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Is ICH Score the Best for Predicting Outcome in Patients with Intracerebral Hemorrhage?

Vikram Londhey

Acute intracerebral hemorrhage (ICH) is one of the common causes of stroke which has a high morbidity and mortality across the globe ranging from 10 to 15 percent. The mortality rate of patients suffering from ICH is as high as 30 to 50% within the first month as compared to cerebral infarction or subarachnoid hemorrhage. Predicting outcome after ICH is a challenging task which is based on clinical, biochemical, haematological and radiological parameters. Not only the medical parameters; but also the socioeconomic factors like financial status and affordability of the patient to the medical care and the availability of expertise during the acute setting are equally important on which the outcome of ICH depends in the public as well as the private sector.

The causes of ICH are trauma, ruptured arteriovenous malformations and aneurysms, patients on anticoagulants, coagulopathy related hemorrhage, uncontrolled hypertension presenting as hypertensive crisis. The common sites of ICH are basal ganglia, thalamocapsular region, brainstem and cerebellum. The outcome of ICH can be predicted by using various scoring systems that have been developed like ICH score, Rankin score, modified Rankin score, FOUR score, and APACHE II score. These scores are valuable as they offer standardized assessment. These scores can be used for risk stratification while selecting the treatment of such cases and as research tools in the setting of clinical trials. There are various studies which have compared one score with the other in predicting the outcome of ICH.

The ICH score is one such predictive tool for assessing mortality at 30 days after hemorrhagic stroke.1 The ICH score is a 6 point calculation based on 5 clinical parameters. Depending on the clinical parameters, the scoring system is developed. Each parameter is given a score from 0 to 1; except GCS which ranges from 0 to 2.

1. Age ≥ 80 years: Yes = 1; No = 0.
2. Glasgow Coma Scale (GCS): GCS Score 3 to 4 (=2 points); GCS score 5 to 12 (=1); GCS score 13 to 15 (=0).
3. Volume of hematoma on baseline CT Scan of Brain: ICH Volume ≥ 30cm³ (=1); ICH Volume ≤ 30cm³ (=0).
4. Location of Hematoma (infratentorial or supratentorial): Infratentorial origin (Yes = 1) (No = 0).
5. Presence of intraventricular extension: Yes = 1; No = 0.

Thus, the score ranges from 0 to 6. As the score increases from 0 to 6, it indicates worsening in the outcome. The ICH score has been validated for 30 day and one year functional outcome in some studies.2,3 Studies have also assessed its utility as a predictor of in hospital mortality and discharge outcome in spontaneous ICH.4 The ICH score is simple, less time consuming in its calculation, reliable, reproducible, user friendly (does not require any special training in Neurology) and is validated to predict 30 day mortality.4,6

Gupta VP and colleagues have compared various scores for predicting the outcome after ICH. Two separate scoring systems (Intracerebral Hemorrhage Outcomes Project [ICHOP 3] and [ICHOP12]) were developed for 3-month and 12-month functional outcomes using GCS, National Institutes of Health Stroke Scale, Acute Physiology and Chronic Health Evaluation II, premorbid modified Rankin Scale (mRS) and hematoma volume. The hematoma volume was considered only in ICHOP3 and not included in ICHOP12 as it would have resolved till then. Patient outcomes were divided as good when mRS score was between 0 to 3 and poor when mRS score was between 4 to 6. The ICHOP scores may provide more comprehensive evaluation of a patient’s long-term functional prognosis by taking into account systemic physiologic factors as well as premorbid functional status.7

Pan K and the co-investigators conducted a prospective observational study in which they compared the ICH and APACHE II scores in patients with spontaneous ICH for predicting 30 day mortality outcome. In this study it was observed that ICH score had a better discriminating power for predicting the 30-day mortality in spontaneous ICH as compared to the APACHE II score.8

The Full Outline of Unresponsiveness (FOUR) score is a validated scale describing the essentials of a coma examination, including motor response, eye opening and eye movements, brainstem reflexes and respiratory pattern. In a study by Braksick et al, they incorporated the FOUR Score into the existing ICH Score and evaluated its accuracy of risk assessment in spontaneous ICH. The FOUR Score was used as a substitute for the GCS to form an ICH Score FS. The ability of the 2 scores to predict mortality at 1 month was then compared in this study. The ICH Score and the ICH Score FS predict 1-month mortality with comparable accuracy as reported by the authors in this study. As the FOUR score provides additional clinical information regarding patient status, it may be a reasonable and valuable substitute for the GCS while calculating the ICH score.9

In this current Issue of JAPI,10 a study titled “Clinical Profile of patients with...
Acute Intracerebral Hemorrhage and ICH score as an Outcome predictor on discharge, 30 days and 60 days follow up", by Piyush Oza is being published. This study was done to prospectively evaluate the predictive utility of ICH score, to predict the outcome in patients presenting with acute ICH at the time of discharge, 30 days and 60 days. The ICH score was calculated at the time of admission. In a study reported by Aimee et al the ICH score calculated at 24 hours after admission has a better predictive value than the ICH score calculated at the time of admission. By 24 hours, the hematoma has been stabilised and definitive therapies have been provided by then. The present study by Oza et al has a small sample size as compared to the commonness of the clinical condition and they have assessed the ICH score on admission and not after 24 hours as recommended in the study by Aimee. GCS was also an independent predictor for the survival and morbidity outcome in this study. The patients in this study were also assessed by mRS. Thus there was utilisation of the various existing scoring systems for predicting outcome following ICH. Nevertheless, this study has helped to add our existing knowledge about the outcome of ICH and plan strategies for the medical care providers, patient and their relatives.

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Clinical Profile of Patients with Acute Intracerebral Hemorrhage and ICH Score as an Outcome Predictor on Discharge, 30 Days and 60 Days Follow-up

Piyush Ojha¹, Vijay Sardana², Dilip Maheshwari³, Bharat Bhushan³, Sumit Kamble¹

Abstract

Background: Intracerebral Hemorrhage (ICH) is one of the most common causes of morbidity and mortality worldwide accounting for 10-15% of all strokes types. ICH score is a validated tool to predict mortality and morbidity at 30 day follow up period.

Objective: To prospectively evaluate the predictive utility of ICH score in patients presenting with Acute ICH on discharge, 30 days and 60 days follow-up period.

Design: Prospective observational study

Materials and Method: This study was conducted in the Department of Neurology, Government Medical College, Kota, Rajasthan, India from January 2016 to August 2016. 120 consecutive patients presenting with acute ICH were studied. Data collected included demographics, clinical parameters, cranial Computed Tomography (CT) findings and ICH score on presentation. Primary outcome was defined as mortality/morbidity during hospitalisation, on discharge, 30 days and 60 days follow-up. Modified Rankin score (mRS) was used to assess the outcome.

Statistical analysis used: SPSS 19 statistical software

Results: Of the total 120 patients with Acute ICH (108 supratentorial and 12 infratentorial) studied, 48 (40%) patients died during hospitalisation. Mean age was 66.9 ± 13.5 Years. Hydrocephalus, midline shift and IV extension on presenting CT scan was observed in 20 (16.6%), 44 (36.6%) and 48 (40%) patients respectively. The independent predictors of increased mortality with statistical significance (p<0.001) were presence of vomiting, seizures, loss of consciousness, lower GCS (≤ 8), higher ICH score and ventilator requirement. Statistically significant (p≤0.001) radiological features associated with mortality included infratentorial location, presence of hydrocephalus, higher midline shift (58.3% vs 22.2% OR=2.6), intraventricular extension of hematoma and a higher baseline hematoma volume. ICH score on admission was significantly (p<0.001) positively correlated with the mRS score on discharge (R=0.667), 1 month (R=0.66) and 2 months (R=0.765) follow-up.

Conclusions: ICH Score is a useful tool to predict outcome during hospitalisation, on discharge, 1 month and 2 month follow-up. We suggest that ICH score assessment and documentation should become standard procedure in acute care and follow up of patients with Intracerebral Hemorrhage.

Introduction

Spontaneous Intracerebral Hemorrhage (ICH) accounts for approximately 4-14% of all strokes with a higher reported incidence in Asian countries compared to west and is associated with a high mortality and morbidity.¹ ² Between 32% and 50% of patients die within the first month and only 20% are independent at 6 months.³ ⁴ The burden of stroke occurrence, morbidity and mortality is much higher in developing nations. There has been considerable interest in predicting outcome after ICH and a number of studies have investigated the relationship of various clinical and radiological factors and poor outcome.⁵ ¹⁰ Few hematological and biochemical parameters at the time of onset of ICH have also been associated with outcome in these patients.

The Intracerebral hemorrhage (ICH) score was developed as a predictive tool for mortality at 30 days after hemorrhagic stroke.⁸ The ICH score is a 6-point calculation based on five clinical indicators: age > 80 years, Glasgow coma scale (GCS), volume of hematoma on baseline CT scan, location (infratentorial or supratentorial) and the presence of intra-ventricular extension. The ICH score has been validated for 30-day and one-year functional outcome in additional studies.¹¹,¹² Studies have also assessed its utility study as a predictor of inhospital mortality and discharge outcome in spontaneous intracerebral hemorrhage.¹³

Majority of the studies have correlated the ICH score with the in-hospital mortality, morbidity at discharge, 30 days and 12 months functional outcome. Also there is a paucity of Indian literature on the utility of ICH scores in patients with Acute Intracerebral haemorrhage.

This prospective observational study was designed to study the clinical profile of patients presenting with Acute Intracerebral Hemorrhage (ICH) at Government Medical College, Kota and to assess the predictors of mortality in patients with spontaneous ICH. We also aimed to assess the utility
Materials and Method

This study was conducted in the Department of Neurology, Government Medical College, Kota, Rajasthan, India from January 2016 to August 2016. 120 consecutive patients presenting with acute ICH were studied after obtaining written informed consent.

Inclusion and exclusion criteria were as follows:

Inclusion Criteria
- All patients diagnosed to have acute spontaneous Intracerebral Hemorrhage.

Exclusion Criteria
- History of trauma
- Patients with subdural and epidural hematoma
- Aneurysmal, arteriovenous malformation (AVM), anticoagulant or coagulopathy-related hemorrhage
- Patients who denied informed consent.

Data collected included demographics, risk factors, clinical parameters, cranial Computed tomography (CT) findings and ICH score on presentation. Detailed history of the presentation including headache, vomiting, seizures, loss of consciousness and focal neurological deficits was obtained. On admission, detailed examination including vitals, systemic examination, Glasgow Coma Scale (GCS) and ICH score were recorded. Baseline hematological and biochemical parameters were assessed. All subjects underwent a plain computed tomography (CT) head at the time of admission. Imaging details on CT scan including volume of hematoma (using formula ABC/2), site of hematoma, intraventricular extension (present or absent), hydrocephalus (present or absent), mid line shift (measured as maximum deviation of septum pellucidum in millimetres from midline) were recorded. During hospitalisation, the reason for and details of mechanical ventilation, presence of any infection and details of neurosurgical intervention (if performed) were also recorded.

Primary outcome was defined as mortality/morbidity during hospitalisation, on discharge, 30 days and 60 days follow-up. Modified Rankin score (mRS) was used to assess the outcome.

Statistical Analysis

SPSS software version 19 was used to analyse the data. Continuous variables were analysed using unpaired ‘t’ test for normally distributed data and MannWhitney U test for skewed data. Categorical variables were analysed using Chi-square test. The relation of ICH score to mRS score at discharge, 1 month and 2 month follow up was analysed by Kendall’s correlation test. Area under curve was derived of ICH score and ICH volume by ROC curve. Bivariate and multivariate logistic regression analysis using stepwise forward regression was performed to find independent predictors of mortality. Odds ratio (OR) and 95% confidence intervals (CI) were calculated. A P value < 0.05 was taken as significant.

Results

During the study period, total 120 patients were enrolled after considering the inclusion and exclusion criteria. The mean age of patients (range 40-88 years) was 66.9 ±13.5 years (Table 1). Of all the patients, 72(60%) patients survived and were discharged while 48 patients (40%) died.

Out of all the patients, hemorrhage was supratentorial location in 108 patients while 12 patients had infratentorial hemorrhage.

There was no statistically significant difference in age and sex between ICH patients who survived and those who died. There was increased number of patients with poor treatment compliance among patients who died compared to the survived patients.

The independent predictors of increased mortality with statistical significance (p<0.001) were presence of vomiting, seizures, loss of consciousness, lower GCS (< 8), higher ICH score.

We also observed that there was a statistically significant higher incidence of ICH score as an outcome predictor as assessed by modified Rankin scale (mRS) at the time of discharge from the hospital, 30 days and 60 days follow up.

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- Aneurysmal, arteriovenous malformation (AVM), anticoagulant or coagulopathy-related hemorrhage
- Patients who denied informed consent.

Data collected included demographics, risk factors, clinical parameters, cranial Computed tomography (CT) findings and ICH score on presentation. Detailed history of the presentation including headache, vomiting, seizures, loss of consciousness and focal neurological deficits was obtained. On admission, detailed examination including vitals, systemic examination, Glasgow Coma Scale (GCS) and ICH score were recorded. Baseline hematological and biochemical parameters were assessed. All subjects underwent a plain computed tomography (CT) head at the time of admission. Imaging details on CT scan including volume of hematoma (using formula ABC/2), site of hematoma, intraventricular extension (present or absent), hydrocephalus (present or absent), mid line shift (measured as maximum deviation of septum pellucidum in millimetres from midline) were recorded. During hospitalisation, the reason for and details of mechanical ventilation, presence of any infection and details of neurosurgical intervention (if performed) were also recorded.

Primary outcome was defined as mortality/morbidity during hospitalisation, on discharge, 30 days and 60 days follow-up. Modified Rankin score (mRS) was used to assess the outcome.

Statistical Analysis

SPSS software version 19 was used to analyse the data. Continuous variables were analysed using unpaired ‘t’ test for normally distributed data and MannWhitney U test for skewed data. Categorical variables were analysed using Chi-square test. The relation of ICH score to mRS score at discharge, 1 month and 2 month follow up was analysed by Kendall’s correlation test. Area under curve was derived of ICH score and ICH volume by ROC curve. Bivariate and multivariate logistic regression analysis using stepwise forward regression was performed to find independent predictors of mortality. Odds ratio (OR) and 95% confidence intervals (CI) were calculated. A P value < 0.05 was taken as significant.

Results

During the study period, total 120 patients were enrolled after considering the inclusion and exclusion criteria. The mean age of patients (range 40-88 years) was 66.9 ±13.5 years (Table 1). Of all the patients, 72(60%) patients survived and were discharged while 48 patients (40%) died.

Out of all the patients, hemorrhage was supratentorial location in 108 patients while 12 patients had infratentorial hemorrhage.

There was no statistically significant difference in age and sex between ICH patients who survived and those who died. There was increased number of patients with poor treatment compliance among patients who died compared to the survived patients.

The independent predictors of increased mortality with statistical significance (p<0.001) were presence of vomiting, seizures, loss of consciousness, lower GCS (< 8), higher ICH score.

We also observed that there was a statistically significant higher incidence of ICH score as an outcome predictor as assessed by modified Rankin scale (mRS) at the time of discharge from the hospital, 30 days and 60 days follow up.
of infection observed in patients who died than who survived.

Statistically significant (\[p \leq 0.001\]) radiological features associated with mortality included infratentorial location of hemorrhage, presence of hydrocephalus, higher midline shift (58.3% vs 22.2% OR=2.6), intraventricular extension of hematoma and a higher baseline hematoma volume.

Patient who died had a shorter stay as compared to those who survived. (median 3.5 vs. 8 days, \[P < 0.0001\]).

Ventilator requirement was also observed to be a poor prognostic factor with statistical significance. Majority (91.7%) had a ventilator requirement among the patients who died, while only 5.6% patients among those who survived required ventilator support.

Figure 2 represents the number of patients presenting with different ICH scores on admission. Maximum number (n=40) had ICH score 2, which was followed by patients with ICH score 0 (n=24), 1 (n=24), 3 (n=8), 5 (n=4) and 6 (n=4).

We also recorded modified Rankin scale (mRS) of all the patients on discharge/death, at 1 month and 2 months follow up. Among the survived patients who were discharged, the number of patients with mRS of 1,2,3,4 and 5 were 4(5.6%), 12(16.7%), 16(22.2%), 28(35.7%) and 28(35.7%) respectively, i.e. majority of them falling between mRS 3-5, being moderate to severely disabled. During the follow up, the percentage of patients having mRS of 1-2 gradually increased, suggesting gradual improvement in these patients. Figure 2 shows the trends of mRS of all the survived patients during the follow-up.

The mortality rates observed with individual ICH scores (Figure 4) were as follows : 0 (16.7%), 1 (0%), 2 (30%), 3 (57.2%), 4 (62.5%), 5 (100%) and 6 (100%). Thus, with increasing ICH scores, mortality rates increased, reaching 100% in patients with ICH scores of 5 and 6.

To assess the utility of ICH scores in predicting mortality/moderate to severe disability on discharge, 1month and 2 months follow-up, we used receiver operating characteristics (ROC) curves (Figure 5). ICH score on admission was significantly (\[p<0.001\]) positively correlated with the mRS score on
discharge (R=0.667), 1 month(R=0.66) and 2 months (R=0.765) follow-up. So our study results suggest that ICH scores can be used to predict outcome on admission, discharge, 1 month and 2 months follow-up.

