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Contents

EDITORIAL

» Cryptococcal Antigen Detection in Serum: Significance as a Screening Modality for Indian PLHIV
Smrati Bajpai ........................................................................................................... 11

ORIGINAL ARTICLE

» Asymptomatic Cryptococcal Antigenemia in People Living with HIV (PLHIV) with Severe Immunosuppression: Is Routine CrAg Screening Indicated in India?
S Anuradha, Abhaya Narayana H, Richa Dewan, Ravinder Kaur, K Rajeshwari .................................................. 14

» Efficacy of Betahistine by Patient-Reported Outcomes and its Tolerability Profile in Indian Patients with Vestibular Vertigo
MV Kirtane, Anirban Biswas ................................................................. 18

» Study of Bone Mineral Density (BMD) in Patients with Rheumatoid Arthritis and its Co-relation with Severity of the Disease
Liyakat Ali Gauri, Qadir Fatima, Sharanbasu Diggi, Asim Khan, Ambreen Liyakat, BR Ajay .................................................. 26

» Prognostic Indicators of Response to Plasmapheresis in Patients of Guillain Barré Syndrome
HB Prasad, RT Borse, AN Avate, Neelkesh Palasdeokar ............... 32

» Evaluation of the Association between CD4, CD8 and CD25 Cell Counts and SLE in Active Disease and in Remission
Archana Sonawale, Vinay Bohara, LS Bichile ................................................ 37

REVIEW ARTICLE

» Pharmacotherapy of Insomnia and Current Updates
Arup Kumar Misra, Pramod Kumar Sharma ........................................... 43

STATISTICS FOR RESEARCHERS

» Principles of Regression Analysis
NJ Gogtay, SP Deshpande, UM Thatte ........................................................ 48

POINT OF VIEW

» Twelve Commandments to Prevent Tsunami of Cardiometabolic Syndrome in India by 2025
Ramchandra Lele .............................................................................................. 57

CONSENSUS STATEMENT

» Consensus on Initiation and Intensification of Premix Insulin in Type 2 Diabetes Management
Viswanathan Mohan, Sanjay Kaira, Jothdev Kesavadev, Awadhesh Kumar Singh, Ajay Kumar, Ambika Gopalakrishnan Unnikrishnan, Rajeev Chawla, Jagat Jyoti Mukherjee, Rakesh Kumar Sahay, JS Kumar, Anil Bhoraskar, Arthur J Asirvatham, Jayanta Kumar Panda, Abdul Hamid Zargar, Ashok Kumar Das ........................................... 59

PICTORIAL CME

» Giant Unruptured Sinus of Valsalva Aneurysm Arising from Left Coronary Cusp
Varun Vishwas Nivargi, Manuel Durairaj, Chandrareshkar Makhale .................................................. 74

» Headcheese Sign: A Useful Radiological Marker
Rathinendranath Sarkar, Rudrajit Paul, Rajesh Pandey, Indranil Thakur, Angan Karmakar .................................................. 76

CASE OF THE MONTH

» Isolated Renal Mucormycosis
R Sriranga, Satyajeet Pawar, Wasim Khot, Neeraj Nischal, Manish Soneja, HA Venkatesh, Ragesh R Nair, Raj Kanna, Mehar C Sharma, SK Sharma ........................................... 77

CASE REPORT

» Oculo-otological Manifestations in a Case of Granulomatosis with Polyangiitis
Archana Sonawale, Anjali Rajadhynksha, Shreepryaa Mangalgi ..... 82

» Lymphocytic Hypophysitis Mimicking Pituitary Macroadenoma
Tarun Kumar Ratol, Jitesh Aggarwal, Raghavendra Haniadka, Kushal Gehlot, Nikhil Dongre, Swapnil Patil ........................................ 85

» Metastatic Crohn’s Disease
Deepak N Amarapurkar, Amey Sonavane, Anjali D Amarapurkar .............................................................................. 86

» Gaucher Disease Presenting in an Adult with Intracerebral Bleed
Sandeep Nemani, Bhumi Agrawal, Sumita Danda, Biju George ............................................................... 89

» Cerebral Venous Sinus Thrombosis and Posterior Reversible Encephalopathy Syndrome Coexisting in a Woman: A Rare Coincidence
Surekha Dabla, Himanshu Juneja, Anubha Garg, Renu Bansal, Surender Kumar .................................................................................. 90

» Chorea and Orofaciolingual Dystonia in a 40 Year Old Male
Lulup Kumar Sahoo, Kali Prasanna Swain, Ashok Kumar Mallick, Geeta Mohanty, Maheswar Samanta, Srikantha Kumar Sahoo ........................................................................... 93

MEDICAL PHILATELY

» Gila Monster Lizard & Incretin-mimetics
Jayanta Pai-Dhungat .................................................................................. 96

CORRESPONDENCE

» Rare Cause of Type 2 Respiratory Failure: Arnold Chiari Malformation
Divendu Bhushan .................................................................................. 97

» Paroxysmal Nocturnal Hemoglobinuria in a Case of Chronic Anemia
Arun Agerwal, Aakanksha Agerwal, Mala Airun ........................................ 97

ANNOUNCEMENTS

» Dr. Vithalrao Nadgouda Best All India Annual Thesis Award ....... 12

» Elections of API, ICP and PRF .................................................................. 99

» Eligibility Criteria for the Award of Fellowship of Indian College of Physicians .................................................. 100

OBITUARY ............................................................................................................ 30
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Cryptococcal meningitis (CM) is indeed a debilitating and an opportunistic infection with high mortality in PLHIV. The mortality due to CM ranges from 13% to 44% in resource limited countries including India. One of the main reasons for this high mortality has been the delay in diagnosis of CM, a large number of patients present late with severe clinical features who could have been detected early if rapid and sensitive tests were used to detect it. Antifungal treatment which has high toxicity and financial constraints to safer options, with high antifungal resistance and complications due to raised intracranial tension are other factors which lead to greater mortality in these patients.

Detection of Cryptococcal antigen (CrAg) in serum or CSF has shown to have predictive value for future Cryptococcal meningitis thus it has an important significance in management of PLHIV. The prevalence of CrAg in serum or CSF has shown to have predictive value for future Cryptococcal meningitis thus it has an important significance in management of PLHIV.²

CrAg is detectable at least about 3 weeks (median) before the onset of symptoms of CM thus its detection and treatment of patients positive for the same is an important area which could lead to reduction in mortality of PLHIV.³ Existing prevalence data for CrAg antigenemia are mostly from resource-limited settings and range from as low as 2% in northern Vietnam to 21% in Benin City, Nigeria On the basis of this data WHO in 2011 recommended that countries with a prevalence of CrAg of more than 3% in their population should consider routine screening and treatment for cryptococcal antigenemia even before ART initiation for ART-naïve adults with a CD4 T-cell count <100 cells/µL. This recommendation currently is followed only in South Africa, Rwanda and Mozambique.

Cost effectiveness of this test is also a factor which needs to be assessed, A study from Uganda by Meya et al,⁴ concluded that the benefits of screening exceeded the costs. Such studies are warranted in India as well to be able to support or refute the recommendations. Morbidity and Mortality outcomes of treating the asymptomatic patients who are positive for CrAg with antifungal therapy also should be studied so as to provide robust strength to the screening recommendations.

Internationally very few studies are available who have reported the outcome statistics of treating these asymptomatic patients.⁵

With above caveats in mind the study conducted by Indian group from New Delhi in the current issue provides limited information although it is still significant because of paucity of local information in the published domain. The prevalence of CrAg positivity of 3% in their local cohort puts it into high prevalence group. The absence of development of CM over the 6 month follow up in all of their patients is also an observation which needs consideration, although the numbers are small to give any significance to it. The all cause mortality of CrAg positive patients in the study published in current issue was significantly high as reported by them, this fact needs to be further explored to determine the etiology of the patients who died so as to comment on the benefits vs hazards of antifungal therapy.

The investigators have stated that their study was not planned to determine the cost effectiveness of CrAg testing along with use of antifungal therapy but they do state that with respect to the current cost of this test vis a vis the cost of indoor management of patient of Cryptococcal meningitis in Indian scenario the test does seems...
cheaper and they recommend its usage for Indian HIV patients. It is warranted to have more data on the above context and that too from various cohorts so as to conclude on the same.

The current study indeed adds information about the prevalence of CrAg positivity and keeping in mind the evidence from other resource limited setting this screening test indeed seems promising, but it is prudent that WHO guidelines which are currently followed in India by NACO should be followed till further robust data comes up to support the benefits of screening all patients of HIV for CrAg and treating all positive patients. Although we do need more evidence from India to support or refute the international guidelines.

References


Dr. Vithalrao Nadgouda Best All India Annual Thesis Award

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Asymptomatic Cryptococcal Antigenemia in People Living with HIV (PLHIV) with Severe Immunosuppression: Is Routine CrAg Screening Indicated in India?

S Anuradha¹, Abhaya Narayana H¹, Richa Dewan¹, Ravinder Kaur², K Rajeshwari³

Abstract

Background: Cryptococcal meningitis (CM) is a common, life-threatening opportunistic infection (OI) among people living with HIV (PLHIV) in India. Serum Cryptococcal antigen (CrAg) positivity is predictive of future occurrence of CM and pre-emptive treatment reduces its mortality. Routine CrAg screening among PLHIV is not adopted by India’s national programme. This study evaluated the prevalence of CrAg and assessed CrAg positivity in predicting all-cause mortality among PLHIV.

Methods: This prospective study was conducted in a tertiary care, public health facility in New Delhi, India. Prevalence of CrAg was assessed in 128 ART naive adult PLHIV with CD4 < 100 cells/mm³ using a latex agglutination test. Age, gender, weight, body mass index (BMI), CD4 count, haemoglobin, serum albumin, and presence of other OI were evaluated as determinants of CrAg positivity. Subjects were followed up for occurrence of CM and mortality (all-cause) at 12 weeks and 6 months.

Results: The mean age of the subjects was 36.2±9.48 years, 73.4% were men, 21.09% women and 5.46% were transgender. The mean BMI was 18.4±2.53 kg/m² and 64% of subjects belonged to the lower socio-economic strata. Mean CD4 counts of the subjects was 54.9±26.58 cells/mm³ and 42.97% had CD4 < 50 cells/mm³. The prevalence of CrAg in the subjects was 3.125 % (4/128). None of the factors assessed showed statistically significant difference between the 2 groups, though CD4 count <50 cells/mm³, low serum albumin and presence of oral candidiasis had a stronger association with CrAg positivity. None of the subjects developed CM during follow up. At 12 weeks, 3/4 (75%) CrAg positive patients were alive compared to 118/124 (95.16%) of CrAg negative subjects. At 6 months, 50% (2/4) CrAg positive patients had died compared to 10.48% (13/124) CrAg negative (p<0.01)

Conclusions: Though CrAg prevalence in PLHIV with CD4<100 cells/mm³ is moderate, asymptomatic CrAg positivity among PLHIV with CD4 < 100cells/mm³ is significantly associated with higher all-cause mortality. CrAg testing is very cost effective and India’s National AIDS Control Programme should seriously consider routine screening among the severely immunosuppressed PLHIV.

Editorial Viewpoint

• Asymptomatic cryptococcal antigenemia is increasing in India and hence CrAg screening in asymptomatic PLHA is recommended.
• Treatment of these patients having high immunosuppression can prevent early death.

Introduction

Cryptococcal meningitis (CM) is an important, serious life-threatening Opportunistic Infection (OI) among PLHIV in India, especially among the severely immunosuppressed (CD4<100cells/mm³). The estimated global prevalence of CM is 1.9 to 4.57% among PLHIV and the worldwide annual burden of CM is estimated at 957,900 cases, resulting in an estimated 624,700 deaths within 3 months of cryptococcal infection.¹ The highest prevalence of CM is seen in sub-Saharan Africa followed by Southeast Asia. The prevalence of CM in PLHIV is estimated at 2.79% in India.² CM is associated with high mortality. In sub-Saharan Africa mortality rates of up to 70% have...
been reported. High mortality rates of 55% in other low- and middle-income countries and nearly 20% in high income countries are estimated. Some of the reasons for these high mortality rates include delayed clinical suspicion and diagnosis due to subtle clinical manifestations, lack of access to lumbar puncture and cerebrospinal fluid (CSF) analysis, low sensitivities of diagnostic techniques used in these settings like India ink preparation, and non availability of Amphotericin B-based treatment regimen. Early and prompt diagnosis of CM and timely initiation of treatment are paramount in reducing the CM related mortality. CM presents as a sub acute to chronic meningitis and the diagnosis is often delayed in resource limited settings. To complicate matters, the clinical features of CM closely resemble tubercular meningitis, which is also endemic in these regions.

Hence it is important to screen for CM with a sensitive, specific, easily accessible and inexpensive test that will identify CM early. The detection of Cryptococcal antigen (CrAg) in serum is a simple test that is dramatically changing the screening protocols for CM among PLHIV. Serum CrAg has high sensitivity and specificity for the diagnosis of asymptomatic Cryptococcal infection among PLHIV. CrAg can be detected in serum or plasma weeks before the onset of the clinical features of CM and is estimated to precede the onset of CM symptoms by an average of 22 days and 11% of patients will have detectable CrAg >100 days prior to the onset of CM.

Routine screening for CrAg in PLHIV with advanced immunosuppression (CD4<100/mm^3) to detect asymptomatic Cryptococcal infection has been extensively studied in Africa. The reported prevalence of asymptomatic CrAg varies from 2% in Ghana, to 8.8% in Uganda and 13% in South Africa. In studies from Thailand and Cambodia, the prevalence of CrAg in PLHIV was 12.9% and 17.7 % respectively in those with low CD4 counts. The WHO is also now recommending routine screening for CrAg in PLHIV with CD4 <100 /mm^3 in regions with prevalence of CrAg > 3% and pre-emptive treatment with fluconazole. There is no published data on the prevalence of serum CrAg from India. The National AIDS Control Programme of India does not recommend screening for CrAg among asymptomatic PLHIV. This study, the first of its kind from India, assessed the prevalence and the determinants of CrAg among PLHIV with CD4 < 100/mm^3 and the outcome among these patients.

**Material and Methods**

This study was conducted in the Department of Medicine and ART center of the Maulana Azad Medical College and associated Lok Nayak hospital, New Delhi. The institution is a designated Center of Excellence in HIV Care by the National AIDS Control Organization, Ministry of Health and Family Welfare, Govt. of India. The study was approved by the institutional Ethics Committee. ART naïve PLHIV >18 years of age, with CD4 < 100/mm^3 who consented to participate in the study were assessed. All subjects with history of being treated for Cryptococcus (definitive or presumptive) in the past or currently receiving fluconazole were excluded. All subjects were evaluated clinically by history and examination and WHO staging of HIV infection was done. Socio-demographic data was collected and baseline haematological and biochemical investigations as per NACO guidelines were done.

All subjects who fulfilled the study criteria were screened for CrAg detection in serum by Latex Agglutination (LAT) assay. CrAg detection was done using Meridian Bioscience, Inc., kits. Three to 4 ml of blood was taken and the clotted blood was centrifuged for 15 minutes. The serum separated was aspirated and 200 microlitres of serum was treated with 200 microlitres of pronase solution. This mixture was incubated at 56°C for 15 minutes. The mixture was then placed in a boiling water bath for 5 minutes. 25 microliters of this mixture was placed on a disposable reaction card. The card was then centrifuged for 5 minutes at 125 rpm and the results were read immediately. Those serum specimens with 2+ or greater reaction on a scale of 1-4 were considered to be positive for CrAg.

All subjects who were CrAg positive received antifungal treatment as per the 2011 WHO advisory.

The subjects were followed up for 6 months for outcome measures: whether they were alive or dead and whether they had developed an episode of CM in the intervening period. The first assessment was done at 12weeks and final outcome assessment was done at 6 months.

Statistical analysis: The mean, median, frequency distribution and the standard deviation were calculated using the subject characteristics. The prevalence of CrAg positivity was calculated. Among the PLHIV, comparison between the two groups (CrAg positive and CrAg negative) for quantitative data of determinants was done using unpaired t test and qualitative data of determinants was done using Fischer exact test to calculate the p value. Binary logistic regression was used to determine factors associated with positive serum CrAg. A p value <0.05 was considered statistically significant. The statistical analysis was done using SPSS software version 20.

**Results**

The study group comprised of 128 ART naïve PLHIV. The mean age of the subjects was 36.2±9.48 years, 73.4% were men,
21.09% were women and 5.46% were transgender. Most patients (42.2%) were in the age group of 31 to 40 years. Among the subjects, 60.16% had either primary school education (37.5%) or were illiterate (22.66%) and 64.8% belonged to low socioeconomic status according to the modified Kuppuswamy classification. Heterosexual route of transmission was the most common route of HIV transmission in the subjects- 83.6%. Majority of the patients had fever as their presenting complaint at diagnosis of HIV infection (74 / 128) while 42 subjects were asymptomatic. Tuberculosis was the most common opportunistic infection (57 / 128) followed by oral candidiasis (17 / 128). Majority of the subjects belonged to WHO clinical stage 4 (n=48) followed by stage 3 (n=42). While 82% of the subjects had anaemia, 91% of the subjects had serum albumin <3.5g/dl. Ten subjects had Hepatitis B co-infection and 3 were co-infected with Hepatitis C infection.

All subjects had CD4 <100 cells/mm³. The mean CD4 counts of the study subjects was 54.9±26.58 cells/mm³ and 42.97% had CD4 < 50 cells/mm³.

The prevalence of serum CrAg in the subjects was 3.125% (4/128). Table 1 compares the clinical, demographic and laboratory data between CrAg positive and negative patients. There were no significant differences between CrAg positive and negative groups in terms of age, WHO clinical stage and Body weight/ BMI and CD4 count.

While assessing the determinants of CrAg positivity, none of the factors were statistically significant for association with serum CrAg positivity. However, age (p=0.26), CD4 count (p=0.105), and presence of oral candidiasis (p=0.284) had greater association with CrAg positivity than other determinants when assessed by binary logistic regression.

None of the subjects (CrAg positive or negative) developed CM during the follow up period of 6 months. At the follow up assessment at 12 weeks, 1 / 4 CrAg positive subjects died at home within the first week of diagnosis of HIV. Another CrAg positive subject had died due to disseminated tuberculosis at the end of 6 months of follow-up. The other 2 CrAg positive subjects who were started on both ART and prophylactic antifungal therapy were alive at 6 months. Among the CrAg negative subjects, 118/124 were alive at 12 weeks and 111 / 124 were alive at 6 months (Table 2).

Table 1: Comparison of demographic, clinical and laboratory data among the CrAg positive and CrAg negative subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CrAg positive (n = 4)</th>
<th>CrAg negative (n = 124)</th>
<th>p value</th>
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<tbody>
<tr>
<td>Age in years</td>
<td>43.5 ± 9.76</td>
<td>36.04 ± 9.38</td>
<td>0.26</td>
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<tr>
<td>Male gender</td>
<td>75%</td>
<td>73.44%</td>
<td>1.00</td>
</tr>
<tr>
<td>BMI in kg/m²</td>
<td>18.2 ± 0.83</td>
<td>18.4 ± 2.57</td>
<td>0.79</td>
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<tr>
<td>WHO clinical stage 3</td>
<td>50%</td>
<td>32.25%</td>
<td>0.597</td>
</tr>
<tr>
<td>WHO clinical stage 4</td>
<td>25%</td>
<td>37.9%</td>
<td>1.00</td>
</tr>
<tr>
<td>CD4 cells/mm³</td>
<td>35.25 ± 19</td>
<td>55.53 ± 26.52</td>
<td>0.105</td>
</tr>
<tr>
<td>Other co-existing OI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>50%</td>
<td>47.43%</td>
<td>0.99</td>
</tr>
<tr>
<td>Candidiasis</td>
<td>25%</td>
<td>13%</td>
<td>0.284</td>
</tr>
</tbody>
</table>

Table 2: Outcome assessment among the study subjects

<table>
<thead>
<tr>
<th>Outcome parameter</th>
<th>CrAg positive (n=4)</th>
<th>CrAg negative (n=124)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Development of CM</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Survival at 12 weeks</td>
<td>75%</td>
<td>95.16%</td>
<td>0.08</td>
</tr>
<tr>
<td>Mortality rate at 6 months</td>
<td>50%</td>
<td>10.48%</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Discussion

Screening for serum CrAg has emerged as one of the most important tools to prevent Cryptococcal infections in PLHIV. The prevalence of CrAg among PLHIV is variable and depends upon the endemicity of Cryptococcal infections in the geographical region and also on the study population. It is recognised that 80% of CrAg positivity occurs among PLHIV with CD4<100 cells/mm³. Therefore routine screening for CrAg is recommended among PLHIV with CD4<100 /mm³ as a priority among resource limited countries. In the WHO advisory released in 2011 for Cryptococcal disease, it has been conditionally recommended that universal screening for CrAg among PLHIV with CD4<100 /mm³ should be adopted in all countries with a CrAg prevalence of >3%. In our study the prevalence of CrAg was documented to be 3.125%.

CrAg screening and treatment strategy has been shown to have a significant impact on reducing mortality among these patients. In a study by Meya et al it was found that CrAg-positive PLHIV without a history of CM, treated with fluconazole had higher odds of survival (OR: 34.6, 95% CI: 1.7 to 703) compared with those not treated with fluconazole. However, in a study by Meyer et al, there was no significant mortality benefit from CrAg screening demonstrated. In the present study also, CrAg positive patients had a significantly higher mortality both at 12 weeks and 6 months (p<0.01). In a recent review of all studies on CrAg screening, it was concluded that that impact of “CrAg screen and treat strategy” on mortality overall was moderate. CrAg screening has also been demonstrated to be a highly cost effective strategy in the management of PLHIV. Meya et al demonstrated that the number needed to test and treat with CrAg screening to prevent 1 case of CM...
was 11.3 persons and the cost per disability-adjusted life year (DALY) saved was $21. Jarvis et al.\textsuperscript{13} in a study from South Africa showed that CrAg screening followed by treatment with fluconazole cost USD 51 per person per year compared to USD 207 per person per year for no screening at all. The most significant finding was that this impact was seen even in situations with prevalence of CrAg antigenemia as low as 0.6%.

Though our study did not do a formal cost effectiveness analysis, it is estimated that the approximate cost of performing 1 CrAg test is $4, compared to $2400 for the in-hospital care of 1 patient with CM. This is the scenario when the test used for CrAg determination in this present study was latex agglutination (LAT).

The CrAg screening strategy has been boosted by the development and approval of the newer Lateral flow assay (LFA) technique. LFA is a rapid diagnostic test that has emerged as an ideal point of care test for detection of CrAg.\textsuperscript{14} The test is simple to perform, does not require any specialised equipment or techniques or any training of lab personnel. Only 1 drop of body fluid (serum, plasma, CSF or urine) is required for the test which does not require any refrigeration also. Most significantly LFA costs only approximately 1-2 USD per test which is affordable in the resource limited settings. LFA has demonstrated high sensitivity and specificity for CrAg.\textsuperscript{14}

**Conclusions**

The present study is the first published study from India on CrAg detection in asymptomatic PLHIV. There is no published data from India on the prevalence of CrAg among PLHIV. This study has important implications for the National AIDS Control programme. Though this is a single center study, it still highlights the increased risk of mortality among PLHIV with CrAg positivity. A larger, multicentre study using LFA based CrAg screening will provide more data. The programme must consider implementation of universal, routine CrAg screening of PLHIV with CD4 <100/mm\textsuperscript{3} followed by pre-emptive fluconazole treatment for CrAg positives to prevent CM and its associated mortality.

**References**

Efficacy of Betahistine by Patient-Reported Outcomes and its Tolerability Profile in Indian Patients with Vestibular Vertigo

MV Kirtane¹, Anirban Biswas²

Abstract

Objective: Patients with vestibular vertigo suffer from disabling symptoms which affect their quality of life. This article presents the efficacy and safety profile of betahistine hydrochloride in Indian patients suffering from vestibular vertigo (OSVaLD study).

Methods: Study included patients suffering from vertigo, who were prescribed betahistine (48 mg/day) according to local label. Safety and efficacy populations of this study included 80 and 75 subjects respectively. The study included three visits: an initial baseline visit, and two follow-up visits (one month and three months [final visit] post-commencement of betahistine therapy). Efficacy was assessed by administering three patient-reported outcomes (PROs) namely, Dizziness Handicap Inventory (DHI), Hospital Anxiety and Depression Scale (HADS), and Medical Outcome Study Short Form-36 version 2 (SF-36 v2). Safety assessment was made by reports of Suspected Adverse Drug Reactions (SADRs) which began during the study.

Results: Mean changes in total DHI score for Indian efficacy population at follow-up and final visits were 31 and 44 points respectively. These changes indicated significant improvements in self-perceived impairment associated with vertigo. Similar improvements in quality of life were observed by HADS subscales (HADS-A and HADS-D) and SF-36 v2 summary scores (PCS [physical component summary] and MCS [mental component summary]). There was only one report of SADR in this study in a female subject receiving betahistine 16 mg t.i.d. This SADR was gastritis of mild severity and was probably not related to betahistine.

Conclusion: A significant number of vestibular vertigo patients reported fair degree of spontaneous recovery. Betahistine treatment improved quality of life, was safe and well-tolerated by Indian patients suffering from vertigo.

Introduction

Vertigo is an illusion of movement (mostly spinning) caused due to imbalance of the vestibular system. In spite of being a common symptom associated with varying underlying diseases, there are very few reports in literature about prevalence of vertigo in India.¹² Vertigo significantly impairs general health status and quality of life in patients with vestibular disorders.³⁴ Therefore quality of life instruments may be used as an important tool to determine efficacy of different treatment options.

Betahistine is commonly used in the management of vestibular disorders. Several studies have demonstrated efficacy of betahistine in comparison with placebo and different anti-vertigo drugs,⁵⁻¹⁰ but its impact on health related quality of life (HRQoL) has been rarely investigated.⁷,⁸ Thus, with the central objective of obtaining real world data about efficacy profile of betahistine using patient related outcomes (PROs), an international study, OSVaLD, (A Three-Month Observational Study in Patients Suffering from Recurrent Peripheral Vestibular Vertigo to Assess the Effect of Betahistine 48 mg/day on Quality of Life and Dizziness Symptoms) was conducted. Three instruments: Dizziness Handicap Inventory

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(DHI), Hospital Anxiety and Depression Scale (HADS), and Medical Outcome Study Short Form-36 version2 (SF-36v2) were used in this study. Final primary findings from OSVaLD, and initial baseline data including an extensive by-country analysis from this study have been reported in individual publications. The present article presents the efficacy and safety of betahistine under routine clinical practice in Indian geographical and ethno-cultural conditions.

**Methods**

**Study design**

OSVaLD was an international, multicenter, open-label, study of betahistine under real-life conditions in patients with vertigo of peripheral vestibular origin. The study was carried out as a world-wide programme across 13 countries between April, 2005 and October, 2006. The data reported in this article was collected across 23 centers located in India.

Betahistine 48 mg/day (24 mg tablet b.i.d. or 16 mg tablet t.i.d) was initiated as monotherapy or as an adjuvant therapy when the current anti-vertigo therapy was not sufficient or tolerated. Prior or concomitant medications could be used as needed.

The study included three clinic visits: an initial baseline visit to the treating physician, one follow-up visit (one month post-commencement with betahistine therapy), and a final evaluation visit (at three months post-commencement with betahistine therapy or early termination of betahistine). This study schedule was matched with the treating physician’s usual consultation pattern.

**Subjects**

The study included patients who were being prescribed betahistine according to local labeling, and who had history of vertigo attacks of peripheral vestibular origin not exceeding 5 years, with baseline total Dizziness Handicap Inventory (DHI) score ≥40. Patients who had contraindications to betahistine as described by local labeling were excluded from the study.

**Efficacy and safety assessments**

The study used three well-established PRO instruments, namely DHI, HADS, and SF-36v2 to evaluate effect of betahistine on dizziness symptoms, symptoms of anxiety and depression, and quality of life, respectively, in patients with peripheral vestibular vertigo. These instruments were administered on scheduled study visits.

The primary outcome measure of the study was to determine the effect of betahistine on dizziness, measured as change in total DHI score at 3 months from baseline. DHI is a self-report questionnaire used to assess the degree of disability associated with dizziness regardless of its underlying cause(s). It consists of 25 items (questions) covering three subscales with functional (9 items), emotional (9 items) and physical (7 items) aspects. “Yes” scores 4 points, “sometimes” 2 points and “no” 0 points. Total DHI-score ranges from 0 to 100. Maximum scores for functional, emotional and physical aspects are 36, 36, and 28 respectively. Higher scores indicate greater perceived disability.

HADS is a self-report scale used to measure anxiety and depression symptoms. It consists of 14 items covering two mood subscales: HADS-A (contains 7 items for anxiety) and HADS-D (contains 7 items for depression). Each item is rated on a four-point scale (scored 0-3), giving maximum scores of 21 for each of these subscales. HADS-A and HADS-D are interpreted as follows: 0-7 points = normal, 8-10 points = mild, 11-14 points = moderate, and 15-21 = severe.

For DHI and HADS, if at least 50% of items were complete in the subscale, the missing values were assumed as equal to the mean of subscale. Otherwise the subscales and scale scores were not calculated.

SF-36v2 is a widely used generic instrument for measurement of health-related quality of life (HRQoL). It contains 8 scales and 2 summary scales based on 36 items which measure physical and mental health status. These scales are: physical functioning (PF), role limitations due to physical health (RP), bodily pain (BP), general health perceptions (GH), vitality (VT), social functioning (SF), role limitations due to emotional problems (RE), and mental health (MH). Scores from these scales can be combined into physical and mental component summary (PCS and MCS). Responses to each item were scored and summed to yield scale and summary scores from 0 to 100. Higher scores represent better self-perceived health. Instead of using original scores ranging from 0 to 100, norm-based scoring results were used. Data were scored in relation to the 1998 U.S. general population norms. Using norm-based scoring method, easier and meaningful interpretation of scale and summary scores can be made. All scores above or below 50 can be interpreted as above or below the general population norms. Standard deviations are equalized at 10, therefore it is easy to see exactly how far above or below the average score any result is in standard deviation units. The rules of scoring were as per SF Health Outcomes Scoring Software of Quality Metric Incorporated. An important rule for scoring was that an incomplete scale score may be estimated if answers exist for at least 50% of the items within that scale. The average score of the completed items replaces any missing responses within the scale.

At the end of the study, patient’s and investigator’s impression of the treatment was assessed as “excellent”, “good”, “moderate”,
and “poor” and scored with 1, 2, 3, and 4 points respectively.

For safety assessments reports of suspected adverse drug reactions SADRs were obtained during month 1 and month 3 visits.

Statistical considerations

Based on results of previous studies conducted on betahistine, OSVaLD study targeted 200 patients per country for robust results. The efficacy population included all subjects allocated to treatment who received a prescription of betahistine at baseline, and (i) who had at least one subsequent clinic visit (follow-up visit, final visit or endpoint visit), (ii) who had a score calculated for at least one of the three outcome scales (DHI total, SF-36®v2 [both summary scores] or HADS [both anxiety and depression scales]) at the baseline visit or at least one post-baseline visit. Scores on each of the three scales (and scores on the different subscales) were summarized by descriptive statistics by visit including last visit on-treatment. Changes from baseline for all efficacy parameters were presented by descriptive statistics, including 95% confidence intervals and one-sample t-test. Analyses were done on efficacy population as a whole, as well as for subgroups based on gender, disease (baseline cause of vertigo) and betahistine monotherapy vs. combination therapy.

Safety was assessed in the safety population that included all subjects allocated to treatment who received a prescription of betahistine at baseline, and who had at least one subsequent clinic visit.

Exposure was described by total treatment duration. Safety was assessed by reports of SADRs which began during the study. All SADRs were coded according to Medical Dictionary of Regulatory Activities (MedDRA) classification version 9.0 (presentation of primary SOC [System Organ Class], HLT [High Level Term] and PT [Preferred Term]) and were presented in summary tables, with number and percentage of subjects who reported SADR by preferred term. These SADRs were also presented according to their severity and their relationship to the study drug as judged by the investigator.

