in a Young Female

R Jayanthi, K Monica, K Raja, CS Gauthaman, PP Arunkumar

Abstract

Neurofibromatosis type 2 (NF2) is a genetically inherited disorder characterized by the presence of multiple central nervous system tumours, most pathognomonic being bilateral vestibular schwannomas with or without peripheral manifestations in the form of cataract or cutaneous neurofibromas. NF2 is an uncommon disorder compared to NF1. We describe a classical case of neurofibromatosis type 2 with florid clinical manifestations and characteristic neuroimaging features. We also briefly describe the literature pertaining to this rare disorder. The case also emphasizes the fact that NF2 should be considered in the list of differentials for ataxia especially when it is associated with sensory neural hearing loss.

Introduction

Neurofibromatosis type 2 (NF2) is a rare disorder. Bilateral vestibular schwannomas are pathognomonic of type 2 neurofibromatosis. This is an autosomal dominant inherited disease results from mutations involving NF2 gene on chromosome 22. NF2 diagnosis is based on the constellation of clinical and imaging features. Despite advancements in imaging modalities and surgical techniques, prognosis is rather grim and many with NF2 still die young. We report a classical case of NF2 with some unique features and briefly review the literature on this rare disorder.

Case Report

A 25 year female presented with defective hearing, visual impairment and gait unsteadiness. It was progressive hearing loss affecting both ears right more than left and progressive loss of vision more pronounced in the left eye. Eventually she developed unsteadiness while walking. She also had history of difficulty in getting up from squatting position; however there was no history suggestive of distal muscle weakness in lower limb or any motor weakness in the upper limb. Her past, personal and family history were not contributory.

General physical examination revealed two subcutaneous hemispherical swellings one in the paraspinal region 3*3 cm and another one in the pectoral region 6*4 cm. Neurological assessment showed features suggestive of bilateral cerebellar dysfunction, second, fifth and eighth cranial nerve involvement and sensorimotor involvement. Direct ophthalmoscopy revealed papilledema right and optic atrophy left (Figure 1). FNAC of swelling came as neurofibroma. Pure Tone Audiometry revealed right profound and left mild sensory neural hearing loss. Contrast MRI of brain revealed bilateral large sized cerebello pontine angle tumours with obstructive hydrocephalus and brainstem compression (Figure 2). To substantiate sensorimotor involvement a nerve conduction study was done, which showed axonal type of sensory motor polyneuropathy. According to NIH and Manchester diagnostic criteria a diagnosis of Neurofibromatosis type 2 was made.

She underwent retromastoid suboccipital subtotal excision of the tumour and the lesion was sent for histopathologic examination. It revealed Verocay bodies pathognomonic of schwannoma (Figure 3).

Discussion

The neurofibromatoses consist of at least two distinct autosomal dominantly inherited disorders, neurofibromatosis 1 (NF1) and neurofibromatosis 2 (NF2).

Historically, these conditions were aggregated as generalized neurofibromatosis (von Recklinghausen disease). NF2 was first described by Wishart in 1822. The heritable nature of NF2 was reported in 1920 by Feiling and Ward, who described a three-generation family with vestibular schwannomas (VS). The autosomal dominant transmission (i.e. a 50 percent risk of transmission from an affected parent) was confirmed in a large family reported by Gardner and Frazier in 1930. NF1 was delineated by von Recklinghausen in the late nineteenth century. Harvey Cushing aggregated NF1 and NF2 in 1916, and his scientific stature was such that, despite reports that the conditions were different, many decades were to pass before the distinction between the two diseases was widely recognized.

NF2 is a dominantly inherited genetic disorder resulting from mutations involving NF2 gene in chromosome 22.1 The disease first described by Wishart in 1822 is indeed arare condition and has prevalence estimated to be about 1 in 60,000. The hallmark phenotypic manifestation...
is vestibular schwannoma which is often bilateral. Vestibular schwannoma occurs in as high as 95% of adult patients with NF2. Epidermomas, meningeomas, and schwannoma involving other cranial nerves are all well-described. Skin manifestations like café au lait spots and neurofibromas may occur in NF2 but are less florid compared with its type 1 counterpart. Axillary or inguinal freckling, Lisch nodules, and malignant transformation of tumors practically never occur in NF2. Instead patients with NF2 may have posterior subcapsular lenticular opacities. Clinical diagnosis is used to be based upon the National Institutes of Health (NIH) criteria.