Discussion

Clinical grading scales play an important role in the evaluation and management of patients with acute neurological disorders, especially traumatic brain injury and various types of stroke. Such scales serve several valuable purposes that follow from the standardization of assessment afforded by these tools. While many grading scales are used for prognostication and treatment selection in neurological disease, the foremost purpose of these scales is to improve communication and consistency among healthcare providers. Another utility of these scales is the ability to use these scales for risk stratification for treatment selection in clinical care and enrolment criteria for clinical research. To be generally applicable, a clinical grading scale must be simple enough to use without significant special training, statistical knowledge, or extensive time commitment. It also must be reliable in patient stratification and should be composed of elements that are associated with outcome and that would likely be assessed, in general, as part of routine clinical care.

Examples of widely used clinical grading scales include the GCS for traumatic brain injury (and other disorders), the Hunt-Hess and World Federation of Neurological Surgeons (WFNS) scales for aneurysmal SAH, the National Institutes of Health Stroke Scale (NIHSS) for ischemic stroke, and the Spetzler-Martin scale for arteriovenous malformations.

Despite the common occurrence and high morbidity of ICH, there remains few widely used clinical grading scales for ICH. Accurate prediction of outcome after spontaneous intracerebral hemorrhage (ICH) is necessary to estimate the prognosis and prepare a treatment plan accordingly. Various scales have been developed to estimate prognosis in patients with spontaneous ICH.\(^{14,15}\) Of them, the ICH score has proven to be reliable in predicting 30-day mortality in different populations and clinical circumstances.

The ICH Score is a clinical grading scale composed of factors related to a basic neurological examination (GCS), a baseline patient characteristic (age), and initial neuroimaging (ICH volume, IVH, infratentorial/supratentorial origin). The purpose of this grading scale was to provide a standard assessment tool that can be easily and rapidly determined at the time of ICH presentation, even by physicians without special training in stroke neurology and that will allow consistency in communication and treatment selection in clinical care and clinical research.

When individual parameters of ICH score are considered, GCS score has shown to be an independent prognostic marker in patients with acute ICH. In our study also, we observed that GCS ≤ 8 was an independent predictor of mortality and long term morbidity when compared to patients with GCS > 8.

Although age has been found to be an independent predictor of ICH outcome in some prior prediction models, we did not find it to be an independent prognostic marker similar to many earlier published studies.

Other parameters of ICH score i.e. ICH volume, presence of intraventricular extension and infratentorial haemorrhage origin were the other factors independently associated with 30-day mortality in the earlier studies and therefore were included in the ICH Score. All the three parameters were also found to be statistically significantly associated with prognosis in our study as well.

The purpose of this study was not to develop a new ICH outcome prediction model or to test whether various prediction models were more accurate with regard to predicting individual patient outcome. Rather, the point of this study was to assess the validity of an existing, simple, and previously validated scale, the ICH Score in patients of Intracerebral haemorrhage in our patients.

As observed in previous studies, mean ICH and ICH scores were significantly higher in patients who died in the present cohort. The mortality rates observed with individual ICH scores were as follows: 0 (16.7%), 1 (0%), 2 (30%), 3 (57.2%), 4 (62.5%), 5 (100%) and 6 (100%).

The 30-day mortality from ICH in various studies has been found to vary from 35 to 52%, with one-half of these deaths occurring within the first 2 days.\(^{16-18}\) In a study conducted by Rohit Bhatia et al, the in-hospital mortality was found to be 32.7%.\(^{13}\) In our study, 48 (40%) patients died during hospitalisation.

More recent studies have also identified lesion size, level of
concerns, midline shift, blood pressure or pulse pressure, kidney dysfunction, IVH and pupillary abnormality, as factors influencing outcome in ICH patients.19,20

In our study, the independent predictors of increased mortality with statistical significance (p<0.001) were presence of vomiting, seizures, loss of consciousness, lower GCS (≤8), higher ICH score.

Statistically significant (p ≤ 0.001) radiological features associated with increased mortality included infratentorial location of hemorrhage, presence of hydrocephalus, higher midline shift (58.3% vs 22.2% OR=2.6), intraventricular extension of hematoma and a higher baseline hematoma volume.

Some studies suggest that early prognostication of outcomes should be avoided whenever possible, and using an ICH score calculated at a later time (24 hours) during the ICH admission is a better indicator of patient outcomes, after the hematoma has been stabilized and definitive therapies have been provided.19 In our study, 40% patients died during hospitalisation, majority of them within initial 48 hours. Moreover, a lot of patients didn’t present within the initial 24 hours of symptom onset. So to keep a uniformity of the data collection and analysis, we calculated ICH score at the time of admission only. A prospective study of the impact of time from symptom onset to calculation of the ICH score may be warranted to determine when, after ICH, the ICH score becomes reliable.

The ICH Score has been validated for 30 days as well as for long-term functional outcome after acute intracerebral hemorrhage (ICH).11 Studies have also analysed its utility to predict in-hospital mortality.13 In our study also, we found a significantly (p<0.001) positive correlation of ICH score on admission with the mRS score on discharge (R=0.667), 1 month (R=0.66) and 2 months (R=0.765) follow-up.

Many ICH patients improve after hospital discharge and this improvement may continue even post-ICH.

The study has few limitations including a relative small number of patients. Another important limitation was that we calculated only ICH score on admission.

However, even with these limitations, this study clearly demonstrates that the ICH Score is a valid clinical grading scale for outcome considered as mortality or functional outcome throughout the first 2 months after acute ICH.

Our study demonstrates that the ICH Score is a valid clinical grading scale for stratifying likelihood of favorable functional outcome after hospitalisation and during follow-up at 1 and 2 months. This is in addition to prior studies which have demonstrated the ICH Score as a validated predictor of risk of 30-day mortality. Our study results also show that a substantial proportion of patients with acute ICH improve after hospital discharge as assessed by mRS. This study has also helped to elucidate the course of improvement (or lack thereof) after acute ICH. This is important clinically because it helps patients, families, and providers plan for ongoing care needs.

**Conclusion**

ICH Score on admission is a useful tool to predict outcome during hospitalisation, on discharge, 1 month and 2 month follow-up. The independent predictors of increased mortality with statistical significance in the present study were presence of vomiting, seizures, loss of consciousness, lower GCS (≤8), higher ICH score and ventilator requirement. Statistically significant (p<0.001) radiological features associated with mortality included infratentorial location, presence of hydrocephalus, higher midline shift, intraventricular extension of hematoma and a higher baseline hematoma volume. A prospective study of the impact of time from symptom onset to calculation of the ICH score may be warranted to determine when, after ICH, the ICH score becomes reliable.

We suggest that ICH score assessment and documentation should become standard procedure in acute care and follow up of patients with Intracerebral Hemorrhage.

**References**

13. Cheung RT, Zou LY. "Use of the original, modified, or new intracerebral hemorrhage score to predict mortality and morbidity after intracerebral hemorrhage. Neurology India 2013; 61:3.
When it comes to Protection Quality makes the Difference

According to the WHO, each year hundreds of millions of patients are affected by healthcare associated infections (HAIs) around the world. When it comes to infection control, the practice of appropriate hand hygiene and the proper use of medical gloves as a standard precaution are important measures in minimising and preventing HAIs.

MALAYSIA: WORLD'S NO. 1 FOR MEDICAL GLOVES
Association between Non-alcoholic Fatty Liver Disease and Left Ventricular Diastolic Dysfunction in Patients of Type 2 Diabetes

Manoj Saluja¹, Kamlesh Kumar², Yogesh Kumar Swami²*, SR Meena¹, Saket Goyal³

Abstract

Objective: The purpose of the study was to assess if non-alcoholic fatty liver disease (NAFLD) in diabetic patients increases the risk and/or severity of diastolic dysfunction

Research design and methods: We studied 70 type 2 diabetic individuals without a history of ischemic heart disease, hepatic diseases, or excessive alcohol consumption, in whom NAFLD was diagnosed by ultrasonography. All patients had normal left ventricular systolic function and blood pressure values under medication. Left ventricular diastolic dysfunction was assessed by pulsed wave Doppler and tissue Doppler imaging, studying mitral inflow patterns and E wave, E’ wave velocities, E/A and E/E’ ratios.

Results and Conclusions: Fifty seven patients (81.43%) had NAFLD, and when compared with the other 13(18.57%) patients, age, sex, BMI, waist circumference, hypertension, smoking, diabetes duration, microvascular complication status, and medication use were not significantly different. In addition, the left ventricular (LV) mass and volumes, ejection fraction, systemic vascular resistance, arterial elasticity, and compliance were also not different. NAFLD patients had lower E’ (8.42±0.89 vs. 9.72±0.54, P <0.0001) tissue velocity, higher E-to-E’ ratio (9.64±1.83 vs. 7.78±0.89, p<0.001), higher LV–end diastolic pressure (EDP) (15.52 ± 0.69 vs. 14.40±0.9 p <0.0001), higher LV EDP/end diastolic volume LV EDP/EDV (mmHg/mL) (0.19 ±0.15 vs. 0.17±0.02 p < 0.001) and higher glycosylated haemoglobin (HbA1C) (8.53±1.02 vs.7.65±0.66 p<0.01) than those without steatosis.

All of these differences remained significant after adjustment for hypertension and other cardio metabolic risk factors. Our data show that in patients with type2 diabetes and NAFLD, even if the LV morphology and systolic function are preserved, early features of LV diastolic dysfunction detected. The frequency of diastolic dysfunction was significantly higher in diabetic patients with NAFLD versus controls.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is recognized as the hepatic expression of the metabolic syndrome, a cluster of cardiovascular risk factors, including type 2 diabetes mellitus. Observational studies have connected NAFLD with insulin resistance, suggesting that the presence of fatty liver and especially that of non-alcoholic steatohepatitis, promotes the development of glycoregulation disorders.¹ The addition of NAFLD to glycoregulation disorders may increase the cardiovascular risk of these patients, independently of the presence of other components of the metabolic syndrome.² Diastolic dysfunction in diabetic patients is the main characteristic of diabetic cardiomyopathy and represents a prognostic factor for the development of diastolic heart failure with preserved ejection fraction.³ The prevalence of diastolic dysfunction is higher in patients with metabolic syndrome compared with the general population, reaching 60% in diabetic patients.⁴ Diastolic dysfunction impairs life quality, reducing exercise capacity and accounting for up to 50% of acute heart failure hospitalizations in patients with preserved ejection fraction.⁵ Recently it was proven that diastolic dysfunction is a frequently met in patients with NAFLD and type2 diabetes or arterial hypertension.⁶

Diabetic cardiomyopathy may induce changes in cardiac structure such as myocardial hypertrophy, fibrosis, and fat droplet deposition. Early changes in cardiac function are also manifested as abnormal diastolic function that with time can lead to loss of contractile function.⁷ In parallel, it is recognized that non-alcoholic fatty liver disease (NAFLD) is largely prevalent in subjects who are obese or have type2 diabetes.⁸⁻¹⁰ Nowadays, growing evidence suggests that NAFLD is linked to increased risk of CVD (Cardio Vascular Disease) events in non diabetic and type 2 diabetic individuals.¹⁰ Several investigators have examined the association of NAFLD with markers of subclinical CVD (e.g., carotid artery intima-media thickness) or clinical CVD.¹⁰ Conversely, the information regarding abnormalities in cardiac function among NAFLD patients is limited and controversial. It has been shown that non diabetic, normotensive patients with NAFLD have echo-cardiographic features of early left ventricular (LV) diastolic dysfunction as measured by tissue Doppler echocardiography¹¹,¹² and impaired LV energy metabolism, as measured by cardiac 31P-magnetic resonance spectroscopy (MRS), compared with control subjects without steatosis.¹³ In a recent study involving type 2 diabetic men, Rijzewijk et al.¹⁴ found that, compared with those with lower intrahepatic fat content, patients with higher intra hepatic fat content, as measured by 1H-MRS, had impaired myocardial perfusion and lower high energy phosphates but similar values,...
obtaining informed consent.

3. Abnormal thyroid function test

Inclusion Criteria

1. The patients of Diabetes Mellitus, who wishes to participate in the study. ADA (American Diabetes Association) criteria for diagnosis of diabetes mellitus:
   i. Random plasma glucose concentration >11.1 mmol/L (200 mg/dl) accompanied by classic symptoms of Diabetes Mellitus (polyuria, polydipsia, polyphagia, weight loss)
   ii. Fasting plasma glucose >7.0 mmol/L (126 mg/dl) on two separate occasions.
   iii. Two hours plasma glucose >11.1 (200 mg/dl) during an oral glucose tolerance test with 75 grams of oral glucose.

2. Diabetic patients who were on lifestyle modification and treatment (oral medication or insulin) with an ejection fraction of more than 50% (Normal E/A) on echocardiogram with no evidence of cardio-respiratory illness.

Exclusion Criteria

1. Patients who had a prior history of ischemic heart and valvular disease, chronic heart failure, cirrhosis, or overt nephropathy.
2. Those who had known causes of chronic liver disease (i.e., alcohol or drug-induced liver disease, hemochromatosis, or autoimmune viral hepatitis). All women were of postmenopausal status and did not take hormonal replacement therapy
3. Abnormal thyroid function test

Method

We studied 70 type 2 diabetic patients who attended the MBS Hospital, Kota. A 12-lead standard resting electrocardiogram, 24-h Holter monitoring, bicycle ergometry and cTMT were performed in all patients to exclude the presence of silent myocardial ischemia or significant disturbances of sinus rhythm; no patients had any abnormal test results. Of the 70 participants included in the study, 57(81.43%) patients met the clinical criteria for a diagnosis of NAFLD (i.e., hepatic steatosis on ultrasound among persons who did not drink alcohol and who did not have viral hepatitis, drug-induced liver disease, iron overload, or other known causes of liver disease) and 13(18.57%) patients did not. All participants gave written informed consent for participation in medical research. BMI was calculated by dividing weight in kilograms by height in meters squared BMI=18-25 – Normal, 25-29.9 – Overweight, ≥30 –Obese (WHO). Waist circumference was measured midway between the lower-rib margin and the superior anterior iliac crest. Blood pressure was measured in duplicate by a physician with a mercury sphygmomanometer (at the right upper arm using an appropriate cuff size) after participants had been seated quietly for at least 5 min.

In all participants, the presence of microvascular complications such as sensory neuropathy (by biothesiometer) and nephropathy (by serum creatinine and albumin urea measurements) were also recorded. Information on smoking and alcohol consumption was obtained from all participants by a validated questionnaire. Blood samples were drawn in the morning after an overnight fast. Serum liver enzymes, ferritin, creatinine, thyroid function test and other biochemical blood measurements were determined by standard laboratory procedures. Fasting and PP plasma glucose (Glucose peroxidase enzyme) Serum total cholesterol, HDL, LDL, and triglycerides were determined by enzymatic kinetic assay method, using semi autoanalyser (Transasia model no, erba – chem 5) after overnight fasting. Blood urea (Berthelot method based on urease enzyme) Serum creatinine (Joffe’s alkaline picrate method).

HbA1c was measured by a high-performance liquid chromatography analyzer. All patients had negative hepatitis B and C viral markers. Conventional echocardiography was used to measure LV diameters, wall thickness and mass according to standard criteria. LV end diastolic (EDV) and end systolic volumes and ejection fraction at rest were measured at the apical two chamber and four-chamber views (by modified Simpson rule). Left atrial maximal volume was measured at the end of LV systole from the apical two-chamber and four-chamber views (by modified Simpson rule). Measurements were indexed to body surface area when appropriate. Pulsed-wave Doppler was used to measure trans mitral peak early diastolic velocity (E), peak late diastolic velocity (A), and E-wave deceleration time (Dte). Isovolumetric relaxation time (IVRT) was also calculated. Each value was obtained from the average of three measurements.

2D-Echocardiography (pulse wave) grading

1. Impaired relaxation (grade I diastolic dysfunction).
   1a. Normal filling pressure-
      DT- 160-240ms, IVRT- 70-90 ms; E/A- 1-2, Mitral A duration >PVa duration, PVs2 >PVd (PVs2 can be <PVd in young person), No anatomical abnormalities.
   1b. Increase filling pressure-
      DT- >240 ms, IVRT- >90 ms, E/A- < 1.0, PVs2 > PVd, Mitral A duration > or <PVa duration.

2. Pseudonormal pattern (grade II diastolic dysfunction) –
   DT- 160-200ms, IVRT < 90 ms; E/A - 1- 1.5 PVs2 < PVd, Mitral A duration <PVa duration, PVa velocity increase (> 35 cm/s), 2D echocardiographic evidence of structural heart disease (EF, LA andLVH) Reversal of E/A ratio (<1.0) with Valsalva maneuver.
3. Restrictive pattern (grade iii and 4 diastolic dysfunction) –
   DT < 160 ms, IVRT < 70 ms; E/A > 1.5
   PVS2 < PVD
   Mitral A duration < PVa duration,
   PVa velocity increase (>35 cm/s,
   usually but not always),
   2D echocardiographic evidence of
   structural heart disease, decreased E/A ratio with preload reduction (Valsalva
   maneuver). PVa, PVD, PVS2, velocity
   components pulmonary vein). 19

**Tissue Doppler imaging**

Tissue Doppler imaging was performed in all patients by a single experienced cardiologist, who was blinded to NAFLD details of participants. Systolic function was evaluated measuring the left ventricular ejection fraction and the systolic myocardial velocity (S') by tissue Doppler imaging. Diastolic function was assessed by establishing the mitral inflow pulsed-wave Doppler pattern and by measuring the early diastolic myocardial velocity by tissue Doppler (E'), as well as the E/E' ratio. The time interval between the QRS complex and the onset of mitral E-wave velocity was subtracted from the time interval between the QRS complex and E' onset to derive T E-E' which strongly depends on the time constant of LV relaxation and minimal pressure. The ratio of IVRT to T E-E' was then calculated; this ratio provides incremental information as to the E-to-E' ratio on LV filling pressure in subjects with normal ejection fraction and E-to-E' ratio between 8 and 15[21].