Study conduct and organization

The study was conducted according to International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Harmonized Tripartite Guideline for Good Clinical Practice (GCP), and Declaration of Helsinki and its subsequent revisions. The protocol and informed consent were approved by the ethics committee at each center prior to study initiation as per national regulatory requirements. Investigator(s) in this study were general practitioners and specialists.

Data management and statistical analysis were conducted by the FOVEA Group, Rueil Malmaison, France. Data entry was performed using Access version 9.0. Quality control was performed using SAS version 8.2. Statistical analysis was performed using SAS version 8.2 and SF Health Outcomes™ Scoring Software of Quality Metric Incorporated (Enhanced module + utility index).

Results

OSVaLD study included 2168 subjects, of which 2032 and 1898 were included in safety and efficacy populations respectively. In India, 100 patients were included in this study, of which safety population consisted of 80 subjects and efficacy population included 75 subjects. Baseline demographic characteristics of these populations are presented in Table 1. As can be seen from Table 1, there were no substantial differences in baseline demographic characteristics of efficacy and safety populations.

There were almost equal proportions of males and females (52% and 48% respectively) in efficacy population. Subjects in Indian efficacy population were prescribed betahistine predominantly because of Ménière’s disease (34.7% cases) followed by benign paroxysmal positional vertigo (BPPV, 29.3% cases) and peripheral vestibular vertigo of unknown pathophysiology (16% cases). This was in contrast to overall OSVaLD efficacy population wherein peripheral vestibular vertigo of unknown pathophysiology was the predominant cause (38.4% cases), followed by BPPV (22% cases), and Ménière’s disease (13.9% cases) (Figure 1).

Principal reasons for a prescription of betahistine were new diagnosis (65.3% cases), insufficient efficacy of current therapy (30.7% cases), and inability to tolerate other
medications (4% cases). Betahistine was prescribed as monotherapy and in combination with other therapies for vertigo in 57.3% and 42.7% cases respectively. Almost equal proportions of patients were prescribed betahistine 24 mg b.i.d. (52% cases) or 16 mg t.i.d. (48% cases).

Efficacy outcomes

DHI

The mean baseline values for the physical, emotional, functional, and total scores were 19.6 ± 5.4, 17.9 ± 6.6, and 24.0 ± 5.2, and 61.6 ± 11.8 respectively. Statistically significant decrease (p < 0.0001) regardless of gender, however mean change in total score was numerically greater in males as compared to females. Subgroups of patients with vertigo due to Ménière’s disease and benign paroxysmal positional vertigo (BPPV) showed statistically significant improvements at the follow-up and final evaluation visits (p < 0.0001 vs. baseline). Mean changes from baseline in DHI response scores of subgroups receiving betahistine as monotherapy, or as combination with other therapies were also statistically significant at the follow-up visit and final evaluation visit (p < 0.0001).

HADS

Mean baseline HADS-A score of efficacy population was 10.0 ± 4.9; 31.9% (23/72) patients had normal anxiety level, 30.6% (22/72) patients had moderate anxiety level, 23.6% (17/72) had mild anxiety level, and 13.9% (10/72) patients had severe anxiety level (Fig. 3). Proportion of patients having severe anxiety was lower among Indian efficacy population compared to overall OSVaLD efficacy population (15.9% [296/1858]). Proportion of patients with normal anxiety level increased from 31.9% (23/72) at baseline to 66.2% (47/71) at the follow-up visit, and to 82.8% (53/64) at the final visit (Figure 3). Higher proportion of males (86.5% [32/37]) had normal anxiety level compared to females (77.8% [21/27]) at final visit.

Mean baseline HADS-D score was 8.4 ± 5.2; 40.3% (29/72) patients had normal depression level, 29.2% (21/72) patients had mild depression level, 22.2% (16/72) had moderate depression level, and 8.3% (6/72) patients had severe depression level. Proportion of patients having severe depression was numerically lower among Indian efficacy population compared to overall OSVaLD efficacy population (9.3%
Among Indian efficacy population, proportion of males having severe depression was higher compared to females (10.5% [4/39] vs. 5.9% [2/36]). Proportion of patients with normal depression level increased from 40.3% (29/72) at baseline to 74.6% (53/71) at the follow-up visit, and to 84.4% (54/64) at the final visit. Similar to our observation in HADS-A, a higher proportion of males (89.2% [33/37]) had normal depression level compared to females (77.8% [21/27]) at final visit.

Changes from baseline at final visit in HADS-A and HADS-D scores were statistically significant (p <0.0001) in efficacy population (Figure 3) and across subgroups based on gender, and monotherapy vs. combination therapy.

### SF-36®v2

At the baseline visit, the mean PCS and MCS scores were 42.5 ± 8.0 and 34.6 ± 12.4 respectively. These scores were below the U.S. general population norm, indicating a reduced HRQoL status. Change from baseline at follow-up and final evaluation visits in both PCS and MCS scores were statistically significant (p <0.0001) (Figure 4). Improvements in PCS and MCS at final visit from baseline were statistically significant across subgroups based on gender (Table 2), and monotherapy vs. combination therapy. Changes observed in Indian efficacy population were numerically higher as compared to total OSVaLD efficacy population (Table 2).

### Overall efficacy assessment

The impression of treatment was excellent for 44.6% (29/65) subjects, good for 49.2% (32/65) subjects, and moderate for 6.2% (4/65) subjects. None of the patients assessed the treatment as poor. Proportion of subjects who assessed the treatment as excellent was higher in Indian efficacy population compared to overall OSVaLD efficacy population (44.6% vs. 36.6%). Indian efficacy population, higher proportion of females in rated the treatment as excellent compared to males, and higher proportion of males rated the treatment as good compared to females. When items “excellent”, “good”, “moderate”, and “poor” were scored with 1, 2, 3, and 4 points, the mean score for subject’s impression of the treatment was determined to be 1.6 ± 0.6.

The investigators’ impression of the treatment was excellent for 36.9% (24/65) subjects, good for 56.9% (37/65), and moderate for 6.2% (4/65) patients. Treatment of none of the patient was found to be poor. The investigator’s impression of the treatment was 1.7 ± 0.6 (mean ± SD). Statistically significant correlation existed between physician’s opinion and subject’s opinion (r = 0.63, p <0.0001).

Subgroup analysis of subject’s and investigator’s impression scores indicated similarity regardless of gender. Subject’s and investigator’s impression scores were numerically higher for peripheral vestibular vertigo of unknown pathophysiology and Ménière’s
The mean betahistine treatment duration was 93.8 ± 42.5 days.

Only one SADR was reported from India in a female subject receiving betahistine 16 mg t.i.d. This SADR was gastritis of mild severity, and was judged to be probably related to betahistine.

**Discussion**

Efficacy and tolerability of betahistine for the treatment of peripheral vestibular vertigo is supported by various clinical studies reported previously. In most of these studies efficacy of betahistine has been established by evaluating its effect on frequency, duration, and severity of vertigo attacks. Another method which has been less utilized to assess the treatment outcome is use of PROs before and after treatment. This becomes particularly important for conditions like vertigo which is accompanied by incapacities influencing daily life. However, to the best of our knowledge, only few studies are reported which have utilized PROs for assessing the efficacy of betahistine.

OSVaLD study provided a unique opportunity to capture extensive real-world data of effect of betahistine on HRQoL of a large patient population across 13 countries. The study used both disease-specific as well as generic instruments for efficacy assessments. Overall results of OSVaLD study have been published previously by Benecke et. al. The results presented in present article provide a deeper insight to efficacy and safety of betahistine in Indian population. A substantial proportion of Indian efficacy population was with peripheral vestibular vertigo of unknown pathophysiology (16%). Although this proportion was lower in comparison with the overall OSVaLD efficacy population (38.4%), it was much higher in comparison to other reports wherein diagnosis for vertigo could not be specified only for 1.5% patients. Etiological diagnosis in vertigo patients is possible only through collection of detailed medical history and performing clinical examinations, which is quite a time consuming procedure. Moreover, for performing the clinical neuro-otological and vestibular function tests, sophisticated investigations such as Videoeyonystagmography [VNG], Electronystagmogram [ENG], Video Head Impulse Test [VHIT], Subjective Visual Vertical [SVV], Posturography, and ECOG [Electroocochleography] are required. The present study was conducted in busy OPD settings, where physicians were unable to collect the detailed medical history and at most places infrastructure required for performing necessary investigations was not available, therefore a substantial proportion of efficacy population was with peripheral vestibular vertigo of unknown pathophysiology.

It is to be noted that at the time of conduct of this study, the qualifying diagnosis for patient population included BPPV; however recent guideline intended for diagnoses and management of BPPV do not recommend the routine treatment of BPPV with vestibular suppressant medications such as antihistamines. Data suggests that 40-70% of patients with migraine related vertigo have positional vertigo in the course of the disease which is not benign positional vertigo. During the completion of this study, published epidemiological data regarding the high prevalence about migraine related vertigo was not available; hence there is a high possibility that many cases of recurrent vertigo were actually migraine related vertigo but were diagnosed otherwise. Further, the improvement in these patients also opens a new possibility that betahistine therapy may be beneficial in this class of patients.

DHI and its various adaptations have been used previously in several studies to investigate the severity of dizziness in various populations, and effect of treatments on dizziness of different etiologies. Dizziness can cause substantial impairment in patients; therefore the primary criterion evaluated was absolute change in mean total DHI score between three month visit and baseline. The baseline total DHI score of Indian efficacy population was approximately 62 which suggested severe functional impairment. Mean change in total DHI score at follow-up and final visits were approximately 31 and 44 points respectively. These improvements were substantially higher than threshold of 18 points which is known to be a significant change in patient’s self-perceived health. The improvements in individual health aspect (physical, emotional, and functional subscores) and in total scores at follow-up and final visits were statistically significant across subgroups based on gender and betahistine monotherapy vs.

### Table 2: HRQoL status as determined by SF-36 v2 in efficacy population

<table>
<thead>
<tr>
<th>SF-36 v2 scale (PCS and MCS)</th>
<th>Male (N = 39)</th>
<th>Female (N = 36)</th>
<th>Efficacy population (India) (N = 75)</th>
<th>Efficacy population (N = 1898)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At baseline visit</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCS</td>
<td>45.0 ± 8.6</td>
<td>40.0 ± 6.7</td>
<td>42.5 ± 8.0</td>
<td>39.8 ± 7.9</td>
</tr>
<tr>
<td>MCS</td>
<td>33.8 ± 12.8</td>
<td>35.4 ± 12.2</td>
<td>34.6 ± 12.4</td>
<td>35.5 ± 11.5</td>
</tr>
<tr>
<td>At final evaluation visit*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCS change from baseline</td>
<td>7.7 ± 8.8</td>
<td>11.6 ± 8.0</td>
<td>9.5 ± 8.6</td>
<td>7.8 ± 8.8</td>
</tr>
<tr>
<td>MCS change from baseline</td>
<td>18.4 ± 16.3</td>
<td>14.9 ± 15.2</td>
<td>16.8 ± 15.8</td>
<td>10.8 ± 12.7</td>
</tr>
</tbody>
</table>

All values: Mean±SD; *p (intra-group) <0.0001; HRQoL = Health related quality of life, MCS = Mental Component Summary, PCS = Physical Component Summary, SD = Standard Deviation, SF-36 v2 = Short-Form 36 Health Survey Version 2
combination therapy. Patients with baseline MD or BPPV (64% of efficacy population) also showed statistically significant improvement in DHI subscores and total score at follow-up and final visits. A comparison of results obtained from Indian population subset with other 13 countries participating in OSVaLD revealed that improvement in total DHI score was highest in India. Efficacy of betahistine as determined by DHI for overall OSVaLD population and Indian subset were in line with other studies reported previously.²⁷

Very often vertigo patients deliberately impose limitations on their daily routine activities in order to avoid embarrassment, which may ultimately lead to co-morbid depression. Clinically relevant levels of depression have been indicated in vertigo patients.²⁵ It has also been suggested that vertigo patients with abnormal depression feel more disabled than those without depression,²⁶ resulting in poor quality of life. All three instruments used in this study to evaluate quality of life in vertigo patients, i.e., disease specific (DHI) as well as general (HADS and SF-36™v2) included assessment of depression.

Correlations between assessments made by DHI, HADS, and SF-36™v2 have been reported in several other studies.³,²⁶ In our study, improvements recorded by generic instruments after completion of betahistine treatment are indicative of poor HRQoL caused by vertigo, though the contribution of non-vertigo factors to these scores cannot be ignored.

Betahistine was found to be safe and tolerable because there was only one incidence of SADR reported in the Indian safety population. The target population-pool of 200 subjects per country could not be achieved in India but the results obtained for efficacy parameters are statistically significant and consistent with results obtained for overall OSVaLD population and other participating countries. This suggests that results presented in this article are true indicator of efficacy and safety of betahistine.

Acknowledgement
Aniket Raje (Abbott Pharmaceuticals, India) provided writing assistance during the development of this manuscript.

References
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Study of Bone Mineral Density (BMD) in Patients with Rheumatoid Arthritis and its Correlation with Severity of the Disease

Liyakat Ali Gauri¹, Qadir Fatima², Sharanbasu Diggi³, Asim Khan⁴, Ambreen Liyakat⁵, BR Ajay³

Abstract

Introduction: Rheumatoid arthritis (RA) is a chronic inflammatory disease of unknown etiology marked by a symmetric, peripheral polyarthritis.¹⁻³ People with rheumatoid arthritis are at increased risk of osteoporosis. Hence this article intends to highlight the importance of BMD measurement in patients with RA as a tool for assessment of disease activity and severity.

Objectives: To evaluate Bone Mineral Density in patients of Rheumatoid Arthritis and Co-relate it with severity of disease.

Materials and Methods: Hand bone density was measured on the plain radiographs of the right hand using digital x-ray radiogrammetry (Pronosco Xposure System 2.0). This BMD was correlated with markers of disease activity using DAS 28 Scoring system.⁴

Results: In our study there were 200 patients with equal number of controls. 70 patients in study group and 131 patients in control group were <45 years old and had normal Z-score while in age group >45 years 26 and 20 cases in study and control groups respectively had their Z-score within normal range. There were total 21 and 2 cases of study and control groups respectively (age <45 years) who had osteoporosis while in age group >45 years 12 and 10 cases in study and control groups respectively had osteopenia.

Conclusion: Patients with RA are more susceptible for bone loss in comparison to normal age and gender related subjects. Patients with longer duration and higher disease activity are more susceptible for developing osteopenia and osteoporosis. Occurrence of joint deformities increases with longer disease duration. Limitation of physical activity impairs the bone mineral density. Patient taking anti-rheumatic therapy (steroids and Disease-modifying anti-rheumatic drugs) are at increased risk of bone loss. All these factors contribute to bone loss independent of each other.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease of unknown etiology marked by a symmetric, peripheral polyarthritis. It is the most common form of chronic inflammatory arthritis and often results in joint damage and physical disability. Because it is a systemic disease, RA may result in a variety of extra articular manifestations, including fatigue, subcutaneous nodules, lung involvement, pericarditis, peripheral neuropathy, vasculitis, and hematologic abnormalities.¹⁻³

The incidence of RA increases between 25 and 55 years of age, after which it plateaus until the age of 75 and then decreases. The presenting symptoms of RA typically result from inflammation of the joints, tendons, and bursae. Patients often complain of early morning joint stiffness lasting more than
1 hour and easing with physical activity. The earliest involved joints are typically the small joints of the hands and feet. The initial pattern of joint involvement may be monoarticular, oligoarticular (2-4 joints), or polyarticular (>5 joints), usually in a symmetric distribution. Some patients with an inflammatory arthritis will present with too few affected joints and other characteristic features to be classified as having RA—so-called undifferentiated inflammatory arthritis.

Increased bone loss is only part of the story in RA, as decreased bone formation plays a crucial role in bone remodeling at sites of inflammation. Recent evidence shows that inflammation suppresses bone formation. The proinflammatory cytokine Tumor necrosis factor-α plays a key role in actively suppressing bone formation by enhancing the expression of dickkopf-1 (DKK-1). DKK-1 is an important inhibitor of the Wnt pathway, which acts to promote osteoblast differentiation and bone formation.

Osteoporosis is a condition in which the bone becomes less dense and more likely to fracture. The World Health Organization (WHO) operationally defines osteoporosis as a bone density that falls 2.5 standard deviations or more below the mean peak bone mass (average of young, healthy adults) as measured by DXA; the term “established osteoporosis” includes the presence of a fragility fracture. 4

Aims and Objectives
1. To evaluate bone mineral density in patients of Rheumatoid arthritis and equal number of controls.
2. Correlation of BMD with severity of the disease.

Material and Methods

The present study was a case control study conducted in the Rheumatology Division, Department of Medicine, S.P, Medical College, Bikaner during July 2009 to January 2012 after explaining the objective of the study and taking an informed consent from the patients or from guardian family members. Hand bone density was measured on the plain radiographs of the right hand using digital x-ray radiogrammetry (Pronosco Xposure System 2.0) a computerized version of the traditional technique of radiogrammetry. A standard x ray image of the hand scanned by an x ray scanner into a PC. In order to estimate the BMD value, the digitized image analysed via PRONOSCO SOFTWARE 5. mean surrogate bone density value was calculated from cortical thickness from regions of interest measured at the center of the second, third, and fourth metacarpals. This surrogate bone density measurement (expressed as grams per square centimeter) was based on measurement of the outer and inner diameter, measuring combined cortical thickness. This BMD was correlated with markers of disease activity using DAS 28 Scoring system 6. Other laboratory investigations (eg. Complete blood count, renal function test, liver function test, random blood sugar, serum lipid profile, thyroid function test, erythrocyte sedimentation rate, Rheumatoid factor, C-reactive protein etc.) were done. Appropriate statistical analysis was applied as and when required using statistical software (SPSS version 10.0).

Number of patients: Over 200 controls subjects with no known history of disease and equal number of cases recruited as per the following inclusion and exclusion criteria.

Inclusion Criteria
Patients of rheumatoid arthritis diagnosed as per American College of Rheumatology (ACR) criteria 1987 were included in the study.

Exclusion Criteria
1. All patients of rheumatoid arthritis with association illnesses like malignancy, renal failure, liver failure, bronchial asthma, chronic obstructive pulmonary disease, diabetics, coronary artery disease, hypertension, thyroid disorders, dyslipidemia or any other endocrinopathy excluded from this study.
2. Patients of RA with other connective tissue disorders like scleroderma, systemic lupus erythematosus, polyomyelitis etc. (overlap syndrome) excluded from this study.
3. All pregnant and lactating mothers having RA excluded from this study.
4. All patients of RA who smoke excluded from this study.

Observations

Mean age in study group was 43.59±13.00 and in control group 42.79±12.87 years. Mean hemoglobin was 9.77±1.52 and 10.03±1.44 in study and control groups respectively. Mean BMD was 0.53±0.01 and 0.57±0.08 in study and control groups respectively while mean T-score was -1.42±1.94 in study group and -0.15±0.08 in control group. Mean Z-score in study group was -0.50±1.79 and in control group 0.51±1.54.
### Table 1: Distribution of cases and controls according to Z-score in relation to age

<table>
<thead>
<tr>
<th>Z Score</th>
<th>Age group</th>
<th>Study group</th>
<th>Control group</th>
<th>Study group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;45 years</td>
<td>No. (%)</td>
<td>No. (%)</td>
<td>No. (%)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>Normal (≥-0.99)</td>
<td>70 (56.9)</td>
<td>131 (92.3)</td>
<td>26 (33.8)</td>
<td>20 (34.5)</td>
<td></td>
</tr>
<tr>
<td>Osteopenia (-1 to -2.49)</td>
<td>32 (26.0)</td>
<td>9 (6.3)</td>
<td>39 (50.6)</td>
<td>28 (48.3)</td>
<td></td>
</tr>
<tr>
<td>Osteoporosis (≤-2.5)</td>
<td>21 (17.1)</td>
<td>2 (1.4)</td>
<td>12 (15.6)</td>
<td>10 (17.2)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>123 (100)</td>
<td>142 (100)</td>
<td>77 (100)</td>
<td>58 (100)</td>
<td></td>
</tr>
<tr>
<td>Mean Z-score</td>
<td>-0.26</td>
<td>1.09</td>
<td>-0.88</td>
<td>-0.89</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>1.91</td>
<td>1.08</td>
<td>1.52</td>
<td>1.61</td>
<td></td>
</tr>
<tr>
<td>T</td>
<td>-7.179</td>
<td>0.026</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.001</td>
<td>0.980</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

On statistical comparison, the difference was statistically highly significant in BMD, T-score, Z-score between study and control groups (p<0.001) while it was insignificant in age, hemoglobin and platelet count (p>0.05).

Among the male, there were total 29 patients each in study and control group who had normal Z-score while 67 and 95 cases in study and control groups respectively had their Z-score within normal range and there were total 22 patients each in study and control group who had osteopenia while among females, 49 and 31 cases in study and control groups respectively had osteopenia.

There were total 13 patients each in study and control group who had osteoporosis in male group while among females, 20 and 10 cases in study and control groups respectively had Osteoporosis. On statistical comparison of study vs control groups, there was highly significant difference in Z-score among males and females (p<0.001).

There were total 96 cases who had their Z-score within normal range and out of these 96 patients joint deformity was present in 23 patients. Out of these 23 patients 4 had their disease duration <1 years while remaining 19 patients had their disease duration 1-5 years.

In osteopenia group, there were total 71 patients were found and out of them joint deformity was present in 39 patients. Out of these 39 patients 30 patients had their disease duration >10 years while 7 patients had their disease duration 1-5 years. One patient each was also found in disease duration groups <1 and >5-10 years.

In osteoporosis group, there were total 33 patients were found and out of them joint deformity was present in 23 patients. Out of these 23 patients 18 patients had their disease duration >10 years while 3 patients had their disease duration >5-10 years and 2 patients had their disease duration 1-5 years while no patient was found in disease duration <1 year. There were total 96 cases who had their Z-score within normal range and out of these 96 patients joint deformity was present in 9 males and 17 females.

Out of these 39 patients with deformities, 14 were males and 25 were females. In osteoporosis group there were total 33 patients were found and out of them joint deformity was present in 23 patients. Out of these 23 patients 11 were males and 12 were females. Rheumatoid factor was positive in total 148 patients out of them 37.2% patients had osteopenia, 20.9% had osteoporosis while in patients with negative rheumatoid factor 30.8% had osteopenia and 3.8% had osteoporosis. On statistical comparison t’ test was applied and the difference was statistically highly significant between Z-score and rheumatoid factor (p<0.001).

Rest all the co relations are depicted and presented in Tables 1-3.

### Discussion

Osteoporosis and fragility-related fractures are one of the most common complications seen in patients with RA and dramatically affect quality of life. The present study was designed to evaluate BMD changes in patients with RA, as well as the effect of severity and drugs (steroids and Disease-modifying antirheumatic drugs) on these changes. In our study, there were 200 patients with equal number of controls. There were total 70 patients in study group and 131 patients in control group who
had their age <45 years had normal
Z-score while in age group >45
years 26 and 20 cases in study and
control groups respectively had
their Z-score within normal range.

There were total 32 and 9 cases
of study and control groups
respectively (age <45 years) who
had osteopenia while in age group
>45 years 39 and 28 cases in study
and control groups respectively
had osteopenia. There were total
21 and 2 cases of study and control
groups respectively (age <45 years)
who had osteoporosis while in
age group >45 years 12 and 10
cases in study and control groups
respectively had osteopenia.

On statistical comparison of
study vs control groups, there
was highly significant difference
in Z-score in age <45 years group
and in age group >45 years the
difference of Z-score between study
and control group was insignificant
(p>0.05).

There were total 51 newly
diagnosed cases. There was no
specific treatment history in these
patients. On the basis of duration of
symptoms, patients were divided
into 4 groups i.e. <1, 1-5, >5-10 and
>10 years. On the basis of age we
divided patients into two groups
i.e. <45 and >45 years.

Among females there were total
40 newly diagnosed cases out of
them 28 were from age group
<45 years while remaining 12
cases were from >45 years of age
group. Out of total 28 patients
who had their age group <45 years
23 patients who had their Z-score
within normal range and out of
these 23 patients 13 were from
disease duration <1 years while
remaining 10 patients were from
disease duration 1-5 years.

There were total 12 females who
had their age >45 years out of them
8 females had their Z-score within
normal range and out of them 3
were from disease duration <1 years
and 5 were from disease duration
1-5 years. Out of remaining 4
females, 3 had osteopenia and 1 had
osteoporosis and they came from
disease duration group <1 years
and >10 years respectively.

Among males there were total
11 newly diagnosed cases out of
them 7 were from age group <45
years while remaining 4 cases were
from >45 years of age group. Out
of total 7 patients who had their
age group <45 years all had their
Z-score within normal range and
disease duration <5 years. There
were total 4 males who had their
age >45 years all of these patients
had their Z-score within normal
and disease duration <5 years.

This observation supported
the fact that patients with RA are
more susceptible for bone loss in
comparison to normal age and
gender related subjects. These
findings are in agreement with
those of Brand et al\(^1\) who reported
that patients with RA have a higher
risk of low BMD than normal age-
and gender matched populations.

Similarly, a study reported by
Kim et al\(^1\) showed an increased
risk of osteoporotic fractures in
RA patients in all age groups,
regardless of gender, and at various
anatomical sites compared with
individuals without RA.

In contrast, Curtis et al\(^1\) found
that the proportion of their RA
patients meeting t score criteria
for osteoporosis (t score <-2.5 at
either the lumbar spine or femoral
neck) was only 4%, and Yoon et
al\(^1\) reported that 52% of their
patients with early-onset RA
had osteoporosis and 39% were
classified as having osteopenia.

Our results are also consistent
with those of Güler-Yüksel et al\(^1\)
who reported that RA patients
with early, active, erosive disease
and a positive rheumatoid factor
had more aggressive joint disease
and decreased BMD. Laan et al\(^1\)
PLAN concluded that BMD may
be affected in patients with recent
onset rheumatoid arthritis by
disease dependent mechanism.

Kim et al\(^1\) also observed an
increased risk of osteoporosis
associated with a positive RF and
elevated acute phase reactants,
although this was not statistically
significant. While Solomon et al.\(^1\)
have found that BMD at the total
hip was significantly lower in
rheumatoid factor-positive and
lumbar spine were almost identical
women. However, values at the
lumbar spine were almost identical
for rheumatoid factor-positive and
-negative women.

**Conclusion**

Patients with RA are more
susceptible to bone loss in
comparison to normal age and
gender related subjects. Patients
with longer duration of disease are
more susceptible for developing
osteopenia and osteoporosis.
Patients with higher disease activity are more susceptible for bone loss. Occurrence of joint deformities increases with longer disease duration. Patients who test positive for rheumatoid factor are also more prone to osteopenia and osteoporosis. Limitation of physical activity impairs the bone mineral density. Patient taking anti-rheumatic therapy (steroids and Disease-modifying antirheumatic drugs) are at increased risk of bone loss. All these factors contribute to bone loss independent of each other emphasizing the initiation of osteo-protective therapy in rheumatoid arthritis patients as soon as possible.

References


Obituary

Dr. G.H. Tilve was a Medical Teacher par excellence, he displayed clinical signs effortlessly in all clinical situations - OPD Indoor & ICU exposing the students to the basic principles of Medicine. He emphasized quality of Teaching and took prolonged efforts that are necessary on the part of the teacher; his urge was for improvement and lasting change that promoted patients health well being. He demonstrated concern and patience in clinical interactions. King Edward VII Memorial Hospital being a seminal centre, his vision of medicine was crucial. A personal physicians for local patients, he contributed to treatment of patients all over the country through his teaching and lecturing. He did not carry any preconceived notions. During his career his interest & work spanned genmedicine Rheumatology & Nuclear Medicine. He succeeded in maintaining the standard of his predecessors Drs. K.G. Nair, V.N. Acharya. He was a teacher to the core, determined to make a clinical diagnosis. I could count on him for candid opinion in clinical/academic issues. He was modest to a fault and had an old-wordly sense of humor. Simplicity was his forte. He loved travel particularly the call of Himalayan region.

Dr. M.E. Yeolelekar
Former Dean/Director (ME & R), K.E.M. Hospital, Mumbai.
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Prognostic Indicators of Response to Plasmapheresis in Patients of Guillain Barre Syndrome

HB Prasad¹, RT Borse², AN Avate³, Neelesh Palasdeokar⁴

Abstract

Introduction: Plasmapheresis is an important modality for the treatment of GBS. Moreover the response to this treatment modality is not same in all cases. We therefore studied the various prognostic indicators of response to plasmapheresis in patients of Guillain Barre Syndrome.

Materials and Methods: 40 patients were included in the study. Thorough clinical examination was done. Nerve conduction was done to find out the type of neuropathy. All were then given plasmapheresis. Prognostic indicators with reference to Age, sex, presenting severity, time between onset of illness and arrival to hospital, time taken to start plasmapheresis, number of plasmapheresis cycles, respiratory involvement, and type of neuropathy were studied.

Results: There were 57.5% females and 47.5% males. Majority (82%) patients were in the age group of 20 to 60 years. All the patients had power grade 1 or 2 on admission but on discharge the power was grade 3 to 5 in 29 (80.55%) patients. The number of patients who received 5 cycles was 34(85%) and those who received 4 cycles of plasmapheresis was 6(15%). AIDP (acute inflammatory demyelinating polyneuropathy) was seen in 36 (90%) pts and AMAN (Acute Motor axonal Neuropathy) was seen in 4 (10%) patients. The severity at presentation and improvement was similar for all ages. Those who received plasmapheresis late showed power improvement of 2 to 3 grade in (50%) whereas those who received early showed improvement of 2 or 3 grade power in 82.14% patients indicating better improvement with early plasmapheresis. No difference was seen in grade of power improvement in 4 or 5 cycles of plasmapheresis. The number of patients on mechanical ventilation were 13 (40.62%) AIDP cases and 4 (100%) AMAN cases indicating more respiratory involvement in AMAN patients. All four patients of AMAN put on mechanical ventilation died of Ventilator associated pneumonia.

Conclusion: Early treatment with plasmapheresis has better outcome in patients of GBS. Four and five cycles of plasmapheresis are equally beneficial.

Introduction

Guillain - Barre Syndrome - is an acute and frequently severe type of polyradiculoneuropathy of autoimmune nature. It is also known as Landry’s Paralysis. Guillain - Barre (Ghee-yen-Bah-ray) Syndrome is also known as acute inflammatory demyelinating polyneuropathy (AIDP) and it is an inflammatory disorder of the peripheral nerves. GBS manifests as rapidly evolving are flexic motor paralysis with or without sensory disturbance. The usual pattern is an ascending flacid paralysis. Weakness typically evolves over hours to a few days and is frequently accompanied by tingling dysesthesias in the extremities. The treatment of GBS is either plasmapheresis or IV immunoglobulin (IVIG). IVIG is expensive though easy to administer. Plasmapheresis is the second modality which is cheaper and effective. Moreover the response of plasmapheresis is not the same in all patients.

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30 ml /Kg body weight of plasma was removed using plasmapheresis filter. They were monitored for neurological improvement and need for ventilation and when indicated patients were put on ventilator. Thorough systemic examination for other systems was done. Patients were assessed daily for improvement in power till the completion of cycles of Plasmapheresis and then till discharge.

Statistical Analysis
Statistical analysis was done using SPSS software version 17 for windows. t test was done for age, duration of illness and early or late PP. Chi square and Fisher exact was used to find association between sex, power on admission, type of neuropathy (AIDP, AMAN), neurodeficit on admission and early or late PP. Proportion test was used to find the significance difference of number of plasmapheresis cycles, respiratory involvement and type of neuropathy.

Material and Methods

40 adult patients admitted to wards and MICU of Sassoon general hospitals a tertiary care centre in Maharashtra, India for flaccid paraplegia or quadriplegia were included. Thorough neurological clinical examination was done to assess degree of weakness on admission and associated features like autonomic dysfunction, respiratory muscle weakness, cranial nerve involvement and reflexes. A detailed history of duration of illness and time from onset of illness to arrival to hospital was noted. The diagnosis of GBS was done by nerve conduction studies to see if patient had AIDP (Acute inflammatory demyelinating polyneuropathy) or AMAN (Acute motor Axonal neuropathy). Patients were then put on plasmapheresis. Plasma exchange was done with 8 fresh frozen plasma (50 ml/kg). We therefore took up this study to assess prognostic indicators of response to plasmapheresis in patients with GBS.