NIH diagnostic criteria for NF2 are as follows:  
1. Bilateral masses of the eighth cranial nerve seen with appropriate imaging techniques.  
2. A first-degree relative with and unilateral mass of the eighth cranial nerve.  
3. A first-degree relative with and any two of neurofibroma, meningeoma, glioma, schwannoma, or juvenile posterior subcapsular lenticular opacity.  

However, 50% of patients with NF2 present without the presence of a positive family history and many present with tumors or lenticular opacity prior to development of acoustic neuromas. Hence, the diagnostic criteria were subsequently revised to permit the diagnosis of NF2 in these subgroups of patients. The Manchester clinical diagnostic criteria allow diagnosis of NF2 in the aforementioned subgroups with maximum sensitivity.

Manchester clinical diagnostic criteria  
1. Bilateral vestibular schwannomas  
2. First-degree family relative with neurofibromatosis type 2 and unilateral vestibular schwannoma or any two of the following: meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities  
3. Unilateral vestibular schwannoma and any two of the following: meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities  
4. Multiple meningeomas (two or more) and unilateral vestibular schwannoma or any two of the following: Schwannoma, glioma, neurofibroma, cataract.  

Most common clinical presentation includes hearing loss and tinnitus. Other symptoms include disturbances in balance, headache, reduced vision, and facial numbness. Neuroimaging [computed tomography or magnetic resonance imaging (MRI)] helps in demonstrating the craniospinal tumors. Genetic studies and mutation analysis confirms the diagnosis. Management of NF2 often confers a major challenge to the treating doctor with respect to the timing of surgery, type of surgery, and surgical approach. Despite these dilemmas, surgical removal remains the treatment of choice. Surgical management by an expert team is found to confer significant benefit to the patient. However, surgery even in expert hands is associated with a variety of major complications like complete hearing loss and facial nerve damage. Patients who are poor candidates for surgery or those who refuse surgery may be considered for radiation therapy or experimental therapeutic modalities. Being autosomal dominant disorder, children of affected parents should be screened regularly for the phenotypic manifestations of NF2 mutation. Neurological examination, ophthalmologic evaluation, and annual auditory brain stem response are recommended. Imaging modality of choice for screening for neural tumors is MRI. MRI for screening is recommended every 2 yearly until 20 years of age and after 20 years every 3 yearly.

Our patient fulfilled the diagnostic criteria for NF2. As described classically, the patient has involvement of vestibulocochlear, trigeminal nerves, and evidence of raised intracranial tension. Imaging had also revealed bilateral cerebellopontine angle tumor. The constellation of these clinical features and neuroimaging is consistent with the diagnosis of NF2.

**Conclusion**

This case is reported for certain unique features such as associated sensory motor polyneuropathy of axonal type and chronic papilledema, secondary to obstructive hydrocephalus as a cause of severe visual loss.

**References**

Artery of Percheron Infarction in a Patient with Atrial Fibrillation: A Rare Stroke Syndrome

Amey Beedkar¹, Archana Sonawale²

Abstract

The artery of Percheron uncommon anatomic variant that provides bilateral arterial supply to the paramedian thalami and the rostral midbrain. Occlusion of this artery results in bilateral thalamic and mesencephalic infarctions. The clinical diagnosis is difficult because of the large clinical variability. We report the clinical and MR imaging findings in a patient who developed infarction in the typical distribution of the artery of Percheron.

Introduction

The thalami and midbrain have a complex blood supply. An important anatomic variation of the blood supply of bilateral median part of thalamus is the origin of both paramedian arteries from a single pedicle which is known as the type B artery of Percheron.²

Occlusion of the artery of Percheron causes bilateral paramedian thalamic infarction with or without midbrain infarction. The prevalence of arteries of Percheron is unknown. Due to a large number of blood supply variants, an ischemic infarction in this territory presents with variable and non-specific clinical symptoms. The goal of this paper is to report a case where the diagnosis of an artery of Percheron infarction was made retrospectively, due to an unspecific clinical presentation.

A Case Report

58 yrs. married female who was a known case of Rheumatic heart disease with mitral stenosis and atrial fibrillation presented to our hospital with symptoms of altered sensorium since 3 days.