Global longitudinal strain and strain rate curves were obtained including all six LV myocardial segments from four-chamber, two-chamber, and long-axis apical views. The average values of peak systolic longitudinal strain and peak systolic strain rate from the three apical views were calculated as global longitudinal strain (LSSYS) and global strain rate (SRSYS), respectively. Similarly, the global diastolic strain rate during the early (SRE) and late (SRL) phase of diastole was also calculated. Standard echocardiographic views were obtained using frequency, depth, and sector width adjusted for frame-rate optimization (between 60and 100 frames per second. Tissue Doppler imaging was obtained by placing the Doppler probe at the level of the lateral mitral ring or at the level of the inter-ventricular septum, in four apical chamber view; the obtained velocities are similar, but inverted compared with the traditional mitral inflow by pulsed-wave Doppler, as illustrated in Figure 1.

**Diastolic flow** is represented by two negative waves: E’ corresponding to diastolic relaxation, simultaneous with the T wave on the ECG, a parameter relatively independent of the filling pressures, and A’ wave – the maximal late annular velocity, corresponding to atrial contraction. E’/A’ ratio is normally >1. The E’ velocity decreases with age, from 9 cm s-1 to 6 cm s-1 in subjects over 60 years old at the level of the inter-ventricular septum, and from 11 cm s-1 to 7 cm s-1 at the level of the lateral mitral ring.

The differentiation of the normal pattern from the pseudo-normal one was based on the Valsalva maneuver, which, in patients with diastolic dysfunction decreases the E/A ratio<1 or at least by 50%. The E’ wave velocities was <8 cm s-1 and the E/E’ ratio>15 in the pseudo-normal pattern, whereas in normal subjects the E’ wave velocity was>10 cm s-1 and the E/E’<8 cm s-1. We used the Data Analysis module of Microsoft Excel 2007 ® (for the descriptive statistics and the Student T test, as well as the Fischer test).

**USG Abdomen**

Hepatic ultrasonography was performed in all patients by a single experienced radiologist, who was blinded to the participants’ details. Hepatic steatosis was diagnosed on the basis of characteristic sonographic features, i.e., evidence of diffuse hyperechogenicity of the liver relative to the kidneys, ultrasound beam attenuation, and poor visualization of intrahepatic vessel borders and diaphragm. 22 It is known that ultrasonography has a good sensitivity and specificity for detecting moderate and severe hepatic steatosis (90–95%), but its sensitivity is reduced when the hepatic fat infiltration upon liver biopsy is, 30%. 8-10 The differentiation of the normal pattern from the pseudo-normal one was based on the Valsalva maneuver, which, in patients with diastolic dysfunction decreases the E/A ratio<1 or at least by 50%. The E’ wave velocities was <8 cm s-1 and the E/E’ ratio>15 in the pseudo-normal pattern, whereas in normal subjects the E’ wave velocity was>10 cm s-1 and the E/E’<8 cm s-1. We used the Data Analysis module of Microsoft Excel 2007 ® (for the descriptive statistics and the Student T test, as well as the Fischer test).
Table 1: Clinical and biochemical characteristics of type 2 diabetic patients grouped NAFLD status

<table>
<thead>
<tr>
<th></th>
<th>Without NAFLD</th>
<th>With NAFLD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>13</td>
<td>57</td>
<td></td>
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<tr>
<td>Male/female</td>
<td>7/6</td>
<td>31/26</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>58±11.21</td>
<td>55±10.38</td>
<td>0.28</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>27.85±5.48</td>
<td>29.12±5.33</td>
<td>0.44</td>
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<tr>
<td>Waist circumference</td>
<td>93.4±10.74</td>
<td>95.0±8.85</td>
<td>0.57</td>
</tr>
<tr>
<td>Diabetes duration</td>
<td>9.8±5.38</td>
<td>8.4±4.05</td>
<td>0.61</td>
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</tbody>
</table>

**Hypertension**

<table>
<thead>
<tr>
<th></th>
<th>Without NAFLD</th>
<th>With NAFLD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>138±12</td>
<td>139±13</td>
<td>0.53</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>81±5</td>
<td>79±6</td>
<td>0.19</td>
</tr>
<tr>
<td>Mean blood pressure (mmHg)</td>
<td>100.8±10</td>
<td>98.9±11</td>
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</tr>
<tr>
<td>Pulse pressure (mmHg)</td>
<td>59.8±11</td>
<td>59.4±10</td>
<td>0.85</td>
</tr>
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<td>Heart rate (bpm)</td>
<td>75.9±10</td>
<td>72.2±9</td>
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<td>Current smokers</td>
<td>0.0</td>
<td>0.0</td>
<td>NS</td>
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<tr>
<td>Microvascular complications</td>
<td>32</td>
<td>30</td>
<td>0.78</td>
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<tr>
<td>Carotid stenosis &gt;30% (%)</td>
<td>42</td>
<td>58</td>
<td>0.41</td>
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<tr>
<td>Oral hypoglycemic agents (%)</td>
<td>58</td>
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<tr>
<td>Insulin (%)</td>
<td>26</td>
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<tr>
<td>ACE inhibitors (%)</td>
<td>54</td>
<td>64</td>
<td>0.66</td>
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<tr>
<td>Calcium channel blockers (%)</td>
<td>38</td>
<td>42</td>
<td>0.72</td>
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<tr>
<td>Diuretics (%)</td>
<td>14</td>
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<tr>
<td>Statins (%)</td>
<td>42</td>
<td>44</td>
<td>0.36</td>
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<tr>
<td>Bl. Urea (mg/dL)</td>
<td>25.0±6.37</td>
<td>23.7±7.16</td>
<td>0.57</td>
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<td>Sr. Creatinine (mg/dL)</td>
<td>0.80±0.34</td>
<td>0.81±0.25</td>
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<td>Fasting glucose (mg/dL)</td>
<td>114.3±19.65</td>
<td>129.9±34.90</td>
<td>0.13</td>
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<tr>
<td>HbA1c (%)</td>
<td>8.5±1.02</td>
<td>7.6±0.66</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>181.6±93.45</td>
<td>195.0±76.38</td>
<td>0.23</td>
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<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>104.4±26.41</td>
<td>109.8±23.02</td>
<td>0.46</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>45.3±8.32</td>
<td>43.5±8.46</td>
<td>0.43</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>107.7±27.60</td>
<td>142.0±85.35</td>
<td>0.19</td>
</tr>
<tr>
<td>Alanine aminotransferase (units/L)</td>
<td>39.3±11.36</td>
<td>41.0±14.56</td>
<td>0.70</td>
</tr>
<tr>
<td>g-Glutamyltransferase (units/L)</td>
<td>41.0±11.39</td>
<td>43.5±14.79</td>
<td>0.56</td>
</tr>
</tbody>
</table>

Data are means ± SD or percentages unless otherwise indicated.

**Results**

In this study 70 type-2 diabetes cases of both sexes between 35-65 years of were included.

Subjects were assigned to two groups:

- **Group - 1 Diabetes patients with NAFLD.**
- **Group - 2 DIABETES patients without NAFLD.**

Clinical and biochemical characteristics of participants stratified by NAFLD status are summarized in Table 1.

NAFLD patients had higher plasma triglycerides and HbA1c than those without steatosis. The glycemic control of participants was not so good (mean HbA1c 8.5±1.02%). As expected, they also had higher serum liver enzymes, although the vast majority of our NAFLD patients, i.e., 90%, had serum alanine aminotransferase (ALT) and gamma glutamyl transferase (GGT) concentrations within the reference ranges (normal ranges for alanine amino transferase and gamma glutamyl transferase, in our laboratory, were 10–40 units/L for women and 10–50 units/L for men, respectively). Fifty seven patients (81.43%) had NAFLD, and when compared with the other 13 (18.57%) patients. NAFLD patients had lower E’ (8.4±0.89 vs. 9.7±0.54, p <0.0001) tissue velocity, higher E-to-E’ ratio (9.6±1.83 vs. 7.7±0.89, p=0.01), higher LV–end diastolic pressure (EDP) (15.52±0.69 vs. 14.40±0.9, p <0.0001), higher LV EDP/EDV (0.19±0.15 vs. 0.17±0.02 p=0.001) and higher glycosylated haemoglobin (HbA1C) (8.5±1.02 vs. 7.6±0.66, p<0.01) than those without steatosis. Age, sex, BMI, waist circumference, smoking status, heart rate, systolic/diastolic blood pressure, LDL cholesterol, HDL cholesterol, fasting glucose, duration of diabetes, microvascular complication status (abnormal albuminuria and sensory neuropathy), and treatments for hypertension, dyslipidemia, and diabetes did not differ between the groups. No significant differences were
found in LV EDVs and end systolic volumes and ejection fraction, indexed LV mass, indexed left atria volume. Thus, the final results of this study can be applied to the general population.

Conclusions and discussions

In the metabolic syndrome and type 2 diabetes mellitus diastolic dysfunction is the consequence of metabolic abnormalities and structural remodeling, which result in abnormal relaxation and increased myocardial rigidity (Boudina and Dale 2007). The multiple metabolic abnormalities are the result of insulin signaling, glycol-lipotoxicity and increase in interstitial fat deposits, affecting consequently the myocardial function at tissue level. Endothelial dysfunction is associated as well to these abnormalities, resulting in vascular remodeling and systemic and coronary atherosclerosis. This translates in an increase in arterial rigidity, high blood pressure and pulse pressure. There is an increase in afterload and myocardial oxygen demands, with a decrease in myocardial perfusion, thus diminishing cardiac efficacy. As a consequence, myocardial hypertrophy, autonomic dysfunction and diastolic dysfunction develop, as the first stage of diabetic cardiomyopathy. In late stages, diastolic dysfunction worsens as a result to structural myocardial abnormalities, as cardiac steatosis, interstitial fibrosis and the alterations in extracellular matrix. NAFLD is defined as the fatty infiltration of the liver in patients without significant alcohol consumption, with a spectrum ranging from simple steatosis to steatohepatitis, histologically similar to alcoholic hepatitis, with a possible progression to end stage liver disease (Ludwig et al 1980). Considered at first an incidental finding, NAFLD is accepted today as a component of the metabolic syndrome, associated with significant cardiovascular risk factors like obesity, hypertension, dyslipidemia, diabetes mellitus and insulin resistance. Moreover, NAFLD may be an independent cardiovascular risk factor as well as a detrimental factor for the severity of the other elements of the metabolic syndrome associated with it. Our study showed that NAFLD in type 2 diabetes mellitus was associated with a higher frequency of diastolic dysfunction compared to diabetic patients without NAFLD.

These data suggest the fact that NAFLD, regardless of the presence of diabetes, further impairs the stiffness and relaxation of the left ventricle. This translates in earlier development of diastolic heart failure and a higher cardiovascular risk.

Data from studies performed on small groups of patients have shown that patients with NAFLD, in the absence of other cardiovascular risk factors included in the metabolic syndrome, present alterations in left ventricular geometry and early diastolic dysfunction. Other studies have shown that NAFLD is associated with a significant decrease in E′ wave velocity, this parameter being described as the only one to correlate with NAFLD. In another study, diastolic dysfunction and insulin resistance were independently associated with NAFLD, in multivariate analysis (Brea et al 2005). Poonta et al showed that patients with type 2 diabetes and NAFLD did not present an abnormal intima-media thickness, a known risk factor for cardiovascular events, but their study was performed on a small number of subjects (Poonta et al 2011). In conclusion, in patients diagnosed with NAFLD the assessment of diastolic dysfunction by tissue Doppler imaging detects early changes in myocardial stiffness and compliance, which precede the late stages of myocardial dysfunction.

Acknowledgment

We have not received substantial contributions from non-contributors and no contributor has been omitted.

Ethical Clearance

This study has been conducted in M.B.S. and associated group of hospitals of Govt. Medical College, Kota. This study had been done originally by us after consent from patient and approval of ethics committee. Written informed consent was obtained from the patient and parents for publication of this case, reports and any accompanying images. We are ensuring that, this study manuscript has not been submitted and published elsewhere.

References

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**Fibrotic Cytokine Interplay in Evaluation of Disease Activity in Treatment Naïve Systemic Sclerosis Patients from Western India**

Prasad V Khadilkar¹, Uday S Khopkar², Milind Y Nadkar³, Anjali G Rajadhyaksha⁴, Durga A Chougule⁵, Sunita D Deshpande⁶, Manisha R Madkaikar⁷, Vandana D Pradhan*⁸

### Abstract

**Background:** Systemic sclerosis (SSc) is a demyelinating disease of skin, subcutaneous tissue, muscles and internal organs, with fibrosis as an important pathological event.

**Aim:** To understand cytokine interplay of IL-1β, IL-4 and IL-6 and their association with disease activity in treatment naïve active cases of systemic sclerosis from Western India.

**Methods:** Twenty-five SSc patients as per ACR-EULAR 2013 criteria (classified based on pulmonary fibrosis and generalized fibrosis) and 25 age-sex matched controls were enrolled. Serum cytokine levels of IL-1β, IL-4 and IL-6 were assessed by multiplex bead based immunoassay.

**Results:** Ten patients had Interstitial lung disease (ILD), whereas, 16 patients had generalized fibrosis. Anti-nuclear antibodies were seen in 22 patients (88%); anti-Sc170 in 15 patients (60%) and anti-Centromere antibodies in 5 patients (20%). Serum levels of IL-1β in patients were significantly higher than healthy controls (p=0.0006). IL-4 levels in all SSc patients were marginally raised (p=0.0102), whereas IL-6 levels were significantly raised (p=0.0001). IL-4 was found to be significantly raised in SSc patients with ILD (p=0.021) as compared to patients without ILD. IL-1β (p=0.0293) and IL-4 (p=0.0001) were significantly higher in SSc patients with fibrosis. On the contrary, IL-6 levels in patients with fibrosis were found to be lower than in patients without fibrosis.

**Conclusion:** Significantly raised cytokine levels among treatment naïve systemic sclerosis patients were found to be associated with higher disease severity in our study. Higher levels of IL-1β and IL-6 indicated an active inflammatory status, whereas significantly raised IL-4 levels indicated at higher fibrotic activity.

### Introduction

Systemic sclerosis (SSc) is a connective tissue disease characterized by breakdown of micro and microvasculature and degenerative changes in skin, subcutaneous tissue, muscles and internal organs. Presence of autoantibodies in patient sera is an important diagnostic and classification feature of systemic sclerosis (ACR-EULAR 2013 Criteria).¹ Excessive production of collagen, T cell accumulation and subsequent extensive fibrosis in dermal and subcutaneous layers leads to sclerosis.² SSc is governed by wide spectra of microvascular and immunological aberrations, which leads to progressive skin thickening and fibrosis.³ Fibrosis may be defined as an exaggerated healing response to a tissue injury (scarring). Various soluble factors released by macrophages in response to tissue injury activate pathways which lead to proliferation and activation of fibroblasts. Subsequent degradation of ECM and impairment in regulation of collagen synthesis mechanism and healing response, results in progressive irreversible fibrotic response. The pathological accumulation of connective tissue and extra-cellular matrix proteins, interferes with normal organ function. Clinical manifestations like pulmonary fibrosis ‘Interstitial Lung Disease (ILD) and Pulmonary Arterial Hypertension (PAH), pitting scars, finger thickening which are prominent manifestations in systemic sclerosis are predominantly associated with fibrosis.⁴ IL-1β is a pyrogenic protein secreted by activated macrophages as a proprotein and is proteolysed to active IL-1β by caspase-1. This cytokine mediates the inflammatory response and is involved in cellular activities including cell proliferation, differentiation and apoptosis.⁵,⁶ Although no direct role of IL-1β in fibrosis is known, it is known to stimulate fibroblasts and other cells involved in fibrosis. IL-6 is a (acute phase) cytokine secreted by mononuclear phagocytes, vascular endothelial cells, fibroblasts and other cells and acts as both, a pro-inflammatory cytokine and an anti-inflammatory myokine. An anti-inflammatory role of IL-6 is associated with its inhibitory effect on TNF-alpha and IL-1. Role of IL-6 in fibrosis has been associated with its active release from fibroblasts during inflammatory responses.⁷,⁸ IL-4 induces the differentiation and activation of naïve helper T cells (Th0) to Th2 cells. Th2 cells subsequently produce IL-4 which is similar in function to IL-13.
Table 1: Demographic and Preliminary data of the study group

<table>
<thead>
<tr>
<th></th>
<th>Systemic sclerosis (n=25)</th>
<th>Healthy subjects (n=25)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Mean ± SD) (in yrs)</td>
<td>35.36 ± 10.41</td>
<td>35.48 ± 10.22</td>
<td>NA</td>
</tr>
<tr>
<td>Sex (M / F)</td>
<td>3 / 22</td>
<td>3 / 22</td>
<td>NA</td>
</tr>
<tr>
<td>ANA positivity</td>
<td>22 (88%)</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Anti-dsDNA Ab positivity</td>
<td>0</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Anti-Scl70 Ab positivity</td>
<td>15</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Anti-centromere Ab pos.</td>
<td>5</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Anti-U1-snRNP Ab pos.</td>
<td>0</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>IL-1β (pg/ml) (Mean ± SEM)</td>
<td>319.6 ± 227.4</td>
<td>5.318 ± 1.444</td>
<td>0.0006</td>
</tr>
<tr>
<td>IL-4 (pg/ml) (Mean ± SEM)</td>
<td>20.01 ± 4.08</td>
<td>6.866 ± 2.94</td>
<td>0.0102</td>
</tr>
<tr>
<td>IL-6 (pg/ml) (Mean ± SEM)</td>
<td>14.06 ± 6.957</td>
<td>1.825 ± 0.1235</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

ANA was observed positive in 22 (88%) patients. 3 (12%) patients who were sero-negative were included as they fulfilled the ACR/EULAR 2013 criteria.