Aims and Objectives
To study the various prognostic indicators of response to plasmapheresis in patients of Guillain Barre Syndrome with reference to age, sex, presenting severity, time between onset and arrival to hospital, time taken to start plasmapheresis, number of plasmapheresis cycles, respiratory involvement and type of neuropathy.

Observation Tables

Table 1: Overall improvement of power after plasmapheresis

<table>
<thead>
<tr>
<th>Power change</th>
<th>No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 to 2</td>
<td>7 (28.0%)</td>
</tr>
<tr>
<td>1 to 3</td>
<td>17 (42.5%)</td>
</tr>
<tr>
<td>1 to 4</td>
<td>1 (2.5%)</td>
</tr>
<tr>
<td>2 to 3</td>
<td>1 (2.5%)</td>
</tr>
<tr>
<td>2 to 4</td>
<td>14 (35%)</td>
</tr>
</tbody>
</table>

Table 2: Power improvement in 4 cycles of plasmapheresis patients

<table>
<thead>
<tr>
<th>Power change</th>
<th>No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 to 3</td>
<td>2 (33%)</td>
</tr>
<tr>
<td>2 to 4</td>
<td>4 (66%)</td>
</tr>
</tbody>
</table>

Table 3: Power improvement in 5 cycles of plasmapheresis patients

<table>
<thead>
<tr>
<th>Power change</th>
<th>No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 to 3</td>
<td>15 (44.11%)</td>
</tr>
<tr>
<td>1 to 4</td>
<td>12 (35.29%)</td>
</tr>
<tr>
<td>2 to 3</td>
<td>1 (2.95%)</td>
</tr>
<tr>
<td>2 to 4</td>
<td>6 (17.65%)</td>
</tr>
</tbody>
</table>

Table 4: Power improvement in early plasmapheresis (27 pts)

<table>
<thead>
<tr>
<th>Power change</th>
<th>No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 to 2</td>
<td>4 (14.81%)</td>
</tr>
<tr>
<td>1 to 3</td>
<td>12 (44.44%)</td>
</tr>
<tr>
<td>2 to 3</td>
<td>1 (3.70%)</td>
</tr>
<tr>
<td>2 to 4</td>
<td>10 (37.03%)</td>
</tr>
</tbody>
</table>

Table 5: Power improvement in late plasmapheresis (13 pts)

<table>
<thead>
<tr>
<th>Power change</th>
<th>No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 to 2</td>
<td>3 (23.07%)</td>
</tr>
<tr>
<td>1 to 3</td>
<td>4 (30.76%)</td>
</tr>
<tr>
<td>1 to 4</td>
<td>1 (7.9%)</td>
</tr>
<tr>
<td>2 to 4</td>
<td>5 (38.46%)</td>
</tr>
</tbody>
</table>

23 out of 27 i.e. 85.18% patients showed improvement in power by 2 grades whereas 5 patients ie 18.51% showed improvement of power of 1 grade. 9 out of 13 pts i.e. 69.23% showed improvement in power by 2 grades, 3 out of 13 i.e. 23.07% showed improvement in power of 1 grade. 1 out of 13 i.e. 7.69% showed improvement by grade 3 power.

Results
Most patients were in the age group of 21 to 60yrs (90%). There were 19(47.22%) males and 21 (52.77%) females. 28(77.5%) patients had weakness of 3 to 6 days. 36 patients i.e (90%) came with quadriplegia and 4 (10%) with paraplegia. All the patients had power grade 1 or 2 on admission but on discharge the power was grade 3 to 5 in 33 (82.55%) patients. Thirty-four (85%) patients received 5 cycles and 6 (15%) received 4 cycles of plasmapheresis. AIDP (acute inflammatory demyelinating polyneuropathy) was seen in 36 (90%) pts and AMAN (Acute Motor Axonal Neuropathy) was seen in 4 (10%) patients. The overall grade power improvement after plasmapheresis was 1 to 2 grade in 7 (17.5%) patients and 1 to 3 in 17 (42.5%) pts. 1 to 4 in 1 (2.5%) patients, 2 to 3 in 1 (2.5%) patient and 2 to 4 in 14 (35%) patients. Twenty-seven (67.5%) patients received early plasmapheresis within 4 days and 13 (32.5%) received late plasmapheresis after 4 days. Diarrhoea was preceding illness in 2 (5%) pts, respiratory infection was seen in 1 (2.5%) patient and 37 (92.5%) had none. The prognostic factors - Those who received plasmapheresis late showed power improvement...
of 2 grade in (69.23%) whereas those who received early showed improvement of power by grade 2 or 3 in (85.18%). The P value was <0.05 significant. All 5 patients ie 100% who received 4 cycles showed grade 2 improvement in power whereas 34 (97.14%) patients who received 5 cycles showed grade 2 improvement in power. The p value was <0.05 ie significant. The severity at presentation and improvement was similar for all ages.13 (40.62%) AIDP cases and 4 (100%) AMAN cases were on mechanical ventilation indicating more respiratory involvement in AMAN patients. 4 out of 17 (23.52%) patients put on mechanical ventilation died of ventilator associated pneumonia. Thus Age, sex, preceding illness, duration of weakness, type of neuropathy and power on admission did not significantly affect the response to plasmapheresis. The p value was >0.05.

### Discussion

#### Age

In this study the commonest age group was 21 to 60 yrs (90%). In a study by Dhadke et al the age group commonly affected was 13-40 yrs. whereas in study by Netto et al 2 mean age was 33.5 ± 21 years)

#### Sex

There were 19(47.22%) males and 21 (52.77%) females indicating slight female preponderance. In the study by Dhadke et al the male:female ratio was 1.5:1 and the study by Netto et al out of 173 there were 118 men and 55 women indicating male preponderance in both these studies moreover sex did not affect recovery in all these studies including our study.

#### Plasmapheresis

There are two modalities of treatment for GBS are immunoglobins and plasmapheresis. Immunoglobulins are expensive and most of our patients cannot afford the same hence plasmapheresis was given to all our 40 patients. All the patients who received plasmapheresis improved. Early initiation of plasmapheresis resulted in better power improvement in most of the patients 85% of our pts received 5 cycles of plasmapheresis and 15% received 4 cycles but all showed response confirming the fact that any treatment is effective

A number of studies have shown that PP is associated with faster and better recovery in patients with GBS AK Meena et al in their guidelines for treatment of GBS highlighted the importance of early and adequate PP. In a meta-analysis of 6 class II trials comparing plasma exchange (PE) to supportive care alone for adults with GBS, it was found that PE reduced the risk of developing respiratory failure.4,5

In our study the patients were observed for 10 days minimum and for longer duration according to hospital stay. All of them recovered by 1 to 2 grade power in 10 days

#### Number of Cycles

Most of our patients received 5 cycles ie 85.5% and about 15% received 4 cycles of plasmapheresis The improvement in grade of power by 2 grades was seen in all 5 ie 100% cases who received 4 cycles and in 97.14% cases who received 5 cycles indicating that any number of plasmapheresis started was beneficial (Tables 1, 2, 3). This was also shown by Yuki et al that in mild GBS, two sessions of PE are superior to none. In moderate GBS, 4 sessions are superior to 2. In severe GBS, 6 sessions are no better than 4. In line with these findings they reported that at least 2 PE are needed to significantly reduce the circulating immunoglobulin complexes.6 In developing countries where cost is the limiting factor, small volume PE may be used. In India small volume PE was used by Tharakan et al with comparable results. They used 15 mL/kg body weight/day to be continued till the progression of the disease got arrested or recovery started. This protocol is still performed in various centers in developing countries with good results

In the study by Dhadke et al out of 40 patients, 14 patients received Intravenous immunoglobulin and 4 patients received plasmapheresis. Patients who received IVIg early in the course of disease had faster recovery as compared to patients who received only supportive line of treatment

In a study by The French Cooperative Group on Plasma Exchange in Guillain-Barré Syndrome.8 They randomized 556 GBS patients according to severity and number of exchanges as follows: Zero versus 2 PEs for patients who could walk-with or without aid-but not run, or who could stand up unaided (mild group); 2 versus 4 PEs for patients who could not stand up unaided (moderate group); and 4 versus 6 PEs for mechanically ventilated patients (severe group). In the mild group, 2 PEs were more effective than none for time to onset of motor recovery (median, 4 vs 8 days, respectively). In the moderate group, 4 PEs were more beneficial than 2 for time to walk with assistance (median, 20 vs 24 days) and for 1-year full muscle-strength recovery rate (64% vs 46%). Six PEs were no more beneficial than 4 in the severe cases. Patients with mild GBS on admission should receive 2 PEs. Patients with moderate and severe forms should benefit from 2 further exchanges

The GBS study group compared plasmapheresis with conventional therapy in 245 patients with the Guillain-Barré syndrome of recent onset. Statistically significant differences, favoring the plasmapheresis group, were found in terms of improvement at 4 weeks, time to independent walking, and outcome at 6 months. Plasmapheresis was not effective for all patients, but was particularly effective for patients who received...
this treatment within 7 days of onset and for patients who required mechanical ventilation after entry into the study. They concluded that Plasmapheresis appears to be of benefit in patients with Guillain-Barré syndrome of recent onset.4,5

Another study9 i.e. Randomised trial of plasma exchange, intravenous immunoglobulin, and combined treatments in Guillain-Barré syndrome showed that in treatment of severe Guillain-Barré syndrome during the first 2 weeks after onset of neuropathic symptoms, PE and IVIg had equivalent efficacy. The combination of PE with IVIg did not confer a significant advantage.

Since all our patients received only plasmapheresis we could not compare it with immunoglobulin.

**Plasmapheresis and Respiratory Failure**

In our study 17 patients were on mechanical ventilation indicating respiratory muscle involvement but only 4 died of VAP and 13 recovered well in response to Plasmapheresis. In a meta-analysis of 6 class II trails comparing plasma exchange (PE) to supportive care alone for adults with GBS, it was found that PE reduced the risk of developing respiratory failure.4,5

In the study by Dhadkeetael1 One third (32.5%) patients developed respiratory paralysis and needed ventilatory support.

A study by Sunder et al:10 Comparing the clinical data in the ventilated and non-ventilated groups concluded that early progression to peak disability, bulbar dysfunction and autonomic instability predicted the development of neuromuscular respiratory paralysis in GBS. Early electrodiagnostic studies in this series suggest axonopathic GBS as a predictor of respiratory paralysis, a finding that needs to be evaluated with sufficient data to permit statistical analysis. In our study all 4 cases with AMAN had respiratory paralysis.

In a review study by Archana B Netto et al2 which studied Prognostic factors in patients with Guillain-Barré syndrome requiring mechanical ventilation concluded that that modifiable risk factors, such as pulmonary involvement, autonomic dysfunction, hypokalemia, sepsis, bleeding, and nutritional complications, had prognostic significance and their modification may reduce the mortality and morbidity associated with GBS. We did not study these aspects.

**Timing of Plasmapheresis**

67.5%of our patients received plasmapheresis early ie within 4 days and 32.5% received late ie after 4 days. The grade power improvement by 1-2 grades in early plasmapheresis was better in 85.18% patients as compared to 69.23% patients in late Plasmapheresis (Tables 4, 5).

A better outcome was demonstrated with plasma exchange in French Study Group when compared with North American Study Group.4 This is due to the fact that treatment was initiated within 2 weeks in the former study group and within 4 weeks in the latter. Hence PE is more beneficial when started within 7 days after disease onset rather than later, but was still beneficial in patients treated up to 30 days after disease onset.

**Severity on Admission and Plasmapheresis**

All our patients received plasmapheresis irrespective of initial power on presentation. American academy of Neurology in 2003 concluded that PE hastens recovery in nonambulant patients who get treatment within 4 weeks of onset, and PE hastens recovery of ambulant patients with GBS who are examined within 2 weeks. PE is usually administered as one plasma volume, 50 mL/kg, on 5 separate occasions over 1-2 weeks.4 All patients with mild, moderate, and severe GBS benefit from treatment. Patients who need even minimum assistance for walking, who are steadily progressing and those who are bed- and ventilator-bound should be advised PP. In our study all the patients had power grade 1 or 2 on admission but on discharge the power was grade 3 to 5 in 33 (82.55%) patients. The overall grade power improvement after plasmapheresis was 1 to 2 grade in 7 (17.5%) patients and 1 to 3 in 17 (42.5%) pts. 1 to 4 in 1 (2.5%) patients, 2 to3 in (2.5%) patient and 2 to 4 in 14 (35%) patients. Though these observations were seen clinically the same were not statistically significant.

**Treatment of AMAN and AIDP**

Four patients in our study had AMAN and 36 had AIDP. All the four cases of AMAN were on mechanical ventilation indicating respiratory involvement but the degree of recovery in both groups was same. AIDP is the most common GBS variant in North America and European nations; the axonal variant AMAN is most often seen in Asian nations, including Japan and China. Although there are many clinical trials including patients with the demyelinating AIDP variant from European and North American centers, data outlining the use of immunomodulatory therapies in AMAN are limited. One small retrospective study found that patients who received IVIG recovered more rapidly than those who received PE.6 Similar results were reported elsewhere.12,13 However, another retrospective review reported better outcomes with PE in severe axonal GBS patients, some of whom had failed prior IVIG therapy.14 Another analysis of 44 AMAN patients reported no difference in the rate of recovery between those who received IVIG or PE.13 Because AMAN generally follows a similar clinical course as AIDP, IVIG and PE are assumed to be appropriate treatment interventions, especially in patients with severe presentations.

Plasmapheresis effectively
hastens recovery from AIDP, not all patients will tolerate it. Additionally, some will demonstrate an inadequate response and others may subsequently relapse following initial benefit.

Preceding Illness and GBS

In our study two patients had diarrhoea, one had respiratory infection and 37 had none. Since antecedent infection was absent in most of our cases it could not be correlated.

In the study by Dhadke et al antecedent infection was seen in 55% patients. A history of antecedent events was present in 83 (48%) patients in the study by Nettoet all and all these patients were on mechanical ventilation indicating its correlation to the severity of initial presentation.

Van Koningsveld et al studied 388 patients with GBS and developed a simple clinical scoring system to predict outcome at 6 months i.e. inability to walk independently at 6 months. They included 3 variables that were predictive of poor outcome at 6 months i.e. age, preceding diarrhoea, and GBS disability score at 2 weeks after entry. Scores ranged from 1 to 7, with three categories for age, two for diarrhoea, and five for GBS disability score at 2 weeks. Predictions corresponding to these prognostic scores ranged from 1% to 83% for the inability to walk independently at 6 months. Predictions agreed well with observed outcome frequencies (adequate calibration) and showed a very good discriminative ability (AUC 0.85) in both data sets.

Conclusion

Patients with GBS benefit from plasmapheresis irrespective of initial severity and any number of PP are beneficial. PP should be started early as the benefit is more in terms of recovery. AMAN type of GBS is uncommon and has more respiratory involvement.

References

Evaluation of the Association between CD4, CD8 and CD25 Cell Counts and SLE in Active Disease and in Remission

Archana Sonawale¹, Vinay Bohara², LS Bichile³

Abstract

Aim: To evaluate the correlation between the levels of CD4, CD8 and CD25 cells and SLE disease in active phase and in remission.

Method: A total of 25 SLE patients, aged between 18-60 years, and fulfilling the ACR criteria with preferential Renal and CNS involvement were included in this study. Baseline CD4/CD8 and CD25 counts, lab parameters etc were conducted. Approximately at the end of 6 months with the settlement of the disease activity blood sample was drawn for the CD4, CD8 and CD25 counts and other lab parameters.

Results: ESR showed a statistical significant decrease while the SLEDAI score and proteinuria showed a decreasing trend as the patients underwent remission. The C3 showed an increasing trend, while the C4 showed more or less a stable pattern. Rise in %CD4 and %CD25 count was statistically significant. There was negative correlation between % CD4 count and SLEDAI score, while positive correlation between % CD25 count and SLEDAI score.

Conclusion: %CD4 count is a sensitive, specific, reliable and valid marker of active disease in SLE and can be used to follow disease activity. %CD25 count can also be used as a marker to follow disease activity.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease and it results in the activation of both the innate as well as the adaptive immunity. SLE results due to a disturbance in immune tolerance, which is most likely initiated by a pathogen challenge, which in presence of genetic defects results in autoimmune hyperactivity.¹ SLE is associated with a number of symptoms due to nephritis, nervous system inflammation, arthritis, leukopenia and skin rashes.² Immune homeostasis is maintained mainly by self tolerance. CD4, CD8 and CD25 cells which consist of 5-10% of the peripheral blood count prevent autoimmunity.³ There is recent evidence that show breaks in immune tolerance to self-antigens most likely result in the commencement of end organ disease. Several factors like autoantibodies, immune complex deposition, activation of T cell result in organ specific presentation of the condition.⁴ It has been previously shown that when CD4, CD25 regulatory T cells have been experimentally depleted by thymectomy, there is an increment in auto-reactive T cells and hastened autoantibody production. On the other hand, supplementation of the CD4, CD25 regulatory T cells isolated from normal mice has been shown to decrease the development of autoimmunity.⁵

SLE is marked by frequent relapses and remissions. Even though clinical features are important markers of disease activity, several laboratory parameters like the Hb, ESR, C3, C4 levels serve as more objective markers.⁶ Recurrent defects in immune tolerance leads to disease flares in SLE which is marked by CD4 and CD25 lymphocytopenia.⁷

However, the role of CD4 and CD25 cells in the maintenance of immune tolerance and as a marker

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Editorial Viewpoint

• Recurrent defects in immune tolerance leads to disease flares in SLE which is marked by CD4 and CD25 lymphocytopenia.
• CD4 count is a sensitive, specific, reliable and valid marker of active disease in SLE.
• CD4 and CD25 count can also be used as a marker to follow disease activity.
of disease activity in SLE is not explored. Hence in this study we have tried to evaluate the correlation between the levels of CD4, CD25 cells and SLE in disease activity and in remission.

Materials and Methods

The study was initiated after receiving approval from the Institutional Review board. A total of 25 SLE patients, aged between 18-60 years, and fulfilling the ACR criteria with preferential Renal and CNS involvement were included in this study. Patients suffering from other rheumatological disorders and overlap syndromes were excluded from the study. Patients fulfilling the inclusion criteria were enrolled in the study after taking their informed consent. These study participants were clinically examined and all the routine investigations were conducted. A 4cc peripheral venous sample was collected and processed as per standard protocol for CD4/CD8 and CD25 counts. The study participants were followed up to study overall disease activity, treatment regimen, and laboratory parameters. Approximately at the end of 6 months with the settlement of the disease activity blood sample was drawn for the CD4, CD8 and CD25 counts.

Baseline study participant characteristics was described using descriptive statistics. Parametric data if it passed the tests of normality was analyzed using parametric tests or else non-parametric tests were used for its analysis. Categorical data was analyzed using Chi-square test. Parametric correlation analysis was done using Pearson correlation test while non-parametric correlation analysis was done using Spearman correlation test.

Results

The mean age of the patients included in this study was 26.8 ± 7.1 (mean ± SD) years. Of the 25 patients in this study, 22 were females and 3 were males. The major organ involvement in lupus patients on presentation was such that, 14 patients had renal involvement only, 2 had CNS involvement only and 9 patients had both renal and CNS involvement.

The mean number of ACR criteria at the beginning of the study and the end of the study was 6.16 ± 1.92 and 1.32 ± 0.62 (mean ± SD) respectively. Applying the Wilcoxon matched pair test, it is found that the number of ACR criteria at the end of the study was significantly lesser than the number of criteria at the beginning of the study (p<0.0001).

The mean total leucocyte count (TLC) at the beginning of the study and at the end was 6936 ± 4774 and 7284 ± 2291 (mean ± SD) cells/mm³ respectively. Applying the Wilcoxon matched pair test, it is found that even though there is an increase in the TLC it is not statistically significant (p 0.33).

The mean absolute lymphocyte count (ALC) at the beginning of the study and at the end was 2131 ± 1707 and 2430 ± 846 (mean ± SD) cells/mm³ respectively. Applying the Wilcoxon matched pair test, it is found that even though there is an increase in the ALC it is not statistically significant (p 0.12).

The mean ESR at the beginning of the study and at the end was 52.48 ± 16.25 and 30.08 ± 12.39 (mean ± SD) respectively. Applying the paired t test, it is found the ESR showed a statistical significant decrease by the end of the study (p 0.0001).

The mean serum creatinine level at the beginning of the study and at the end was 1.19 ± 0.56 and 1.24 ± 0.75 (mean ± SD) mg/dL respectively. Applying the Wilcoxon matched pair test, it is found that even though there is an increase in the serum creatinine level it is not statistically significant (p 0.81).

After treatment for the study duration, of the 25 patients included in this study, 21 entered remission while 4 did not. The induction of remission was defined according to the SLEDAI score (Systemic Lupus Erythematosus Disease Activity Index). According to this definition, an SLEDAI score <3 indicates remission while a score of ≥ 3 indicates active disease.

The mean SLEDAI score at 0, 3 and 6 months was 23.48 ± 10.8, 8.32 ± 3.30 and 2.48 ± 1.82 (mean ± SD) respectively. Applying the Friedman test the difference is statistically significant (p<0.0001). Post hoc Dunn test showed that the difference was statistically significant for the difference in proteinuria between 0 & 6 months, 0 and 3 months and 3 and 6 months. The SLEDAI score showed a decreasing trend as the patients underwent remission due to treatment.

The mean proteinuria at 0, 3 and 6 months was 1908 ± 1306, 1044 ± 891 and 444 ± 400 (mean ± SD) mg/24 hrs. Applying the Friedman test the difference is statistically significant (p<0.001). Post hoc Dunn test showed that the difference was statistically significant for the difference in proteinuria between 0 & 6 months, 0 and 3 months and 3 and 6 months. The proteinuria, showed a decreasing trend after treatment.

The mean C3 levels at 0, 3 and 6 months was 54.46 ± 21.20, 63.34 ± 20.88 and 97.96 ± 15.93 (mean ± SD) mg% respectively. Applying the Friedman test the difference was statistically significant for the difference in proteinuria between 0 & 6 months, 0 and 3 months and 3 and 6 months. The proteinuria, showed a decreasing trend after treatment.
The %CD4 count is the absolute CD4 count expressed as percentage of normal CD4 count which is the lower value of the normal range. The %CD4 count at the beginning of the study was 55.84 ± 44.70 and was 107.69 ± 45.44 by the end of the study. Applying the Wilcoxon matched pairs test showed that the rise in %CD4 count was statistically significant (p<0.0001).

The %CD8 count is the absolute CD8 count expressed as percentage of normal CD8 count which is the lower value of the normal range. The %CD8 count at the beginning of the study was 113.61 ± 70.39 and was 134.39 ± 90.43 by the end of the study. Applying the paired t test showed that the rise in %CD8 count was statistically comparable (p 0.37).

The %CD25 count is the absolute CD25 count expressed as percentage of normal CD25 count which is the lower value of the normal range. The %CD25 count at the beginning of the study was 4.76 ± 4.33 and was 11.12 ± 4.75 by the end of the study. Applying the Wilcoxon matched pairs test showed that the rise in %CD25 count was statistically significant (p 0.0006).

Correlation analysis between % CD4 count during active lupus and SLEDAI score at baseline showed that there is a negative correlation between % CD4 count and SLEDAI score with the Spearman correlation coefficient being -0.5554. The two-tailed P value is 0.0039, which is statistically significant.

Correlation analysis between % CD4 count and SLEDAI score at remission showed that there is a negative correlation between % CD4 count and SLEDAI score with the Spearman correlation coefficient being -0.08. The two-tailed P value is 0.68, which is statistically non-significant.

Correlation analysis between % CD8 count during active lupus and SLEDAI score at baseline showed that there is a negative correlation between % CD4 count and SLEDAI score with the Spearman correlation coefficient being -0.6397. The two-tailed P value is 0.0006, which is statistically significant.

Correlation analysis between % CD8 count and SLEDAI score at remission showed that the Spearman correlation coefficient is -0.70, which is statistically non-significant.

Correlation analysis between % CD25 count during active lupus and SLEDAI score at baseline showed the Spearman correlation coefficient being 0.06. The two-tailed P value is 0.76, which is statistically non-significant.

Correlation analysis between % CD25 count at remission and SLEDAI score at remission showed that there is a positive correlation between % CD25 count and SLEDAI score with the Spearman correlation coefficient being 0.50. The two-tailed P value is 0.0096, which is statistically significant.

If the patients were grouped into 3 subgroups according to the number of ACR criteria positive at diagnosis, and the % CD4 count of these patients were compared at both baseline and at remission, it can be seen that there is a steady increase in %CD4 count as the patients went into remission. So we can state that the CD4 count is most depressed in patients with severe flare as indicated by low CD count when 8-11 ACR criteria were
Fig. 3: Correlation between %CD25 count at flare and remission with patients divided according to the number of positive ACR criteria at baseline

Table 2: Correlation between %CD count at flare and remission with patients divided according to the SLEDAI score at baseline

<table>
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<th>Parameters</th>
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<td>Total leucocyte count at diagnosis</td>
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<tr>
<td>&lt;4000 cells/mm³: 5</td>
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</tr>
<tr>
<td>4000-11000 cells/mm³: 17</td>
<td></td>
</tr>
<tr>
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<td>1.3-1.8 mg/dL: 3</td>
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</table>

positive (Figure 1).

Similarly when the %CD8 count was compared between flare and remission it was found out that the CD8 count only mildly increased as the patients went into remission. However, there was correlation with CD8 count and ACR criteria at diagnosis (Figure 2).

The same result was seen when the %CD25 counts were treated similarly (Figure 3).

If the patients were grouped into 2 subgroups according to the SLEDAI score being < or >12 at baseline and the %CD4, %CD8 and %CD25 count was correlated between flare and remission it was found that the count increased once the patients went into remission for both the subgroups (Table 2).

If the patients were grouped into 2 subgroups according to the WHO class of nephritis on renal biopsy and the %CD4, %CD8 and %CD25 count was correlated between flare and remission it was found that the count increased once the patients went into remission for both the subgroups (Table 3).

Discussion

Twenty five patients with active lupus were included in this present study. The same patients in remission acted as their own controls. Of the 25 patients, 3 were males and 22 were females. This sex distribution is similar to the known sex distribution of SLE which is female: male 9:1. Of all the patients, lupus nephritis was the mode of presentation in 9 of the patients, 14 had both CNS and renal involvement on admission and only CNS involvement was seen in 2 patients. This correlates well with the usually described incidences of renal (30-50%) and CNS (50%) involvement.

Out of the total of 25 patients in this study, 5 patients had leucopenia at the onset as shown by a total leucocyte count < 4000 cells/mm³, while it was normal (4000-11000 cells/mm³) in 17 patients (Table 1). The reported incidence of leucopenia in active Lupus varies between 20-70% in different case series. Santiago et al reported the incidence of leucopenia as 75%. In another study conducted by Lertchaisapatpong et al the incidence of leucopenia was around 50%. The apparent discrepancy in different studies with respect to leucopenia appears mainly due to treatment with steroids and immunosuppressive agents prior to the inclusion of these patients in the study. In the present study all the included patients were treatment naïve and hence the reported incidence of leucopenia (20%) may reflect a more accurate and unbiased view.
Lymphopenia is defined as ALC <1500 cells/mm³. In our study lymphopenia was seen in 9 patients, while normal lymphocyte count was seen in 16 patients (Table 1). This correlates well with the work done by Ng et al who showed the incidence of lymphopenia to be about 42% in active lupus patients.

The mean serum creatinine level at the beginning of the study was 1.19 ± 0.56 mg/dL. This is comparable to most of the other studies where the serum creatinine level was <1.5. This shows that renal function of majority of patients is well preserved at presentation. The statistical non-significant change in serum creatinine may be because of the fact that majority of the patients had near normal creatinine levels on presentation.

The proteinuria showed a descending trend on treatment which was statistically significant. This result correlated well with the case series published by Brinmingham et al and Touma et al.

The C3 levels showed an increasing trend during the treatment period which well correlates with the study conducted by Ziakas et al. C4 is a marker of disease activity and should rise as patient enters remission. However, in the present study different results were obtained. The C4 levels were more or less stable during the treatment duration. This low sensitivity and specificity of C4 levels in predicting relapse and remission observed in our study is similar to that seen in another study conducted by Bombardier et al.

The SLEDAI score showed a decreasing trend over the study duration. This is similar to a study conducted by Mirzayan et al which shows that SLEDAI decreases over treatment. In our study the %CD25 count showed an increasing trend on treatment. This was similar to a study conducted by Miyara et al which showed a decrease in the CD25 count.

Correlation analysis between %CD4 count during active lupus and SLEDAI score at baseline showed that there is a negative correlation between %CD4 count and SLEDAI score. This was in line with the study conducted by Ester Rosarie Ben et al in which CD4 +CD25+ Foxp3+Treg cell depletion was reported in 25 patients of SLE which correlated with higher SLEDAI scores. Also Shah et al have shown that the CD4 T cell count was decreased in SLE patients.

Correlation analysis between %CD8 count during active lupus and SLEDAI score at baseline showed that there is a negative correlation between %CD8 count and SLEDAI. This was similar to the study conducted by Dolf et al which showed that there is increase in CD8 cells during active disease. Correlation analysis between %CD8 count and SLEDAI score at remission showed no correlation. However this was in contrast with existing literature where Dolf et al have shown that the CD8 count decreases in remission.

Conclusion

Our data indicates that leucopenia is not a very sensitive marker of disease activity since it is present in about 20% patients with flare even though it has been described as a traditional marker. ESR was high in all patients with flare making it a very sensitive marker albeit a less specific one since it was high even in patients of remission. Creatinine levels were not good markers since patients with active disease had normal creatinine levels. C3 is a very sensitive marker of flare as compared to C4 levels.

Our study results show that the CD4 count has an inverse relation with the SLEDAI score, number of positive ACR criteria and class of lupus nephritis. It is most depressed in patients with severe flare as compared to mild or moderate flare. The %CD4 count rises with the settling of disease activity and reaches to normal on treatment. This proves that %CD4 count to be a sensitive, specific, reliable and valid marker of active disease and can be used to follow disease activity. Our study results show that %CD8 count has got no correlation with the disease activity in mild and moderate as well as severe lupus flares and cannot be used to follow disease activity in lupus. The %CD25 counts tend to be low in all lupus flares and rises to normal in patients with remission. It also correlates inversely with SLEDAI score and number of positive ACR criteria. Hence %CD25 count can also be used as a marker to follow disease activity.

References


Pharmacotherapy of Insomnia and Current Updates

Arup Kumar Misra¹, Pramod Kumar Sharma²

Abstract
Insomnia is highly prevalent and is associated with a range of psychological, psychiatric, and medical conditions. Insomnia affects health by influencing cognitive, emotional and social functioning. Circadian and sleep homeostatic processes play an important role in insomnia development and its maintenance. Several efficacious treatments, both pharmacologic and non-pharmacologic, exist for the management of insomnia. Among non-pharmacologic treatments including stimulus control therapy, sleep restriction, relaxation, sleep hygiene and cognitive therapy have been shown to be efficacious. Pharmacological treatment acts as adjuvant to cognitive behavioural treatment. Despite availability of various classes drugs for insomnia treatment, none can be considered as an ideal agent. Novel therapies are still being explored and tested to arrive at a hypnotic that has acceptable side effects and tolerability profile while still being efficacious.

Introduction: Definition, Epidemiology and Symptoms
The International Classification of Sleep Disorders defines “insomnia as difficulty with the initiation, maintenance, duration, or quality of sleep that results in the impairment of daytime functioning, despite adequate opportunity and circumstances for sleep.”¹ It is a sleep disorder that occurs acutely and may become chronic if not treated in time. It occurs in approximately 10% - 48% of general population and is more prevalent among women and elderly. It affects the social and professional life of individual and results in the high burden for the family and the society. Its presence is associated with a variety of medical and psychiatric conditions and has been found associated closely with anxiety and depression.