Patient was apparently alright 3 days back when she went to sleep, she slept through an entire day and was difficult to arouse. She would wake up to painful stimuli and would lapse back into sleep as soon as stimulus was withdrawn. After much effort when patient was awakened, relatives noticed that the she was disoriented in time and place and had irrelevant talk. Medical help sought on 3rd day of symptoms.

There was no fever, headache, vomiting, convulsions.

On admission, her heart rate was 110/minute and irregularly irregular, blood pressure was 150/100 mm Hg, respiratory rate was 18/minute. On neurologic examination, her Glasgow Coma Scale (GCS) score was 7/15 (E1M5V1).

Cranial nerves examination revealed bilateral ptosis, bilateral divergent squint, no nystagmus, upward gaze palsy was present, pupils bilaterally dilated 5-6 mm, sluggishly reacting to light

Other cranial nerves examination normal

On motor system; all limbs were moving in response to painful stimuli. All brainstem and deep tendon reflexes were present. Plantar reflex was flexor on both sides.

No abnormal involuntary movements were seen

Investigations are shown in Table 1

Chest X-ray was normal

Capillary blood glucose was found to be 123 mg/dL. The electrocardiogram showed atrial fibrillation.

MRI brain showed an abnormal hyperdensity seen in bilateral paramedian midbrain and in bilateral medial part of thalami corresponding with areas of restricted diffusion suggestive of acute infarct in territory of artery of Percheron with mild cortico-cerebellar atrophy (Figures 1 to 4)

MR angiography of brain was normal.

The patient was started on mannitol, aspirin, atorvastatin, metoprolol in standard recommended dosages. Low molecular heparin was also given which was later overlapped with and then switched to oral warfarin, with dose titration to achieve an INR of

<table>
<thead>
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<th>Table 1: Investigations</th>
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<tr>
<td>Hemoglobin 13.8 gm%</td>
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<td>TLC 5400 cumm albumin 4.1 g/dl</td>
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<tr>
<td>Platelets 3.4 lac/</td>
</tr>
<tr>
<td>BUN 8 mg/dl</td>
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<tr>
<td>Creatinine 1.1 mg/dl</td>
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<td>Na+ 145 mg/dl</td>
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<tr>
<td>K+ 3.6 mg/dl</td>
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<td>Cl- 106 mg/dl</td>
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<td>Uric acid 6.8 mg/dl</td>
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</table>

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vertical gaze palsy (65%), memory impairment (58%), confusion (53%), and coma (42%). This patient presented with typical features of this stroke syndrome over her course of time. The changes in mental status may be due to involvement of reticular activating system and the interruption of connections between the thalamus and parts of the prefrontal cortex involved in behavioral control. Early diagnosis is best made by a diffusion-weighted imaging (DWI) sequence MRI.

In the case reported here, conventional MR imaging and the diffusion-weighted imaging confirmed the presence of infarction in bilateral thalamic and left anteromedial midbrain region typically seen in occlusion of the artery of Percheron. These infarcts should be recognized as due to occlusion of a possible single rare artery that is a normal anatomic variant showing its peculiar supply and not be blamed on occlusion of multiple vascular territories or other pathologic conditions such as vasculitis or infectious disease. Performing conventional angiography is usually not indicated in such cases. Because of the small size of the artery and its highly variable origin and course, lack of visualization of the artery does not exclude its presence, however interventional explorations focused on potential treatment of occlusion of the artery of Percheron may be encouraged.

**Conclusion**

- In patients presenting with bilateral paramedian thalamic infarction the possibility of artery of Percheron infarction should be considered.
- In artery of Percheron of infarction, there can be additional involvement of periaqueductal grey matter of the midbrain.
- Clinical features may vary but loss of consciousness, memory impairment, vertical gaze palsy and behavioural disturbances are most common.

**References**

1st time in India

Vobilom
(Voglibose 0.2/0.3 mg + Metformin 500 mg)

Boost PPHG Control

Preserve β-cell function

Control
65% β-cell

T2DM
48% β-cell
Nicolae Paulescu (1869-1931), a Romanian physiologist, was born in Bucharest. A child prodigy, he graduated from Bucharest High School in 1888 and left for Paris, where he enrolled in Medical School and graduated with a Doctor of Medicine degree (1897). He was immediately appointed as Assistant Surgeon at Notre-Dame du Perpetuel Secours Hospital, normally a post difficult to get. Surprisingly, Paulescu returned to Romania in 1900, where he remained Head of the Physiology Department of Bucharest Medical School, as well as Professor of Clinical Medicine at St. Vincent de Paul Hospital, until his death in 1931.