Table 2: Clinical Presentations at the time of participation for the study

<table>
<thead>
<tr>
<th>Clinical Manifestation</th>
<th>Sub-classification</th>
<th>Score</th>
<th>Patients (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thickening of fingers on both hands</td>
<td></td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Skin thickening on fingers</td>
<td>Puffy fingers</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Scleroderactly</td>
<td>4</td>
<td>23</td>
</tr>
<tr>
<td>Finger-tip lesions</td>
<td>Digital tip ulcers</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>Finger-tip pitting scars</td>
<td></td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Telangiectasia</td>
<td></td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Abnormal Nail-fold capillaries</td>
<td></td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Raynaud’s phenomenon</td>
<td></td>
<td>3</td>
<td>21</td>
</tr>
<tr>
<td>Pulmonary Arterial Hypertension / Interstitial Lung Disease</td>
<td></td>
<td>2</td>
<td>10</td>
</tr>
</tbody>
</table>

Fig. 1: Significant contribution of IL-4 observed in SSc patients in pulmonary and generalized fibrosis. IL-4 is seen significantly contributing to fibrosis of lungs and in skin tissues.

Fig. 2: Association of IL-1β serum levels in SSc patients in pulmonary fibrosis and generalized fibrosis. IL-1β is seen significantly contributing to fibrosis in skin tissues; whereas the levels are sharply elevated in pulmonary fibrosis.

Fig. 3: Lower IL-6 serum levels in SSc patients in pulmonary fibrosis and generalized fibrosis. IL-6 is seen in marked low levels among patients with fibrosis.

The cells which initially produce IL-4 have not been identified, but some studies suggest that basophils may be the effector cells for IL-4 synthesis. IL-4, an important cytokine of the adaptive immune response, is an important regulator in the humoral and adaptive immunity. It is a suppressor of production of Th1 cells, macrophages, IFN-gamma and dendritic cells. It promotes alternative activation of macrophages into repair macrophages (M2) instead of classical M1 cells.10, 12 Along with other proteins, IL-4 stimulates the synthesis of extracellular matrix by promoting production of collagen, fibronectin and proteoglycan, and inhibiting the synthesis of specific collagenases, together leading to wound repair and fibrosis.13 IL-4 and other cytokines released from Th2 cells are involved in airway inflammation observed in pulmonary manifestations in patients with autoimmunity and allergic asthma.14
The aim of this study is to understand cytokine interplay of IL-1β, IL-4 and IL-6 and their association with disease activity in treatment naive active cases of systemic sclerosis from India.

**Materials and Methods**

A total of 25 clinically diagnosed treatment naïve systemic sclerosis patients (above 18 yrs. of age) over a period of 12 months were enrolled after clinical assessment following standard protocols. Patients and Healthy controls were enrolled after obtaining Ethical permission from the institute and informed consent from the participants. Patients with an autoimmune overlap were excluded. An equal number of age sex matched controls were also included in this study. Demographic data and available routine investigation reports like pulmonary function test (PFT), skin biopsy, nail-fold capillaroscopy were recorded. Patients were classified into categories based on pulmonary fibrosis involvement (ILD) and also based on clinical manifestations involving fibrosis. Serological assessment for anti-nuclear antibodies (ANA) and anti-dsDNA antibodies was performed by indirect immunofluorescence (IIF) assay [Biorad, USA]. Other autoantibodies like anti-Centromere antibodies, anti-Topoisomerase I (anti-Scl70) antibodies and anti-U1-snRNP antibodies was performed by Line-BLOT assays (Euroimmun, Germany). Flow cytometer (BD FACS ARIA Special Order System, USA) was used for assessing the multiplex bead based assay for estimating serum cytokines IL-4 and IL-1β using Aimplex [YSL Bio, USA]. FCAP Array Software v1.0.0. RC1 was used for calculation of results. IL-6 was detected using ELISA technique. TECAN Infinite 200 multimode reader [Switzerland] was used for reading at 450 nm. GraphPad Prism Version 6.01 was used for all data analysis.

**Results**

**Characteristics of the patient population**

The study group included twenty-five (25) clinically diagnosed treatment naïve systemic sclerosis patients based on ACR-EULAR 2013 criteria (age; 35.36 ± 10.41 years) and equal number of age-sex matched healthy controls (age; 35.48 ± 10.22 years). There were 22 females (88%) and 3 males (12%) where the female : male ratio is 7.33:1 (Table 1). Ten patients (40%) were diagnosed with Interstitial lung disease (ILD), whereas, 16 patients (64%) had clinical manifestations which are governed by fibrosis (Table 2). Three patients (12%) had a history of Tuberculosis infection.

**Autoantibody profile in patients**

Anti-nuclear antibodies (ANA) were present in 22 patients (88%) of which 9 patients (41%) showed nuclear, 5 patients (23%) showed centromere, 3 patients (13%) showed speckled IFA pattern and the remaining 5 patients (23%) showed homogenous pattern. 15 patients (60%) showed anti-Scl70 antibodies, whereas 5 patients (20%) showed anti-Centromere antibodies. None of the patients had anti-dsDNA and anti-U1-snRNP antibodies (Table 1).

**Evaluating sera cytokine levels in patients and comparing them with healthy controls**

Serum cytokine levels of IL-1β in SSc patients (319.6 ± 227.4 pg/ml; Mean ± SEM) were significantly greater than healthy controls (5.318 ± 1.444 pg/ml) (p=0.0006). Serum IL-4 levels in patients (20.01 ± 4.408 pg/ml) were significantly higher in SSc patients as compared to healthy controls (6.866 ± 2.94 pg/ml) (p=0.0102). Serum IL-6 levels in patients (14.06 ± 6.957 pg/ml) were also significantly raised as compared to healthy controls (1.825 ± 0.1235 pg/ml) (p < 0.0001) (Table 1). We did not find any association of the autoantibodies with disease severity as well as cytokine levels.

**Evaluating association between serum cytokines and lung fibrosis (ILD) (n=10)**

SSc patients with ILD (n=10) showed higher levels of IL-1β (724.6 ± 534.0 pg/ml) and IL-4 (21.25 ± 6.462 pg/ml) as compared to SSc patients without ILD (IL-1β : 30.39 ± 19.01 pg/ml) (IL-4 : 4.513 ± 1.640 pg/ml). Only IL-4 was found to be significantly raised in ILD patients (p = 0.021). IL-6 serum levels in SSc patients with ILD (4.487 ± 1.445 pg/ml) were found to be lower as compared to patients without ILD (20.44 ± 11.41 pg/ml) (Figure 1 – 3).

**Evaluating association between serum cytokine levels among patients with clinical manifestations with fibrosis (n=16)**

When patients were classified on basis of generalised fibrosis (n=16), IL-1β levels (505.8 ± 359.6 pg/ml) and IL-4 levels (29.67 ± 5.539 pg/ml) were significantly higher than in patients with generalized fibrosis (IL-1β : 9.345 ± 1.036 pg/ml) (IL-4 : 2.519 ± 1.005 pg/ml). Both IL-1β (p = 0.0293) and IL-4 (p < 0.0001) were found to be significantly raised in patients having fibrosis. IL-6 serum levels in patients with fibrosis (6.425 ± 2.338 pg/ml) were found to be lower than in patients without fibrosis (27.63 ± 18.69 pg/ml) (Figure 1 – 3).

The distribution of cytokine levels within the cutaneous manifestations was insignificant (p>0.05) (Figure 4).

**Discussion**

Cytokines form an important aspect of the immune pathologic response which induce various signaling pathways in fibrosis. The pathogenesis of SSc is incompletely understood because of the multiple partially elaborated events that lead to progression of the disease. The leukocyte-endothelial interactions are mediated by cytokines, which aberrantly recruit inflammatory cells into the perivascular dermal matrix. Cytokines are one of the important cell signaling (regulatory and indicator) proteins released by the various lineages of T-helper cells, which regulate the balance between humoral and cell-based immune response; maturation, growth, and cell response. Some cytokines are also known to enhance or inhibit the action of other cytokines directly or through multiple cascades.

Our study showed marginally raised IL-4 levels in patients as compared to healthy controls. While the IL-1β and IL-6 levels were found to be greatly elevated in patients as compared to healthy controls. Our study group showed 40% incidence of pulmonary fibrosis. This was higher as compared to 12% pulmonary arterial involvement recently reported by McMahan et al (2015) in American SSc patients. Approximately 80% Italian SSc patients had been reported with pulmonary involvement (Scala et al) (2004). Clark et al (2015) reported 42% incidence of pulmonary involvement among SSc patients from UK whereas 31% incidence was noted in Croatian SSc patients that had pulmonary involvement. Presence of antinuclear antibodies (ANA) had been observed in
approximately 95% cases of systemic sclerosis globally. Our data showed slightly lower ANA positivity (88%).

Anti-Topoisomerase I (anti-Scl70) antibodies, which primarily were found associated with diffused systemic sclerosis had been reported in 65% SSc patients. Similar findings were noted in our study where 60% patients had anti-Scl70 antibodies. Our earlier study showed an incidence of 20% for anti-centromere antibodies in limited form of scleroderma with CREST syndrome.

Though earlier studies had reported pathophysiology of systemic sclerosis and fibrosis, no much data is available on the impact of various cytokines among newly diagnosed and treatment naïve cases of systemic sclerosis. Similarly, less information is available for the cytokine interplay and disease activity among SSc patients with ILD and without ILD. We had observed a different pattern of the cytokine profile among Indian SSc patients Most of the studies had reported only IL-6 and/or IL-1β to be significantly raised in SSc patients. IL-4 was reported to be not significantly raised in SSc patients as compared to healthy controls. Clark et al (2015) had reported statistically significant IL-6 levels (p=0.01) and marginally raised IL-4 and IL-1β levels among SSc patients from UK. Scala et al (2004) had reported significantly raised levels of serum IL-4 (p=0.042) and in culture supernatant of PBMCs and T lymphocytes of SSc patients. Higher levels of IL-1β were also reported by Hussein et al (2005) and Beirne et al (2009) in SSc patients. In a study by Gourh et al (2009) in American SSc patients, significantly higher levels of IL-6 were reported (p < 0.0001). The same group reported lower levels of IL-1β and a marginally higher level of serum IL-4 in the SSc patients as compared to healthy controls. Egyptian population IL-6 levels were found significantly raised than healthy controls (p = 0.0001) (Yousif M and Habib R, 2015).

In the present study among SSc patients with pulmonary fibrosis, only IL-6 levels were found to be significantly elevated. IL-6 levels were lower in SSc patients with fibrosis (both pulmonary and generalized) whereas IL-1β and IL-4 levels were significantly elevated in Indian SSc patients with generalized fibrosis (Table 3).

Conclusion

Thus our study on Indian SSc patients showed 40% patients having pulmonary involvement and associated cytokine interplay. Although many studies had reported an association between cytokines and autoantibodies in SSc patients, we did not find such association in our active, treatment naïve SSc patients. It also indicated the possible role of these cytokines in fibrotic activity leading to disease severity. Results also supported active role of IL-1β and IL-6 in proinflammatory conditions indicating the role of IL-1β and IL-6 in disease severity (chronic inflammatory response). However only IL-4 was observed to be contributing to fibrosis indicating the possible role in pathogenesis of the disease. Our study did not indicate involvement of these cytokines in disease progression being one time point study. Further studies are to be conducted in this regard on a bigger cohort of SSc patients to understand the changes in cytokine profile for disease progression and management.

Source of Support

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Assessing the Utility of GeneXpert MTB/Rif Assay in a Tertiary Care Centre in Southern India with Established Microscopy and Liquid Culture Facilities

Aman Bhardwaj¹, Sadia Khan²*, Anil Kumar³, Liju George⁴, Asmita Mehta⁵, Kavitha Radhakrishnan³

Abstract

Background: To evaluate the diagnostic accuracy of the Xpert MTB/RIF assay for the detection of M. tuberculosis in pulmonary and extra-pulmonary specimens and to compare it with conventional techniques.

Methods: A prospective study was conducted with the introduction of GeneXpert in a tertiary care hospital which relied on microscopy and culture for diagnosis of tuberculosis. All patients for whom geneXpert was ordered by the physician were included in the study. Samples which did not have accompanying microscopy or MGIT culture requests were excluded from the analysis of the results. Sensitivity and specificity of GeneXpert was calculated using liquid culture as the reference test.

Results: Xpert MTB/RIF assay was performed on 742 samples of which 116 were positive for Mycobacterium tuberculosis. Rifampicin resistance was seen in 6 samples. The pulmonary samples showed a positivity rate of 16.8% while 17.1% of the extrapulmonary samples were positive by GeneXpert. A comparative analysis of microscopy, liquid culture and GeneXpert could be done for 88 samples. Of the 88 geneXpert positive samples, 42 were positive by smear microscopy and MGIT culture while 46 showed discordant results. Of these, 18 samples were positive by geneXpert but showed no growth in MGIT culture. 15 of these patients had undergone anti-tuberculous treatment (ATT) within the past 12 months. The sensitivity of geneXpert was 89.7% and specificity was 95.1% when compared to liquid culture as a gold standard. Sensitivity for extrapulmonary samples was 85.7% and specificity was 98.05%.

Conclusion: To conclude, though GeneXpert detects tuberculosis within the shortest possible time, it still suffers from intermediate level sensitivity, which makes culture facilities relevant even in settings that offer an Xpert/Rif assay.

Introduction

Tuberculosis continues to be a major global health problem, with 9.6 million new cases diagnosed every year and 1.5 million TB deaths.¹ The World Health Organization (WHO) Global Report states that the TB death rates are unacceptably high despite the fact that with a timely diagnosis all TB cases can be cured.¹ Global tuberculosis control programmes can only be effective when robust diagnostic methods for detecting tuberculosis exist. Until recently, the field of TB diagnostics had seen very little development, with many laboratories relying on techniques which were being used half-a-century ago i.e. conventional staining with Zeihl-Neelsen and use of egg based solid media for culture of Mycobacterium tuberculosis. GeneXpert MTB/Rif assay is a self-contained, fully automated nucleic acid amplification technology, which allows rapid and relatively sensitive diagnosis of tuberculosis.² The Xpert MTB/Rif assay is believed to be a “game-changer” in the field of TB diagnostics. Therefore, it has been endorsed by WHO for the diagnosis of pulmonary TB and is an integral part of its effort to strengthen TB diagnostics in clinical laboratories across the world.³

The Xpert MTB/Rif (GeneXpert) technology can detect Mycobacterium tuberculosis and rifampicin resistance-a surrogate marker for MDR-TB, in approximately 2 hours.⁴ With minimal requirements of training and biosafety measures, GeneXpert can be used closer to point of care than most other diagnostic methods.⁴⁻¹² That the test has high sensitivity and specificity, has been proved by several clinical validation studies and operational trials.¹¹⁻¹² However, much work remains to be performed to ascertain the utility of GeneXpert in various settings and patient population.¹³

We conducted this study to elucidate the role of geneXpert in a tertiary care centre with established liquid culture and microscopy facilities in South India.

Methods

Patient population of the study

This prospective study was conducted at a 1500 bed tertiary care centre in Kochi, Kerala. The hospital caters to a diverse patient population from Kerala, neighbouring states, islands of Lakshadweep and Andaman & Nicobar Islands and international patients from middle-east Asia, parts of Africa and NRIs from diverse locations. GeneXpert was started at this centre in January 2015, before which smear microscopy by Zeihl Neelsen technique and Auramine Phenol method as well as liquid culture by MGIT were used for diagnosing tuberculosis.

The study was conducted between January 2015 and December 2015.