Insomnia is of three types—transient, acute and chronic. Transient insomnia normally last for few days to a week. It can be triggered by excess environmental noise, medications and extreme temperatures. One example of transient insomnia is jet lag, in which traveling through time zones causes a temporary disruption of the body’s circadian rhythm. Acute insomnia is most common and often cause by situations such as stress at work, family pressures or a traumatic event. Acute insomnia may last for weeks. On the other hand, chronic insomnia lasts for months or longer. They are mostly secondary to the symptom or side effect of some other problem.

Chronic insomnia does not resolve spontaneously, although the presenting form of insomnia can vary over a period. Chronic insomnia tends to be unremitting, disabling and may pose a risk for additional medical and psychiatric disorder. Fortunately, there are number of safe and effective treatments for insomnia available today.

Assessment and Diagnosis
A thorough assessment of sleep, medical and psychiatric history is required to confirm the diagnosis of insomnia. The patient should report at least one of the following sleep-related complaints like difficulty initiating sleep, difficulty maintaining sleep, waking up too early, or sleep that is chronically Nonrestorative or poor in quality. It is important to differentiate between primary insomnia from secondary insomnia due to some underlying co-morbid conditions. These conditions may require prior intervention and treated in conjunction with the primary disorder. These include untreated or unstable medical, psychiatric or substance abuse conditions (e.g., gastroesophageal reflux disease, cardiopulmonary disorders, seizure disorders, some neuroendocrine disorders, sleep apnoea, bipolar disorder, severe mental illness, active substance dependence).
Therapy of Insomnia

Variety of remedies including prescription medications, herbal supplements, and sleep aids are available for management of insomnia. In addition, a number of non-pharmacologic approaches, including cognitive and behavioral therapy also exists.

**Non-pharmacological Therapy**

Behavioral and cognitive therapy should always be a part of any first line pharmacotherapy.

**Cognitive therapy**

It is observed that patients with insomnia have negative thoughts and beliefs about their condition and its consequences. These therapies are mainly focused on paradoxical intention,2 cognitive restructuring and safety behaviors. The approaches may differ in procedure but all of this will help patients to challenge the veracity and usefulness of these beliefs. It is the basis of cognitive therapy and is thought to decrease the anxiety and arousal associated with insomnia.

**Stimulus control therapy**

Patient suffering from chronic primary insomnia, stimulus control therapy should be considered as the first line behavioral treatment.3 It consists of instructions which limit the amount of time spend by patient to stay awake in bed or the bedroom. These typical instructions include keeping a fixed wake time 7 days per week, irrespective of how much sleep you get during the night; to avoid any behavior in the bed or bedroom other than sleep or sexual activity; sleep only in the bedroom; leave the bedroom when awake for approximately 10 to 15 min; and return to bed only when sleepy. Thus such instructions help to re-establish the circadian sleep-wake cycle to the desired phase.

**Sleep hygiene**

It is a sleep tip given to the patient to maintain good sleep habits such as keeping an environment and routine conducive to sleep, maintaining a regular bed and wake time, avoiding tobacco, alcohol, large meals and vigorous exercise for several hours prior to bed. It is always helpful when it is given with other non-pharmacological or pharmacological interventions to treat insomnia.4

**Sleep restriction**

Sleep restriction therapy (SRT) helps the patients to maintain the amount of time spend in bed to an amount equal to their average total sleep time. The therapy can be established by maintaining daily sleep diaries for one to two week regarding total sleep time, maintain fixed wake time and adjustments made on the weekly basis until treatment completion.

**Phototherapy**

It has sleep-promoting effects for patients who have difficulty in maintaining the circadian rhythms. Exposure to morning bright light is indicated if the patient is suffering from delay phase component of insomnia (i.e., the patient prefers to go to bed late and wake up late). On the other hand, evening exposure to bright light is indicated if the patient’s insomnia has a phase advance component (i.e., the patient prefers to go to bed early and wakes up early).

**Pharmacotherapy**

Historically, barbiturates and then benzodiazepines were the most commonly used sedative-hypnotics. While both classes have demonstrated efficacy for insomnia but barbiturates have greater levels of tolerance, abuse potential, lethal dose threshold and alterations to sleep pattern. For these reasons, barbiturates are now rarely being used as hypnotics. Though similar attributions were made for the benzodiazepines, albeit with far less evidence.

Many neurotransmitters are involved in the sleep-wake cycle. Sleep-promoting neurotransmitters are adenosine, melatonin, galanin and gamma aminobutyric acid (GABA). On the other hand, wakefulness-promoting neurotransmitters are norepinephrine, orexin, acetylcholine, dopamine and histamine.5 Medications most commonly used for insomnia produce their effects by acting through GABA, melatonin and histamine. Current pharmacological treatment of insomnia consists of mainly three groups namely benzodiazepines; novel benzodiazepine receptor agonists (Z compounds) and melatonin receptor agonist.

### Benzodiazepines (BZDs)

BZDs decrease the onset to sleep and increase the total sleep duration. Benzodiazepines namely flurazepam, quazepam, estazolam, temazepam, triazolam, etc. act by binding to GABA receptor at a site other than GABA (γ-aminobutyric acid) binding site and increase the amount of chloride current through the GABA-chloride ion channel complex.6 These drugs are approved by U.S. Food and Drug Administration (U.S. FDA) to improve sleep maintenance by decreasing the awakening in night.6 BZDs are not suitable especially for the patient with chronic insomnia as they are associated with dependence and tolerance on long term use and used mainly for treating short term insomnia. They are also associated with excessive sedation, motor incoordination, cognitive impairment and anterograde amnesia as common adverse effects. Irrespective of use of BZDs, there is always increase in residual daytime sleepiness and risk of accidental fall and hip fracture.

### Novel Benzodiazepine Receptor Agonists (Z Compounds)

Z compounds bind to the α1 subunit of GABA receptor. It produces sedative and hypnotic effect and provides better efficacy and safety than other previous drugs.7 There are three drugs in this
group namely zolpidem, zaleplon and eszopiclone. Zolpidem is a short acting drug approved for short-term treatment of insomnia. It helps to reduce the time for sleep onset and/or sleep maintenance and has been approved to use for 7-10 days for management of insomnia with difficulty of sleep onset. If taken for an extended period, it has the potential to induce dependence. Zaleplon has a shorter half life and is approved for the patient who has difficulty in falling asleep. Both the drugs have similar degrees of efficacy and have an advantage of no rebound insomnia on abrupt discontinuation. Eszopiclone, an active S(+) enantiomer of zopiclone is effective in both sleep onset and maintenance for the transient and chronic insomnia.

**Melatonin Receptor Agonist**

Melatonin is a hormone secreted by the pineal gland and plays a major role in maintaining circadian rhythm. Melatonin secretion occurs mostly in night hours and it promotes sleep by reducing the effect of wake promoting signals in the suprachiasmatic nucleus of the hypothalamus. Its acts by binding to two receptors namely, MT1 receptors which promotes the onset of sleep; and by binding to MT2 receptors, that shifts the timing of the circadian system. Ramelteon is an agonist for both MT1 and MT2 melatonin receptors. It is primarily used for the sleep onset insomnia and somnolence, dizziness, fatigue, etc. are few adverse effects of the drug. Advantage of melatonin receptor agonist is that there is no sign of withdrawal symptoms or rebound insomnia on discontinuation after long term use.

Tasimelteon is a newer selective agonist for the melatonin receptors MT1, and MT2. It is similar to other members of the melatonin receptor agonist class namely ramelteon and agomelatine.

**Orexin Receptor Antagonists**

Orexin-A and -B, also known as hypocretin-1 and hypocretin -2 are neuropeptides found to have profound effect on arousal and sleep by acting through OX-1 and OX -2 receptors. Orexin receptor antagonists are a novel class of drugs developed for the treatment of insomnia. These neuropeptide that play a key role in promoting wakefulness, appetite, metabolism, reward, stress, autonomic function and regulating the sleep-wake cycle. Suvorexant is the first oral dual orexin receptor antagonist developed by Merck and was approved by the U.S. FDA in August 2014. Food does not interfere with its absorption and is mainly metabolized by the CYP3A4 system. The recommended dose is 10 mg once at night and it can be increased to a maximum of 20 mg. Suvorexant is safe and well tolerated in patients. The most common adverse effect reported has been somnolence on the next day which might be not acceptable in working patients. The higher doses above 20 mg significantly cause motor impairment and driving impairment. It has potential sedative additive effect when used with antidepressants and other sedative drugs. Suvorexant has not yet been compared to other drugs approved for insomnia, so its relative advantages in terms of efficacy or adverse effect profile, will emerge more clearly in future, after head to head comparative trials with the already available drugs. Suvorexant is safe and well tolerated in patients. The most common adverse effect reported has been somnolence on the next day which might be not acceptable in working patients. The higher doses above 20 mg significantly cause motor impairment and driving impairment. It has potential sedative additive effect when used with antidepressants and other sedative drugs. Suvorexant has not yet been compared to other drugs approved for insomnia, so its relative advantages in terms of efficacy or adverse effect profile, will emerge more clearly in future, after head to head comparative trials with the already available drugs. Suvorexant is safe and well tolerated in patients.
Recent Advances in Pharmacotherapy of Insomnia

Pharmacologic therapy that are safe, efficacious and do not possess unwanted side effects are need of the hour. The search is still on for agents that should have properties close to an ideal hypnotic.

5-HT$_{2A}$ Receptor Inverse Agonist

Agents targeting the 5-HT$_{2A}$ serotonin receptor subtype (e.g. volinanserin, eplivanserin, pruvanserin) were being developed. These compounds have been developed with minimal affinity to dopamine, histamine and adrenergic receptors, compared to existing sedating antidepressants. These agents had been associated with improvement in sleep maintenance and increases in slow wave sleep. Despite positive phase III efficacy data, eplivanserin development was discontinued for reasons unknown. Subsequently the development of volinanserin, and pruvanserin were also suspended.

Lorediplon

Lorediplon is a non-benzodiazepine compound of the pyrazolopyrimidine family that is being pursued as a treatment for insomnia but has not yet completed development. It is a novel, longer acting non-BZD drug that modulates the GABA$_A$ receptor. It has demonstrated a potent hypnotic profile and extended systemic half-life; properties that could confer potential clinical benefits in terms of sleep maintenance and sleep architecture. A recent phase I pharmacodynamic study with lorediplon (in a phase advanced model of insomnia) demonstrated that this orally available compound has a best-in-class efficacy profile in terms of sleep maintenance and sleep quality when compared to market leader zolpidem. It is safe and well tolerated, with no residual effects observed up to fourteen hours after dosing. It has no next-day residual effects and other side effects linked to other treatments available in this class. Currently, the drug is in Phase IIa of clinical development.

Serotonin Receptor Modulators

There are reports which suggest that serotonin (5-HT) have role in promoting sleep. LY2624803 (H$_1$ receptor antagonist and 5HT$_{2A}$ receptor antagonist) is under development that can modulate the serotonin receptor and improve insomnia. LY2624803 has completed phase II clinical trial for chronic insomnia. The minor side effects were seen in trials with patients of transient insomnia are headache, dizziness, back pain, diarrhoea and dermatitis. The frequency and profile of the adverse effects seen in the study was less than zolpidem. This drug was associated with less awakenings during sleep, decrease in total time awake and better sleep efficiency than zolpidem.

Newer Orexin Receptor Antagonists

Filorexant (MK-6096) is an orexin antagonist which is or was under development by Merck for the treatment of insomnia. It is a dual antagonist of the OX-1 and OX-2 receptors. It causes dose-dependent decrease in locomotor activity and significantly increased sleep. It represents a novel and selective therapy. It has completed phase II clinical trials. Unfortunately, further development was not pursued due to the cost involved or it might have caused significant unwanted side effects.

Lemborexant (Phase II), MIN-202 (Phase I), SB-649868 (Phase I) and ACT-462206 are the newer orexin receptor antagonists which are in various phases of clinical development. These drugs were found to significantly reduce latency to persistent sleep, wake after sleep onset (WASO), sleep efficiency (SE) and increased total sleep time (TST) as compared to Z-compounds and placebo. As of now, these drugs are considered to have a favourable safety profile as compared to the prototype of this class, suvorexant.

Newer Melatonin Receptor Agonists

Piromelatine (Neu-P11) is an agonist at melatonin MT1 and MT2 and serotonin 5-HT$_{1A}$/5-HT$_{1D}$ receptors. It improves circadian rhythms in primary insomnia. It has demonstrated efficacy and safety in a Phase II clinical trial in patients with primary insomnia. Piromelatine has a good potential for the treatment of primary insomnia characterized by sleep maintenance disturbances. Additionally, it was found to preserve REM sleep and induce deeper sleep with less arousal. It is generally safe and well tolerated as found in the study, with no detrimental effects on next-day psychomotor performance as compared to placebo.

Esmirtazapine

Esmirtazapine, a high-affinity antagonist at 5-HT$_{2A}$ and H$_1$ receptors, was assessed for its hypnotic efficacy. Six weeks of treatment with esmirtazapine was associated with consistent improvements in sleep onset, maintenance, and duration as assessed by polysomnography and patient reported parameters. It was generally well tolerated, and residual daytime effects were minimal and no rebound insomnia was observed. Drowsiness, dizziness, strange dreams, weight gain are some of the minor side effects may not be acceptable to some. In
and may hopefully addressed by such problems are highly desirable impairment, abuse potential, etc. as reducing their overall utility. The about their side effects and thus great leap in treating insomnia Current therapies have shown a is always a part of cognitive and it possible to treat insomnia to availability of drugs from different choices in medications are needed suitable for all patients. Additional as well. All medications are not true in case of insomnia therapy given at the dose of 15 mg.

Conclusion “One size fits all” does not hold true in case of insomnia therapy as well. All medications are not suitable for all patients. Additional choices in medications are needed for different patients. Though availability of drugs from different pharmacological class have made it possible to treat insomnia to a certain extent but still it is far from perfect. Pharmacotherapy is always a part of cognitive and behavioural therapy for insomnia. Current therapies have shown a great leap in treating insomnia but still there are concerns about their side effects and thus reducing their overall utility. The available therapies have sedation, motor incoordination, cognitive impairment, abuse potential, etc. as important side effects. Overcoming such problems are highly desirable and may hopefully addressed by future therapies that are being explored. We should expect that newer drugs that have selective interaction with their receptor and lesser potential to cause undesirable effects for example daytime sedation, tolerance, abuse liability, etc. may be considered a welcome approach. There is immense opportunity for drug companies in the pharmacotherapy of insomnia as it is going to become an important health related issue of the modern society.

References
Principles of Regression Analysis

NJ Gogtay, SP Deshpande, UM Thatte

**Introduction**

While correlation analysis helps in identifying associations or relationships between two variables, the regression technique or regression analysis is used to “model” this relationship so as to be able to predict what will happen in a real-world setting. Let us understand this with something that happens in daily life. As children, we are often told by our parents that education is a vital part of our lives and a “good” education will help us get “good jobs” and thus “good wages”! If we were to explore the relationship between education and wages, we could think up two questions – a) Does a relationship exist between education and wages? And a related but more interesting and important question b) for every extra year spent in education, do wages commensurately increase [and if yes, by how much?]? The latter question is moving into the realm of prediction. Regression attempts to answer these and similar questions regarding relationships between variables.

**Correlation Versus Regression—Understanding the Distinction**

The difference between correlation analysis and regression lies in the fact that the former focuses on the strength and direction of the relationship between two or more variables without making any assumptions about one variable being independent and the other dependent [see below], but regression analysis assumes a dependence or causal relationship between one or more independent variables and the dependent variable. A correlation analysis with a scatter plot and a regression line1 is however a prerequisite to regression and both analyses are often carried out together.

**Dependent and Independent Variables**

An important first step before carrying out a regression analysis is to understand the concept of independent and dependent variables. An independent variable, as the name suggests is a “stand alone” variable, and one that remains unaffected by other variables that are measured in a study. The “dependent” variable is the one that is usually of interest to the researcher and alters in response to change/s in the independent variable.

Let us understand this concept with the following two research questions – 1) “As age increases, does the risk of developing diabetes as measured by HbA1C or blood sugar levels increase? Or b) “Given that a patient has both diabetes and hypertension, what is his risk of developing coronary artery disease [CAD]?” In the former example, we are exploring the relationship between age and diabetes and in the latter, the relationship between two variables with a third variable—i.e., diabetes and hypertension with CAD. In the first example, age would be the independent variable while diabetes, which is dependent on age would become the “dependent” variable. In the second example, since CAD is associated with both diabetes and hypertension, CAD would become the dependent variable and diabetes and hypertension would be the two independent variables. If you will notice, diabetes in one example is a dependent variable and in the other, an independent variable. Thus, what is a dependent and what is an independent variable needs to be defined à priori by the researcher before carrying out the regression analysis. The choice of the variables would in turn be defined by the research question and the hypothesis being explored. Independent variables are often called predictor variables or exogenous variables and dependent variables are called prognostic or endogenous variables.

**Types of Regression**

Essentially in medical research, there are three common types of regression analyses that are used viz., linear, logistic regression and Cox regression. These are chosen depending on the type of variables that we are dealing with (Table 1). Cox regression is a special type of regression analysis that is applied to survival or “time to event” data and will be discussed in detail in the next article in the series.

Linear regression can be simple linear or multiple linear regression while Logistic regression could be Polynomial in certain cases (Table 1).

The type of regression analysis
Table 1: Types of regression

<table>
<thead>
<tr>
<th>Type of regression</th>
<th>Dependent variable and its nature</th>
<th>Independent variable and its nature</th>
<th>Relationship between variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple linear</td>
<td>One, continuous, normally distributed</td>
<td>One, continuous, normally distributed</td>
<td>Linear</td>
</tr>
<tr>
<td>Multiple linear</td>
<td>One, continuous</td>
<td>Two or more, may be continuous or categorical</td>
<td>Linear</td>
</tr>
<tr>
<td>Logistic</td>
<td>One, binary</td>
<td>Two or more, may be continuous or categorical</td>
<td>Need not be linear</td>
</tr>
<tr>
<td>Polynomial (logistic)</td>
<td>Non-binary</td>
<td>Two or more, may be continuous or categorical</td>
<td>Need not be linear</td>
</tr>
<tr>
<td>Logistic hazards regression</td>
<td>Time to an event</td>
<td>Two or more, may be continuous or categorical</td>
<td>Is rarely linear</td>
</tr>
</tbody>
</table>

To be used in a given situation is primarily driven by the following three metrics:

- Number and nature of independent variable/s
- Number and nature of the dependent variable/s
- Shape of the regression line

A. Linear regression: Linear regression is the most basic and commonly used regression technique and is of two types viz. simple and multiple regression. You can use Simple linear regression when there is a single dependent and a single independent variable (e.g. for the research question described above “As age increases, does the risk of developing diabetes increase as measured by HbA1C or blood sugar levels?”). Both the variables must be continuous (quantitative data) and the line describing the relationship is a straight line (linear).

Multiple linear regression on the other hand can be used when we have one continuous dependent variable and two or more independent variables, for example when we want to answer the second question mentioned above, “Given that a patient has both diabetes and hypertension, what is his risk of developing coronary artery disease (CAD)?”. Importantly, the independent variables could be quantitative or qualitative. Both the independent variables here could be expressed either as continuous data (blood pressure or HbA1C values) or qualitative data (presence or absence of diabetes as defined by the ADA 2016 or hypertension as defined by JNC VIII). A linear relationship should exist between the dependent and independent variables.

B. Logistic regression: This type of regression analysis is used when the dependent variable is binary in nature. For example, if the outcome of interest is death in a cancer study, any patient in the study can have only one of two possible outcomes - dead or alive. The impact of one or more predictor variables on this binary variable is assessed. The predictor variables can be either quantitative or qualitative. Unlike linear regression, this type of regression does not require a linear relationship between the predictor and dependent variables.

For logistic regression to be meaningful, the following criteria must be met/satisfied:

- The independent variables must not be correlated amongst each other e.g. if the dependent variable is presence (or absence) of post-operative wound infection and the independent variables are duration of surgery, extent of blood loss and Hb levels at day 7, it is intuitive that all are correlated amongst each other and therefore will lead to erroneous results. What should be taken as the independent variable is only the duration of surgery.
- The sample size should be adequate

If the dependent variable is non-binary and has more than two possibilities, we use the multinomial or polynomial logistic regression.

Step Wise Regression

Stepwise regression is an automated tool that can be used in the exploratory stages of model building to identify a useful subset of predictor variables. The process systematically adds the most significant variable or removes the least significant variable during each step. The idea behind using such automated tools is to maximize the power of prediction with a minimum number of independent variables.

Steps in Conducting a Regression Analysis

Regression analysis is done in 3 steps:

1. Analyzing the correlation [strength and directionality of the data]
2. Fitting the regression or least squares line, and
3. Evaluating the validity and usefulness of the model.

Step 1: This has been described in the article on correlation analysis1

Step 2: Fitting the regression line

Conventionally, in mathematics, the equation of a line is given by the formula “y = mx+c”, where, m is the “slope” or gradient of the line and “c” is where the line “cuts” the y-axis, also called as the “intercept” (Figure 1). In regression, this equation is given by
A scatter plot and regression line of age versus systolic blood pressure

\[ y = 0.889x + 94.61 \]

\[ R^2 = 0.292 \]

**Fig. 1: Regression analysis exploring the relationship between Age and HbA1C**

The intercept \( B_0 \) represents the value of Y or the dependent variable (HbA1C) when the value of the predictor variable is zero (age). In reality age can never be zero, so this is the value of HbA1C that is present regardless of age. The equation \( y = B_0 + B_1 \times x \) classically describes simple linear regression. For Multiple linear regression, the equation would be \( y = B_0 + B_1 \times x_1 + B_2 \times x_2 + B_3 \times x_3 + \ldots + B_k \times x_k \), depending upon the number of predictor variables \( [x_1, x_2, \text{and so on}] \) and \( k \) is the \( k \)th predictor variable.

Step 3: Evaluating the validity of the model

**Validation techniques can be broadly divided into two – numerical and graphical.** An easy numerical technique is to look at the value of \( R^2 \). You will recollect that the coefficient of correlation \( (r) \) is squared to obtain the Coefficient of Determination or \( R^2 \). This is the value that is used for predicting the extent of variability in the dependent variable that can be explained by the independent variable. In our example (Figure 1), the \( R^2 \) is 0.29 or 29% indicating that 29% of the variability in SBP can be explained by age. If the value of \( R^2 \) is high, then we could assume that the model has a high predictive value. The value of 29% indicates that 71% of the variability still remains unaccounted for and thus model may not have a great predictive value. It is also useful to remember that the value of \( R^2 \) is affected by the choice of the independent variables and the presence of outliers\(^1\) and hence researchers need to be careful while using \( R^2 \) alone for validation.

Graphical analysis of residuals is a graphical technique for validation that uses graphs to visually inspect the data to assess its robustness.

**Utility of Regression Analysis**

The example given below highlights the utility of regression analysis. Table 2 has values of systolic blood pressure [SBP] for 30 women with age being presented in an ascending order. Age here would be the independent variables and SBP, the dependent variable.

We first make a scatter plot and eye ball the data and then...
Thus, the equation would read as

\[ y = 0.889x + 94.61 \]

OR

\[ \text{SBP} = 94.61 + 0.889 \times \text{age} \]

The given data set if you will notice does not contain the age 60 or the corresponding SBP. Say we as asking the question, what would be the SBP of a 60-year old woman? We would “fit” 60 into the regression equation and calculate it as

\[ \text{SBP} = 94.61 + 0.889 \times 60 \text{ or } 148 \text{ mm Hg}. \]

It is important to note here that multiple lines can be drawn through the data set and hence we need to define the criterion for drawing the line. The method that is most commonly used is called the “least squares methods”.

When we apply this equation to the population for making a prediction, we would really not be able to predict either the systolic blood pressure perfectly. Hence, we need to taken into account an “error” or “deviation” that is likely to occur when this equation is used. Thus, the equation would read as below

\[ y = B_0 + B_1x + e \]

or

\[ \text{Outcome} = \text{prediction} + \text{deviation} \]

Applications of Regression Analysis

There are three major uses of regression analysis – attributing causality [cause and effect relationship], forecasting, and prediction. These are explained with three examples.

Causality

Palmer KT and colleagues assessed working aged people from the general population in the United Kingdom to estimate the risks of occupational exposure to noise on self reported hearing difficulties and tinnitus using a validated questionnaire. The study showed that, in both sexes, after adjustment [see below] for age, the risk of severe hearing difficulty and persistent tinnitus rose with years spent in a noisy job indicative of a cause-effect relationship.

Forecasting

Efficient management of patient flow in emergency departments (EDs) is a very important issue for hospital administrators. Marcilio I and colleagues studied diverse models in an attempt to forecast the daily number of patients seeking emergency department [ED] services in a general hospital in Sao Paolo, Brazil, using calendar variables and ambient temperature reading as the independent variables. They found that the mean number of ED visits was 389 [166-613] with a seasonal distribution with the highest patient volumes seen on Mondays and lowest on weekends. Calendar variables rather than temperature were better at forecasting. They concluded that this data could be used for better allocation of personnel for the management of ED services.

Prediction

Brazier et al used logistic regression to predict risk factors for colorectal cancer in a community practice where they studied 461 consecutive patients undergoing colonoscopy. Of these, 129 had adenomatous polyps (pre-cancerous) and 34 had colorectal cancer. They randomly chose 292 patients and evaluated the impact of several independent variables in a model that looked at prediction of occurrence of colorectal cancer. Five variables were identified to be predictive- the patient’s age, sex, hematocrit, fecal occult blood test result and indication for colonoscopy. When this model was applied to the remainder of the 169 patients, it was found to be a reliable indicator of risk of colorectal neoplasia.

Understanding what Confounders are and the Concept of “Adjustment”

In study by Palmer and colleagues presented earlier, the relationship between being in a noisy job and the extent of hearing difficulty and tinnitus was assessed. Intuitively, we do know that noise is not the only reason why hearing difficulty can occur. This may be related to stress, gender, tiredness, older age and many more factors. A confounder is defined as that variable that is “hidden” or “lurking” and was not accounted for or thought of initially and impacts the outcome being studied. Confounders [to the extent possible] need to be identified before the start of the study and addressed during analysis by a process called as “adjustment”. This is a statistical technique to eliminate the influence of one or more confounders on
the treatment effect. Simply put, it can be understood as a process of “statistical correction” that is done once the data is gathered. In regression analysis, once a significant association between the independent variable/s and dependent variable has been found, it is important to see if this significance still persists after potential confounders have been adjusted for. In the study by Palmer, age was identified as a potential confounder a priori [since we know the hearing worsens with age] and adjusted for in the final analysis. Post adjustment, in both sexes, the relationship between years spent in a noisy job and severe hearing difficulty continued to remain significant [relative to those in non-noisy jobs].

Conclusion
In summary, regression analysis is a statistical tool that helps evaluate relationships between a dependent variable and one or more independent or predictor variables. More specifically, it helps us understand how the dependent variable changes with changes in the independent variable and thus finds its application in forecasting and predicting. The technique must however be used with clear understanding of the assumptions in each type of regression analysis, their limitations and the potential error that can occur when models are applied to a larger population.

References
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⚠️ An add-on to ongoing CCB/Diuretic therapy

**Azilday**

On BP goal... **All Day**

Azilsartan 40 mg
Twelve Commandments to Prevent Tsunami of Cardiometabolic Syndrome in India by 2025

Ramchandra Lele

For all my physician friends I will like to stress 12 important points with the emphasis on prevention of tsunami of cardiometabolic diseases if we do not want India to be the world capital of Diabetes in 2025.

Prevention must start today and I recommend that every Indian should have the following tests as routine beginning quite early in life at least at age of 18.

1. When you go home measure your abdominal girth. Males more than 90 cm and Females more than 80 cm you have a marker for metabolic syndrome and therefore your exercise should start today that is a first simple thing.

2. Each one of you have a pro-insulin to insulin ratio measured right from the beginning, a ratio more than 18% is a marker of metabolic syndrome.

3. You must have your adiponectin measurement less than 7 milli units is a very form marker of metabolic syndrome. Low adiponectin causes 60-70% reduction of UCP2 gene expression facilitating adipogenesis.

4. You should have your Urine for Microalbuminuria which is a part of metabolic syndrome.

5. All of you must have your Haemoglobin A1C more than 6.5% marks the beginning of metabolic syndrome

6. Diabetes is an Inflammatory* state so hsCRP should be measured as a routine more than 2 is a measurable marker of metabolic syndrome.

7. Vitamin D Deficiency-. Almost 200 genes in human body are activated by Vitamin D.Vitamin D has receptors on all organs including Heart and Blood Vessels and you will be surprised that most of you sitting in this audience are deficient in Vitamin D. At Jaslok hospital, I was in the basement like a parda-lady from Bhendibazar, has no exposure to sunlight so, when I had a fracture my vitamin D was less than 5 and I have done routine vitamin D of all the medical and nursing staff and all were found deficient in Vitamin D. So make sure that you maintain your vitamin D at least 30 units every day or take vitamin supplement. And I recommend 11 o’clock tea break at every hospital should be in sunlight on a terrace. Doctors, Nurses and everybody. A similar exposure can be arranged for school children on daily basis.

I am making some more Practical Suggestions.

8. Atherosclerosis is a pro Inflammatory state. All our cell membranes including the Neurons should have EPADHA Eicosa Pentanoic Acid and Decosa Hexanoic acid at least 6% to 8%. Our cell membranes including the Neurons contain pro-Inflammatory as well as Anti inflammatory cytokines.

RBC EPA DHA represents cell membrane content of all cells. Which can be routinely measured and most of us are having EPA DHA content less than 4%.

So we make more pro-inflammatory cytokines and less of anti Inflammatory cytokines, Lipoxins, Resolvin, protectins including Neuroprotectins, Marecin.

Even the latest edition of Harrison’s Text book of Medicines does not mention anti Inflammatory cytokines.

The Eskimos consume fish oil and they live for 100 years because of their rich Omega 3 content. I recommend cows ghee: 10 grams per day will give you 1.5 gram Omega 3. Dara singh our famous iconic wrestler, who lived up to the age of 88 took 250 grams of cows ghee every day, I am suggesting only 10 to 20 grams.

And last what I suggest is to utilise the tradional experiental wisdom of Ayurveda (science of life) whose primary aim is promotion of positive health and prevention of illness Swasthvrruta for the body and Sadvrruta for the mind.
Ayurveda emphasises breast feeding (since breast milk has maximum omega 6:3 ration of 2:1 hence today’s paediatricians recommend extension of breast feeding from the usual six months to 12 or even 18 months if feasible.

9. India has a unique tradition of ancient medicines and there are 3 Indian drugs which are unique. Pro-insulin to insulin ratio is more than 18% in diabetics.

Vijaysar, an ayurvedic drug converts pro-insulin to insulin so, I urge Diabetologists in India to conduct clinical trial of baseline, Pro-insulin to insulin ratio and after 3 months of Vijaysar.

10. Guggule (Comiphora Mukul) is described in Ayurveda as “Medohar” Gugglesterone it’s active ingredient is an anti obesity drug it blocks the PPR gamma Farscenoid receptors (FXR) and prevents adipogenesis.

A clinical trial can be undertaken to prove Gugglesteron is an anti obesity drug for everybody whose abdominal girth is more than 90 cm.

11. Another suggestion is about Osmotin, (A plant analogue of Adiponectin). In 2013 in a Dubai conference, I recommended that osmotin extracted from Methi seeds and Methi Leaves can be used as nutritional supplements. Karela Juice also contains osmotin in lesser concentration.

Ayurved describes that satvik ahar enabled rishis and Munis to live for 100 years. Satvik ahar contains 400 gms of fruits and vegetables which represents low calories (1300), soluble fiber, vitamins and minerals. I have suggested that the part of benefits of satvik ahar are due to the osmotin contents, which remains stable in the gastrointestinal tract.

12. My last suggestion pertains to glucagon suppression as a primary modality for both type one and type 2 Diabetes.

If Glucagon was discovered earlier than Insulin, Diabetes should be defined as a state of Hyper-Glucagonemia.