1916, Paulescu developed an aqueous (watery) extract of bovine pancreas in salted water, purified with hydrochloric acid and sodium hydroxide, which, when injected into a dog with diabetes, had a normalizing effect on its blood sugar levels. He called it pancrein. Shortly, Paulescu returned to Romania in 1900, where he remained Head of the Physiology Department of Bucharest Medical School, as well as Professor of Clinical Medicine at St. Vincent de Paul Hospital, until his death in 1931.

He submitted an extensive paper “Research on the role of the pancreas in food assimilation” in June 1921 to the Archives Internationale the Physiologie in Liege, Belgium which was published in August 1921. Paulescu also secured the patent rights for his method of manufacturing pancreine (insulin) on April 1922 by the Romanian Ministry of Industry and Trade.

Nobel Prize controversy - Eight months after Paulescu’s publication, Banting, Macleod and Best, from University of Toronto, published their successful use of pancreatic extract for normalizing blood sugar in diabetic dogs and humans. Their work is a mere confirmation of Paulescu’s work. Banting and Best announced their discovery of insulin on December 31 that year (1922) and published it in the February 1923 issue of Toronto’s Journal of Laboratory and Clinical Medicine. Banting and Macleod were awarded the Nobel Prize- Physiology or Medicine for creating usable insulin in 1923. Paulescu wrote to the Nobel committee claiming priority but his claims were rejected. His pioneering work was completely ignored by scientific and medical community.

Banting and Best knew of Paulescu’s paper but misinterpreted it in their 1922 paper, because of inadequate knowledge of French, by saying: ‘He [Paulescu] states that injections of pancreine (insulin) into peripheral veins produce no effect…..?’

Had the Nobel Committee checked Paulescu’s paper, they would have noticed that Banting and Best had read it upside down! In a letter to Professor Ian Murray on 15 October 1969, Charles Best apologized, saying, ‘I would like to state how sorry I am for this unfortunate error and trust that your efforts to honor Professor Paulescu will be rewarded with great success.’

Thanks to British professor Ian Murray, Paulescu’s achievements were recognized as being significant in the history of insulin after 50 years.

It is quite possible that Paulescu’s outspoken criticism of Darwinism and his anti-Semitic views ‘sealed his fate’.
Tetany as a Delayed Manifestation of Cisplatin Toxicity

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1Assistant Professor, Postgraduate, 2Professor, Department of Internal Medicine, Chettinad Hospital and Research Institute, Chennai, Tamil Nadu

Sir,

Cisplatin is a nephrotoxic chemotherapeutic agent and hypomagnesemia due to proximal renal tubular dysfunction is known to occur with cisplatin. However, severe symptomatic hypomagnesemia causing tetany is relatively uncommon. We report a case of cisplatin induced hypomagnesemia presenting as tetany one month after treatment for gastric carcinoma.

A 55 year old lady came with complaints of muscle cramps of 1 week duration. She had been diagnosed with Carcinoma of the stomach for which partial gastrectomy was performed 5 months prior and she had received 3 cycles of cisplatin based chemotherapy. She also had significant loss of appetite cycles of cisplatin based chemotherapy. Her investigations (Table 1) showed marked hypokalaemia and hypocalcaemia, with high urinary losses of potassium, calcium and magnesium. Hence it was diagnosed as a case of renal tubular dysfunction secondary to cisplatin toxicity. Patient showed remarkable improvement with magnesium replacement.

Cisplatin is a potentially nephrotoxic drug, and can cause acute renal failure and dys electrolytemias in a dose dependent fashion. Studies have shown that toxicity of cisplatin may persist even after discontinuation of therapy.

Learning points: Tetany may be the presenting symptom of not only hypocalcaemia but also hypomagnesemia. Cisplatin toxicity may manifest as hypomagnesemic hypocalcemic tetany without renal failure. It is of utmost importance to elicit a detailed drug history from patients since it may provide valuable clues to the etiology of the disorder.