¹Final year MBBS Student, ²Associate Professor, ³Professor, ⁴Resident, Department of Microbiology, ⁵Professor, Department of Pulmonology, Amrita Institute of Medical Sciences, Kochi, Kerala, ²Corresponding Author
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minutes and decolorized using acid alcohol. Potassium permanganate was used to flood the slide for 1 minute and the smears were dried and observed under fluorescent microscope and graded according to guidelines issued by WHO and followed by Central TB division, India.14

### Liquid Culture

Liquid culture of all samples was done in Mycobacterial Growth Indicator Tube (BBL MGIT) which contains Middlebrook 7H9 liquid media and an oxygen-quenched fluorochrome, embedded in silicone at the bottom of the tube. During bacterial growth within the tube, the free oxygen is utilized and is replaced with carbon dioxide. With depletion of free oxygen, the fluorochrome is no longer inhibited, resulting in fluorescence within the MGIT tube when visualized under UV light.15 Samples for liquid culture were decontaminated using NALC-NaOH method as recommended by CDC.16

The decontaminated samples (0.5ml) were added to labelled MGIT tubes with 0.8ml of antimicrobial PANTA solution and left at room temperature for 30 minutes after inoculation. They were incubated in the MGIT960 machine till the instrument flagged it positive. Positive tubes were confirmed for Mycobacterium tuberculosis by performing AFB smear and MPT 64 rapid card test (SDbioline).

### GeneXpert

Samples were processed according to standardized protocol recommended by WHO.17 The sample was mixed with double volume of Xpert MTB/Rif sample reagent and vortexed for 10 seconds followed by 5 minutes of incubation at room temperature. 2ml of sample was transferred to Xpert MTB/Rif cartridge and loaded into the machine. The sample combines with the sample processing control (SPC) in the cartridge. A filter captures the sample and SPC. Ultrasonically lysed cells release the DNA from bacterial cells if present. Eluted DNA combines with dried down bead reagents in the cartridge. PCR and detection occurs in the real time and results are ready to be viewed and printed in 1 hour 52 minutes on an average.

### Statistical Analysis

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of GeneXpert assay was compared to MGIT culture as a reference standard using contingency two-by-two tables. P values less than 0.05 were taken as statistically significant. All statistical analyses were performed using SPSS Statistics 17.0.

### Results

A total number of 742 samples were received for GeneXpert between January to December 2015. These consisted of 339 pulmonary samples and 403 extrapulmonary samples. 116 samples were positive for *Mycobacterium tuberculosis* by GeneXpert. 6 of these samples showed rifampicin resistance also.

The pulmonary samples showed a positivity rate of 16.8% by geneXpert while 17.1% of the extrapulmonary samples were positive by geneXpert (Table 1). Microscopy was done for 110 of the 116 geneXpert positive samples of which 68 were positive for acid fast bacilli. Liquid culture was done for 88 of these samples of which 70 grew *Mycobacterium tuberculosis* (Table 2, 3).

A comparative analysis of all three methods was done (Table 4). Of the 88 geneXpert samples, 42 were positive by smear microscopy and MGIT culture while 46 showed discordant results. The discordant samples were further analysed (Table 5, 6). 18 samples were positive by geneXpert but showed no growth in MGIT culture. Of these 15 patients had undergone anti-tuberculous treatment (ATT) within the past 12 months (Table 5). During the study period 8 samples which were negative by geneXpert and grew *M. tuberculosis* in MGIT culture were also analysed (Table 6).

### Table 1: Distribution of Xpert MTB/Rif positive samples

<table>
<thead>
<tr>
<th>Sample</th>
<th>No. positive</th>
<th>Percentage positive (Sample wise)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary (339)</td>
<td>88</td>
<td>28.6%</td>
</tr>
<tr>
<td>Sputum (n=95)</td>
<td>32</td>
<td>33.6%</td>
</tr>
<tr>
<td>BAL (n=215)</td>
<td>25</td>
<td>11.6%</td>
</tr>
<tr>
<td>Others (n=29)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Extrapulmonary (403)</td>
<td>192</td>
<td>47.8%</td>
</tr>
<tr>
<td>Pleural fluid (n=110)</td>
<td>4</td>
<td>3.6%</td>
</tr>
<tr>
<td>Lymph node (n=25)</td>
<td>19</td>
<td>76%</td>
</tr>
<tr>
<td>Pus (n=40)</td>
<td>20</td>
<td>50%</td>
</tr>
<tr>
<td>Tissue (n=140)</td>
<td>10</td>
<td>7.1%</td>
</tr>
<tr>
<td>Pericardial fluid (n=7)</td>
<td>1</td>
<td>14.2%</td>
</tr>
<tr>
<td>CSF (n=26)</td>
<td>2</td>
<td>7.6%</td>
</tr>
<tr>
<td>Synovial fluid (n=10)</td>
<td>1</td>
<td>10%</td>
</tr>
<tr>
<td>Asctic fluid (n=10)</td>
<td>1</td>
<td>10%</td>
</tr>
<tr>
<td>Urine (n=35)</td>
<td>1</td>
<td>2.8%</td>
</tr>
<tr>
<td>Total (n=742)</td>
<td>116</td>
<td>15.6%</td>
</tr>
</tbody>
</table>

### Table 2: Comparison of Xpert MTB/Rif positive samples and microscopy

<table>
<thead>
<tr>
<th>Sample</th>
<th>No. positive</th>
<th>Percentage positive (Sample wise)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary</td>
<td>88</td>
<td>28.6%</td>
</tr>
<tr>
<td>Sputum</td>
<td>32</td>
<td>33.6%</td>
</tr>
<tr>
<td>BAL</td>
<td>25</td>
<td>11.6%</td>
</tr>
<tr>
<td>Others</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Extrapulmonary</td>
<td>192</td>
<td>47.8%</td>
</tr>
<tr>
<td>Pleural fluid</td>
<td>4</td>
<td>3.6%</td>
</tr>
<tr>
<td>Lymph node</td>
<td>19</td>
<td>76%</td>
</tr>
<tr>
<td>Pus</td>
<td>20</td>
<td>50%</td>
</tr>
<tr>
<td>Tissue</td>
<td>10</td>
<td>7.1%</td>
</tr>
<tr>
<td>Pericardial fluid</td>
<td>1</td>
<td>14.2%</td>
</tr>
<tr>
<td>CSF</td>
<td>2</td>
<td>7.6%</td>
</tr>
<tr>
<td>Synovial fluid</td>
<td>1</td>
<td>10%</td>
</tr>
<tr>
<td>Asctic fluid</td>
<td>1</td>
<td>10%</td>
</tr>
<tr>
<td>Urine</td>
<td>1</td>
<td>2.8%</td>
</tr>
<tr>
<td>Total</td>
<td>116</td>
<td>15.6%</td>
</tr>
</tbody>
</table>

### Table 3: Comparison of Xpert MTB/Rif positive samples and liquid culture (MGIT)

<table>
<thead>
<tr>
<th>GeneXpert Positive (n=116)</th>
<th>Total samples for MGIT culture =88</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culture Positive</td>
<td>70</td>
</tr>
<tr>
<td>Culture Negative</td>
<td>18</td>
</tr>
<tr>
<td>Culture not sent</td>
<td>28</td>
</tr>
</tbody>
</table>

### Table 4: Comparative analysis of positive tuberculosis samples by 3 methods: Xpert MTB/Rif assay, AFB smear and MGIT culture

<table>
<thead>
<tr>
<th>No.of Samples</th>
<th>GeneXpert</th>
<th>AFB Smear</th>
<th>MGIT Culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>42</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>8</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>28</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>10</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
This study was performed to assess the utility of GeneXpert in a centre with established culture and microscopy facilities. The most distinguishable asset of having an Xpert system in the repertoire of tests that a laboratory offers is its rapid turnaround time. As evident from the turnaround time in this study, GeneXpert gives a positive result within 3 hours of sample collection.

Even though, microscopy appears to be faster, it fails to differentiate between *Mycobacterium tuberculosis* and non tuberculous mycobacteria. Liquid culture, though reliable takes longer to be faster, it fails to differentiate between *Mycobacterium tuberculosis* and non tuberculous mycobacteria. Eventhough, microscopy appears to be faster, it fails to differentiate between *Mycobacterium tuberculosis* and non tuberculous mycobacteria. Liquid culture, though reliable takes longer to be faster, it fails to differentiate between *Mycobacterium tuberculosis* and non tuberculous mycobacteria. However, its less than optimal performance in certain populations like HIV positive individuals makes use of an additional test imperative.

**Table 5: Analysis of discordant samples: Xpert MTB Rif Positive, MGIT culture negative samples**

<table>
<thead>
<tr>
<th>GeneXpert ID</th>
<th>Sample</th>
<th>AFB Smear</th>
<th>Relevant details</th>
</tr>
</thead>
<tbody>
<tr>
<td>GX74</td>
<td>BAL</td>
<td>-</td>
<td>Patient on ATT since 3 months</td>
</tr>
<tr>
<td>GX81</td>
<td>LymphNode</td>
<td>-</td>
<td>Received ATT 1 year back</td>
</tr>
<tr>
<td>GX124</td>
<td>BAL</td>
<td>-</td>
<td>Received ATT 6 months back</td>
</tr>
<tr>
<td>GX264</td>
<td>BAL</td>
<td>-</td>
<td>Patient on ATT since 2 months</td>
</tr>
<tr>
<td>GX238</td>
<td>Pus (Neck)</td>
<td>-</td>
<td>Patient on ATT &gt; 2 years; stopped 1 month back</td>
</tr>
<tr>
<td>GX25</td>
<td>Sputum</td>
<td>+</td>
<td>Patient on ATT since 2 months</td>
</tr>
<tr>
<td>GX156</td>
<td>Pleural fluid</td>
<td>+</td>
<td>Patient on ATT since 3 months</td>
</tr>
<tr>
<td>GX246</td>
<td>Pus</td>
<td>+</td>
<td>Data not available</td>
</tr>
<tr>
<td>GX252</td>
<td>Sputum</td>
<td>+</td>
<td>Patient on ATT since 2 months</td>
</tr>
<tr>
<td>GX285</td>
<td>Sputum</td>
<td>+</td>
<td>Patient on ATT since 2 months</td>
</tr>
<tr>
<td>GX236</td>
<td>Pus (Cervical abscess)</td>
<td>+</td>
<td>Patient on ATT &gt; 1 year</td>
</tr>
<tr>
<td>GX342</td>
<td>Ascitic fluid</td>
<td>-</td>
<td>MTB PCR for IS6110 Negative; peritoneal nodes GeneXpert +ve</td>
</tr>
<tr>
<td>GX648</td>
<td>Lymph node</td>
<td>-</td>
<td>Patient on ATT since 7 month</td>
</tr>
<tr>
<td>GX685</td>
<td>sputum</td>
<td>-</td>
<td>Patient on modified ATT(HREZ) after completing 4 months of intensive phase and sputum conversion.</td>
</tr>
<tr>
<td>GX418</td>
<td>Sputum</td>
<td>-</td>
<td>On ATT For 5 months</td>
</tr>
<tr>
<td>GX489</td>
<td>Sputum</td>
<td>-</td>
<td>No ATT, CT suggestive of lower lobe tuberculosis</td>
</tr>
<tr>
<td>GX545</td>
<td>Pus from paravertebral abscess</td>
<td>+</td>
<td>On ATT for skeletal TB since 1 month</td>
</tr>
<tr>
<td>GX595</td>
<td>BAL</td>
<td>-</td>
<td>Treated case of old pulmonary TB.</td>
</tr>
</tbody>
</table>

**Table 6: Analysis of discordant samples: Xpert MTB Rif Negative, MGIT culture positive samples**

<table>
<thead>
<tr>
<th>GeneXpert ID</th>
<th>Sample</th>
<th>Relevant details</th>
</tr>
</thead>
<tbody>
<tr>
<td>GX17</td>
<td>Pericardial fluid</td>
<td>Interlaboratory comparison at Quest,Gurgaon also negative</td>
</tr>
<tr>
<td>GX26</td>
<td>Pericardial fluid</td>
<td>Sample repeated with additional processing steps: Positive</td>
</tr>
<tr>
<td>GX125</td>
<td>BAL</td>
<td>Blood stained specimen</td>
</tr>
<tr>
<td>GX240</td>
<td>Pleural fluid</td>
<td>MTB PCR Negative (for IS6110)</td>
</tr>
<tr>
<td>GX299</td>
<td>Buccal mucosa</td>
<td>Blood stained specimen</td>
</tr>
<tr>
<td>GX344</td>
<td>Ileal biopsy</td>
<td>Blood stained specimen</td>
</tr>
<tr>
<td>GX389</td>
<td>BAL</td>
<td>IGRA-intermediate</td>
</tr>
<tr>
<td>GX661</td>
<td>Mastoid Abscess</td>
<td>MTB PCR Negative (for IS6110)</td>
</tr>
</tbody>
</table>

GeneXpert has an important role to play in intensified case finding scenarios which may have an immediate and sustained effect on TB epidemiology. However, its less than optimal performance in certain populations like HIV positive individuals makes use of an additional test imperative.

Analysis of GeneXpert positive but culture negative samples showed that a majority of these patients were already on anti-tuberculous drug regimes. Therefore, it is imperative that this technology should be used for diagnosing new cases of tuberculosis, as recommended by the manufacturer. Treated cases can be tested for development of rifampicin resistance.

Similarly, our study showed 8 samples which were culture positive but negative by GeneXpert. 2 of these samples were negative by an in-house PCR while1 showed similar results in an inter laboratory comparison done at another laboratory. The other samples were blood stained; one of them gave a positive Xpert result after extensive reprocessing. The limitation of PCR assays in the presence of biological inhibitors such as blood has been well documented. Our experience with blood stained specimens shows that an extended processing step for blood stained specimens can help to reduce the false negatives in geneXpert.

Several studies have pointed out the intermediate level sensitivity of GeneXpert, better than smear microscopy but less than broth culture, making it prone for false negative results. Our study showed a sensitivity of 89.7% comparable to similar studies. It has been inferred from similar research that a single Xpert/Rif assay may be insufficient to rule-out tuberculosis, even though a second test may increase the sensitivity by 62%. Detection of rifampicin resistance is another important advantage of the Xpert/Rif assay. However, in this study even though rifampicin resistance was detected in 6 cases, we could confirm only 1 sample with the MGIT direct susceptibility test. This was a major limitation in our study.

This study also evaluated GeneXpert for extrapulmonary samples. Sensitivity for extrapulmonary samples was 85.7% and specificity was 98.05% which was comparable to other studies. However,
disaggregated sample data could not be analysed due to small sample size.

To conclude, though GeneXpert detects tuberculosis within the shortest possible time, it still suffers from intermediate level sensitivity, which makes culture facilities relevant even in settings that offer an Xpert/Rif assay.

Acknowledgement

We thank Mr. Sreejith CV, Technical supervisor, Mycobacteriology, Amrita Institute of Medical sciences for excellent technical support. We also thank IPAQT of which we are a partner laboratory; which enables us to offer Xpert MTB/Rif assay tests at subsidized costs to our patients.

References

Cardiac Amyloidosis: A Case Series from India

Nikhil Raut¹, Anil Potdar², Satyavan Sharma³

Abstract

Objective: Cardiac amyloidosis (CA) is not well recognized in Indian literature. The aim of this communication is to highlight the difficulties in diagnosis.

Methods: A retrospective analysis of data of six patients of CA diagnosed during 2008 to 2015 was done. Clinical, investigative, management and follow-up data is analyzed.

Results: The mean age was 51 years with male preponderance. Heart failure was the commonest manifestation. Atrial arrhythmias were seen in 33%. Syncope, peripheral neuropathy and macroglossia were striking features. A speckled inter-ventricular septum (66%) or thickened inter-atrial septum (16%) on echocardiography strongly favoured CA. Other echocardiography features include thickened ventricular wall, enlarged atria and pericardial effusion (PE). Late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) was characteristic of CA. Plasma cell dyscrasia confirmed light chain amyloidosis. Abdominal fat pad and rectal biopsy confirmed the diagnosis. Chemotherapy for plasma cell dyscrasia was administered in 50% of patients.

Conclusions: Echocardiography and CMR imaging enable the diagnosis of CA in background of strong clinical suspicion. Abdominal fat pad biopsy is a simple and reliable method for confirming the diagnosis.

Implications and Practice: The awareness of this entity can enable an early diagnosis and improve the survival with timely novel chemotherapy.

Introduction

Systemic amyloidosis is characterized by deposition of insoluble abnormal fibrils in the viscera, blood vessel wall or connective tissue. Cardiac amyloidosis (CA) refers to involvement of heart by amyloid deposition whether as part of systemic amyloidosis (frequently) or as a localized phenomenon.¹ The clinically relevant forms are immunoglobulin-derived light chain (AL) and transthyretin-derived (ATTR) amyloidosis. AL amyloidosis, previously referred as primary amyloidosis is the most common form of systemic amyloidosis resulting from plasma cell dyscrasia. Approximately 90% of patients with AL amyloidosis present with cardiac involvement. Symptomatic heart failure is seen in 50% of patients on presentation and is major factor impacting survival.²

There are scattered reports of CA in Indian literature.¹ ³ ⁴ This series documents the profile of CA encountered in tertiary care practice in our country. The clinical diagnosis remains difficult however meticulous application of echocardiography, cardiac biomarkers and cardiac magnetic resonance (CMR) imaging can enable early recognition. Therapeutic regimens for AL amyloidosis have evolved over the years with improved survival. However, the overall prognosis remains dismal.

Material and Methods

The material for this study is obtained from records of academically interesting patients maintained by the author in a tertiary care referral postgraduate teaching institute. Six cases of CA were diagnosed, treated and followed up during 2008 to 2016.