Glucagon suppressors only recently become available as Gliptins. But in Ayurveda, there is a drug called Triphala, (Aamliki, Haritki, Bethki) which supress CCKA and CCKB receptors and block glucagon release by the Alfa cells of Pancreatic islets. This CCK receptors suppression brings down Glucagon.

So again a study which can be easily done to measure the effect of Triphala before and after 3 months and how it can bring down the Glucagon levels.

Our thinking and approach is heavily dependent on preaching from the west which is classically described as “Para pratyaneeya Buddhi”.

My approach is out of box disruptive thinking, which will surely prevent the disaster of cardio metabolic tsunami in our country in near future.

(Our sincere thanks to Mr. Swaraj Sunil - Anjali Devlalkar for transcripting. Dr. Lele’s convocation address at Diabetic Foot on 18th June, 2016 at Hotel Grand Hyatt, Mumbai)
Consensus on Initiation and Intensification of Premix Insulin in Type 2 Diabetes Management

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Abstract

Introduction: Premix insulin is the most commonly used insulin preparation in India. The first Indian premix guidelines were developed in 2009 and thereafter were updated in 2013. There is a need to revisit the Indian premix insulin guidelines, in view of emerging evidence and introduction of newer co-formulations.

Objective: The present consensus has been developed to evaluate available premix formulations, examine existing evidence related to premix formulations, and evolve consensus statement of recommendations on the topic.

Methods: A meeting of experts from across India was conducted at Chennai in July 2016. The expert committee evaluated each premix insulin regimen with reference to 1) Current recommendations by various guidelines, 2) Approved pack inserts and 3) Published scientific literature. The information was debated and discussed within the expert group committee, to arrive at seven consensus-based recommendations for initiation and intensification with premix insulin.

Results: Recommendations based on consensus on initiation and intensification of premix insulin in type 2 diabetes mellitus (T2DM) management were developed for the following situations. 1) Initiation of premix insulin co-formulation at diagnosis, 2) Initiation of once daily (OD) premix insulin/co-formulation, 3) Initiation of twice daily (BID) premix insulin/co-formulation 4) Intensification with BID and thrice daily (TID) premix insulin/co-formulation. Three recommendations pertained to the use of premix insulin in other forms of diabetes, or in specific situations: 5) Use of premix insulin in gestational diabetes mellitus 6) Use of premix insulin in type 1 Diabetes Mellitus (T1DM) 7) Premix insulin use during Ramadan

Conclusion: In the setting of high carbohydrate consumption in India, or in patients with predominant post prandial hyperglycemia, premix insulin/co-formulation can offer effective and convenient glycemic control. This paper will help healthcare practitioners initiate and intensify premix insulin effectively.

Introduction

Type 2 diabetes mellitus (T2DM) is associated with significant morbidity and mortality across the globe. It is reported that the developing countries will account for 70% of world diabetic population...
by 2025. India with 69.2 million patients living with T2DM, has the second largest diabetic population in the world. By 2040, the number of individuals living with T2DM is predicted to increase to 123.5 million. The rapidly changing lifestyle and growing urbanisation are some of the most important reasons for this rise in numbers. Diabetes accounts for 14.5% of global all-cause mortality among people with diabetes aged 20 to 79 years.

Insulin is the oldest and best available treatment option for managing T2DM and maintaining good glycemic control. There are various types of insulin regimens, including basal insulin, basal-bolus, basal plus, premix insulins and prandial insulins. Premix insulin (also termed as biphasic insulin) formulations are the most widely prescribed insulins in India. The preference for premix insulin regimens over other insulins in India may be due to following reasons:

1. Indians with typical Asian Indian Phenotype i.e., higher waist circumference, higher total and visceral fat, hyperinsulinemia and likely insulin resistance respond better to premix insulins.
2. High intake of carbohydrates, resulting in higher glucose excursions after every meal.
3. Several observational studies have demonstrated high baseline post-prandial glucose (PPG) value in T2DM from India vs others.4
4. There is often delay in initiation of insulin therapy, resulting in higher risk of failure of basal insulins.
5. Convenience and simplicity with premix insulins, allowing physicians to intensify the treatment with same insulin.

Premix insulin formulations provide a combination of rapid/short-acting and intermediate/long-acting insulins in a fixed ratio, addressing both fasting plasma glucose (FPG) and post-prandial glucose (PPG) in a single injection. It represents 6.8% of total global market and 72.7% of the Indian insulin market.5 Premix insulin formulations include both conventional and premix insulin analogues (Table 1). The premix insulins/co-formulation commercially available in India are 1) Biphasic Human Insulin (BHI) (30/70, 50/50): Mixtard® 30, Mixtard® 50, 2) Biphasic insulin aspart (BIAsp) (30/70, 50/50): NovoMix™ 30, NovoMix™ 50, 3) Biphasic insulin lispro (25/75 and 50/50): Humalog Mix™ 25/75 and 50/50 4) Insulin Degludec/insulin aspart (IDegAsp) 70/30: Ryzodeg™ 70/30). IDegAsp is a soluble co-formulation of a basal insulin with an ultra-long duration of action and a short-acting insulin analogue, containing 70% insulin degludec (IDeg) and 30% insulin aspart (IASp) in a single injection.

The global and national guidelines and widely accepted and evaluated consensus statements (evaluated by the expert group) included American Diabetes Association Standard of Care 2017 (hence forth referred to as ADA 2017),10 consensus statement by the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) on the comprehensive T2DM management algorithm-2016 Executive Summary (hence forth referred to as AACE/ACE Consensus statement 2016).11 Global guideline for T2DM IDF (hence forth referred to as IDF 2012 and IDF 2015),12,13 Premix insulin initiation and continuation guidelines for management of diabetes in primary care by the Indian National Consensus Group (INCG) and/or Chapter 51 of...

Various guidelines recommend the use of premix insulin analogues over human premix insulins for lower risk of hypoglycemia, meal time flexibility and lesser weight gain. The first ever India specific guidelines on premix insulins was drafted and published in 2009. In 2013, India National Consensus Group (INCG) reevaluated the available evidences and published an update in 2013. While these guidelines are popular among the Indian physicians and often referred in many congresses, there is a growing demand for further update in view of a newer co-formulation being available. In view of this, 15 experts from across the country met during Dr. V. Mohan’s International Diabetes Update on 30th July, 2016 in Chennai and deliberated on the above subject. The objectives of this meeting were:

- To evaluate the available premix formulations and co-formulation
- Examine the existing evidence related to premix formulations and co-formulation
- Evolve a consensus statement of recommendations on the topic of premix and co-formulation insulins

**Methods**

The expert group identified seven different clinical situations for the use of premix insulins. These are presented in Figure 1. The group agreed that recommendations would be made on each of these seven situations:

1. Initiation of premix insulin at diagnosis
2. Initiation of once daily (OD) premix insulin/co-formulation
3. Initiation of twice daily (BID) premix insulin/co-formulation
4. Intensification with BID premix insulin/co-formulation and TID premix insulin. Three recommendations pertained to the use of premix insulin in other forms of diabetes, or in specific situations:
5. Use of premix insulin in gestational diabetes mellitus
6. Use of premix insulin in type 1 Diabetes Mellitus (T1DM)

**Consensus 1: Initiation of Premix Insulin at Diagnosis**

Biphasic human insulin 30/70 (BHI 30), biphasic insulin lispro 25 (LisproMix 25), biphasic insulin aspart 30 (BIAsp 30) and IDegAsp are the Premix insulins/ co-formulation currently approved for once/twice daily administration.

**Current Place in Guidelines**

ADA 2017, INCG 2013 and CDA 2013 guidelines recommend the use of insulin at the time of diagnosis of diabetes. INCG 2013 considered premix insulin as a reasonable option effective in all stages of the disease with the unique advantage of being simple, safe and easy to initiate. Insulin is preferred at diagnosis, if FPG > 250 mg/dL, PPG > 300 mg/dL and HbA1c > 9% or if patient has systemic infection or sepsis, acute myocardial infarction, unstable angina, diabetic ketoacidosis, pregnancy or peri-operative care. The guideline prefers premix insulin analogues over premix human insulins.

**Published Scientific Literature**

In a systematic review, short-term intensive insulin therapy was
Table 2: Comparison of once daily premix insulin and co-formulation versus once daily insulin glargine for initiation

<table>
<thead>
<tr>
<th>Trial (Reference)</th>
<th>Objective</th>
<th>Duration of Treatment/Total Number of Enrolled Subjects</th>
<th>Trial arms</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open-label, randomized Treat-to-target trial on T2DM patients poorly controlled on Met+ insulin secretagogue for 6 months (Yang et al 2013)</td>
<td>To investigate non-inferiority of OD BIAsp 30 to OD IGlar among Chinese and Japanese patients</td>
<td>24 weeks/521</td>
<td>• BIAsp 30 (261)</td>
<td>• Mean HbA1c reduced by -0.78% with BIAsp 30 and -0.65% with IGlar [ETD: -0.12% (95% CI: -0.25, -0.02) confirming superiority of BIAsp 30 to IGlar]</td>
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<td></td>
<td></td>
<td></td>
<td>• IGlar (260)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Hypoglycemia event rates (per subject-year):</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Severe: 0 (BIAsp 30) and 0.01 (IGlar). Similar risk between groups</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Nocturnal: 0.84 (BIAsp 30) and 0.55 (IGlar). Similar risk between groups</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Documented symptomatic: 3.08 (BIAsp 30) and 2.4 (IGlar)</td>
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<tr>
<td>Multinational, open-labelled, randomized, parallel-group, treat-to-target trial in Insulin-naïve T2DM patients (Strojek et al 2009)</td>
<td>To assess efficacy and safety of BIAsp 30 and IGlar administered OD in subjects with type 2 diabetes</td>
<td>26 weeks/480</td>
<td>• BIAsp 30 (239)</td>
<td>• Mean HbA1c reduced by -1.41% with BIAsp 30 and -1.25% with IGlar [ETD: -0.16% (95% CI: -0.3, 0.02) confirming non-inferiority of BIAsp 30 to IGlar]</td>
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<td></td>
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<td></td>
<td>• IGlar (241)</td>
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<td></td>
<td></td>
<td></td>
<td>Hypoglycemia event rates (per subject-year):</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Severe: 3 episodes in each group</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>• Nocturnal: 1.1 (BIAsp 30) and 0.5 (IGlar); RR: 2.41 (p = 0.003)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Overall: 6.5 (BIAsp 30) and 4.8 (IGlar); RR: 1.41 (p = 0.034)</td>
<td></td>
</tr>
<tr>
<td>Multinational, open-labelled, randomized, parallel-group, treat-to-target trial in Insulin-naïve Asian T2DM patients (Kalra et al 2010)</td>
<td>To compare the glycemic efficacy of BIAsp 30 and IGlar as assessed by change from baseline HbA1c</td>
<td>26 weeks/155</td>
<td>• BIAsp 30 (76)</td>
<td>• Mean HbA1c reduced by -1.22% with BIAsp 30 and -0.87% with IGlar [ETD: -0.36% (95% CI: -0.64, -0.07) confirming superiority of BIAsp 30 to IGlar]</td>
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<td>• IGlar (79)</td>
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<td>Hypoglycemia event rates (per subject-year):</td>
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<td></td>
<td></td>
<td></td>
<td>• Severe: 1 episode with BIAsp 30 and 3 with IGlar</td>
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<td></td>
<td></td>
<td>• Nocturnal: 0.9 (BIAsp 30) and 0.9 (IGlar); RR: 0.81 (p = 0.61)</td>
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<td></td>
<td></td>
<td></td>
<td>• Overall: 6.2 (BIAsp 30) and 4.5 (IGlar); RR: 1.54 (p = 0.15)</td>
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<tr>
<td>Open-label, treat-to-target trial on Insulin-naïve Japanese adults with T2DM (Onishi et al 2013)</td>
<td>To demonstrate the non-inferiority of IDegAsp to IGlar in terms of change from baseline HbA1c</td>
<td>26 weeks/296</td>
<td>• IDegAsp (147)</td>
<td>• Mean HbA1c reduced by -1.4% with IDegAsp and -1.2% with IGlar [ETD: -0.28% (95% CI: -0.46, -0.10) confirming superiority of IDegAsp to IGlar]</td>
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<td></td>
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<td></td>
<td>• IGlar (149)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Hypoglycemia event rates (per subject-year):</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Severe: No events in either group</td>
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<td></td>
<td></td>
<td></td>
<td>• Nocturnal confirmed: 0.39 (IDegAsp) and 0.53 (IGlar); RR: 0.75 (p = NS)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Overall confirmed: 1.91 (IDegAsp) and 2.71 (IGlar); RR: 0.75 (p = 0.73)</td>
<td></td>
</tr>
</tbody>
</table>

| BIAsp 30=Biphasic insulin aspart 30; OD=Once daily; BID=Twice daily; BHI=Biphasic human insulin; BMI=Body mass index; HbA1c=Glycosylated haemoglobin; IDegAsp=Insulin degludec/Insulin aspart; ETD: Estimated treatment difference; IGlar=Insulin Glargine; IGlu=Insulin glulisine; Mix25=25% soluble and 75% protaminated insulin lispro; OAD=Oral anti diabetic drugs; T2DM= Type 2 diabetes mellitus; NS=Not significant |
reported to improve the underlying pathophysiology in early T2DM. This meta-analysis of 7 studies showed that intensive insulin therapy leads to an increase in Homeostasis Model Assessment of β-cell function (HOMA-B) and a decrease in Homeostasis model Assessment of Insulin Resistance (HOMA-IR) as compared to baseline data. The glycemic remission was assessed in 4 studies (n=559 participants) and the proportion of participants in drug-free remission was about 66.2%, 58.9%, 46.3% and 42.1% after 3, 6, 12 and 24 months of follow-up, respectively. Currently, there is no published literature on specific role of premix insulin/co-formulation and its impact on beta cell function or remission of diabetes.

**Expert Group Recommendation 1: Premix Insulin Initiation at Diagnosis**

- In newly diagnosed T2DM patients with symptomatic hyperglycemia and/or metabolic decompensation (glucoxicity), short-term therapy with premix insulin is recommended.
- Premix insulin analogues are preferred over human premix insulins in view of the lower incidence of major and nocturnal hypoglycaemia and flexibility of administration as seen in treatment naïve patients (dose 0.2 to 0.3 U/kg body weight in 2 divided doses).
- IDegAsp may be preferred over premix insulin analogues in view of the lower incidence of overall and nocturnal hypoglycaemia and superior fasting plasma control as seen in treatment naïve patients (6 U BID).

**Consensus 2: Initiation of Once Daily Premix Insulins/Co-formulations**

BHI 30/70, 50/50, Lispro Mix 25/75, 50/50, BIAsp 30/70, 50/50 and IDegAsp are the Premix insulins which are currently approved for once daily administration.

**Current Place in Guidelines**

IDF 2012 recommends initiation of premix insulin OD or BID when first or second line therapies fail to achieve glycemic target of HbA1c < 7%. Doses can be increased by 2 U every 3 days once or biweekly (IDF 2012). As per National Institute for Health and Care Excellence guideline, OD premix insulin should be considered when HbA1c level is ≥ 9%.

INCG 2013 recommends premix insulin OD as an add-on therapy to metformin when HbA1c level is > 7.5% to ≤ 8.5% (failure to reach HbA1c target < 7% after > 3 months of metformin monotherapy). If HbA1c > 7% and FPG > 110 mg/dL, then premix insulin is titrated to achieve FPG < 110 mg/dL. The guideline also recommends initiation with premix insulin therapy at a starting dose of 10 U either before breakfast, if pre-dinner glucose is high or before dinner, if the pre-breakfast glucose is high. The dose should be split when the starting dose is > 30 U.

CDA 2016 recommends initiation of premix insulin at 5-10 U OD or BID (pre-breakfast and/or pre-supper). The doses can be titrated by adding 1-2 U to pre-breakfast and/or pre-supper dose daily until target pre-breakfast and pre-supper blood glucose values are achieved (72-126 mg/dL).

JAPI 2014 recommends premix insulin/co-formulation OD in patients with HbA1c > 9% and high FPG and PPG.

**Published Scientific Literature**

Three open label randomized studies have shown that OD premix insulin is superior to OD basal insulin in terms of achieving HbA1c (Table 2).

A systematic review of 28 randomized controlled trials (N=30588) evaluated the effectiveness of insulin analogues to reach the HbA1c target of < 7% in T2DM patients. The results reported that higher proportion of patients treated with BIAsp 30 achieved the glycemic target than the patients treated with basal insulin (46.5% versus 41.4%).

In a 26-week, open-labelled, randomized, parallel group trial which included participants from India as well, the efficacy and safety of OD BIAsp 30 was compared to IGlar, both in combination with metformin and glimepiride in 480 insulin naïve T2DM patients. The results indicated a significantly higher HbA1c reduction with BIAsp 30 than insulin glargine (IGlar) (-1.41% versus -1.25%). In a 24-week treat-to-target trial, OD BIAsp 30 was compared to OD IGlar in Chinese and Japanese insulin-naïve T2DM patients, who were poorly controlled on Metformin and insulin secretagogues for 6 months. The estimated between-group difference in HbA1c change was -0.12% and BIAsp 30 was noninferior to IGlar. However, BIAsp 30 provided better coverage of glycemic control post-dinner compared to IGlar group.

However, a 24-week open-label randomized GALAPAGOS study reported a comparable proportion of insulin-naïve T2DM patients (inadequately controlled on OADs) achieving a HbA1c target < 7% at study end after treatment with OD or BID BIAsp 30 and IGlar ± insulin glulisine (IGlu) OD (55.7% versus 57.6%).

In a phase 3, 26-week, open label, treat-to-target trial, Onishi et al evaluated the efficacy and safety of IDegAsp versus IGlar in Japanese T2DM patients who were inadequately controlled with oral anti-diabetic drugs (OADs). After 26 weeks, IDegAsp was associated with superior glycemic control (7% versus 7.3%) with numerically lower rates of overall confirmed (27%) and nocturnal confirmed hypoglycaemia (25%) as compared to IGlar, with similar FPG levels and end of trial insulin doses.

**Consensus 3: Initiation of Twice Daily Premix Insulins/Co-formulations**

BHI 30/70, 50/50, Lispro Mix 25/75, 50/50, BIAsp 30/70, 50/50 and IDegAsp are currently recommended for twice daily administration.

**Current Place in Guidelines**

IDF 2012 suggests premix insulin BID, particularly for patients with elevated HbA1c and who were already on premix insulin OD.
**Expert Group Recommendation 2: Once Daily Premix Insulins/Co-Formulations for Initiation**

- It is recommended to initiate insulin early in the course of disease when non-insulin drugs prove inadequate in achieving the desired glycemic goals.
- In the setting of high carbohydrate consumption or in patients with predominant post prandial hyperglycemia, premix insulin analogues could be preferred over basal insulins for insulin initiation (10 U pre-breakfast or pre-dinner).
- In the setting of high carbohydrate consumption or in patients with predominant post prandial hyperglycemia, IDegAsp could be preferred over premix insulin analogues and basal insulins for insulin initiation for achieving recommended glucose targets (10 U pre-breakfast or pre-dinner).
- It is recommended to titrate the dose once/twice a week based on pre-meal value. It is recommended to modify the dose based on the lowest/mean value of the 3 most recent values if available. Frequency of monitoring may be reduced in the maintenance phase.

**Recommendation on Titration:**

<table>
<thead>
<tr>
<th>Pre-breakfast/pre-dinner value*(mg/dL)</th>
<th>Pre-dinner/pre-breakfast dose change (Dose adjustment (units))</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 80</td>
<td>-2</td>
</tr>
<tr>
<td>80-130</td>
<td>0</td>
</tr>
<tr>
<td>131-160</td>
<td>+2</td>
</tr>
<tr>
<td>161-180</td>
<td>+4</td>
</tr>
<tr>
<td>&gt; 180</td>
<td>+6</td>
</tr>
</tbody>
</table>

*Lowest/mean of the three recent self-measured blood glucose values

**Note:** For patients initiated on pre-breakfast dose, titrate according to predinner values and vice versa.

**NICE T2DM guideline 2008** considers premix BID when HbA1c >9%.

**INCQ 2013** recommends premix insulin BID as an add-on therapy to Metformin when HbA1c > 8.5% (failure to reach Hba1c target < 7% after 3 months of metformin monotherapy).

**JAPI 2014** recommends premix insulin BID to patients already receiving OD regimen, if FPG is persistently high and there is failure to reach target HbA1c.

**Published Scientific Literature**

Two clinical trials postulated

that BID premix insulin is superior to OD basal insulin in achieving glycemic targets.23 A multicentre, open-label, parallel-group, treat-to-target trial in insulin naıve subjects with T2DM reported that BID BIAsp 30 was more effective in achieving Hba1c targets (< 7% [ADA goal]/ ≤ 6.5% [AAACE and IDF goal] than OD IGlar in subjects with Hba1c > 8.5%.23 Similar results were reported in another randomized controlled 60-week trial involving 582 patients with or without OAD comparing OD IGlar and BID BIAsp 30.23 Another multinational, open-label, parallel-group, treat-to-target trial in insulin naïve T2DM patients reported the superiority of BID IDegAsp over BIAsp 30 in terms of FPG control, nocturnal and overall hypoglycaemia.24 An open-label, randomized, single-dose, three-way crossover trial, reported that BIAsp 30 provided significantly better PPG control by 10% than Lispro Mix 25 (16.6 versus 18.9 mmol/L per hour; p<0.05) and by 17% when compared to BHI 30 (16.6 versus 20.1 mmol/L per hour; p<0.0016) (Table 3).

In the 1-2-3 study, 41% of the T2DM participants achieved the glycemic target (HbA1c<7%) after taking OD BIAsp 30 over the period of 16 weeks. The proportion of patients achieving the glycemic target increased after taking BID BIAsp 30 (70%) and TID BIAsp 30 (77%).25

**Consensus 4: Intensification with Twice/Thrice Daily Premix Insulins/Co-Formulations**

**Current Place in Guidelines**

Various guidelines recommend intensification of OD premix regimen to BID/TID premix regimen (ADA 2017, IDF 2012, NICE 200926, CDA 2013, JAPI, INCG).

ADA/EASD 2016 guidelines provide the option of transitioning from basal insulin to BID premix insulin in patients with T2DM who have failed to reach glycemic targets on basal insulin. The guideline recommends to start BID premix insulin as per the previous basal insulin dose and split the total basal dose either as 2:1 (2/3rd of the dose in the morning [AM] and 1/3rd of the dose in the evening [PM]) or 1:1 (½ of the dose in the morning and ½ of the dose in the evening). The doses may be titrated by 1-2 U or 10-15% once or twice weekly until self-measured blood glucose (SMBG) target is reached. In case of hypoglycaemia, the corresponding dose can be reduced by 2-4 U or 10-20%. The recently updated ADA 2017 guidelines have further strengthened the importance of twice daily premix insulins following the failure of basal insulin regimen. This regimen is recommended at the same level as basal plus regimen. Similarly, thrice daily administration of premix insulins is recommended at par with basal bolus therapy, when further insulin intensification is necessary. IDF 2012 recommends...
### Table 3: Twice daily premix insulin/co-formulation for initiation

<table>
<thead>
<tr>
<th>Trial (Reference)</th>
<th>Objective</th>
<th>Duration of Treatment/Total Number of Enrolled Subjects</th>
<th>Trial arms</th>
<th>Results</th>
<th>Safety (Hypoglycemia)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multicentre, open-label, parallel-group, treat-to-target insulin naive subjects with T2DM (INITIATE study Raskin et al 2005)</td>
<td>To compare safety and efficacy of BIAsp 70/30 to IGLar</td>
<td>28 weeks /233</td>
<td>BIAsp30 BD (117)</td>
<td>Mean HbA1c reduced by -2.79% with BIAsp 30 and -2.36% with IGLar [p&lt;0.01; BIAsp 30 significantly better than IGLar]</td>
<td>Hypoglycemia event rates (per subject-year): Severe: 1 event with IGLar and none with BIAsp 30 Overall minor: 3.4 (BIAsp 30) and 0.7 (IGlar) (p&lt; 0.05)</td>
</tr>
<tr>
<td>Randomised, open label, parallel group study in Insulin-naive T2DM (EUROMIX study Kann et al 2006)</td>
<td>To demonstrate the non-inferiority of BIAsp 30 BD to IGLar OD</td>
<td>26 weeks/258</td>
<td>BIAsp 30 BD (128)</td>
<td>Mean HbA1c reduced to 7.5% with BIAsp 30 and 7.9% with IGLar [ETD: -0.5% (95% CI: -0.8, -0.2) p=0.0002]</td>
<td>Hypoglycemia event rates (per subject-year): Severe: 1 event each with IGLar and BIAsp 30</td>
</tr>
<tr>
<td>Multinational, open-label, parallel-group, treat-to-target trial in insulin naive T2DM patients (Franek et al 2015)</td>
<td>To demonstrate non-inferiority of IDeGAsp to BIAsp 30 in terms of change from baseline HbA1c</td>
<td>26 weeks/394</td>
<td>BID IDeGAsp (197)</td>
<td>Mean HbA1c reduced by -1.71% with IDeGAsp and -1.73% with BIAsp 30 [ETD: 0.02% (95% CI: -0.12, 0.17) confirming non-inferiority of IDeGAsp to BIAsp 30]</td>
<td>Hypoglycemia event rates (per PYE): Severe: 0.05 (IDegAsp) and 0.03 (BIAsp 30) Nocturnal confirmed: 0.63 (IDegAsp) and 2.77 (BIAsp 30); RR: 0.25 (p &lt; 0.001) Overall confirmed: 5.8 (IDegAsp) and 13.01 (BIAsp 30); RR: 0.46 (p &lt; 0.001)</td>
</tr>
</tbody>
</table>

BIAsp 30=Biphasic insulin aspart 30; BID=Twice daily; BHI=Biphasic human insulin; BMI=Body mass index; HbA1c=Glycosylated haemoglobin; IDeGAsp=Insulin degludec/insulin aspart; ETD: Estimated treatment difference; FPG: fasting blood glucose IGLar=Insulin Glargine; IGlu= Insulin glulisine; Mix25=25% soluble and 75% protaminated insulin lispro; OAD=Oral anti diabetic drugs; PPG=post prandial glucose; T2DM=Type 2 diabetes mellitus; PYE: Patient-years of exposure

intensification of the therapy from OD premix insulin to BID/TID to reach targets of HbA1c <7%, FPG <115 mg/dL and PPG <160 mg/dL. CDA 2013 recommends intensification of the therapy from OD premix insulin to BID to reach targets of HbA1c ≤7%, FPG 72-126 mg/dL and PPG 90-180 mg/dL.

NICE 2009 recommends intensification of the therapy from OD premix insulin to BID/TID to reach HbA1c target ≤7%.

INCG 2013 recommends intensification of premix insulin therapy from OD to BID, if HbA1c >7% and FPG >110 mg/dL. If a patient on premix insulin (OD/ BID) has HbA1c >7%, though the pre-meal blood glucose is within target, intensification to BID or TID should be considered. When the TDD of insulin in an OD regimen nears 40-50 U, the regimen should be intensified to BID and the total premix insulin dose should be split into equal breakfast and pre-dinner doses (50:50). When BID premix insulin is to be intensified to TID, 2-6 U or 10% of total daily BIAsp 30 dose before lunch, which may require down titration of morning dose (-2 U to 4 U) is recommended.

JAPI 2014 recommends premix insulin OD to BID/TID to reach targets of HbA1c ≤7%, FPG <110 mg/dL and PPG <180 mg/dL.