References

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Comparison of Dyslipidemia in Pre-diabetes and Diabetes-A Pilot study

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Dear Sir,

We read with interest the original article “Lipid Profile in Prediabetics” by Suboth Kansal and TK Kamble, March 2016, Vol 64, issue of journal of the association of physician of india. We did a similar study in which patterns of lipid profile in prediabetic and diabetics were compared. Total 60 cases were taken (30 Pre-diabetic and 30 Diabetic). Pre-Diabetics and Diabetics who met the criteria (for pre-diabetes FBS >100 to 125 mg/dl and PPBS >140 to 199mg/dl, HbA1c 5.7 to 6.4% and for diabetics, FBS>126mg/dl and PPBS ≥200mg/dl, HbA1c ≥6.5%). The fasting total cholesterol and triglyceride level of two groups were compared. The mean value of total cholesterol in Prediabetics was 170.57 ± 26.18 mg/dl and diabetics was 171.23 ± 33.79 mg/dl, which was statistically not significant (p=0.746). While the fasting value of triglyceride in pre-diabetics was 131.1 ± 29.36mg/dl and in diabetics 164.95±73 mg/dl which was statistically significant (p<0.01). Thus we concluded that as pre-diabetes progress to diabetes, the fasting triglyceride level rises significantly whereas total cholesterol is not much affected.

In study done by Suboth Kansal and TK Kamble, total cholesterol values was 184.75±46.02 mg/dl, and triglyceride values was 139.5±47.24 mg/dl in prediabetics, while in our prediabetics both total cholesterol and triglyceride values were much lower, i.e. total cholesterol 170.57±26.18 mg/dl and Triglyceride-131.1±29.36mg/ dl. This may be due to 1-Difference in selection criteria for Prediabetes used by Suboth Kansal and TK Kamble is WHO criteria and we have used ADA criteria. 2-Regional differences in cultural and eating habits between Mumbai and Delhi may be other contributing factor.

In our study total cholesterol values (total cholesterol 170.57±26.18 mg/dl) are similar to study done by Williams et al, from National health and nutritional examination survey done in 1999-2000 (NHANES) in which mean Total cholesterol was 174.2mg/dl in prediabetics.

When we look into the results of both studies together, we can infer that as the blood sugar level progress from normal to prediabetes and diabetes, the level of lipids also show rise in their value, specially triglyceride.

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Table 1: Laboratory Parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>At admission (cells/cubic mm)</th>
<th>Day 10 (mg/dl)</th>
<th>Day 20 (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>6.8</td>
<td>8.5</td>
<td>9.7</td>
</tr>
<tr>
<td>Total leucocyte count</td>
<td>10600</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet count (lakh)</td>
<td>3.26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RBS (mg/dl)</td>
<td>94</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BUN (mg/dl)</td>
<td>5</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>0.69</td>
<td>0.61</td>
<td></td>
</tr>
<tr>
<td>Total protein (gm/dl)</td>
<td>4.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum albumin (gm/dl)</td>
<td>2.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum sodium (mEq/L)</td>
<td>133</td>
<td>133</td>
<td>137</td>
</tr>
<tr>
<td>Serum potassium (mEq/L)</td>
<td>2.1</td>
<td>3.7</td>
<td>3.6</td>
</tr>
<tr>
<td>Serum calcium (corrected) (mg/dl)</td>
<td>6.8</td>
<td>9.5</td>
<td>8.7</td>
</tr>
<tr>
<td>Serum phosphorous (mEq/L)</td>
<td>3.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum magnesium (mEq/L)</td>
<td>0.7</td>
<td>1.4</td>
<td>2.5</td>
</tr>
<tr>
<td>24 Hour urinary calcium (mg/24 hours)</td>
<td>406</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact PTH (pg/ml)</td>
<td>3.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Olmesar
Olmesartan Medoxomil 10 / 20 / 40 mg Tablets
BP control...every hour, 24 hours

Rosumac Gold
Rosuvastatin 10 / 20 mg + Aspirin 75 mg + Clopidogrel 75 mg
3D Magic

Nexovas
Cilnidipine 5/10/20 mg Tablets
The Nex... for Cardio Renal Protection

Etizola
Etizolam 0.25 / 0.5 / 1 mg
Shorter action... Lesser side effects
X Protection at 50% reduced price

Start EARLY in Hypertension

Zilarta 80, Zilarta 80
24 potent & persistent BP control