The diagnosis of amyloidosis was based on clinical presentation, measurement of serum immunoglobulin free light chain assay and histopathology. Skigram chest, electrocardiogram (ECG), routine blood investigations, N-terminal pro-brain natriuretic peptide (NT-pro BNP) and serum immunoglobulin free light chain assay (4 patients) were analysed. Detailed echocardiography and Doppler data was available in all whereas tissue Doppler, speckled tracking and 3 dimensional echocardiography in case 4. CMR (case 4, 5) and cardiac catheterization and hemodynamic data (case 1, 3 and 6) was reviewed. Histopathological diagnosis was achieved with abdominal fat pad biopsy in cases 1 to 5 and additional rectal biopsy in cases 3 and 4. Management details including chemotherapy (3 patients) and pacemaker therapy (1 patient) are available.

Results

Clinical data is summarized in Table 1. There was male preponderance and age ranged from 22 to 72 years (mean-51). Heart failure was the commonest manifestation. The blood pressure was frequently in lower range (90/70 to 110/80 mmHg) with 30 mmHg postural drop in case 5. Atrial arrhythmias were seen in two patients. Case 1 had atrial fibrillation (AF) and presented with syncope due to slow ventricular rate. Case 2 displayed a variety of rhythm abnormalities including brady-arrhythmias, atrio-ventricular dissociation and AF. Chronic diarrhoea prompted case 3 to seek hospitalization in gastroenterology unit. Symptoms due to peripheral neuropathy dominated the clinical presentation in case 5 and 6. Autonomic neuropathy with postural hypotension resulted in syncope in case 5. Macroglossia was striking.

¹Cardiologist, ²Director, Department of Cardiology, H.J. Doshi Hindusabha Hospital, Mumbai, Maharashtra; ³Professor and Head of Cardiology and Interventional Cardiologist, Bombay Hospital Institute of Medical Sciences, Mumbai, Maharashtra; ⁴Corresponding Author

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were invariably elevated (1600–9724, pg/ml). NT-pro BNP levels in case 6. Skiagram chest displayed varying degree of cardiomegaly with or without signs of pulmonary venous and arterial hypertension. ECG showed atrial arrhythmias, repolarization changes, low voltage complex and poor progression of ‘R’ waves in precordial leads. NT-pro BNP levels were invariably elevated (1600–9724, pg/ml).

Table 1: Clinical data

<table>
<thead>
<tr>
<th>Case number</th>
<th>Year of presentation</th>
<th>Presenting features</th>
<th>NT-pro BNP (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, (22/ M)</td>
<td>2008</td>
<td>Presyncope, AF with slow rate, dyspnea</td>
<td>1600</td>
</tr>
<tr>
<td>2, (72/ M)</td>
<td>2012</td>
<td>LHF, atrial arrhythmias, conduction block</td>
<td>5606</td>
</tr>
<tr>
<td>3, (46/ F)</td>
<td>2015</td>
<td>Chronic diarrhea, bi-ventricular failure</td>
<td>9274</td>
</tr>
<tr>
<td>4, (51/ M)</td>
<td>2015</td>
<td>LHF</td>
<td>4729</td>
</tr>
<tr>
<td>5, (55/ F)</td>
<td>2015</td>
<td>Syncope, peripheral neuropathy</td>
<td>2332</td>
</tr>
<tr>
<td>6, (65/ M)</td>
<td>2016</td>
<td>Peripheral neuropathy, macroglossia, RHF</td>
<td>3114</td>
</tr>
</tbody>
</table>

Table 2: Therapeutics and outcome

<table>
<thead>
<tr>
<th>Case number</th>
<th>Therapeutics</th>
<th>Survival after diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Diuretics, VVI pacemaker</td>
<td>6 months</td>
</tr>
<tr>
<td>2</td>
<td>Diuretics, Bortezomib, Lenalidomide, Prednisolone</td>
<td>6 weeks</td>
</tr>
<tr>
<td>3</td>
<td>Diuretics, ACEI</td>
<td>2 months</td>
</tr>
<tr>
<td>4</td>
<td>Diuretics</td>
<td>6 months</td>
</tr>
<tr>
<td>5,6</td>
<td>Diuretics, Bortezomib, Lenalidomide, Prednisolone, supportive (pregabalin, fludrocortisone)</td>
<td>Alive at 1 year</td>
</tr>
<tr>
<td>6</td>
<td>Diuretics, Bortezomib, Lenalidomide, Prednisolone, supportive (pregabalin)</td>
<td>Alive at 6 months</td>
</tr>
</tbody>
</table>

Table 3: Trans-thoracic echocardiography

<table>
<thead>
<tr>
<th>Case number</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BAE, thickened PW and IVS (speckled appearance), DD, mod PH, LVEF-70%</td>
</tr>
<tr>
<td>2</td>
<td>BAE, thickened IAS and PW, DD, LVEF-60%</td>
</tr>
<tr>
<td>3</td>
<td>LVH, thickened IVS (speckled appearance), DD, mod PH, mod TR, mild PE, LVEF-20%, RV EF</td>
</tr>
<tr>
<td>4</td>
<td>LVH, DD, mod PH, mild PE, LVEF-45%</td>
</tr>
<tr>
<td>5</td>
<td>LVH, thickened IVS (speckled appearance), DD, LVEF-55%</td>
</tr>
<tr>
<td>6</td>
<td>BAE, LVH, thickened IVS (speckled appearance), DD, mod PH, mild PE, LVEF-60%</td>
</tr>
</tbody>
</table>

Table 4: Invasive hemodynamic data

<table>
<thead>
<tr>
<th>Chamber</th>
<th>Case 1 (Pressure mmHg)</th>
<th>Case 3 (Pressure mmHg)</th>
<th>Case 6 (Pressure mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>m-18</td>
<td>m-16</td>
<td>m-8</td>
</tr>
<tr>
<td>RV</td>
<td>70/18</td>
<td>30/16</td>
<td>40/12</td>
</tr>
<tr>
<td>MPA</td>
<td>70/30, m-40</td>
<td>30/16, m-18</td>
<td>40/10, m-20</td>
</tr>
<tr>
<td>Ao</td>
<td>100/70, m-82</td>
<td>90/50, m-65</td>
<td>110/50, m-85</td>
</tr>
<tr>
<td>LV</td>
<td>Syst-100</td>
<td>Syst-90</td>
<td>Syst-110</td>
</tr>
<tr>
<td></td>
<td>LVEDP-20</td>
<td>LVEDP-18</td>
<td>LVEDP-16</td>
</tr>
</tbody>
</table>

Table 5: Cardiac magnetic resonance showing sub-endocardial late gadolinium enhancement of left ventricle (arrow). Abbreviations: LV- left ventricle, LA- left atrium

Abbreviations: VVI - single chamber pacemaker, ACEI- angiotensin converting enzyme inhibitor
was administered in 3 patients. Four patients died within 6 weeks-6 months (average-3.8 months) of diagnosis. One patient (case 5) is alive at one year. At the end of 6 months, case 6 has completed 4 cycles of chemotherapy.

Haematological assessment confirmed plasma cell dyscrasia (lambda chain gammopathy in cases 1, 4, 5 and 6 and Waldenstrom’s macroglobulinemia in case 2). Abdominal fat pad (cases 1 to 6) and rectal (case 3 and 4) biopsy revealed congophilic amorphous eosinophilic material demonstrating apple green birefringence under polarized light.

Discussion

Amyloidosis involves kidney, heart, gut, peripheral nerves and skin with associated organ dysfunction². This case series is the largest data on CA from our country. CA is a restrictive cardiomyopathy which is difficult to diagnose and treat. The delay in recognition further adds to the poor prognosis. The diagnosis is difficult due to diverse manifestations and patients present to different specialities (Table 1). Most of the patients were over the age of 50 years. There were subtle clues that raised the possibility of AL amyloidosis. In one-third of the patients peripheral neuropathy was encountered. Symmetrical sensory neuropathy is common and a thorough neurological examination is vital for a proper diagnosis. Autonomic nervous system dysfunction causing significant postural hypotension was observed in one case. Macroglossia was seen in one patient (16%). In literature, approximately 10% of the patients are reported to have changes in tongue which may vary from tooth indentation to obvious enlargement. Peri-orbital bruising in the setting of heart failure, although not seen in this study is pathognomic of amyloidosis.⁷

In this study, heart failure with preserved ejection fraction, syncope or atrial arrhythmias raised the possibility of CA. Reduced ejection fraction was uncommon. The blood pressure was invariably low due to combination of low cardiac output and reduced vascular tone. Blood pressure should be measured in both supine and standing postures because autonomic disturbance can manifest as significant postural hypotension as in case 5. Skiagram chest provided useful information about cardiac size, pulmonary venous and arterial hypertension. A variety of ECG changes including low voltage, pseudoinfarction pattern, atrial arrhythmias and atrio-ventricular block were observed. These reflect the generalized infiltrative nature of this disease and are well known in the literature.⁸

NT pro BNP estimation was useful and supported the diagnosis of CA. All patients had marked elevation (mean-4442 pg/ml) and co-related with mortality within 6 months. The disproportionate elevation as seen in this series has been attributed to the cellular release caused by direct myocardial compression in addition to high cardiac filling pressure. NT pro BNP can fall significantly after chemotherapy and has been associated with improved survival though it doesn’t correlate with objective assessment on echocardiogram.⁹

Echocardiography provides crucial information, however it cannot confirm the diagnosis in isolation and the images should be interpreted in the context of clinical picture and other investigations. A comprehensive TTE involving M mode, two and three dimensional, tissue Doppler and speckled tracking should be performed. Figure 1 and table 2 show features suggestive of CA. Thickening of the left ventricular (LV) wall in absence of systemic hypertension is the commonest finding and is often reported as “hypertrophy”. The right ventricular free wall can also be thickened. The pathological process is actually an infiltration and should not be interpreted as hypertrophy.¹⁰⁻¹⁵ A thickened IVS with speckled or granular (sparkling) appearance (66%) and thickened IAS (16%) strongly favoured CA in this study. A grossly thickened IAS as observed in case2 has 100% specificity for diagnosis of CA and is usually seen in advanced stage of the disease.¹⁶ Other features helpful in diagnosis include enlarged atria, thickened valves and PE. All patients had a restrictive pattern on mitral inflow assessment. Newer modalities can detect abnormal ventricular relaxation prior to appearance of morphological abnormalities.¹⁷ Speckle tracking, tissue Doppler and three dimensional imaging demonstrated baso-apical gradient with preserved systolic function at the apex and decreased LV torsion. These findings enabled us to make an early diagnosis of diastolic dysfunction in case 4.

The availability of CMR has enhanced our diagnostic abilities in the last two years. CMR due to its superior tissue characterization facilitates diagnosis and assists in sub-classification of CA. CMR demonstrated two features characteristic of CA. Both patients had sub-endocardial pattern of LGE within the atrial and ventricular myocardium and difficulty in nulling the myocardium following gadolinium injection. The sub-endocardial pattern and scoring of LGE helps in differentiation of sub-types.²⁷⁻⁸⁻¹⁹ Sub-endocardial LGE is more prevalent in AL variety, whereas trans-mural is more prevalent in ATTR. Four patients in this series has AL amyloidosis, a sub-type potentially amenable to chemotherapy.

The combination of plasma cell dyscrasia with a typical echocardiographic appearance with or without CMR imaging is highly suggestive of AL amyloidosis. However, the definitive diagnosis requires a tissue biopsy that demonstrates amyloid deposits with apple-green birefringence when stained with Congo red. The biopsy can be performed from any affected organ. In this study, fine-needle aspiration of the abdominal fat proved to be a simple procedure and provided diagnosis in majority. Rectal biopsy too proved extremely useful. Endo-myocardial biopsy is not necessary if the echocardiographic and CMR appearances are typical and histological diagnosis has been made from another tissue. The AL sub-type was diagnosed in 66% by detecting free light chain abnormal protein in the blood using immunofixation technique.

Cardiac amyloidosis has a poor prognosis and four patients (66%) died within a short period. The reported median survival from onset of heart failure is approximately six months. Treatment may be classified as supportive (heart failure therapy) and therapies that suppress production of respective amyloid fibril precursor protein. Chemotherapy that targets the underlying plasma cell dyscrasia has changed considerably in the last decade. There is a need for cardiologists to be involved in the treatment and evaluate patients during chemotherapy to adjust concomitant medications.
Modern therapies using a bortezomib (proteasome inhibitor), lenalidomide and dexamethasone causes remission andextends survival by few years.\textsuperscript{2,7,20} Bortezomib was well tolerated in our patients without any cardiotoxicity. Two patients who received chemotherapy are doing well at one year (case 5) and six months (case 6). Standard heart failure therapy may be of limited benefit or even detrimental due to low blood pressure and arrhythmias. Pacemaker and other devices provide limited benefit. Cardiac transplant in AL amyloidosis has been performed but the outcome depends on extremely careful selection of patients.

Conclusions

CA is rarely diagnosed in our country and this series should create awareness amongst physicians and cardiologists about challenges in diagnosis. Modern techniques like advanced echocardiography and CMR should be utilized liberally to facilitate an early recognition. The prognosis of this hopeless disease is changing.

References

Comparative Evaluation of Continuous Veno-venous Hemodiafiltration and Continuous Arterio-Venous Hemodiafiltration in Patients of Hepatic Failure and / or Hepatorenal Syndrome

Nitya Nand1*, Preeti Verma2, Deepak Jain3

Abstract

Objectives: Continuous renal replacement therapies (CRRT) are the most favoured form of renal replacement therapies (RRT) in patients of decompensated liver cirrhosis and hepatorenal syndrome (HRS). The role of CRRT has been limited only to acute kidney injury and HRS in prior studies. We therefore aimed to evaluate the role of two different modes of CRRT- CVVHDF and CAVHDF in patients of hepatic failure and / or hepatorenal syndrome in reducing hyperbilirubinemia, uremia and fluid overload.

Methods: 30 critically ill patients of hepatic failure and /or HRS were randomly divided into two groups of 15 cases each. Group A patients received continuous veno-venous hemodiafiltration (CVVHDF), whereas group B patients underwent continuous arterio-venous hemodiafiltration (CAVHDF). The inclusion criteria were hepatic failure and / or hepatorenal syndrome (HRS) with hyperbilirubinemia and fluid overload in hemodynamically unstable patients, who were unfit for conventional hemodialysis.

Results: Despite hemodynamic fragility of the subjects, both the procedures were effective in achieving biochemical and clinical improvements. There was a significant fall in blood urea, serum creatinine and serum bilirubin at the end of procedures. After mean 27.32 h of CVVHDF and 27.02 h of CAVHDF, blood urea decreased to 39.54 ± 28.6 mg/dl and 45.11 ± 31.9 mg/dl in respective groups. Serum bilirubin decreased to 7.01 ± 6.4 mg/dl and 3.21 ± 1.99 mg/dl in group A and B. All the patients had gradual and steady improvement in pH and bicarbonate concentration towards normal. Urea clearance was 24.98 ± 1.09 ml/min and 22.72 ± 1.58 ml/min respectively in the two groups, whereas bilirubin clearance was 27.77 ± 1.38 ml/min and 28.74 ± 0.3 ml/min in group A and B respectively. Ultrafiltration rate had mean value of 141.66 ± 22.33 ml/h in group A and 134.26 ± 38.71 ml/h in group B. Both the modes of CRRT were well tolerated without any new episodes of hypotension secondary to the procedures and requirement of inotropes didn’t change significantly. Symptomatic relief and improvement in clinical and biochemical parameters were observed in all the cases. There were no significant differences between the results of two groups. Complication rate was less and survival was 30%.

Conclusion: Continuous hemodiafiltration is probably the best available modality of CRRT to treat hemodynamically unstable and critically ill patients of hepatic failure and/ or hepatorenal syndrome and it should be advocated more frequently.

Introduction

Acute fulminant hepatic failure and decompensated cirrhosis are the major challenging global public health concerns. Renal dysfunction in liver disease, and hepatorenal syndrome (HRS) being its most severe form has a very poor prognosis.1,2 The only definitive treatment at this stage is liver transplantation.3 However, renal replacement therapies (RRT) are life saving and have a crucial role as bridge therapies. Conventional intermittent hemodialysis is less effective and is associated with a number of disadvantages. A variety of RRTs have been proposed to prolong the life span and improve prognosis of such critically ill patients.4 However, there are very scarce prospective studies regarding the use of continuous renal replacement therapies (CRRT) in patients of hepatic failure or HRS.5-7 These studies concluded that CRRT was effective in providing metabolic and biochemical correction in AKI, in the setting of multi-organ failure and was technically feasible even when conventional hemodialysis or peritoneal dialysis could not be performed. No study has been carried out regarding the role of CRRT in hepatic failure in reducing hyperbilirubinemia. Therefore, in order to evaluate and compare the efficacy and outcome of continuous hemodiafiltration, this prospective study was undertaken. In this study, we are reporting our experience of use of two modalities of CRRT in critically ill patients of hepatic failure and/ or hepatorenal syndrome requiring urgent hepatic and renal supportive intervention.