Published Scientific Literature

Various studies have reported BID/TID premix insulins to be similar to basal plus or basal bolus therapies in terms of glycemic control, risk of overall hypoglycemia, insulin dose and weight gain (Table 4).
### Table 4: Twice/thrice daily premix insulin/ co-formulation for intensification

<table>
<thead>
<tr>
<th>Trial (Reference)</th>
<th>Objective</th>
<th>Duration of Treatment/Total Number of Enrolled Subjects</th>
<th>Trial arms</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multinational Open-label, trial on Insulin naive T2DM patients (GALAPAGO5 Study Aschner et al 2015)</td>
<td>To demonstrate superiority of insulin glargine (± glulisine) Vs premix strategy</td>
<td>weeks/923</td>
<td>Premix insulin OD/BID (461)</td>
<td>• Mean HbA1c reduced by –1.64% with premix insulin and –1.48% with IGlar ±IGlu [ETD: -0.16% in favour of premix (95% CI: 0.04, 0.27) p=0.008]</td>
</tr>
<tr>
<td>Multinational randomized, open-label trial in T2DM patients (Tinahones et al 2015)</td>
<td>To assess non-inferiority, and then superiority, of Biphasic insulin lispro 25 (LM 25) versus insulin glargine once daily and insulin lispro once daily (IGL) in terms of change in HbA1c from baseline</td>
<td>24 weeks/476</td>
<td>BID LM25 (236)</td>
<td>• Mean HbA1c reduced by –1.3% with LM25 and –1.08% with IGL [ETD: -0.21% (95% CI: −0.38,−0.04) confirming non-inferiority of LM25 to IGL]</td>
</tr>
<tr>
<td>Multicentre randomized active-comparator parallel group open-label non-inferiority trial on T2DM patients (Jin et al 2015)</td>
<td>To demonstrate non-inferiority of the basal-prandial insulin treatment vs premixed insulin-based therapy in terms of change from baseline in HbA1c levels</td>
<td>24-weeks/161</td>
<td>BIAsp 30 BID (83)</td>
<td>• Mean HbA1c reduced by –1.04% with BIAsp 30 and –0.94% with IGlar +IGlu [ETD: -0.09% (95% CI: −0.35, 0.16) confirming non-inferiority of basal-prandial therapy to premixed insulin therapy]</td>
</tr>
</tbody>
</table>

#### Efficacy (HbA1c) Safety (Hypoglycemia)

- Hypoglycemia event rates (per subject-year):
  - Severe: 9 events with IGlar ±IGlu and 15 events with premix insulin
  - Nocturnal symptomatic: 1.07 (IGlar ±IGlu) and 2.28 (Premix insulin); RR=0.47 (p < 0.001)
  - Overall symptomatic: 4.51 (IGlar ±IGlu) and 8.37 (Premix insulin); RR=0.54 (p < 0.001)

Contd...
### Table 4: Twice/thrice daily premix insulin/ co-formulation for intensification

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<th>Trial (Reference)</th>
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<th>Results</th>
<th>Safety (Hypoglycemia)</th>
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</thead>
<tbody>
<tr>
<td>Open-label trial on T2DM patients (LANSCAPE Vora et al 2015)</td>
<td>To test non-inferiority 24 weeks/335 of basal plus regimen with BID premix as assessed HbA1c reduction from baseline</td>
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<td>Hypoglycemia event rates (per subject/year):</td>
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<td></td>
<td></td>
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<td></td>
<td>• BIDAsp 30 BID (165)</td>
<td>• Severe: 13 patients with IGlar +IGlu and 9 patients BIDasp 30 experienced severe hypoglycemia</td>
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<td></td>
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<td></td>
<td>• IGlar + IGlu (OD) (170)</td>
<td>• Nocturnal: 3.6 and 5.7 events/patient-year with BIDasp 30 and IGlar +IGlu; RR=1.57 (p=0.019); significantly lesser with BIDasp 30</td>
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<td></td>
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<td>• Mean HbA1c reduced by –1.0% with IGlar +IGlu and -1.22% with BIDasp 30 [ETD: -0.21% (95% CI: UL=0.38) confirming non-inferiority of basal-prandial therapy to premixed insulin therapy]</td>
<td>• Overall: 18.2 and 15.3 events/patient-year (p=0.22); Similar between groups</td>
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<td>• Proportion of patients achieving HbA1c &lt;7%: 27.9% and 20.6% with BIDasp 30 and IGlar +IGlu respectively (p=0.12)</td>
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<td>Hypoglycemia event rates (per subject/year):</td>
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<td></td>
<td></td>
<td>• Severe: 11 episodes with IDet+IAsp and none with BIDasp 30</td>
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<td>• Nocturnal: 0.013 and 0.010 with IDet+IAsp and BIDasp 30 respectively; similar between groups</td>
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<td>• Minor: 0.035 and 0.037 with IDet+IAsp and BIDasp 30 respectively; similar between groups</td>
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Table 4: Twice/thrice daily premix insulin/ co-formulation for intensification

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<th>Results</th>
<th>Safety (Hypoglycemia)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multinational, open-label, randomized, parallel-arm treat-to-target trial on T2DM patients not controlled by OADs (Malek et al 2015)</td>
<td>To demonstrate the non-inferiority of stepwise insulin intensification of basal–bolus insulin analogues to BIAsp30 in reduction in HbA1c from baseline</td>
<td>50-week/403</td>
<td>• BIAsp 30 (1-2-3) (203) • IDet + IAsp (1-2-3) (200)</td>
<td>• Mean HbA1c reduced to 7.4% with IDet + IAsp and 7.3% BIAsp1-2-3 (ETD: 0.1% (95% CI: -0.1, 0.3) confirming non-inferiority of IDet+IAsp to BIAsp 30</td>
<td>Hypoglycemia event numbers: • Major: 37 and 36 with IDet+IAsp and BIAsp 30 respectively • Nocturnal: 90 and 88 with IDet+IAsp and BIAsp 30 respectively • Overall: 725 and 651 with IDet+IAsp and BIAsp 30 respectively</td>
</tr>
<tr>
<td>Multinational Open-label, treat-to-target trial on T2DM patients ≥18 years of age inadequately controlled OD or BID pre- or self-mixed insulin with or without OADs (Fulcher et al 2014)</td>
<td>To demonstrate non-inferiority of I DegAsp to BIAsp 30 in terms of change in HbA1c</td>
<td>26-week/447</td>
<td>• BID I DegAsp (224) • BID BIAsp 30 (223)</td>
<td>• Mean HbA1c reduced to 7.1% with both I DegAsp and BIAsp 30 (ETD: -0.03% [95%CI -0.18, 0.13]) confirming non-inferiority of I DegAsp to BIAsp 30</td>
<td>Hypoglycemia event rates (per patient-year of exposure): • Severe: 0.09 and 0.25 with I DegAsp and BIAsp 30 respectively; similar between the groups • Nocturnal confirmed: 0.74 and 2.53 with I DegAsp and BIAsp 30 respectively; RR: 0.27 (p&lt;0.0001) • Overall confirmed: 9.72 and 13.96 with I DegAsp and BIAsp 30 respectively; RR: 0.68 (p=0.0049)</td>
</tr>
<tr>
<td>Open label, treat to target trial in insulin experienced T2DM patients (Rodbard et al 2015)</td>
<td>To demonstrate the non-inferiority of I DegAsp compared to basal bolus therapy for change in HbA1c from baseline</td>
<td>26 weeks/274</td>
<td>• I DegAsp BID (138) • I Deg OD + I Asp (2-4 times daily) (136)</td>
<td>• Mean HbA1c reduced by -1.31% with I DegAsp and -1.50% I Deg + I Asp (ETD: 0.18% [95%CI -0.04, 0.41]) not confirming non-inferiority of I DegAsp to I Deg + I Asp</td>
<td>Hypoglycemia event rates (per patient-year of exposure): • Severe: 0.47 and 0.24 with I DegAsp and I Deg + I Asp respectively • Nocturnal confirmed: 1.2 and 1.6 with I DegAsp and I Deg + I Asp 30 respectively; RR: 0.8 (p=NS) • Overall confirmed: 11.6 and 13.6 with I DegAsp and I Deg + I Asp 30 respectively; RR: 0.81 (p=NS)</td>
</tr>
</tbody>
</table>

BIAsp 30=Biphasic insulin aspart 30; BID=Twice daily; BHI=Biphasic human insulin; BMI=Body mass index; HbA1c=Glycosylated haemoglobin; IDet:Insulin Detemir; I DegAsp=Insulin Degludec/insulin Aspart ETD: Estimated treatment difference; I Glar=Insulin Glargine; I Glu=Insulin glulisine; I Asp=Insulin aspart; ITT=intent to treat; Mix25/ LM25=25% soluble and 75% protaminated insulin lispro; OAD=Oral anti diabetic drugs; SMBG Self-Monitoring of Blood Glucose T2DM= Type 2 diabetes mellitus

In a recent meta-analysis, based on 13 randomized control trials (RCTs) on T2DM patients (≥18 years old), the efficacy and safety of basal bolus (including basal plus) was compared with premixed insulin (≤3 injections/day). The mean HbA1c decrease from baseline is comparable for both the treatment groups (basal bolus and premixed groups; -1.56%, and -1.47% respectively, p = 0.13). Further, the
Expert Group Recommendation 4: Twice/thrice Daily Premix Insulins/Co-Formulations for Intensification

- Twice daily premix analogue provide comparable glycemic control and safety versus basal plus strategy with the additional benefit of simplicity (one device vs 2 devices).
- When intensifying premix analogue therapy from once daily to twice daily, split the once daily dose into equal breakfast and dinner doses and titrate further.
- When intensifying premix analogue from twice daily to thrice daily, consider adding 2–6 U or 10% of total daily premix insulin dose before lunch which may require down titration of morning dose (-2 to 4 U).
- Premix insulin analogue thrice daily is comparable to basal bolus regimen, and offers more convenience as an option for intensive insulin therapy.
- IDegAsp twice daily is comparable to basal bolus regimen and offers for a convenient alternative to intensive insulin therapy.
- Twice daily IDegAsp can be recommended over premix analogues in view of superior fasting glucose control and lower risk of major and nocturnal hypoglycemia.
- Twice daily IDegAsp can be recommended over premix analogues for patients where basal insulin analogue is inadequate for superior fasting glucose control.
- The recommended target for titration is pre-meal value of 80-130 mg/dL, pre-breakfast dose if titrated based on pre-dinner values and vice-versa.

Recommendation on Titration:

<table>
<thead>
<tr>
<th>Pre-breakfast/pre-dinner value (mg/dL)</th>
<th>Pre-dinner/pre-breakfast dose change</th>
<th>Dose adjustment (units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 80</td>
<td></td>
<td>-2</td>
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<tr>
<td>80-130</td>
<td></td>
<td>0</td>
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<tr>
<td>131-160</td>
<td></td>
<td>+2</td>
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<tr>
<td>161-180</td>
<td></td>
<td>+4</td>
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<tr>
<td>&gt; 180</td>
<td></td>
<td>+6</td>
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</table>

*Lowest/mean of the three recent self-measured blood glucose values

Note: For patients initiated on pre-breakfast dose, titrate according to pre-dinner values and vice versa

A study group analysed 9 RCTs and reported no significant difference in event rate of overall hypoglycemia (12.1 Vs. 12.2 episodes per patient per year with mean difference 0.16) and body weight gain (2.4 kg Vs. 2.2 kg with mean difference of 0.21). The analysis of daily insulin dose based on two RCTs in the same study reported mean difference to be -0.54U/day and -0.02U/day favouring premixed insulin group. The authors suggested basal bolus insulin therapy up to 4 injections/day as the intensification of basal plus and TID premix as the intensification of BID premix insulin analogues is similar. Since premix analogue insulins (up to 3 injections per day) have been established to be non-inferior to basal-bolus insulin therapy (up to 4 injections per day) in terms of efficacy, weight and overall hypoglycemia, it was anticipated that these options would be suggested after basal insulin insufficiency as a revision in ADA Standards of Care in Diabetes 2017. Highlighting this much anticipated change has now been updated in the ADA Standards of Care 2017.

In a 26-week, randomized, open-label, multinational, treat-to-target trial, IDegAsp was found to be superior to BIAsp30 in T2DM patients inadequately controlled with OD/BID pre/self-mixed insulin with/without OADs in terms of significantly lower FPG levels (estimated treatment difference [ETD] −20.52 mg/dL mmol/L [95% CI −27.56 to −13.69], p < 0.001) and mean daily insulin dose (estimated rate ratio 0.89 [95% CI 0.83–0.96], p = 0.002). Additionally, fewer confirmed, nocturnal confirmed, and severe hypoglycemia episodes were reported in IDegAsp group compared with BIAsp 30 group.

In a randomized, open-label, treat-to-target, phase III non-inferiority study of BID IDegAsp with basal bolus insulin therapy (IDeg once daily administered with IAsp 2–4 times daily) in type 2 diabetes previously treated with basal insulin with/without OADs reported comparable reduction in HbA1c with both treatment groups and numerically lower overall and nocturnal confirmed hypoglycemia with IDegAsp in comparison to basal bolus therapy.

Consensus 5: Premix Insulins In Gestational Diabetes

Premix insulins BHI 30 and BIAsp30 have been reported to provide tight glycemic control with fewer injections in women with GDM.

Current Place in Guidelines

As per DIPSI guidelines 2006 for Indian GDM patients, combination of short acting insulin and intermediate acting insulins was suggested for GDM patients in morning and evening. In this regimen, 2/3rd of the total daily dose (TDD) of insulin is given in the morning and 1/3rd in the evening. For each combination, 1/3rd of the dose should be regular insulin and 2/3rd should be intermediate acting insulin. If a patient continues to have fasting hyperglycemia, the intermediate acting insulin should be given at bedtime instead of before dinner. Use of premix insulin analogues in pregnancy should be individualized and physician-based.

Published Scientific Literature

BIAsp 30 was reported to be safe during pregnancy and allows considerable flexibility in the meal time insulin dosing without disturbing patient’s routine life pattern.

In a single-center, randomized, open-label, parallel group trial, the efficacy and safety of 6 U of BIAsp 30 (Group A) was compared with 6 U of BHI 30 (Group B) in 323 patients with GDM. Both the groups were comparable in terms of glycemic (FPG and PPG) levels, rates of hypoglycemia, adverse events and neonatal macrosomia. Patients in Group A had significantly lower mean total insulin dose at the end of the study compared to Group B patients, indicating a lower dose requirement by Group A patients to achieve the similar degree of glycemic control. Hence, BIAsp 30 was considered as non-inferior to BHI 30, producing similar glycemic
and neonatal outcomes and was well-tolerated during pregnancy.\textsuperscript{32}

Consensus 6: Premix Insulins in Type 1 Diabetes Mellitus

Premix insulin formulations BIAsp 30, LisproMix 25 and IDegAsp are recommended for achieving the glycemic control in patients with type 1 diabetes mellitus (T1DM).

Published Scientific Literature

In a 26-week, multicentre, open-label, two-arm, parallel study, the efficacy and safety of OD IDegAsp + mealtime IAAsp was compared to OD IDet + mealtime IAAsp in T1DM patients aged >18 years. A total of 548 patients with T1DM were randomized 2:1 to IDegAsp or IDet + IAAsp. Non-inferiority for IDegAsp versus IDet was confirmed; A1C improved by 0.75% with IDegAsp and 0.70% with IDet to 7.6% in both groups (estimated treatment difference IDegAsp - IDet: -0.05% [95% CI –0.18 to 0.08]). There was no statistically significant difference between IDegAsp and IDet + IAAsp in the rates of severe hypoglycemia (0.33 and 0.42 episodes/patient-year, respectively) or overall confirmed (plasma glucose, 56 mg/dL) hypoglycemia (39.1 and 44.34 episodes/patient-year, respectively). Nocturnal confirmed hypoglycemia rate was 37% lower with IDegAsp than IDet (3.71 vs. 5.72 episodes/patient-year, P<0.05).\textsuperscript{33}

Expert Group Recommendation 6: Premix Insulins in T1DM

- In T1DM patients aged more than 18 years where basal bolus is not feasible, biphasic insulin analogues are preferred over human premix insulins in view of their safety profile.
- In T1DM patients aged more than 18 years where basal bolus is not feasible, IDegAsp based regimen provides similar efficacy as compared to basal bolus therapy.

Consensus 7: Premix Insulins During Ramadan

Current Place in Guidelines

IDF 2016 recommended the use of premix analogues over biphasic human insulin due in view of the lower incidence of hypoglycemia. In case of OD dosing, the normal dose should be taken at iftar. For BD dosing, the normal dose should be taken at iftar and suhur dose should be reduced by 25–50%. For TID dosing, an afternoon dose should be omitted and iftar and suhur doses to be adjusted based on the FBG levels.\textsuperscript{34}

SAFES guidelines also recommend premix analogues in patients with diabetes during Ramadan owing to its multiple advantages of safety and flexibility. The guideline also recommends that if a patient is already on premix insulin, the usual morning dose should be used at the sunset meal and the usual evening dose should be halved at predawn meal.\textsuperscript{35}

Published Scientific Literature

Premix insulins are more convenient for T2DM patients since they require fewer injections than basal-bolus regimens (Table 5). In an open-label randomised trial, the effects of LisproMix25 and BHI 30/70 was compared during Ramadan in terms of glycemic control. Patients treated with insulin lispro Mix25 had lower overall glycemia than patients on BHI 30/70. However, there was no difference in the number of hypoglycemic episodes between treatments\textsuperscript{36}. A regimen of insulin lispro Mix50 in the evening and regular human insulin with NPH (30:70) in the morning was compared with regular human insulin with NPH (30:70) given twice daily during Ramadan in a small observational study. Switching the evening meal dose to insulin lispro Mix50 significantly improved glycemic control without increasing the incidence of hypoglycemic events\textsuperscript{37}. A new regimen in which 40% of the daily insulin dose was given as IDet at suhoor and 60% was given as NovoMix70 before iftar was assessed in another randomised study. The new regimen was found to be non-inferior to standard care with a significantly lower hypoglycemic event rate\textsuperscript{38}. A prospective observational study in Indonesia found that BIAsp significantly reduced all glycemic indices following Ramadan without an increase in body weight or risk of hypoglycemia; however, there were no significant changes in body weight or body mass index (BMI).\textsuperscript{39}

Expert Group Recommendation 7: Premix Insulins during Ramadan

- It is recommended to use premix analogues over human premix during Ramadan in view of improved safety and flexibility of dosing.
- Patients on once daily premix insulin/co-formulations need not modify dose but have to administer the dose at the time of breaking the fast.
- Patients on twice daily premix insulin/co-formulations should take usual pre-dinner dose at night meal and reduce morning dose by 25-50%.

Conclusion

Appropriate management of glycemic levels in patients with T2DM is important in delaying long-term complications associated with this disease. The principal factors important in optimal glycemic control include choice of an appropriate insulin regimen and timing of initiation and intensification/optimisation of insulin therapy. Premix insulin formulations are the most widely prescribed insulins in India due to typical Indian phenotype, high
carbohydrate intake and high PPG levels. There is a need to update premix guidelines with respect to newer evidence and newer co-formulations. The recommendations put forth are based on the existing established guidelines and published evidence.

The recommendations presented in this paper can be further simplified as follows:

- **In the setting of high**
carbohydrate consumption or in patients with predominant post prandial hyperglycemia like in India. IDEgAsp could be preferred over premix insulin analogues and basal insulins for insulin initiation, to achieve recommended glucose targets without increasing the risk of overall and nocturnal hypoglycemia.

- Twice daily IDEgAsp is recommended over BIAsp 30 in view of lower risk of hypoglycemia and superior fasting glucose control. It is also recommended where premix/basal insulin analogues are considered inadequate for superior fasting glucose control.

- Both premix insulin analogues thrice daily and IDEgAsp twice daily are comparable to basal bolus regimen and offers a convenient alternative to intensive insulin therapy.

- When intensifying premix analogue therapy from once daily to twice daily, the once daily dose should be split into equal breakfast and dinner doses and titrated further. When intensifying premix analogue from twice daily to thrice daily, consider adding 2–6 U or 10% of total daily premix insulin dose before lunch. This may require down titration of morning dose.

- Premixed insulin analogues are more effective than human premix insulin in lowering PPG levels in patients with GDM.

- IDEgAsp based regimen provides similar efficacy versus basal bolus therapy in TIDM patients aged > 18 years where basal bolus regimen is not feasible.

- Premix insulin analogues are recommended over human premix insulin during Ramadan in view of their safety and flexibility.

The strength of the current consensus is that it is evidence based, and concordant with globally acceptable guidelines. It includes evidence based discussion of modern insulin coformulation, and covers the complete spectrum of premix insulin use in various clinical presentations of diabetes, including type 1 diabetes, type 2 diabetes, GDM and symptomatic hyperglycemia.

We hope that these consensus recommendations will be a useful reference tool for physicians and that their impact will be validated through observational research, involving large number of physicians and in the setting of routine outpatient care of T2DM in India.

Acknowledgement

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References


Giant Unruptured Sinus of Valsalva Aneurysm Arising from Left Coronary Cusp

Varun Vishwas Nivargi¹, Manuel Durairaj², Chandrashekhar Makhale³

Sinus of Valsalva aneurysm is a rare cardiac anomaly, and arises mainly from a congenital defect of the aortic media or may follow bacterial endocarditis. It occurs in between 0.09 and 0.15% of cases, and comprises up to 3.5% of all congenital cardiac anomalies.¹ Coexisting cardiac lesions, especially a ventricular septal defect or aortic valve regurgitation, may both be present in about 30 to 40% of patients.²,³

A congenital sinus of Valsalva aneurysm is usually clinically silent but may vary from a mild, asymptomatic dilatation detected in routine 2-dimensional echocardiography to symptomatic presentations related to the compression of adjacent structures or intracardiac shunting caused by rupture of the sinus of Valsalva aneurysm into the right side of the heart. Approximately 65-85% of sinus of Valsalva aneurysms originate from the right sinus of Valsalva, 10-30% from non-coronary and left sinuses (< 3%) are rare. We describe a young 26 years old male who presented to us with recurrent syncope. 12-lead electrocardiogram was suggestive of monomorphic ventricular tachycardia epicardial in origin (Figure 1). On further investigation cardiac Doppler showed a giant unruptured sinus of Valsalva aneurysm arising from left coronary cusp with mild aortic regurgitation (Figure 2) which was confirmed and better outlined with a complete cardiac catheterisation (Figure 3).

Patient was started on antiarrhythmics and was advised surgery for the aneurysm. Patient was lost to follow up.

References


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This information is intended for healthcare professionals.
Headcheese Sign: A Useful Radiological Marker

Rathindranath Sarkar¹, Rudrajit Paul², Rajesh Pandey³, Indranil Thakur², Angan Karmakar³

A 40 year old woman presented with progressive dyspnoea for three months. She had earlier been treated for asthma with inhalers for a long time. However, the medication gave only partial relief. She worked as a jute bag designer. On examination, she was tachypnic with respiratory rate of 33/minute and oxygen saturation of 81% on room air. There was no cyanosis. Chest examination revealed scattered crepitations in both lungs. An initial chest X-ray showed fluffy opacities in both lung fields. However, sputum for GeneXpertTM was negative. An HRCT scan of thorax was done which showed (Figure 1) a heterogeneous appearance of upper and middle zones of both lungs with juxtaposition of low, normal and high attenuated regions. This is called “headcheese sign” of thorax.

The name of this sign is derived from “headcheese” which is a European dish consisting of meat pieces. The name indicates the heterogeneous mosaic appearance of thorax. This occurs due to infiltration of inflammatory cells in parenchyma (ground glass opacity) in a patchy distribution with normal lung in between. There is also a bronchospastic component of the underlying disease which causes distal air trapping. This gives rise to the low attenuation regions. Thus, headcheese sign indicates a dual pathophysiology: lung parenchymal infiltration and obstruction of small airways.

The commonest cause of this radiological appearance is hypersensitivity pneumonitis. It usually occurs after prolonged exposure to the culprit allergen. In our patient, the exposure to jute was probably responsible for the lung pathology. Now, it has been found that the “headcheese sign” may occur in other conditions like atypical lung infections with bronchiolitis or sarcoidosis. But infections are mostly of short duration, whereas hypersensitivity pneumonitis is a chronic condition. Thin section CT scans are the best in identifying the radiological appearance. The air trapping component may sometimes be missed in normal scans. Expiratory films are needed to delineate the low attenuation parts better.

We present this case to sensitize clinicians to this radiological sign. In doubtful clinical situations, this may help in diagnosing the underlying lung disease.

References


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Concrete Renal Mucormycosis

R Sriranga, Satyajeet Pawar, Wasim Khot, Neeraj Nischal, HA Venkatesh, Ragesh R Nair, Raj Kanna, Mehar C Sharma, SK Sharma

Abstract

Mucormycosis in humans has been described as early as 1885 in literature. Isolated renal mucormycosis is rare as it has been mainly described in developing countries like India and China. It is rarer still to find this entity in immunocompetent young males without any risk factors. Specific guidelines on the treatment is not yet known but combined surgical and medical therapy is considered the best modality for its management. We describe a young male who presented with bilateral hydroureteronephrosis. He was initially treated as a case renal tuberculosis which is relatively more common in TB endemic country like ours. However when he did not respond to the anti-tuberculosis drug (ATT), a biopsy revealed mucormycosis. He was treated with nephrectomy and liposomal amphotericin B and oral posaconazole. On follow up of 2 years he is healthy and leading his normal life.

Introduction

Mucormycosis, an emerging fungal infection, is the 3rd most common among the invasive fungal infections. It is seen commonly among the immunosuppressed, post-transplant patients, and diabetics. Herein we report a very rare case of isolated renal mucormycosis in a young immunocompetent male.

Case Report

A 25-year-old male, a resident of Uttar Pradesh with no known comorbidities, tailor by occupation, ex-smoker (smoking index of 70) presented to with a history of multiple episodes of right sided flank pain since 8 month and painless hematuria since last 6 months. Flank pain was colicky in nature, radiating from loin to groin and relieved with analgesics and antispasmodics. It was associated with high grade fever with chills. Hematuria was painless, present throughout the stream of urine and was associated with occasional passage of clots in urine. There was no history of pyuria, dysuria, weight loss, anorexia, IV drug abuse or working in fields. He was evaluated in private setup for these complaints and found to have a nodular lesion on posterior wall of urinary bladder and left hydroureteronephrosis. He was subsequently referred to higher center for management. At the time of presentation he also had anuria for last 3 days and uremic symptoms in form of recurrent vomiting, anorexia.

At admission, he was pale, afebrile and normotensive. There was no icterus, clubbing, cyanosis, lymphadenopathy or skin rash. Facial puffiness and bilateral pedal edema was also present, suggesting fluid overload. The ocular fundus examination was normal. The sternal tenderness was not present. Examination of respiratory system revealed decreased breath sounds in bilateral infra-axillary and infrascapular areas. There were no adventitious sounds. Examination of abdomen revealed a lump
in hypogastrium. It was firm, non-tender, smooth and dull on percussion. Shifting dullness was present. Rest of the abdominal examination and examination of cardiovascular and central nervous system was within normal limits.

His investigations done at the time of admission showed leucocytosis with eosinophilia (Table 1).

Urgent non-contrast CT scan of abdomen revealed bilateral hydronephrosis with diffuse circumferential urinary bladder wall thickening suggesting inflammatory strictures at vesicoureteral junction. In addition, right kidney was bulky with multiple areas of hypodense lesion within parenchyma suggesting secondary inflammatory or infective lesions. He underwent two sessions of hemodialysis followed by bilateral percutaneous nephrostomy.

His viral markers was negative, urine routine, culture sensitivity and stool routine culture sensitivity was sterile.

Repeat CECT of chest and abdomen was done which showed diffusely enlarged right kidney with loss of architecture and multiple areas of hypo density within the parenchyma. In addition, perinephric fat stranding with collections were seen. No contrast excretion was seen in delayed scans on right side. Left kidney was normal with drainage tube in situ and pelvicalyceal system decompression. Diffuse urinary bladder thickening was persisting with adjacent areas of fat stranding (Figure 1).

He underwent USG guided trucut biopsy from bladder mass which revealed predominantly necrotic tissue along with acute inflammatory exudate. He was evaluated rigorously for etiology of his illness. Pleural fluid was transudative in nature (Table 2).

Though there were no confirmatory evidence he was started on category I ATT empirically. Within 10 days of starting ATT he had elevation in liver enzymes and ATT was modified. During this course his absolute eosinophil count showed gradual decline from initial 5100/mm$^3$ to 1700/mm$^3$ (Graph 1).

Renal functions gradually improved from initial urea/creatinine of 212/18.6 mg/dl to 30/1.3. Right sided PCN was draining less than 50 ml of urine.

### Table 2: Fluid analyses

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<th>Pleural fluid analysis</th>
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<td>Transudative Transudative</td>
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<td>Predominant PMN Predominant PMN</td>
<td>Gene Xpert – Gene Xpert –</td>
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<tr>
<td>Negative Negative</td>
<td>ADA - Normal ADA - Normal</td>
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Graph 1: Eosinophil counts
per day. DTPA scan showing right sided non-functioning kidney so PCN was removed.

Cystoscopy guided biopsy from bladder mass was done which revealed ulceration of mucosa along with necrosis of muscularis layer, dense acute on chronic inflammatory infiltrate predominant eosinophils. Bone marrow biopsy was also done in view of persistent eosinophilia which revealed myeloid predominance with predominance of eosinophilic precursors with eosinophilia.

Patient was started on anti-parasitic agents. Absolute eosinophil count also decreased from 1700/mm$^3$ to normal (Graph 2).

He was discharged with same treatment and advice to follow-up in outpatient department.

But after 2 months from his discharge he again presented to us with complaints of on and off low grade fever and pyuria. There was no history of abdominal pain, haematuria or dysuria. Left sided PCN was in situ with adequate drainage per day. He was admitted again for re-evaluation in view of persistent bladder symptoms. His investigations revealed anemia with lymphocytosis (Table 3). His autoimmune work up and immunodeficiency work up was negative (Table 4). Left nephrostogram showed stricture at left ureterovesical junction with no further passage of contrast. CECT was repeated for better characterisation of renal lesion showed shrunken right kidney.

<table>
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<th>Table 3: Investigations on readmission</th>
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<tr>
<td><strong>Time</strong></td>
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<td>Hb (gm/dl)</td>
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<tr>
<td>Platelet Count(per ml)</td>
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<td>TLC (per ml)</td>
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<td>Bilirubin(T) (mg/dl)</td>
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<td>SGPT (&lt;50 IU/mL)</td>
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<td>ALP (IU/mL)</td>
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<th>Table 4: Auto-immune workup</th>
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<td><strong>Auto-immune workup</strong></td>
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<tr>
<td>RF – Negative</td>
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<tr>
<td>ANA – Negative</td>
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<tr>
<td>ANCA – Negative</td>
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<tr>
<td>Anti dsDNA – 4 (0-50 IU/ml)</td>
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<td>C3 levels – 99 (70-240 mg/ml)</td>
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**Workup for eosinophilia**
- PDGFR/FIL, P, P1, TIMP – Negative
- Serum IgE levels – 11000 IU/l
- Aspergillus serology – Negative
- HbA1c – 5.1
- NBT test – Negative

**Immunodeficiency workup**
- CD4 – Normal
- IgG : 1757 (960-1986)
- IgA : 397 (125-386)
- IgM : 137 (90-242)

**Fig. 2**: CECT axial (a and c) and coronal reformatted images (b) shows shrunken right kidney with hypodense lesion in right kidney with perinephric extension and significant pelvic fat stranding (arrow head)
with non-enhancing solid lesion having perinephric extension at upper pole possibly inflammatory/infective in nature. Urinary bladder wall thickening had significantly decreased however significant pelvic fat stranding was seen suggesting oedema and adhesions (Figure 2).

Ultrasound guided renal biopsy was done. It showed mucormycosis with renal abscess, healed acute cortical necrosis with chronic tubulointerstitial nephritis (Figure 3). Bladder mass biopsy was reviewed which showed predominantly necrotic tissue along with acute inflammatory exudate and few broad a septate hyphae seen under special stains.

Sigmoidoscopy was undertaken to look for possibility of infiltration in rectum which showed mucosal oedema and ulceration with formation of small recto-vesical fistula. Rectal biopsy showed unremarkable inflammatory granulated tissue and acute inflammatory exudate.

Patient was started on Liposomal Amphotericin B based on these findings. He was monitored with serial abdominal imaging for treatment response. As right kidney was non-functional a decision to perform right nephrectomy along with cystectomy was taken. Patient underwent nephrectomy without any complications but plan form cystectomy was deferred in view of extensive pelvic adhesions. His postoperative condition remained stable. His follow-up investigations showed improvement in platelet count and mild increase in creatinine levels (Table 5). He was discharged on oral posaconazole. Due to economic reasons he didn’t take oral posaconazole. He was on weekly amphotericin for 3 months post discharge following which he stopped his medications. 2 years post discharge he is healthy on regular quarterly OPD visits.

**Discussion**

Mucormycosis, a ubiquitous filamentous fungal infection caused by fungus of order Mucorales which belongs to a class of Zygomycetes. It was first described in literature in 1885 [1]. Based on the anatomical location of infections it can be classified into 1) Oculo rhino cerebral mucormycosis 2) pulmonary 3) cutaneous 4) gastrointestinal 5) disseminated 6) uncommon forms.

There is considerable epidemiological differences in the presentation of the disease. In western countries it is common to be seen among HIV positive patients and also in transplant recipients.2

In India it is commonly among uncontrolled diabetics and trauma patients and rhino oculo cerebral type is MC.3 This change in presentation is because of differences in prevalence,
risk factors and causative agents involved. There are a few case reports wherein there was iatrogenic cause (contaminated bandages and adhesive dressings). Most of case reports from India are culture or histopathology proven. The prevalence of isolated renal mucormycosis is 5 to 14%.

Rhinocerebral mucormycosis has the highest mortality followed by disseminated which is followed by pulmonary mucormycosis. Cutaneous mucormycosis has least mortality.

Although most of the rhinooculocerebral mucormycosis is seen in patients with diabetes as a risk factor, isolated renal mucormycosis is seen in healthy individuals. In India 29% of those with mucormycosis are healthy individuals. In disseminated mucormycosis kidney is involved in almost 22% cases. But isolated renal mucormycosis is described rarely in literature. Case reports on isolated renal mucormycosis come from India and china with the phenomenal difference of them seen in healthy subjects in India as compared to those with risk factors in China.

The portal of entry of the fungus to kidney is not clear. Based on the presence of additional foci in Lungs noticed during autopsy it may be hypothesized that lungs may be the portal of entry. In a recent literature ascending route may be the portal of entry as the lesion was also seen in urinary bladder. Once the fungi gains entry into the renal vessels, they cause cortical and medullary infarction leading to renal failure. Mortality of different types of mucormycosis reaches 75% to 100% in many case series. Survival for isolated renal zygomycosis is estimated to be 65%.

Our patient being a young immunocompetent male had atypical indolent presentation unlike florid presentation of mucormycosis as described in case reports. Imaging features of features of renal mucormycosis are nonspecific and shows diffuse enlargement of kidney, multiple hypodense areas secondary to abscess or infarct by vascular invasion, per nephric collection. Sometimes they may simulate xanthogranulomatous pyelonephritis with absence of renal calculi.

Although the presentation was benign but outcome would be favorable only with the aggressive management with the combination of surgical and medical modalities.

References

Oculo-otological Manifestations in a Case of Granulomatosis with Polyangiitis

Archana Sonawale¹, Anjali Rajadhyaksha², Shreepriya Mangalgi³

Abstract

A 44 year old lady presented with acute onset of loss of vision in the right eye and cough with mucopurulent expectoration for two months. Ophthalmic examination revealed central retinal artery occlusion (CRAO). Chest radiograph showed multiple cavitatory nodules with fluid levels. Sputum was negative for AFB and ANCA was strongly positive suggestive of a diagnosis of Granulomatosis with Polyangiitis (GPA). Within the next few weeks the patient had rapid detenoration due to left eye CRAO, progressive bilateral hearing loss, facial palsy and retro orbital mass. The aggressive disease responded well to steroids and cyclophosphamide.

Introduction

Granulomatosis with polyangiitis is an ANCA-associated small vessel vasculitis characterised by granulomatous necrotising inflammatory lesions of the upper and lower respiratory tract and also ocular and otological involvement. Eye involvement is frequent and may range from mild conjunctivitis to dacrocystitis, scleritis, episcleritis, granulomatous uveitis, ciliary vessel vasculitis and retro-orbital mass. Retinal vasculitis is rarely seen. Otological involvement may occasionally be the first and only sign of the disease with presentations like serous otitis media, sensorineural hearing loss, otalgia and otorrhoea with middle ear involvement. We present a case of GPA with rapidly progressive oculo-otological manifestations which were much more florid than the pulmonary symptoms.

Case History

A 44 year old post-menopausal lady residing in rural Maharashtra, farmer by occupation presented to the ophthalmology department with sudden onset loss of vision in the right eye. She also had 2 month history of moderate grade fever, cough with mucoid expectoration. Initial ophthalmologic examination revealed the presence of pale disc with pale retina, attenuated arterioles with cattle trucking in veins and ghost vessels. A cherry red spot was also seen on the macula. A diagnosis of central retinal artery occlusion was made and right eye anterior chamber paracentesis was done under local anaesthesia. Patient was started on aspirin, vasodilators (pentoxiphylline, xanthinol nicotinate), oral acetazolamide, topical dorzolamide, antibiotics, and labetolol and referred to us for her systemic complaints.

On presentation to us patient had tachycardia, with a pulse rate of 120 beats per minute, other vitals were stable. Respiratory system examination revealed the presence of vesicular breath sounds, with coarse crepitations in bilateral infra-axillary and infra-scapular areas. Rest of the systemic examination was unremarkable. Preliminary investigations revealed a haemoglobin of 8.6 g%, ESR of 55 mm at the end of first hour, TLC of 36,700/mm³ with 88% polymorphs and 12% neutrophils, a platelets count of 4.0 lakhs/mm³. Her BUN was 9.0 mg/dl with a serum creatinine of 0.9 mg/dl. Blood sugar levels, liver function tests, complete lipid profile were within normal limits. ECG showed the presence of sinus tachycardia. A chest radiograph (Figure 1) was performed which showed the presence of multiple cavitatory nodules with fluid levels in bilateral lung fields, largest in the right parahilar region. The preliminary differential diagnoses were multiple lung abscesses of possible bacterial, mycobacterial or fungal etiology, cavitative metastasis or granulomatosis with polyangiitis (Wegener's granulomatosis). Sputum examination was negative for acid fast bacilli by Ziehl Neelsen staining as well as NAA method. Sputum culture yielded growth of Klebsiella pneumoniae sensitive to amikacin and piperacillin+tazobactum. Sputum mycobacterial culture and fungal culture were negative. Sputum cytopathology showed numerous WBCs with few alveolar macrophages, without any atypical cells. A high resolution CT was done (Figure 2) which showed presence of multiple cavitative lesions.

Her serum C reactive protein levels were 155.0 mg/L. Urine examination was negative for protein, casts or active sediments. HIV, HBsAg and anti-HCV markers were negative.

Fig. 1: Chest X-ray PA view s/o multiple cavitatory nodules with fluid levels in bilateral lung fields
ANA, anti-ds DNA were negative. C3 and C4 complement levels were normal. Samples were sent for anti-neutrophil cytoplasmic antibodies. 2D-echocardiography showed an ejection fraction of 60%, with a structurally normal heart. There were no thrombi or vegetations. Carotid arterial doppler revealed no e/o plaque or thrombus in bilateral carotid arteries. CT guided biopsy of lung lesions showed the presence of organizing haemorrhage within the lung parenchyma, without any evidence of malignancy. Patient was started on IV antibiotics (piperacillin+tazobactum and amikacin), Inj. dexamethasone 4 mg od. Acetazolamide 250 mg tds, along with aspirin, vasodilators, topical antibiotics, labetolol and dorzolamide were continued. 6 days after the initial presentation, patient complained of sudden onset vision loss in left eye. Fundus examination was s/o ill-defined margins of disc with attenuated arterioles, dilated tortuous veins with cattle trucking, ghost vessels and the presence of a cherry red spot (Figure 3).

The impression was that of left central retinal artery occlusion. MRI Brain with MRA showed presence of chronic ischemic changes in periventricular white matter, minimal T2 hyper intense signal in the left optic nerve s/o neuritis with diminished calibre of right optic nerve s/o atrophy. In lieu of optic neuritis, patient was started on Inj. Methylprednisolone 1g for three days i/b oral prednisolone 1mg/kg. Meanwhile patient’s ANCA titres came positive with titres 1:40 (+4), cytoplasmic pattern by immunofluorescence. Anti-PR-3 ANCA levels were strongly positive by E.I.A with titres of 186.38 RU/ml (negative <20 RU/ml). ENT examination showed normal nasal cavities, nasopharynx, external auditory canal and tympanic membrane. Diagnostic nasal endoscopy showed normal mucosa with no e/o granulation. A screening CT scan of the paranasal sinuses showed mild thickening of mucosa of the left frontal sinus, with normal maxillary, ethmoid and sphenoid sinuses. A final diagnosis of granulomatosis with polyangiitis was made and patient was started on pulse cyclophosphamide therapy and was discharged on oral prednisolone.

Twenty days later this patient presented with progressive bilateral hearing loss and left facial asymmetry of 7 days duration. On examination patient had left infranuclear facial palsy and bilateral conductive hearing loss, which was subsequently confirmed by pure tone audiometry (mild to moderate in right ear and moderate to severe in left ear). Otoscopic examination showed presence of an intact, bulging tympanic membrane.

HRCT of the temporal bone suggested fluid in the middle ear with intact ossicular chain. A diagnosis of serous otitis media was made and patient underwent myringotomy with grommet insertion. Subsequently, a second pulse of cyclophosphamide was administered and patient was discharged on oral glucocorticoids and advised to return after a month for the third cycle.

Subsequently our patient did not follow up as per our advice. She came back to us only 3 months later, that too after stopping all medications and treatment by various alternative medicine practitioners. This time she presented with weakness in left hand since one week which was causing her difficulty in buttoning and unbuttoning clothes, difficulty in making a fist with the left hand and thus causing difficulty in doing household chores. She also had diplopia and that she had difficulty in seeing sideways objects necessitating that she turn her head around every time. On examination there was lagophthalmos, hypertropia and restricted extra ocular movements in bilateral eyes. Bilateral LMN type facial paralysis and a weak left hand-grip were also present. Sensory loss was also noted over medial aspect of left hand. Fundus examination showed bilateral optic atrophy.

A CT scan of the orbit showed the presence of a 10*20 mm well circumscribed intracranal mass in the left orbit extending up to the orbital apex and orbital canal leading to the compression and displacement of the optic nerve (Figure 4).

A MRI was performed which showed the presence of a left orbital mass, which was intracranal in location compressing the optic nerve and pushing it medially. The mass showed dark signal on T2 and T1, with brilliant post-gadolinium enhancement. Similar enhancing ill-defined masses were seen along bilateral cavernous sinuses with extension along the petrous apex to involve the medial pterygoids and parapharyngeal space as well as both pterygopalatine fossae. There was also an ill-defined T2/flair hyperintense lesion 1cm in diameter in the right half of posteroinferior cerebellum projecting into the 4th ventricle. The lesion showed restricted diffusion and post-contrast enhancement. MR Spectroscopy revealed a lactate peak in the lesion (Figure 5).

A nerve conduction study was also performed which showed reduced CMAPs in left median, left ulnar, bilateral common peroneal nerves and reduced SNAPs in left median nerve suggestive of mononeuritis.
Granulomatosis with polyangiitis (previously Wegener’s granulomatosis) is a multisystem autoimmune disorder associated with antineutrophil cytoplasmic antibodies (ANCA), predominantly c-ANCA or PR3-ANCA. It predominantly affects the upper and lower respiratory tracts and kidneys. However, it is also known to involve eyes, ears, heart, gastrointestinal system, central and peripheral nervous systems. The pathology of GPA comprises of necrotizing granulomas and vasculitis of small to medium sized blood-vessels. Our case is atypical as it had predominant ophthalmologic and otologic involvement with bilateral central retinal artery occlusion at the initial presentation, orbital, naso-pharyngeal and cavernous sinus pseudotumors, cavitatory lung lesions, bilateral facial nerve palsy, mononeuritis multiplex, cerebellar granuloma, and the conspicuous lack of renal involvement till date.

Ophthalmologic involvement occurs in 28–58% of patients of GPA. Ocular GPA can either manifest de novo, as disease spread from contiguous structures such as the sinuses, or as a part of systemic GPA. Ocular inflammation can occur with or without systemic manifestations. Ocular manifestations may be the initial presentation of GPA in 8–16% of patients and visual loss occurs in up to 8% of patients. Eye involvement can be in the form of keratitis, conjunctivitis, scleritis, episcleritis, uveitis, retrobulbar granulomatous disease, ocular palsies, lacrimal duct obstruction, optic neuritis and retinal vascular occlusions. Our patient had bilateral central artery occlusion, optic neuritis and left orbital pseudotumor.

The ear may be involved in nearly 40% of patients of GPA. Otologic involvement may be in the form of otitis media; usually of serous type, granulomatous involvement of middle ear and mastoid mucosa, tympanic membrane perforation, inflammation of the auricle etc. Conductive as well as sensorineural hearing loss can occur and may lead to profound deafness. Facial nerve palsies are also common, caused by either necrotizing vasculitis of the vasa nervorum or neuritis due to granulomatous involvement of the middle ear. Our patient had bilateral deafness with facial paralysis.

Nervous system involvement is seen in a significant proportion of patients, either the peripheral nervous system (PNS) involvement due to vasculitis or with central nervous system (CNS) involvement due to infiltrating granulomatous manifestations (10–45%). Peripheral neuropathy, cranial neuropathy, external ophthalmoplegia, cerebrovascular events, seizures, cerebritis, spastic paraparesis, temporal arteritis, Horner’s syndrome, and papilledema have been known to occur. Peripheral neuropathy could either present as mononeuritis multiplex, distal symmetrical polyneuropathy or unclassified peripheral neuropathy. Cranial neuropathies frequently involved the second, sixth, and seventh cranial nerves, occasionally with simultaneous multiple cranial nerve involvement.

Apart from cavitatory lung lesions and predominant ophthalmologic and otologic involvement, our patient had mononeuritis multiplex and granulomatous lesion in right posterior-inferior cerebellum. Additionally, she also had inflammatory granulomatous masses in the left orbit, bilateral cavernous sinuses and pterygopalatine fossae. However, there was no evidence of renal involvement till date. Renal involvement could occur in due course and hence patient needs regular evaluation for the same.

Conclusion

Predominant oculo-otological involvement as an initial presentation of GPA can of ten confound the diagnosis.

References

Lymphocytic Hypophysitis Mimicking Pituitary Macroadenoma

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Abstract

Lymphocytic hypophysitis is an inflammatory/autoimmune disorder that primarily involves the pituitary gland and the pituitary stalk. The common clinical presentations include headache, nausea, vomiting, fatigue, features of hypopituitarism and diabetes insipidus as well as diplopia, orbital pain and bitemporal hemianopia. We report a case of lymphocytic hypophysitis which presented as hemichorea. Neuroimaging showed a mass in the sella turcica region which, on histopathological examination was suggestive of lymphocytic hypophysitis. After excision of this mass, patient showed marked improvement in his symptoms albeit he developed panhypopituitarism. The patient was treated with pituitary hormonal replacement therapy and is currently asymptomatic.

Introduction

Lymphocytic hypophysitis is a rare disease and represents an inflammatory/autoimmune disorder that primarily involves the pituitary gland and in many cases the pituitary stalk.¹,² The clinical presentation of this inflammatory condition may mimic a pituitary adenoma,³ the spectrum of which includes headache, nausea, vomiting, fatigue, features of hypopituitarism, diabetes insipidus, diplopia, orbital pain and bitemporal hemianopia.⁴ Lymphocytic hypophysitis is most commonly diagnosed in women during pregnancy or in the post-partum period and can be associated with other types of autoimmune diseases like autoimmune thyroiditis, orbital pseudotumour, pernicious anemia, type I diabetes mellitus and primary biliary cirrhosis.¹,³,⁵-¹⁰ Although most commonly occurring in women during the child bearing years, lymphocytic hypophysitis has now been recognized to affect men and women of any age.¹¹

Case Report

A 76 years old male presented to us with history of fever, headache, and right sided abnormal limb movements for seven days. There was no history of head injury, loss of consciousness, vomiting, convulsion, bladder or bowel disturbances, or visual difficulty. There was no history of similar complaints in the past or any other medical disease like hypertension or diabetes. On examination, patient had choreoathetoid movements in right upper limb and lower limb. Rest of neurological and other systemic examinations were normal. Routine blood investigations were normal. Patient underwent an MRI brain which revealed a well-defined enhancing soft tissue intensity mass lesion in the sellar region including the infundibulum, extending into suprasellar region and inferiorly into the right sphenoid sinus associated with right sphenoid sinusitis. Cerebrospinal fluid (CSF) examination, thyroid function test, peripheral blood film for acanthocytes and serum angiotensin converting enzyme (ACE) levels of this patient were normal. Patient was treated with sodium valproate, haloperidol and clobazam with no respite from symptoms. Transnasal endoscopy and excision of pituitary macroadenoma was performed by a team comprising of experts from otorhinolaryngology and neurosurgery. Histopathological examination of the tissue fragment in the right posterior ethmoidal sinus and sphenoid sinus revealed respiratory mucosa lined by pseudo stratified columnar epithelium with focal areas of necrosis. The underlying stroma exhibited moderate to heavy mixed inflammatory infiltrate of lymphoplasmacytic cells and eosinophils along with Periodic acid Schiff (PAS) positive branching septate mycelia filaments, morphological resembling Aspergillus species (Figures 1 and 2).

Fig. 1: Periodic acid schiff (PAS) staining shows PAS positive branching septae mycelia filaments suggestive of Aspergillus

Fig. 2: H & E stain of biopsy shows inflammatory infiltrate of lymphoplasmacytic cells and eosinophils suggestive of lymphohypophysitis

Few pieces were taken from the pituitary gland; its histopathological examination revealed tumor cells with uniform round nuclei and plasmacytoid appearance. Cells formed solid sheets with sinusoidal arrangement.
Vascularity was of moderate nature, hence mimicking a pituitary adenoma. After surgery, patient’s choreoathetoid movements subsided completely. Patient also developed pan hypopituitarism in the form of apathy, hypotension, and features of hypothyroidism like constipation, dry skin and sluggish reflexes. Further investigations revealed henceforth: thyroid stimulating hormone (TSH) =0.04µIU/mL, tri-iodothyronine (T3) =1.38µg/dL, thyroxine (T4)=7.4µg/dL, serum cortisol =1.80µg/dL, serum testosterone= 0.16nmol/L and serum prolactin =19.98ng/mL. Antineutrophil cytoplasmic antibody (ANCA) and antinuclear antibody (ANA) were negative.

Patient was treated with anterior and posterior pituitary hormone replacement therapy in the form of hydrocortisone, levothyroxine and voriconazole for two months. Currently this patient is asymptomatic.

Discussion

Hemichorea refers to choreiform movements in one half of body. It sometimes occurs after lesions that selectively involve the caudate nucleus, putamen, and globus pallidus. Some common causes being acute stroke, non-ketotic hyperglycaemia, and systemic lupus erythematosus. Lymphocytic hypophysitis is an autoimmune condition in which the pituitary gland becomes infiltrated by lymphocytes, resulting in pituitary enlargement and impaired function. It demonstrates a wide spectrum of presentations, imaging results and treatment strategies.

This case presented to us with the symptom of hemichorea which can be attributed to the autoimmune process found in association with lymphocytic hypophysitis. As per our knowledge and reviewing of literature this is the first case of lymphocytic hypophysitis which is presenting as hemichorea. There is also a variation in the response to therapy, in particular corticosteroids. Those patients who have partial responses and relapses continue to represent therapeutic challenges. Longitudinal follow up and diligent anterior and posterior pituitary hormonal replacement therapy are essential for successful management of this condition.

Conclusion

Hemichorea could be a rare clinical manifestation of lymphocytic hypophysitis. Autoimmunity can thought to be the common denominator in both these conditions. We urge researcher to report more such associations to confirm our hypothesis.

References


Metastatic Crohn’s Disease

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Abstract

Metastatic cutaneous involvement is a rare extraintestinal manifestation of Crohn’s disease. Presence of cutaneous noncaseating granulomas that are anatomically noncontiguous in location with a fistula or the gastrointestinal tract is a diagnostic hallmark. We present a case of inflammatory bowel disease initially diagnosed as ulcerative colitis, but later manifesting as intra-abdominal abscesses and ulcerated cutaneous lesions that on biopsy proved to be metastatic Crohn’s disease. The patient promptly responded to corticosteroid therapy.

Introduction

Establishing a diagnosis of Ulcerative Colitis (UC) or Crohn’s disease (CD) can be occasionally challenging in children and adolescents as a phenotypic overlap exists between the two disease entities. Furthermore, metastatic CD (MCD) is also an uncommon extraintestinal manifestation. Here, we report a case diagnosed as UC in adolescence, but later presented with several spontaneous intra-abdominal abscesses and multiple skin lesions which proved to be MCD.
Case Report

A 28 year old gentleman presented with complaints of high grade fever with chills and abdominal pain for one month. Abdominal pain was gradual in onset, progressive, intermittent in nature and periumbilical in location. It was localised and severe with no aggravating or relieving factors. He complained of nausea and non-projectile, non-bilious vomiting associated with abdominal pain. He also complained of passage of blood intermixed with stools. Fifteen days prior to presentation at our centre, he noticed skin lesions over the right shin and abdomen that gradually ulcerated and developed a necrotic base.

He had been diagnosed with UC twelve years back. He had presented with blood in stools and abdominal pain at that time. During initial evaluation, an ileocolonoscopy had revealed diffuse colonic erythema and innumerable polyps in the right colon with normal appearing ileum. Colonic biopsies from suspected areas were suggestive of UC. He was started on oral 5-aminosalicylic acid agents and corticosteroids, following which he improved symptomatically. Through the initial five years after diagnosis, he had five flares of the disease, each time treated with a short course of oral corticosteroids. He was symptom-free for the last seven years. He had history of smoking cigarettes (5/day) since ten years. His father was a case of muscular dystrophy.

Presently, he was investigated at another center a week back where CT abdomen had revealed mural wall thickening in the terminal ileum, ileoceleal region, ascending and proximal transverse colon and necrotic lymphadenopathy in the periportal, mesenteric, greater omental and periduodenal regions, the largest node being 2.1 X 1.5 centimeters. CT chest was normal. There was no free fluid in the pleural and peritoneal cavity. He had further undergone laparoscopy-guided mesenteric lymph node biopsy which exhibited reactive hyperplasia on histopathology. He had been started on empiric anti-tubercular therapy for a week. He presented to us without any symptom relief.

Physical examination revealed pallor, bilateral pitting pedal edema and multiple elevated necrotic lesions over the shin and abdomen (Figure 1). Per abdominal and other systemic examination was normal.

At our center, a complete blood count revealed hemoglobin of 10.1 g/dl; total leucocyte count of 13,400 cells/µL (82% Neutrophils) and a platelet count of 5,30,000/µL. Liver and renal function tests were normal. Erythrocyte sedimentation rate was 49 mm at end of one hour. C - reactive protein (CRP) was positive. He had low serum total proteins, albumin and vitamin D levels. Anti-Saccharomyces cerevisiae IgA and IgG were positive. Stool examination revealed presence of blood, mucus and pus cells. The Interferon-gamma release assay and Mantoux skin test for tuberculosis were negative. A transabdominal ultrasound revealed multiple intraabdominal abscesses. An ultrasound guided aspiration from one of the largest abscess showed frank pus. Microscopic analysis of the aspirate revealed plenty of polymorphonuclear leukocytes. The aspirate did not grow any pathological organisms in culture. The polymerase chain reaction for detection of M. Tuberculosis was negative.

A colonoscopy revealed extensive pseudopolyposis in the transverse and right colon till the caecum with minimal friability. The left colon and ileum were normal (Figure 2). Colonic biopsy was suggestive of irregular glands, occasional crypt abscesses and inflammatory cell infiltrate in the lamina propria with congestion and focal fibrosis suggestive of ulcerative colitis with moderate activity. There was no atypia or dysplasia. Biopsy
from the skin lesion revealed chronic inflammation of the dermis mixed with epithelioid and giant cells with evidence of chronic non-caseating granulomas (Figure 3). Fungal and Ziehl-Neelsen stain for Acid Fast Bacilli, TB Gene X-pert and TB MGIT culture of the skin biopsy were negative. The diagnosis of metastatic crohn’s disease was thus apparent.

He received intravenous corticosteroids and broad spectrum antibiotics. Fever subsided within 48 hours. He was then administered oral prednisolone for four weeks. Prednisolone was tapered and concomitantly azathioprine was started along with vitamin-D supplements. His skin lesions gradually improved and the intra-abdominal abscesses resolved. Six months on maintenance azathioprine therapy, his skin lesions had completely healed and CRP was negative.

Discussion

Crohn’s disease (CD) is a chronic inflammatory condition of the gastrointestinal (GI) tract. CD may manifest with a variety of skin lesions like fissures and fistulae, pyoderma gangrenosum, aphthous ulcers, erythema multiforme, erythema nodosum and necrotizing vasculitis. Prevalence of skin lesions is reported to be around 14% - 44%. Mucocutaneous lesions associated with CD can be classified as CD-specific, reactive or associated. CD-specific lesions are most common and manifest as oral disease, perianal and peristomal fissures and fistulae. Metastatic Crohn’s Disease (MCD) is a rare manifestation that is specific to Crohn’s disease. Most common reactive lesions include aphthous ulcers and erythema nodosum and are considered to arise as a result of cross-antigenicity between skin and gastrointestinal tract. Palmoplantar pustulosis, palmar erythema, hidradenitis suppurativa and vitiligo are commonly reported skin disorders associated with CD. Skin lesions due to nutritional deficiencies associated with malabsorption include acrodermatitis enteropathica (zinc deficiency), pellagra (nicotinic acid deficiency) and hair and nail disorders (biotin deficiency).

Noncaseating granulomatous inflammation involving predominantly the papillary and reticular dermis is a characteristic lesion of MCD. Epithelioid cells and multinucleated giant cells against a background of lymphocytes are pathognomonic. Presence of granulomas around dermal blood vessels (granulomatous perivasculitis) suggests a vasculitis-mediated etiopathogenesis. Sarcoidosis is a close differential diagnosis on histopathology. Histopathological examination of the skin lesion clinches the diagnosis especially in the absence of GI symptoms.

The skin lesions may manifest prior to clinical presentation (3 months - 8 years) or may be seen along with an established gastrointestinal disease. Occasionally, the lesions may exhibit scaling and crusting. Skin lesions appear more frequently along with a colonic disease than an ileal predominant disease and are usually poor predictors of gastrointestinal activity of CD. They commonly involve the genitalia (especially in children), legs, abdomen, trunk and dermal folds.

There are no established guidelines for the treatment of MCD. Both topical and systemic therapeutic modalities have been tried with varying success. Topical corticosteroids and tacrolimus have been used to successfully treat single lesions or localized disease. Systemic therapy with metronidazole, corticosteroids, methotrexate, azathioprine, mycophenolate mofetil, cyclosporine and thalidomide have been used successfully in various case reports. Recently, biological agents like infliximab and adalimumab have also been used efficaciously with complete resolution of skin lesions over 2 weeks to 6 months.

10-30% patients with CD develop intra-abdominal or pelvic abscesses in their life time which can evolve spontaneously or post-operatively and clinically present with spiking fever and focal abdominal tenderness.

Conclusion

Accurate diagnosis of IBD in children and adolescents should thus be based on a combination of precise history taking, relevant physical and laboratory examination, esophagogastroduodenoscopy (EGD) and ileocolonoscopy with histology, and imaging of the small bowel. In this particular patient, there were three unique features - 1) A phenotypic overlap of UC and CD; 2) spontaneous appearance of intra-abdominal abscesses and 3) multiple skin lesions diagnosed as MCD.

References

Gaucher Disease Presenting in an Adult with Intracerebral Bleed

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Abstract
Gaucher disease (GD) is the most common lysosomal storage disorder, caused by deficiency of acid beta glucosidase. GD usually presents in children but occasional cases can present in adulthood. Here we report a case of type I GD in a 37 year old female who presented with intracerebral bleed due to long standing thrombocytopenia. She underwent splenectomy in view of limited resources for enzyme replacement therapy. With splenectomy her platelet counts normalised and neurological status also improved.

Introduction
Gaucher disease (GD) is the most common lysosomal storage disorder. It presents mainly in childhood or early adulthood. Type I disease (non neuronopathic form) can rarely be asymptomatic till adulthood. Here we report a case which presented to us in adulthood with intracerebral bleed due to thrombocytopenia, which on further evaluation found to have type I GD.

Case
A 37 year old female, who had recurrent episodes of headache and intermittent involuntary movements of the left upper limb, was referred to us with a probable diagnosis of cystic glioma in the right frontoparietal region with secondary bleeding into the tumour due to thrombocytopenia. She was having borderline thrombocytopenia with splenomegaly diagnosed thirteen years ago (platelet count remaining between 30 x 10⁹/L to 50 x 10⁹/L). She never had any bleeding episodes in the past and had two childbirths which were uneventful, but platelet rich concentrates were transfused during the same. During her period of evaluation she developed sudden onset weakness of left upper limb and clinical examination revealed left sided faciobrachial stroke and a massive splenomegaly. On investigation she had haemoglobin of 109 gm/L, WBC count of 4.9 x 10⁹ cells/L with a normal differential count and platelet count of 38 x 10⁹/L. The coagulation parameters and liver and kidney function tests were normal. Ultrasound abdomen showed a spleen size of 24 cm with no focal lesions. Brain imaging showed a well defined rounded lesion with acute and subacute stages of bleed in the right frontal lobe with the possibility of an underlying cavernoma. She was treated conservatively for the stroke. During evaluation of thrombocytopenia, a bone marrow analysis showed hypercellular marrow with adequate megakaryocytes and aggregates of histocytes, with possibility of storage disorder like GD (Figure 1). Considering a possibility of Type I GD, beta glucosidase level was done which was 0.88 nmol/ml/hr (Normal range- 2.3- 14.1 nmol/ml/hr) confirming the diagnosis of GD. She underwent splenectomy (Figure 2) for improving the platelet counts, as she could not afford enzyme replacement therapy (ERT). With this, her platelet counts normalised and she was discharged with no further complications.

Discussion
GD is an autosomal recessive disorder caused by mutation in gene encoding lysosomal enzyme glucocerebrosidase (acid beta-glucosidase). This leads to accumulation of glucocerebroside, in the macrophages.¹ GD has three phenotypic subtypes, type 1 is non neuronopathic type while type 2 and type 3 occur with acute and chronic neurological manifestations respectively.² Type I GD is most common in Ashkenazi Jews, 1 case in 850, compared to 1 in 40000³ to 1 in 86000 in general population.⁴ Type I GD usually presents with hepatosplenomegaly, bone disease, anemia and/or thrombocytopenia in children, but rarely adult presentation is also known.⁵ Indication to treat in case of type I GD depends on severity of clinical manifestations. ERT is the first choice in such cases. Considering the high cost of ERT and its limited utility in developing countries, other treatment options are offered to such patients. Splenectomy was preformed routinely for patients with symptomatic splenomegaly and thrombocytopenia before the availability of ERT. In the present era, there are limited indications for performing splenectomy viz massive symptomatic splenomegaly, splenic rupture and thrombocytopenia with bleeding manifestations where ERT is not feasible. There

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are reports where splenectomy has been curative in patients with immune thrombocytopenia with GD.\textsuperscript{3} Splenectomy is known to increase bony complications including avascular necrosis in GD.\textsuperscript{6,7} Partial splenectomy was considered to be associated with less complications, but the results are conflicting.\textsuperscript{8}

Other treatment options for GD include substrate reduction therapy with drugs like Miglustat and Eliglustat.\textsuperscript{5,7} Hematopoietic stem cell transplantation can be curative but it is associated with higher morbidity and mortality. In the era of ERT, it is rarely offered for non-neuronopathic form. Gene therapy\textsuperscript{11} and enzyme enhancement therapy\textsuperscript{12} are still in animal studies and clinical trials phase and have a potential for future therapeutic use.

**Conclusion**

Though GD is most common in children, it needs to be considered as a differential diagnosis in adults presenting with cytopenias and splenomegaly.

**References**


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**Cerebral Venous Sinus Thrombosis and Posterior Reversible Encephalopathy Syndrome Coexisting in a Woman: A Rare Coincidence**

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**Abstract**

Cerebral venous sinus thrombosis (CVST) and posterior reversible encephalopathy syndrome (PRES) are two rare diseases which may present with similar symptoms and signs. We report a case with coexisting PRES and CVST in a 34 years old postpartum female presented with multiple episodes of generalized seizures and bilateral vision loss after delivery. MRI brain and venography revealed left transverse sinus, sigmoid sinus and internal cerebral vein thrombosis with vasogenic edema in bilateral parieto-occipital, right temporal and left frontal area, which was suggestive of posterior reversible encephalopathy syndrome (PRES). She was treated with antihypertensive, low molecular weight heparin (LMWH), oral anticoagulant and responded well to the treatment.

**Introduction**

Posterior reversible encephalopathy syndrome and cerebral venous sinus thrombosis presents with similar kind of symptoms. A clinical diagnosis of PRES includes the presence of headache, seizures, encephalopathy and visual disturbances as well as radiologic findings of focal reversible vasogenic edema best seen on magnetic resonance imaging (MRI) of the brain. The syndrome is most commonly encountered in association with acute hypertension, preeclampsia or eclampsia. The clinical presentation of CVST is similar to PRES, diagnosed best on magnetic resonance venography brain as occlusion of one or more of venous sinuses and, or cerebral vein by thrombus. Although both conditions have similar clinical features but, treatment is entirely different; hence we need to differentiate between these two conditions. Here we present a case of a 34 year old female who presented with postpartum eclampsia and diagnosed as a case of PRES with CVST.
Fig. 1: (A-L) Magnetic rasonance images of brain: - T2 (Images A to C) and flair (Images D-G) shows hyperintense lesions in bilateral parietooccipital, right temporal and left frontal region which shows diffusion restriction on DWI (Image H-I). ADC (Images J-L) shows hypointense (diffusion restriction) at right parietooccipital and left occipital region but there were no restriction at other areas and there were signal changes in diffusion compatible with vasogenic oedema

Fig. 2: MRI venography image: Left transverse sinus, sigmoid sinus and cerebral veins not visualized

Case Presentation

A 34 year old female who was postpartum day one, had multiple episodes of generalized seizures. There was no history of fever, ear or nasal discharge, head injury, neck stiffness or limb weakness. There was no past history of hypertension, diabetes, cerebrovascular accident, epilepsy, oral contraceptive use, any other chronic illness or similar complaints in the past. She also had one full term normal vaginal delivery six years back. There was no past history of preeclampsia or eclampsia. On examination patient was confused, partially responding to verbal commands. Her blood pressure was 180, 110 mm of Hg with pulse rate of 90, min and temperature of 99 °F. On central nervous system examination, higher functions were impaired. Pupils were equal and reacting to light. Cranial nerves examination was normal. No meningeal irritation were present. On motor examination, bulk and tone was normal in all four limbs. Power was 4, 5 in all four limbs. Deep tendon reflexes were exaggerated in all four limbs. Plantars were withdrawal on both sides. Sensory examination was normal. No cerebellar signs were present. No significant finding was present on cardiovascular and respiratory examination. Per abdomen, uterus was palpable at 16 weeks height and bleeding P/V was minimal. For the control of seizures intravenous magnesium sulphate (1 gm, hr) was given along with antihypertensive drugs (IV Labetalol). Laboratory findings revealed hemoglobin 11.2 gm, dl, total leukocyte count 9000, mm³, platelet count 1.8 lac, mm³. Serum levels of liver enzymes were aspartate transaminase 23 U/L, alanine transaminase 37 U/L, alkaline phosphatase 127 U/L and serum bilirubin levels of 0.7 mg/dl. Renal profile revealed blood urea 32 mg/dl, serum creatinine 1.0 mg/dl, serum uric acid 4.3 mg/dl with serum calcium and phosphate levels 10.6 mg,
dl and 3.5 respectively. Serum sodium and potassium levels were 141 mEq/L and 3.6 mEq/L with blood sugar level 126 mg/dl. Urine examination revealed 2+ proteinuria.