Material and Methods

Thirty critically ill patients of hepatic failure and / or hepatorenal syndrome were randomly divided into two groups of fifteen cases each. Group A patients received continuous veno-venous hemodiafiltration (CVVHDF), whereas in group B, continuous arterio-venous hemodiafiltration (CAVHDF) was done. The inclusion criterion was patients of hepatic failure and / or HRS who were hemodynamically unstable and unfit for conventional hemodialysis. A written consent for the procedures...
Table 1: Demographic parameters in two groups

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/Female</td>
<td>13/2</td>
<td>13/2</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>95.6 ± 6.05</td>
<td>97.33 ± 6.44</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>64.93 ± 6.96</td>
<td>64.66 ± 5.98</td>
</tr>
<tr>
<td>Icterus</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>CVP (cm H2O)</td>
<td>5.93 ± 1.27</td>
<td>7.13 ± 0.91</td>
</tr>
<tr>
<td>Fluid overload</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Ascites</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Hepatic encephalopathy (Grade I-IV)</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Hgb (g/dl)</td>
<td>8.55 ± 1.49</td>
<td>9.25 ± 1.66</td>
</tr>
<tr>
<td>Blood urea (mg/dl)</td>
<td>179.66 ± 74.45</td>
<td>171.86 ± 72.15</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>4.22 ± 1.60</td>
<td>3.48 ± 1.60</td>
</tr>
<tr>
<td>Serum bilirubin (mg/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>18.98 ± 12.14</td>
<td>9.49 ± 4.27</td>
</tr>
<tr>
<td>Direct</td>
<td>8.18 ± 6.45</td>
<td>3.43 ± 2.89</td>
</tr>
<tr>
<td>Indirect</td>
<td>10.21 ± 7.86</td>
<td>6.06 ± 4.27</td>
</tr>
<tr>
<td>PT/PTTK (s)</td>
<td>31.64/65.15</td>
<td>25.41/59.2</td>
</tr>
<tr>
<td>pH/ HCO3 (mmol/l)</td>
<td>7.31/14.33</td>
<td>7.31/13.79</td>
</tr>
<tr>
<td>APACHE II</td>
<td>18.86 ± 5.69</td>
<td>16.86 ± 4.74</td>
</tr>
<tr>
<td>MELD</td>
<td>37.33 ± 5.67</td>
<td>31 ± 4.65</td>
</tr>
<tr>
<td>Oliguria (&lt; 400ml/d)</td>
<td>12</td>
<td>10</td>
</tr>
</tbody>
</table>

was taken from all the subjects prior to enrollment in the study.

The study patients were evaluated for signs and symptoms of hepatic failure or HRS like hyperbilirubinemia, ascites, pedal edema, hepatic encephalopathy, azotemia and oliguria. Fluid overload was assessed by raised jugular venous pressure (JVP > 8 cm H2O) and pulmonary crackles. Patients with low central venous pressure (CVP < 4 cm H2O) were considered in hypovolemic shock and were adequately rehydrated before initiating vasopressor support. Baseline investigations including renal and hepatic functions were done in every patient before the start of the procedures. The overall assessment of illness severity at the admission was done by APACHE II score, whereas disease severity of hepatic failure was assessed by MELD score. A 1.3 m² hollow fibre, high flux, polyethersulfone hemofilter with high transmembrane pressure of 500 mmHg was connected bedside at the level of right atrium, to the venous access with pump during CVVHDF and to the arterial and venous access in pump less circuit during CAVHDF. Standard peritoneal dialysis fluid (sodium- 132 meq/l, chloride- 98 meq/l, calcium- 3.5 meq/l, magnesium- 0.5 meq/l, lactate- 40 meq/l, glucose- 1360 mg/dl) was run counter-current to the blood flow at a controlled rate of 1litre/h to achieve diffusive and convective clearance. In this study, ultrafiltration rate was kept less than 150 ml/h to avoid procedure induced hypotension. The rapidity and quantity of the fluid removal was individualized, depending on the patient’s clinical profile. The exact volume of ultrafiltrate removed was calculated in the graduated bag and the ultrafiltrate flow rate could be controlled by adjusting the height of the bag and varied on regular basis as the clinical picture dictated. The excess of ultrafiltrate was replaced with 0.9% normal saline, that was used as replacement fluid. Depending upon vital parameters of the subjects, a net negative balance of 100-200 ml/h was attempted. An initial loading dose of heparin (50 IU/kg) was given systemically five minutes prior to hemodiafiltration and continuous heparin was then infused into arterial/ venous line at the rate of 600 IU/h or 10 IU/kg sufficient to maintain partial thromboplastin time (PTT) twice the control value.

The biochemical parameters in the blood were monitored every four hourly. Dialysate urea, creatinine and bilirubin were repeated over same intervals. Vital signs, ultrafiltration rate, urine output and net negative balance were monitored every hour. Adequacy of HDF was finally assessed by using simplified Barth formula (kt/v).9

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation and the discrete variables as percentage. Student’s t-test (paired and unpaired) was employed to find out

the significance of difference between the means. The chi- square test with appropriate modification (Fisher’s exact test) was used to examine the significance of difference between the proportions.

Results

The patients in both the groups were alike in terms of mean age, clinical symptoms and signs and baseline biochemical parameters; except that central venous pressure (CVP) was lower, while serum bilirubin, PTI and MELD scores were significantly higher in group A patients. The most common etiology of hepatic failure in our patients was alcoholic cirrhosis (43.3%) followed by viral cirrhosis (30%), sepsis with multiorgan dysfunction (13.3%), toxins, autoimmune cirrhosis and ischemic hepatitis. The mean APACHE II score was comparable in both the groups; MELD score was higher in group A. Twelve patients out of thirty (40%) were on the vasopressor support at the time of initiating HDF. Baseline investigation profile of the two groups is shown in Table 1. The mean duration of CRRT in group A was 27.32±1.58 h and in group B was 27.02±1.5 h. Ultrafiltration rate was 141.66 ± 22.33 ml/h in group A and 134.26 ± 38.71 ml/h in group B. During the procedures, blood urea decreased by 29.6% in first 8h, 73% at 24h and 78.2% at the end of CVVHDF in group A. In group B, it decreased by 67.9% at 24h and 73.2% at the end of CAVHDF. Similarly, fall in serum creatinine was 76.5% in group A and 64.9% in group B after the procedures. The difference between both the groups was insignificant at all the intervals. There was significant difference in mean bilirubin values in two groups from the beginning and the difference persisted till the end of the study. The fall in mean bilirubin was 60.16% at 24h and 63.7% at the end of CRRT in group A. In group B, there was 63.3% fall at 24h and 67.1% at the completion. Serum bicarbonate also improved as compared to baseline in both the groups. There was no significant change in mean arterial pressure (MAP) throughout the procedure (Table 2, Figures 1, 2).

From the observations, it can be inferred that, inspite of the fact that most of the patients were critically ill and hemodynamically fragile, both the modalities of CRRT were...
Moreover, the development of renal dysfunction in CLD significantly decreases survival and prognosis. CRRTs have now been in use for more than a decade in the management of patients with combined hepatic and renal failure. In this present study, we evaluated and compared two modalities of HDF successfully, in terms of efficacy and outcome, without any significant complication of the procedure per se. CRRT was given in these patients because conventional intermittent hemodialysis would have proved deleterious in these critically ill and hemodynamically unstable patients in controlling fluid overload, hyperbilirubinemia and azotemia.

During HDF, all the patients of both the groups remained hemodynamically stable with no significant disturbance in their vital parameters, despite the fact that 40% of the patients were on inotropic support before initiation of the procedures. This is presumed to be due to slow and gradual removal of the solutes and water, which allowed time to optimize intravascular and left ventricular filling, leading to maintenance of cardiac output. A significant fluid removal could be achieved without any episodes of hypotension in all the patients, whereas, hypotension is frequently encountered in conventional hemodialysis.

Continuous HDF was found to be extremely efficient procedure in clearance of small molecular weight solutes (urea, creatinine) by convection and middle molecular weight solutes (direct and indirect bilirubin) by convection even in patients with hemodynamic instability. This fact is borne out by our experience as we achieved a significant fall (p < 0.001) in these biochemical parameters i.e. urea, creatinine, direct and indirect bilirubin. Metabolic acidosis also improved gradually as seen with the rise of pH and bicarbonates in both the groups. The improvement in consciousness level in patients of hepatic encephalopathy was secondary to correction of metabolic and hemodynamic factors by CRRT. The mean clearance of urea, creatinine and bilirubin over 24 h was = 25ml/min in both the procedures. The actual values compare favourable with the clearance as achieved with conventional hemodialysis over 4 hours. Therefore, HDF is physiologically superior to intermittent hemodialysis in correction of hyperbilirubinemia, fluid overload and azotemia.

The most important surrogate marker of dialytic efficiency and safety “adequacy of dialysis” was calculated by using simplified Barth method in form of k/t/v. Value of k/t/v in CVVHDF was 2.49 and in CAVHDF it was 1.67. As these values were more than one in both the groups, it confirmed the adequacy of HDF in the management of our critically ill patients. Studies with single pass albumin dialysis have been done for treatment of hyperbilirubinemia, however, to the best of our knowledge, there have been no studies regarding the use of continuous HDF without albumin dialysate in the treatment of hyperbilirubinemia in patients of hepatic failure. The most encouraging finding in our study was that the hepatic and renal functions improved in 100% patients. Out of 30, a total of 9 patients (30%) survived and were discharged from the hospital. In our study, mean APACHE II score was >16 and mean MELD score was >30, thus predicting high mortality and indicated an urgent need for liver transplantation. Though, continuous HDF led to improved survival and prognosis in critically ill patients of hepatic failure, no control groups with alternate form of RRT were compared, as it was considered unethical to subject unstable patients to intermittent hemodialysis.

Table 2: Hemodynamic and biochemical parameters after 24 hours of hemodiafiltration

<table>
<thead>
<tr>
<th>Parameters</th>
<th>0 hour</th>
<th>24 hour</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Arterial Pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group A</td>
<td>75.11 ± 5.12</td>
<td>72.74 ± 4.91</td>
<td>0.206</td>
</tr>
<tr>
<td>Group B</td>
<td>75.18 ± 4.89</td>
<td>72.29 ± 4.23</td>
<td>0.094</td>
</tr>
<tr>
<td>Blood Urea (mg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group A</td>
<td>179.66 ± 74.45</td>
<td>48.46 ± 42.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Group B</td>
<td>171.86 ± 72.15</td>
<td>55.06 ± 38.74</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Serum Creatinine (mg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group A</td>
<td>4.22 ± 1.60</td>
<td>1.18 ± 0.67</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Group B</td>
<td>3.48 ± 1.60</td>
<td>1.46 ± 1.07</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Serum bilirubin (mg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group A</td>
<td>18.98 ± 12.14</td>
<td>7.34 ± 2.28</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Group B</td>
<td>9.49 ± 4.27</td>
<td>3.47 ± 2.28</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Serum bicarbonate (mmol/l)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Group A</td>
<td>14.33 ± 3.76</td>
<td>16.78 ± 2.66</td>
<td>0.048</td>
</tr>
<tr>
<td>Group B</td>
<td>13.56 ± 3.98</td>
<td>18.12 ± 4.50</td>
<td>0.006</td>
</tr>
</tbody>
</table>
Role of Diagnostic Splenectomy in Patients Presenting with Pyrexia of Unknown Origin with Splenomegaly and Non-Contributory Pre-surgical Evaluation

Muralidharan J1, Ralph R2, Mathuram A3, Prakash V4, Nayak S5, Zachariah A3

Abstract

Aims: To describe the clinical and laboratory profile, post-surgical complications and longitudinal outcomes in a historical cohort of pyrexia of unknown origin (PUO) patients with splenomegaly who underwent a diagnostic splenectomy following non-contributory extensive pre-surgical laboratory and radiological evaluation.

Materials and Methods: This retrospective study was conducted in a 2700 bed teaching hospital in South India, in eligible patients, over a 10-year period.

Results: Out of 38 PUO patients who underwent diagnostic splenectomy, a final diagnosis was established in 30 patients. Overall, infections contributed to 44% (13/30), and neoplasia to 56% (17/30) of all cases. Of PUO patients with infections 3/13 (23%) were diagnosed with disseminated tuberculosis, 7/13 (54%) with melioidosis, 1/13 (8%) with Candidal splenic abscess with infective endocarditis and 2/13 (15%) with Colistin-resistant E. coli splenic abscess. Amongst PUO patients with neoplasia 13/30, all patients were diagnosed with hematological neoplasia. Of these 94% (16/17) were diagnosed with Non-Hodgkin’s lymphoma and 6% (1/17) with Hodgkin’s disease. Splenectomy was non-contributory in 21% (8/38) patients. Post-operative complications were seen in 6/38 patients who required monitoring in the intensive care unit (ICU). In-hospital mortality was noted in 10.5% (4/38) patients.

Conclusions: Diagnostic splenectomy has high diagnostic utility in the evaluation of PUO patients with reticuloendothelial system involvement after an extensive negative investigative workup. The diagnosis of lymphoma in such patients is more common than an infective cause.
**Introduction**

Pyrexia of unknown origin (PUO) remains a diagnostic challenge to the physician. The Durack and Street classification defines classical PUO as fever greater than 101°F on several occasions for more than three weeks and failure to reach a diagnosis despite one week of in-patient investigation.1 The true incidence and prevalence of pyrexia of unknown origin remains uncertain.2 Broadly, causes may be divided into infections, neoplasia or connective tissue disease. Indian studies show that despite detailed clinical and investigative evaluation, up to 27% of PUO patients remain undiagnosed.3

With the advent of modern interventional radiological techniques today, more invasive investigations like diagnostic laparotomy and splenectomy have been relegated to the last line of a series of tests for PUO evaluation. However, in the patient subset that remains undiagnosed despite extensive laboratory and radiological investigations, surgical exploration may assume a more significant role. Furthermore, in PUO patients with associated splenomegaly, diagnostic splenectomy may contribute significantly to establishing the etiological diagnosis.4,5

A 2008 Chinese retrospective review of the medical records of 54 PUO patients with splenomegaly, who subsequently underwent a diagnostic splenectomy, revealed that a definite etiological diagnosis was made in 72.2% of patients.4 A similar study conducted at a Chinese tertiary care center in 2017, involving 83 PUO patients with splenomegaly scheduled for a diagnostic splenectomy following non-contributory initial evaluation, revealed that a definitive etiological diagnosis was made in 89.2% (74/82) of patients.5 Given the paucity of information from India, we set out to study the diagnostic role of splenectomy and its associated complications, in a historical cohort of Indian PUO patients with splenomegaly and a non-contributory preliminary laboratory and radiological evaluation.

**Material and Methods**

This study was conducted in a historical cohort of classical PUO patients with splenomegaly, admitted for diagnostic splenectomy, between March 2006 and March 2016 at a tertiary care referral center in South India, receiving an average of 2500 inpatients and 8000 outpatients/day. The predominant catchment area for the hospital includes the districts of Vellore and Tiruvannamalai in Tamil Nadu state and Chittoor district of Andhra Pradesh. The study was approved by the institutional review board and the human research ethics committee (Minute No: 10162, May 2017). The study protocol followed the principles of the Declaration of Helsinki.

**Inclusion and exclusion criteria**

Patients included were aged 18 years or older; had been diagnosed with classical PUO; had a non-contributory pre-surgical etiological work-up and had subsequently undergone a diagnostic splenectomy. Pregnant patients and those with fever related to other PUO categories (nosocomial, neutropenic and HIV-associated) were excluded from the study.

**Definitions**

Classical PUO was defined according to the Durack and Street criteria as, (1) an axillary temperature of >38.0°C which corresponds to an oral temperature of >38.3°C; (2) illness duration more than 3 weeks; (3) a lack of a definite diagnosis after three outpatient visits or 3 days in the hospital; (4) fever not related to other categories of PUO (nosocomial, neutropenic and HIV associated).1

**Variables and Outcomes**

Clinical information from paper and electronic case records of eligible patients was collected using a systematic data abstraction form. To maintain confidentiality, all patients were assigned a serial number at enrollment. Data was subsequently collected by identifying patients using these serial numbers. Demographics, presenting symptoms and signs, preliminary investigations preceding splenectomy, and outcomes were documented. Pancytopenia was defined as hemoglobin <10g/dl, white cell count < 4000 cells/cumm and platelet count <100,000/cumm. Elevated serum transaminase levels were defined as serum glutamic oxaloacetic transferase levels > 40U/L with or without serum glutamic pyruvic transferase levels > 35 U/L.

The primary outcome was definitive etiological diagnosis post-splenectomy. Secondary outcomes included post-operative complications, post-operative intensive care unit (ICU) admission; length of ICU stay and in-hospital mortality.

Pre-surgical etiological workup for patients with PUO and splenomegaly

All patients included in the study had undergone a preliminary work-up to rule out a delayed diagnosis of an acute febrile illness. Potential diagnostic clues had been identified and a diagnostic work-up had been initiated along those lines. An attempt had been made to evaluate patients without initiating empirical therapy. All patients included, had undergone a computed tomography scan (CT) scan of the thorax, abdomen and pelvis; blood culture and sensitivity; and trans-thoracic echocardiography as part of the initial diagnostic work-up.

**Diagnostic laparotomy**

After obtaining informed consent, a long midline incision was made. Viscera were carefully examined and any suspicious area biopsied. In addition to splenectomy, a wedge biopsy of the liver and sampling of significant
And hepatosplenomegaly in 39%, generalized lymphadenopathy in 24%, nausea and vomiting in 22%, included loss of weight and appetite as additional presenting complaints.