On 3rd postpartum day, patient complained of headache and blurring of vision. Fundus examination was done which revealed bilateral papilledemna. plain CT scan brain showed, showing hypodensities in bilateral parietooccipital, right temporal and left frontal region. MRI brain with venography brain (Figure 1, Images A to L) was performed which revealed a hyperintense lesion on T2W, Flair images in bilateral parietooccipital, left temporal and right frontal region which were hypointense on T1W image and showed diffusion restriction on DWI. On ADC maps, hypointensity at right parietooccipital and left occipital region, hyperintense lesions in other areas which were hyperintense on DWI (findings compatible with vasogenic edema) were seen. On MR Venography brain left transverse sinus, sigmoid sinus and cerebral veins were occluded (Figure 2).

Based on the above imaging findings, a diagnosis of PRES (due to uncontrolled hypertension, eclampsia) with CVST (likely due to thrombophilic postpartum state) was made. She was treated with low molecular weight heparin, Labetalol, Mannitol and Dexamethasone. She improved symptomatically after 1 week of treatment and discharged on warfarin. She was asymptomatic on follow up after 1 week.

Discussion

Cerebral venous sinus thrombosis (CVST) and posterior reversible encephalopathy syndrome (PRES) usually present with similar symptoms and signs such as headache, nausea, vomiting, visual disturbances and seizures. PRES is caused by dysregulation of cerebral blood flow and disruption of blood brain barrier leading to vasogenic edema in brain. The predisposition for posterior circulation in PRES could be due to sparse sympathetic innervation to posterior vasculature. Uncontrolled hypertension (most common risk factor), as in this case, leads to hyperperfusion and cerebral vessel damage due to inadequate autonomic sympathetic response, resulting in interstitial extravasation of proteins and fluids, causing vasogenic edema.² MRI is the gold standard for diagnosis and should be performed when PRES is suspected like in this case. Treatment includes aggressive management of hypertension, use of antiepileptic drugs to treat seizures and corticosteroids for vasogenic edema. The prognosis of PRES is excellent if promptly diagnosed and treated.³

CVST is the presence of thrombosis in the cerebral veins and, or dural venous sinus that prevents blood from draining out of the brain leading to cerebral ischemia, infarction, hemorrhage, edema, neuronal dysfunction and hyperexcitability. The incidence of CVST is about 3–4 persons per million affecting female more than male. The predisposing factors to CVST are genetic (factor V Leiden, protein C, S deficiency, hyperhomocysteinemia, antithrombin III deficiency, prothrombin gene mutations etc) and acquired prothrombotic states (pregnancy, postpartum, antiphospholipid antibody syndrome, oral contraceptive use, hormonal replacement therapy), polycythemia, sickle cell disease, thrombocytopenia, paranasal sinus infection, otitis media, dehydration, uncontrolled diabetes, thyroid dysfunction, connective tissue disease, vasculitis, inflammatory bowel disease, liver disease, smoking head injury, folic acid and vitamin B12 deficiency (acquired hyperhomocysteinemia) etc.⁴ A clinical diagnosis of CVST should be made on the basis of clinical presentation and in the presence of predisposing factors for venous thrombosis. The most sensitive technique for the diagnosis of CVST is magnetic resonance venography seen as occlusion of one or more venous sinus and, or, cerebral vein. Other findings like cerebral ischemia, infarction with diffusion restriction on DWI and diminution of ADC values (suggestive of cytotoxic edema) and vasogenic edema similar to PRES can be seen.

Treatment includes identification and elimination of the underlying cause, management of raised intracranial pressure and anticoagulation, initially with low molecular weight heparin, after three to four days warfarin is started and both overlapped for two to three days then heparin is withdraw. Anticoagulants are usually given for a period of six months after a first episode or longer when there is persistence of predisposing factors. Other treatment modalities in the form of endovascular thrombolysis and mechanical thromboaspiration alone or in combination can be tried in patients with poor prognosis.⁵

Here we have presented a case of 34 years old female with postpartum eclampsia having PRES with CVST, although two different clinical entities, with different etiopathogenesis and treatment, but similar clinical and neuroimaging features. Two common complications in postpartum period, CVST and PRES coexisting in one patient as in our case is a rare coincidence.

Conclusion

PRES and CVST are two diseases which have similar manifestations but different treatment modalities. These two diseases can have similar clinical and neuroimaging features involving posterior circulation, also clinical setting to develop venous thrombosis and reversible encephalopathy. These should be borne in mind while evaluating postpartum headache, vision loss and, or, seizures. Early diagnosis and treatment of PRES and CVST have excellent outcomes and prognosis.

References

Chorea and Orofaciolingual Dystonia in a 40 Year Old Male

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Abstract

Neuroacanthocytosis is a heterogeneous group of disorders which result in progressive neurodegeneration, predominantly of the basal ganglia, and erythrocyte acanthocytosis. We report a case of neuroacanthocytosis with typical phenotype of choreoacanthocytosis. A 40 year male presented with features of chorea with orofaciolingual dystonia producing eating and speech difficulties. There were features of self mutilation in form of lip and tongue biting. Peripheral blood smear examination revealed acanthocytes in our patient. Neuroimaging showed bilateral caudate atrophy and nerve conduction study showed motor axonal neuropathy. This case report describes the typical features and investigations to diagnose this rare disorder which is usually underdiagnosed.

Introduction

Neuroacanthocytosis is a rare genetic movement disorder. This clinical entity was described by Edmund Critchley from two families, one from USA, the other from UK¹ and was initially named as Levine- Critchley syndrome. It is characterised by movement disorder, behavioural and cognitive changes. The movement disorder consists of chorea, dystonia and tics. There is prominent orofacial dystonia with dystonic tongue movement interfering with eating. Many patients develop lip and tongue biting with prominent dysphagia and dysarthria. The term “acanthocyte” is derived from the Greek word for “thorn”. Acanthocytes are contracted erythrocytes with unevenly distributed thorny projections. These acanthocytes are distinct and unique for neuroacanthocytosis. We report a case with typical features of neuroacanthocytosis and how by simple clinical examination and peripheral blood smear study we can diagnose this rare disorder.

Case Report

A 40 year old male presented with abnormal, repetitive, involuntary, non-purposeful movements of the whole body including head, face and neck for one year. These movements disappeared during sleep and were not suppressed with voluntary action. These movements were associated with shrinking of shoulder and spasmodic movements of the neck. He also had difficulty in eating due to abnormal twisting movement of the tongue while eating. He used to eat by pushing the food bolus with fingers inside mouth. Occasionally, he had nasal regurgitation of liquids with resultant choking and coughing. He had frequent lip and cheek biting. Since last six months, he had slurring of speech with a twang. There was history of significant weight loss. There was no history of any psychiatric manifestation or behavioural changes or change in cognition. There was no history of blurring of vision, limb weakness or sensory symptoms. Bowel and bladder habit was normal. There was history of similar illness in younger sister.

General examination showed cachexia with lip biting and cheek biting marks (Figure 1) suggestive of self-mutilation and orofacial dyskinesia.

He was conscious, oriented with normal memory and behaviour. There was dysarthria with nasality of voice. There was generalised hypotonia with power of 5/5 in all limbs. Generalised areflexia with flexor plantar response was present. There was chorea in form of abnormal, repetitive, involuntary, non-purposeful movements of limbs, trunk and neck. He walked with bizarre gait with abnormal movements of the trunk. There was orofacial and lingual dyskinesia. Sensory, cerebellar and autonomic nervous system examination revealed no abnormalities. Other systemic examination was normal.

The routine investigations, complete blood count, renal function tests, liver function tests, serum electrolytes, serum ceruloplasmin, serum copper and 24 hour urinary copper were within normal limit. Creatinine phosphokinase, aldolase, transferrin, serum ferritin were normal. There was no retinitis pigmentosa. Magnetic resonance imaging (MRI) of brain showed atrophy of the brainstem, cerebellum and basal ganglia. Genetic confirmation of diagnosis could not be made due to unavailability of facility for analysis of VSP13A gene. It was supported by presence of acanthocytes in peripheral blood smear with typical bilateral caudate atrophy.

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With the classical clinical features of chorea, orofaciolingual dystonia and feeding dystonia in the background of positive family history, the clinical diagnosis of autosomal recessive choreo-acanthocytosis was made. It was supported by presence of acanthocytes in peripheral blood smear with typical bilateral caudate atrophy in neuroimaging. Genetic confirmation of diagnosis could not be made due to unavailability of facility for analysis of VSP13A gene. He was treated symptomatically with dopamine depleter tetrabenazine. The patient responded well to treatment with gross reduction in abnormal movements and he could eat properly.

Fig. 1: Cheek bite marks

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Discussion

Neuroacanthocytosis (NA) is a syndrome consisting of movement disorder, behavioural and cognitive changes. The core neuroacanthocytosis syndrome includes autosomal recessive choreo-acanthocytosis and X-linked Mcleod syndrome. Autosomal recessive choreo-acanthocytosis (ChAc) is characterised by adult onset at around 35 yr of age. The movement disorder consists of chorea, dystonia and tics. Parkinsonism may occur in more advanced stages. There is also prominent orofaciolingual dystonia producing frequent lip and tongue biting. It also interferes with eating due to feeding dystonia. Neuropsychiatric symptoms are prominent in neuroacanthocytosis and may appear several years before the onset of neurological manifestations. The gait of choreo-acanthocytosis patients may have a “rubber man” appearance with truncal instability and sudden, violent truncal spasms. Psychiatric manifestations are common. Most choreo- acanthocytosis patients have elevated levels of creatinine phosphokinase. In contrast to Mcleod syndrome, myopathy and axonal neuropathy are usually mild. Clinical neuromuscular manifestations include areflexia, sensory-motor neuropathy, variable weakness and atrophy. In at least one third patients, seizure, typically generalised, are the first manifestation of the disease. It is due to mutation of VPS13A gene which encodes for the protein chorein.

Mcleod syndrome, an X-linked disorder, begins at around 50 yrs of age and slowly progressive. Neuromuscular and cardiac involvement is more common in Mcleod syndrome. In contrast to Choreo-acanthocytosis, only exceptional Mcleod syndrome patients have lip or tongue biting, dysphagia, dystonia or parkinsonism. Huntington’s disease closely resembles neuroacanthocytosis and has similar phenotype of chorea, behaviour and cognitive deficits.

Conclusion

Neuroacanthocytosis, though a rare movement disorder, should be suspected in patients with typical features of chorea with orofaciolingual dystonia in the back ground of positive family history. By simple test like demonstration of acanthocytes in peripheral blood smear can lead us to diagnosis of this rare disorder.

References

1st time in India

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

Boost
PPHG Control

Preserve
β-cell function

Control
65% β-cell

T2DM
48% β-cell

Avior Therapeutics
Discovery of incretin hormones and incretin effect was postulated in the early 20th Century, when Murce administered duodenal extract to diabetic patients and demonstrated reduction in glycosurea. However, the specific substance responsible for action of incretin remained elusive for a long time. With discovery of insulin and later of its available assays, studies were carried out by measuring insulin levels in blood after administering an intravenous load of glucose and comparing it with oral ingestion of the same. Surprisingly insulin levels were higher after oral ingestion of glucose than after I.V administration. It became clear that a sequence of physiological responses is activated following meal intake. The G.I. tract has a significant role in absorption, digestion and assimilation of ingested nutrient with Incretins, mainly GIP and GLP. Purification and characterization of the first incretin GIP-(Glucose dependent insulinotropic polypeptide) was done in 1973. Studies on GIP indicated that another gut-derived biological active factor also played a significant role in glucose metabolism.

The second peptide with incretin activity, a glucagon like peptide (GLP-1) was discovered in 1987. Both GIP and GLP-1 are extremely short-acting. Plasma half-life of GLP is 1-2 minutes. This rapid inactivation is due to a ubiquitous enzyme, dipeptidyl peptidase-IV (DPP-IV). Hence the search was on for a synthetic GLP-1 and an inhibitor of DPP-IV enzyme.

In 1992, J. Eng, J P Raufmann and co-workers identified a breakthrough in the most unusual place, after considerable research. They found a peptide in the venom of a poisonous lizard- the ‘Gila monster’ (Heloderma suspectum), seen in Arizona and Mexican deserts. The peptide was mainly in the saliva of this lizard and was called extendin-4. It is a potent agonist at the GLP-1 receptor of insulin secreting beta cells in pancreas and remains effective for much longer than human GLP-1. Later it was renamed Exenatide and after clinical trials by pharmaceutical company Lilly it was approved by FDA in 2005 for treatment of type-2 diabetes. Exenadite offered further advantage of acting on the brain to reduce sensation of hunger thus aiding weight loss.

The pharmaceutical giant Merck began to investigate DPP-IV enzyme inhibitors by using computer mathematical models. The outcome was sitagliptin, the first DPP-IV inhibitor to be approved by FDA (2006) for type-2 diabetes. The manufacturing rights are with M S D. The importance of computer simulation in chemistry was recognized and 2013 Nobel Prize for chemistry was won by Michael Levitt, Martin Karplus and A. Warshel.

There has been some concern that both exetinide and sitagliptin may present risk of acute pancreatitis. This is because of the observation that the Gila monster eats only 5-10 times a year, and between meals its metabolism is very slow, and digestive system becomes dormant. When it eats, the GLP-1-like hormone in its saliva causes its pancreas to grow very quickly as much as 50%. Similar pancreatic growth has been observed in rodents who received exenatide and sitagliptin. Hence these drugs have come under increasing scrutiny. Further studies on this aspect are progressing, with many newer gliptins appearing in the market.
Rare Cause of Type 2 Respiratory Failure: Arnold Chiari Malformation

Divendu Bhushan
Consultant Physician, Paras HMRI, Patna, Bihar

Sir,

Chronic obstructive airway disease is the foremost cause of type 2 respiratory failure, but there are other causes of this including chest wall disease, impaired neuromuscular transmission and diminished drive.

Syringomyelia i.e. Impaired neuromuscular transmission is a rare cause (0.01%) of type 2 respiratory failure. Here I am discussing a case who presented with hypercapnic respiratory failure and on evaluation was found to be afflicted with extensive syrinx involving cervical spinal cord. A pre diabetic 45 yrs old lady presented in our casualty with complaints of cough with expectoration, generalized body weakness, unable to walk since 10 days prior to admission, and swelling over feet since 2 days. On investigations she was found to have type 2 respiratory failure with cor pulmonale. There was no evidence of pulmonary embolism. CBC, liver and kidney function tests were normal. RA factor, and ANA were negative. She was managed with nebulization, BIPAP, antibiotics, iv steroids and other supportive treatment. She responded well and discharged on BIPAP 20/10 and other supportive management. On follow up visit she was doing well with respect to her respiratory effort, but still she was not able to stand and walk on her own and complained of increase weakness in both upper arms. MRI brain and spine was ordered for her neurological weakness. This revealed a syringomyelia with myelomalacia at cervical cord. Syringomyelia and other neuromuscular disorders leads to increased load versus strength in respiration. This type of hypoventilation causes symptoms like excessive day time somnolence, poor quality sleep, and orthopnea.

In retrospect we should give a thought of rare disorders if diagnosis of COAD was not confirmed as a cause of type 2 respiratory failure. It is a surgically correctable cause.

Neuromuscular disorders usually present as sensory motor weakness. Their presentation as respiratory failure is very rare. There are only few case reports of syringomyelia presenting as respiratory failure.\(^1\) The clinical course of chronic hypoventilation follow a typical sequence: an asymptomatic stage + PaO\(_2\) and PaCO\(_2\) normal→ nocturnal hypoventilation →Finally if vital capacity drops further, daytime hypercapnia develops. This increase in PaCO\(_2\) leads to compensatory increase in plasma bicarbonate and obligatory decrease in PaO\(_2\), resulting in hypoxemia. This can further leads to secondary erythropyoeisis. The combination of chronic hypoxemia and hypercapnia induces pulmonary vasoconstriction, leading to pulmonary hypertension, right ventricular hypertrophy and right heart failure.\(^2\)

Take home massage is to keep our vision wide until you get a suitable diagnosis.

References


Paroxysmal Nocturnal Hemoglobinuria in a Case of Chronic Anemia

Arum Agarwal\(^1\), Aakanksha Agarwal\(^2\), Mala Airun\(^3\)

\(^1\)Senior Consultant and HOD, Department of Internal Medicine, Narayana Multispeciality Hospital, Jaipur, Rajasthan; \(^2\)Intern, B.J. Medical College, Ahmedabad, Gujarat; \(^3\)Clinical Director, Narayana Multispeciality Hospital, Jaipur, Rajasthan

Sir,

Paroxysmal nocturnal hemoglobinuria (PNH) is a very rare and progressive acquired disorder of hemopoiesis characterized by hemolytic anemia (due to acquired intracorpuscular defect), pancytopenia (due to marrow failure) and tendency to have venous thrombosis. Hemolysis occurs throughout the day but patients usually present by passing red concentrated urine in the morning when color is more pronounced. The gold standard diagnostic test for PNH is flow cytometry of RBCs to demonstrate absent or reduced expression of both CD55 and CD59).

We present a case of coombs negative hemolytic anemia with pancytopenia who presented with symptomatic severe anemia and was diagnosed with PNH. The case underlines the need for increased awareness of PNH among relevant healthcare specialties.

Mr GM, 28 years was admitted to our institution on 23.02.2016 with complaints of shortness of breath, fatigue, weight loss, and general weakness of 1 month duration. He had no history of ecchymosis, visible blood loss, fever, jaundice, dark colour urine, abdominal pain, or headache. He had a past history of blood transfusions in 2010 and 2014 for anemia and was also hemodialysed for acute renal failure in 2010. Perusal of some old records showed very high LDH(>10000 IU), reticulocytosis (>10%) and multiple Gall Bladder stones with a tentative diagnosis of Hemolytic anemia in 2014 and no further work-up was done. On examination his temperature was normal, pulse rate was 132 per minute, Blood Pressure 110/80 mm Hg and respiratory rate 25 per minute. On systemic examination he had an early systolic murmur, mild hepatosplenomegaly, and clear lung fields. Rest of the systemic examination were essentially normal. On evaluation he had Pancytopenia, indirect hyperbilirubinemia, mildly low serum B12, raised LDH, normal serum iron, low serum haptoglobin, low serum ferritin and Grade 1 bone marrow iron stain. There was no reticulocytosis this time. His coombs test and anti nuclear antibody were negative. His inflammatory markers were raised. On USG there was also mild hepatosplenomegaly and cholelithiasis. With all these findings he was diagnosed to have coombs negative severe hemolytic anemia with impaired hemopoiesis and features of iron deficiency anemia (IDA). Bone marrow aspiration was normocellular with erythroid hyperplasia and mild megaloblastic features. He was managed with four units of packed red blood cell transfusion, Injection hydroxycobalamin, iron sucrose and...
other supportive treatment. With unremarkable peripheral blood smear and severe hemolytic anemia we evaluated him further and flowcytometry was done to rule out PNH (Table 3). It showed a PNH clone within the granulocytes (94.3%), monocytes (85.7%) and RBCs(26.9%), findings consistent with a diagnosis of PNH. The treatment options were discussed with the family and he was discharged and referred for allogenic bone marrow transplantation on 27.02.2016. Eculizumab was not available.

In PNH as the defect is at the level of the pluripotent stem cells, red blood cell (RBC) precursors, platelets and granulocyte series are all affected, as seen in this case (pancytopenia). Iron deficiency anaemia is common in these patients as a result of blood loss due to haemoglobinuria and accounts for the abnormal RBC morphology, as observed in our patient. Urine for hemisidenuria also occurs with chronic intravascular hemolysis. Severity of anaemia varies depending on the number of defective cells and it was severe in our patient necessitating blood transfusion. In general, the higher the clone size, the more symptomatic is the patient. This not only includes hemolysis but also the chance of developing thrombosis. However, there are no absolute rules and patients with low clone size can still develop a thrombosis, and patients with high clone size can be relatively asymptomatic. Our patient had no evidence of thrombosis.

The diagnosis of PNH was thought in view of coomb’s negative severe hemolytic anemia with a history of passing dark colour urine at times and flowcytometry confirmed the diagnosis. He was managed with supportive care and blood transfusions. Our patients did not show reticulocytosis as is usually seen in hemolytic anemia but instead showed erythroid hyperplasia with megaloblastic bone marrow and this could explain the absence of reticulocytosis (megaloblastic crisis). Hemolysis can be ongoing even in the absence of overt symptoms as is suggested in our patient by a fall in hemoglobin at follow up. Chronic hemolysis and platelet activation may also lead to chronic renal failure and dialysis, as well as recurrent nonfatal thrombotic events. Our patient did not have any evidence of thrombosis, erectile dysfunction or dysphagia. He did have dialysis done in 2014 due to acute renal failure.

For patients with classical PNH, allogeneic hematopoietic cell transplantation (HCT) and complement inhibition with eculizumab are the only established therapies. Eculizumab is recommended for patients with significant disease manifestations attributable to hemolysis, including disabling fatigue, transfusion-dependence, frequent pain paroxysms, thrombosis, worsening renal insufficiency, or other end-organ complications. It needs to be given intravenously every 12-14 days. Eculizumab (soliris® 300 mg vial) is not available in India and if imported costs around 7370 euro per vial. Our patient could not afford the drug and was managed with blood transfusion and supportive care. He has been advised allogenic bone marrow transplantation.

To conclude, the course of PNH is unpredictable and increased awareness of the disease among clinicians should enable early diagnosis of this rare disease. It may be diagnosed at an early stage and in more number of patients, only if higher index of suspicion is maintained. One must keep the diagnosis of PNH in differential diagnosis while treating cases of chronic and/or refractory anaemias, Coomb’s negative hemolytic anaemia, pancytopenia with a cellular marrow, unexplained iron deficiency anemia (confirm with bone marrow iron staining) and venous thrombosis of obscure aetiology.

References

ELECTIONS OF API, ICP AND PRF

(Full details Circular No. 1 & 2/2017)

Election for Governing Body of API, Faculty Council of ICP and Board of PRF are announced for following posts:

**Governing Body of API:**
- President-Elect – One; Vice President – One; Elected Members – Four posts

**Faculty Council of ICP:**
- Dean-Elect – One; Vice Dean – One and Elected Members – 4 posts

**Board of PRF**
- Director Elect – One; Board members – Two posts

Separate nominations must be submitted for each post.

**Rules Relating to Qualification for Election to Governing Body of API**
1. President Elect: To contest for the post of President Elect the candidate should be a life member of API for at least 10 years and have completed atleast two full terms of 3 years each in any elected position in the Governing Body.
2. Vice President: To contest for the post of Vice President the candidate should be a life member of API for at least 5 years and should have completed atleast one continuous full term of 3 years in any elected position in the Governing Body.
3. To contest for elected members and one zone member of the Governing Body, continuous membership of the Association of atleast 3 years is mandatory.

Nominations shall be made on prescribed forms stating the office for which nominations are filled. The nominations for API posts shall be proposed by one valid member and seconded by another valid member of API and duly signed by them and shall also be signed by the candidate signifying his/her willingness to stand for election and serve on the Governing Body if elected.

**Requirements for eligibility for the contests of**
- **Dean Elect:**
  1. A member of API for at least 15 years and
  2. A Founder Fellow or a Fellow of the College of 7 year standing and
  3. Any person who has held the position of President/Secretary of API or served as Vice Dean for one full term or elected member of the Faculty Council for one term.

- **Vice – Dean:**
  1. A member of API for at least 12 years and
  2. A Founder Fellow or a Fellow of the College of 5 year standing and
  3. Any person who has held the position of Secretary of API or has been a Jt Secretary from HQ for one full term or a member of the Faculty Council

- **Elected Members:**
  A member of API for at least 10 years and a Founder Fellow or a Fellow of the college of 3 year standing.

**Requirements for eligibility contest of election to Board of PRF**
- **Director Elect:**
  A member of API for at least 10 years with research experience and having 10 research publication in peer reviewed indexed journals.

- **Board Member:**
  Member of API for at least 10 years with research experience and having 5 research publication in peer reviewed indexed journals.

Nominations shall be made on prescribed forms stating the office for which nominations are filled. The nominations for ICP posts shall be proposed by one valid member and seconded by another valid member of ICP and duly signed by them and shall also be signed by the candidate signifying his/her willingness to stand for election and serve on the Faculty Council of ICP if elected.

A member shall not contest simultaneously for more than one post (i.e President-Elect, Vice-President, Elected members, North Zone Member of the Governing Body) (Dean-Elect; Vice Dean and Elected Members of Faculty Council) and also (Director Elect, Board members of PRF) Post means not only an office-bearer but also member of the Governing Body of API or Faculty Council of ICP of Board of PRF.

Every member is supplied with a nomination form. The nomination form completed in all respects should reach the API Office not later than 31st May 2017. For every post on the Governing Body / Faculty Council / Board of PRF, the nomination must be accompanied by a sum of Rs. 2,500/- (Rupees two thousand five hundred only) non refundable in the form of Demand Draft payable at Mumbai. The nomination paper NOT accompanied by the Bank Draft of Rs. 2,500/- will be deemed invalid.

**Important**
Canvassing in any form should not be done by the candidate for the election. Instead, they are requested to send a short bio-data NOT MORE THAN 200 words along with the nomination paper which will be printed and circulated along with the ballot paper. Excess of bio-data beyond the first two hundred words shall be deleted. Canvassing in any form or in favour of the candidate shall not be permitted.

THE CANDIDATE WILL HAVE TO CERTIFY AND SIGN THAT THE INFORMATION PROVIDED IN HIS/HER BIODATA IS CORRECT.

The results will be declared at the end of counting of votes and announced in the subsequent issue of JAPI. The report will be placed before the Governing Body for intimation.

**DEAD LINES OF ELECTION PROCEDURE**
- Last date to receive the nomination at API Office: 31st May 2017
- Last date for withdrawal: 20th June 2017
- Last date to receive ballot papers at API Office: 31st August 2017

The full API circular No. 2/2017, ICP circular No. 1/2017 and Board of PRF 1/2017 are on API and JAPI website.

Dr. Mangesh Tiwaskar
Hon. General Secretary
Indian College of Physicians

Eligibility Criteria for the Award of Fellowship of Indian College of Physicians

5.2.1.1 Minimum experience of 10 years after Post Graduation.
5.2.1.2 Continuous membership of the Association of Physicians of India for not less than 7 yrs.
5.2.1.3 Should have made a significant contribution to research / teaching / development in the field of medicine.
5.2.1.4 Should have contributed to API by way of scientific or Organizational works.

To make the selection objective, a point system has been followed in assessing the suitability of the applications.

The Criteria used by the Credentials Committee for the award of fellowship are:
1. Qualification
2. Experience in Medical Profession
3. Publications
4. Honours / Awards
5. Research work
6. Contribution to API
7. CME & Conference (API/ICP)
8. Social welfare/ community service

The Fellowship form should be proposed and seconded by Founder Fellow / Fellow of ICP only.

- The Proposer / Seconder should not propose / second more than 3 nominees for award of ICP in a particular year.
- It is responsibility of the Nominee / applicant to get the proposal completed by the proposer and seconder along with the citation.
- API Membership No. of the proposer / seconder should be entered by the proposer / seconder themselves.
- The proposer should satisfy the requirements for proposal as under:-
  - The Nominee is a life member of API
  - The Nominee has completed 10 years after post-graduation
- The Nominee should read the Form carefully before filling the columns, to project their achievements appropriately.
- The Nominee should list their achievements in appropriate columns.
- Proof of qualifications, publications, honours, awards, must be submitted as supporting data. The supporting data should be numbered parawise (eg 1., 2., 3. , etc). For more than one supporting documents, the numbering should be in alphabets (eg 1 (a), (b), (c), etc).
- No hand written applications will be accepted.
- One original and seven Xerox copies to be submitted
- Last date for receiving application form is 31st May, 2017.

Dr. Mangesh Tiwaskar
Hon. General Secretary

Dr. A.M. Bhagwati
Jt. Secretary

Available on API and JAPI Websites : www.apiindia.org & www.japi.org
Format for Submission of Bio - Data of The Nominee for Consideration for Award of Fellowship of Indian College of Physicians.

1. Name in Full (Surname First) (in Block Letters)

2. A. P. I. Membership No. and date of joining

3. Date of Birth

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<tr>
<th>Address Residence</th>
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4. Tel.: Fax : Mobile E-mail:

5. Postgraduate degree in Medicine Year of passing Institute University

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<th>Other Professional Qualifications</th>
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<th>Speciality / Subjects</th>
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6. Experience in Medical Profession after Postgraduation in Medicine

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<th>Name of Hospital / Clinic / Organisation &amp; Location</th>
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7. Publications: List below. (If number of publications in Journals exceeds 8, publications which can qualify as research papers may be listed under Research section 9.)

   a) Number of Publications in Indexed National / International Journals.  
      Attach title page / Abstract as Appendix

   b) Number of Chapter in Books / monograms

   c) Editorship of National level or State level: Book / Monogram / Update Series

8. Honours And Awards (list below with photocopy of proof)

   a) Oration in National / State Association Meeting

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<th>Title of Oration</th>
<th>Organisation</th>
<th>Year</th>
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### (b) Award National / International / or State level

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<th>Title of Award</th>
<th>Organisation</th>
<th>Year</th>
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9. **Research work** (list below)

(a) Research sanctioned & funded by Research Agency

Attach Letter of sanction.

(b) Departmental Research. (To qualify, the findings should be published in National/International Journal) Do not include papers already listed under Publications

Attach title page / Abstract

10. **Contribution to API** (list below and attach proof)

<table>
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<th>Post held in Organisation / Meeting</th>
<th>Name of Organisation / Meeting / CME</th>
<th>National / Zonal / Under API/ICP</th>
<th>Year</th>
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11. **Participation in CME or Scientific Sessions of API or ICP as Faculty**

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<tr>
<th>Speaker / Chairperson / Other</th>
<th>Title of Talk / Session</th>
<th>Name of Meeting</th>
<th>Year</th>
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12. **Social welfare / Community service.** (Include under the headings given below, with documentary evidence)

(a) Emergency services during National calamities (Quakes/ Floods/Cyclones, etc)

(b) Public education Programme (Radio), TV talk/ writing in newspapers

(c) Service in Rural Areas

Service | Evidence

---

N.B : No handwritten application will be accepted. *To be typed on separate page

*One original and seven Xerox copies of sets to be submitted

Last date for receiving the application form is 31st May 2017.

Address : Turf Estate, No. 006 & 007, Dr. E. Moses Road, Opp. Shakti Mill Compound, Mahalaxmi (West), Mumbai – 400 011.
Indian College of Physicians

Citation

The Fellows proposing and seconding the nomination for Fellowship of Indian College of Physicians should highlight the professional / scientific achievements of the candidate and the contribution to A. P. I. from personal knowledge in 200 words, in the format given below:

<table>
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<tr>
<td>Signature Proposer</td>
<td>Signature Seconder</td>
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Note:- The Fellowship form should be proposed and seconded by Founder Fellow / Fellow of ICP only. In case there are more than 3 nominations by any proposer/seconder, the first three nominations in order of receipt in API Office and complete in all respects will be considered for award of Fellowship of ICP and the others rejected for consideration.
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Cilnidipine 10mg + Telmisartan 80mg Tablets

In Hypertension with IHD

RX CILACAR-M10/25
Cilnidipine 10mg + Metoprolol Succinate ER 25mg Tablets

RX CILACAR-M10/50
Cilnidipine 10mg + Metoprolol Succinate ER 50mg Tablets

In Uncontrolled Hypertension with LVH/CHD/Stroke

RX CILACAR-C6.25
Cilnidipine 10mg + Chlorothalidone 6.25mg Tablets

RX CILACAR-C
Cilnidipine 10mg + Chlorothalidone 12.5mg Tablets

In Uncontrolled & Complicated Hypertension

RX CILACAR-TC6.25
Cilnidipine 10mg + Telmisartan 40mg + Chlorothalidone 6.25mg Tablets

RX CILACAR-TC12.5
Cilnidipine 10mg + Telmisartan 40mg + Chlorothalidone 12.5mg Tablets

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¹ Int J Basic Clin Pharmacol 2013 Apr;2(2):160-164
² Kidney International (2007) 72,1543-1549