Table 1. Characteristics are summarized in the study population was 46.5 (16.2) years. 50% included. The mean age of the study population was 46.5 (16.2) years. 50%

36. Results

Of 230 patients admitted with classical PUO during the study period, 38 consecutive patients (21 males) with splenomegaly and non-contributory pre-surgical etiological work-up were included. The mean age of the study population was 46.5 (16.2) years. 50% (19/38) had febrile illness duration of > 6 months. 15/38 patients were from West Bengal, 8/38 patients from Tamil Nadu, 6/38 patients from Orissa, 4/38 patients from Tripura, 3/38 patients from Jharkhand, 1/38 patients from Kerala and 1/38 from Bihar. Patient characteristics are summarized in Table 1.

Apart from prolonged fever, additional presenting complaints included loss of weight and appetite in 80% (31/38), night sweats in 55% (22/38), nausea and vomiting in 22% (8/38), early satiety in 48% (18/38), generalized lymphadenopathy in 24% (10/38) and hepatosplenomegaly in 39% (15/38). 31.6% (12/38) patients had co-existent diabetes mellitus, 29% (11/38) hypertension, 5.3% (2/38) chronic liver disease and 2.6% (1/38) chronic lung disease. Common presenting laboratory abnormalities included pancytopenia in 32% (12/38) and elevated serum alkaline phosphatase with concomitantly elevated serum gamma-glutamyl transferase levels in 39% (15/38) patients (Table 1). None of the patients in this subset had features suggestive of intra-hepatic bile radicle dilatation (IHBDR) on ultrasound abdomen examination.

In addition to CT thorax, abdomen and pelvis; blood culture and sensitivity; and trans-thoracic echocardiography additional diagnostic tests of utility included PET-CT (2/38); bone marrow aspiration and trephine biopsy (35/38); and peripheral lymph node biopsies (10/38). PET-CT imaging revealed multiple intra-abdominal lymph nodes with hepatosplenomegaly with increased FDG uptake in both patients. Subsequent ultrasound guided lymph node biopsies in both patients were non-contributory to the etiological diagnosis. Bone marrow trephine biopsy was repeated from the contralateral iliac bone in 23/38 patients. Image (CT/USG) guided lymph node or lesion biopsy was attempted in 4 patients and ultrasound guided splenic aspiration in 5 patients respectively. The tissue obtained was either insufficient for analysis or non-contributory to the diagnosis both by histopathology and culture. All patients were administered one dose of pneumococcal conjugate vaccine PCV13, one dose of meningococcal polysaccharide vaccine (against Group A, C, Y and W135 strains) and one dose of split virion trivalent inactivated influenza vaccine as intramuscular injections at different sites, at least 2 weeks prior to laparotomy.

A definitive etiological diagnoses based on diagnostic splenectomy was established in 79% (30/38) patients. Overall, infections contributed to 44% (13/30), and neoplasia to 56% (17/30) of all cases. Of PUO patients with infections (13/30), 3/13 (23%) were diagnosed with disseminated tuberculosis, 7/13 (54%) with melioidosis, 1/13 (8%) with Candidal splenic abscess with infective endocarditis and 2/13 (15%) with Colistin-resistant E. coli splenic abscesses. Amongst PUO patients with neoplasia (17/30), all patients were diagnosed with hematological neoplasia. Of these 94% (16/17) were diagnosed with Non-Hodgkin’s lymphoma and 6% (1/17) with Hodgkin’s disease (Table 2).

In 21% (8/38) patients, splenectomy was non-contributory to the etiological diagnosis. Of these, an etiological diagnosis could be established based on liver or lymph node specimens obtained during laparotomy in 3/8 patients. All 3 patients were diagnosed with high grade Non-Hodgkin’s lymphoma. 5/8 patients continued to remain undiagnosed following laparotomy. Their clinical status and reports were reviewed at 6-weeks following discharge.

On review at 6-weeks post-splenectomy, one patient was diagnosed with Non-Hodgkin’s lymphoma based on repeat bone marrow examination done following negative laparotomy. The other 4 patients were contacted via telephone and reported defervescence. They were lost to follow up and could not be examined in person.

Post-operative complications were seen in 6/38 patients who required monitoring in the intensive care unit (ICU). The average ICU stay was 11±8.2 days and median ventilator free days at day 28 were 18 (0-28) respectively. In-hospital mortality was noted in 10.5% (4/38) patients (Table 2). Of these, one patient was diagnosed with high-grade Non-Hodgkin’s lymphoma and died of neutropenic sepsis 72 hours post-splenectomy; two patients died of a refractory septic shock possibly secondary to an infected collection in the post-operative surgical site while the fourth patient succumbed to ventilator associated pneumonia. Two patients were noted to have developed incisional hernias on post-operative follow-up at 6-weeks.

Discussion

Based on the results of our study, there appears to be a low rate of diagnostic splenectomy in PUO patients, with 38 cases over 10 years. The most common clinical profile leading to diagnostic splenectomy in our study population was that of a disease process involving the reticuloendothelial system (hepatosplenomegaly, lymphadenopathy, pancytopenia with liver infiltration), with a non-contributory pre-surgical work-up (bone marrow aspirate smear and...
terephine biopsy, lymph node biopsy or image guided biopsy of involved sites for histopathological examination and microbiological culture).

Of the patients who underwent the procedure, definitive diagnosis was achieved in 79% (30/38) patients. This finding is similar to that of a 2008 retrospective study on 54 PUO patients with splenomegaly which revealed that definitive diagnosis was made in 72.2% of patients undergoing splenectomy. Diagnostic splenectomy contributed to a diagnosis of hematological neoplasia in more than 50% study patients. A majority of study patients diagnosed with hematological neoplasia had B-cell NHL. None of the patients were diagnosed with any solid organ malignancies.

The most common infectious disease diagnosed based on splenectomy was melioidosis (54%). Tuberculosis was diagnosed in less than 30%, in contrast to the higher prevalence demonstrated in western studies. A possible explanation is that current investigative approaches including culture, molecular diagnosis and guided biopsy are able to achieve an etiological diagnosis in most PUO patients with tuberculosis, seldom requiring a diagnostic laparotomy with splenectomy.7,8 Autoimmune diseases such as systemic lupus erythematosus and sarcoidosis did not account for any of the diagnosed cases. This is a surprising observation since these diseases are characterized by prominent reticuloendothelial system involvement. They often present with prolonged fever, pancytopenia and hepatosplenomegaly and demonstrate characteristic splenic histopathological findings which include non-caseating granulomas in sarcoidosis and concentric perivascular laminations of fibrous tissue in small penicillar arteries resulting in the typical “onion skin” lesion of lupus spleen.9,10

Another important observation in our study is the identification of an etiological diagnosis in approximately 40% (3/8) of patients with a non-diagnostic splenectomy, based on liver or lymph node specimens obtained during laparotomy. This observation highlights the importance of obtaining biopsy specimens from other intra-abdominal sites in addition to performing splenectomy during diagnostic laparotomy in PUO patients. In a study by Ozaras et al in 2005, the authors noted 17 diagnostic laparotomies for PUO were done over a 20-year period. Of these, a diagnosis was established in 13 patients with the most common diagnosis being tuberculosis (4 patients) and lymphoma in 6 patients (NHL in 3 patients, and HL in 3 patients). Laparotomy helped to exclude other causes in 2 patients diagnosed as Still’s disease. Overall, they reported a diagnostic rate of 88% in their study.6 Other studies report a laparotomy diagnostic rate ranging from 27% to 100%,11-14

While none of the patients in our cohort suffered direct procedural complications, 10.5% died in the post-operative period. A majority of deaths appeared to be related to complications arising from the preceding systemic illness rather than from the procedure itself. In a 2017 study by Zhang et al, surgical complications occurred in 25.9% of patients and the 1-month operative mortality was 16.7%.5 Post-splenectomy complications may range from acute events such as intra-abdominal hemothorax, pleural effusions, pulmonary atelectasis and pancreatitis to long-term complications that include overwhelming sepsis due to encapsulated organisms and enhanced atherosclerosis.11

A few limitations merit mention. The small sample size of our cohort limits study generalizability. Also, the findings of our study may only be representative of those regions from where a majority of referrals were derived. The relatively short follow-up period of 6-weeks limits us from documenting the rate of sepsis due to encapsulated organisms, which is a well recognized long term complication in asplenic patients. The likelihood of this event occurring however would be low given the universal pre-surgical coverage with vaccines against encapsulated organisms in our cohort.

Conclusions

In conclusion, diagnostic laparotomy with splenectomy appears to have a high utility in evaluating PUO patients presenting with splenomegaly, especially when manifesting features of reticuloendothelial system involvement, in the setting of a negative extensive pre-surgical laboratory and radiological workup. The diagnosis of lymphoma appears more likely than an infectious cause in this subset of patients. Amongst infections, melioidosis is an important etiological differential to be considered in the Indian context.

References

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discussion

The study aimed to evaluate the effectiveness of Jalra-M in managing Type 2 Diabetes Mellitus (T2DM) patients. The results showed significant reductions in HbA1c levels, which is a key indicator of blood glucose control. Over 15 million patients have experienced benefits from using Jalra-M, indicating widespread positive outcomes. The drug is approved for use across all food types, ensuring flexibility in its use. It has also been shown to be safe for cardiovascular health. Packed with evidence, Jalra-M is a reliable partner in the treatment of T2DM patients.

Conclusion

Jalra-M demonstrates significant benefits in the treatment of T2DM, with proven efficacy in reducing HbA1c levels and safety for cardiovascular health. Its availability across all food types makes it a versatile option for patients. Further research could explore long-term effects and potential interactions with other medications.
Development of Non-alcoholic Fatty Liver Disease (NAFLD) in Young Obese Tribal Subjects of Tripura: Link between Low 25 (OH) Vitamin-D Levels and Immune Modulators

Avik Chakraborty1*, Arkadip Choudhury2, Animesh Saha3

Abstract

Background: There have been many studies conducted so far on Non Alcoholic Fatty Liver Disease (NAFLD) with its many aspects including its association with 25 hydroxy Vitamin D levels and its rather complex interplay with pro-inflammatory cytokines such as Interleukin-1α (IL-1α), Interleukin-6 (IL-6) and Tumour Necrosis Factor-Alpha (TNF-α), Interleukin-17a (IL-17a) and anti-inflammatory cytokines such as Interleukin-4 (IL-4) and Interleukin-10 (IL-10). This study was designed to show the development of NAFLD in the young tribal population of Tripura and the link between 25(OH) Vitamin D and pro-inflammatory cytokines (IL-1α, IL-6, IL-17a and TNF-0) and -inflammatory cytokines such as IL – 4 and IL - 10 and the development of NAFLD while at the same time throws light on the prevalence of 25(OH) Vitamin D deficiencies and the levels of pro-inflammatory cytokines in the study group.

Methods: The study is an analytical cross-sectional study with final population of 94 cases between 18 to 40 years of age fulfilling inclusion and exclusion criteria and an equal number of subjects from same tribal community age and sex matched taken as control population.

Results: There was a significant relationship between level of 25(OH) Vitamin D and fatty liver (OR: 9.46, 95% CI: 4.82 – 18.59; p < 0.001). The mean serum 25(OH) Vitamin D level in the cases was significantly higher than the controls (17.21 ng/ml ± 6.34 ng/ml vs 26.56 ng/ml + 10.63 ng/ml; p < 0.001). There was a significant difference between the mean serum levels of IL-1α (11.50 Pg/ml ± 2.75 Pg/ml vs 8.28 Pg/ml ± 2.08 Pg/ml; p < 0.001),IL-4 (0.69 Pg/ml ± 0.43 Pg/ml vs 0.84 Pg/ml ± 0.36 Pgm/l; p = 0.009), IL-6 (2.99 ± 1.11 Pg/ml vs 2.22 ± 1.08 Pg/ml; p < 0.001), IL-10 (6.50 ± 2.76 Pg/ml vs 5.23 Pg/ml ± 2.67 Pg/ml; p = 0.002), IL-17a (5.33 Pg/ml ± 2.22 Pg/ml vs 3.64 Pg/ml ± 1.99 Pg/ml; p < 0.001) and TNF-α (6.99 ± 2.81 Pg/ml vs 5.40 ± 3.08 Pg/ml; p < 0.001) of the cases and the controls Low serum 25(OH) Vitamin D levels and its rather complex interplay with pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1, IL-6 and interferon; whereas the main Th2 anti-inflammatory cytokines are IL-4 and IL-10. In general, Th1 cytokines induce Th1 cytokines and inhibit Th2 cytokine production and vice versa. Normally, there is a balance between proinflammatory and anti-inflammatory cytokines. 6-8 IL-6 though initially considered as a hepatoprotector in liver steatosis, capable of reducing oxidative stress and preventing mitochondrial dysfunction, was however was found to be a key element in the acute phase response, mediating the synthesis of several acute phase proteins. It has been seen that not only the cytokine itself but also its soluble receptor is significantly increased in patients with NASH. 6-8 TNF-α receptor polymorphism is one

Conclusions: 25(OH) Vitamin D concentration are lower while that of IL-1α, IL-4, IL-6, IL-10, IL-17a and TNF-α are higher in subjects with fatty liver in comparison to those without. 25(OH) Vitamin D deficiency and high levels of serum IL-1α were independently associated with the risk of development of NAFLD.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a disorder that is characterized by a group of histological abnormalities identified on liver biopsy similar to those seen in alcoholic liver disease but occurring in patients who consume little or no alcohol. It has a spectrum that ranges from simple fatty liver (steatosis) to non-alcoholic steato-hepatitis (NASH) and NAFLD associated cirrhosis. 1 Worldwide prevalence reports of NAFLD vary widely between 2.8 % to 46.0 %. 2 Laboratory and clinical evidence supports the fact that peripheral insulin resistance and hyperinsulinemia are associated with NAFLD, even in lean patients without obvious glucose intolerance. Vitamin D is capable to reduce FFA-induced insulin resistance both in peripheral tissues and in hepatocytes. Therefore, low serum vitamin D may predispose to intrahepatic lipid accumulation leading to NAFLD. A strong epidemiological overlap exists between NAFLD and hypovitaminosis D prevalence, as both conditions are widely spread among obese dysmetabolic individuals. 3,4 Evidence suggests that endotoxin-mediated cytokines are important mediators of hepatic steatohepatitis. 5 Cytokines are classified as T helper 1 (Th1) and T helper 2 (Th2) subtypes. The main proinflammatory Th1 cytokines are tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1, IL-6 and interferon; whereas the main Th2 anti-inflammatory cytokines are IL-4 and IL-10. In general, Th1 cytokines induce Th1 cytokines and inhibit Th2 cytokine production and vice versa. Normally, there is a balance between proinflammatory and anti-inflammatory cytokines. Th1 cytokines are Th1 cytokines and inhibit Th2 cytokine production and vice versa. Normally, there is a balance between proinflammatory and anti-inflammatory cytokines. Th1 cytokines are Th1 cytokines and inhibit Th2 cytokine production and vice versa. Normally, there is a balance between proinflammatory and anti-inflammatory cytokines. 6-8 IL-6 though initially considered as a hepatoprotector in liver steatosis, capable of reducing oxidative stress and preventing mitochondrial dysfunction, was however was found to be a key element in the acute phase response, mediating the synthesis of several acute phase proteins. It has been seen that not only the cytokine itself but also its soluble receptor is significantly increased in patients with NASH. 6-8 TNF-α receptor polymorphism is one

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type of genetic polymorphism which is over expressed in patients with NAFLD who move on to NASH. One of the major mechanisms by which TNF-α plays its role in NAFLD is by creating a state of insulin resistance by inhibiting the tyrosine kinase activity of the insulin receptor. The connection between TNF-α expression and insulin resistance in NAFLD was first described by Hotamisligil et al. in a study in which adipose tissue was presented as a significant cause of obesity induced inflammation, mainly by TNF-α expression inducing inflammation and insulin resistance. IL-17a is another pro-inflammatory cytokine which has been studied in relationship to the development of NAFLD. IL-17A signaling, via IL-17A, plays an important role in obesity-induced NAFLD pathogenesis.

Aim and Objectives

The aim of the present study is to investigate the relationship of Vitamin D status and Immunomodulators (TNF-α and IL-1a, IL-4, IL-6, IL-10, IL-17a) as the indicators of NAFLD in middle aged tribal subjects of Tripura. The objectives were to determine the status of 25 (OH) Vitamin D concentration in middle aged non-alcoholic tribal subjects of Tripura with and without fatty liver disease and to evaluate whether the risk of development of NAFLD in these subjects has any association with the level of Immunomodulators and Vitamin D status.

Materials and Methods

The study is an analytical cross-sectional study where a consecutive type of sampling was employed. In this study, a total of 94 tribal subjects from different communities across the state fulfilling inclusion and exclusion criteria and having ultrasound evidence of fatty liver were taken as cases. An equal number of age, sex and demography matched healthy volunteers as control subjects. The study was funded by ICMR and the study protocol was approved by the Human Ethics Committee of the Tripura Medical College and Dr. BRAM Teaching Hospital and written informed consent was obtained in all cases.

Inclusion Criteria

1. Referred for assessment of abnormal liver function test (LFT) or hepatic steatosis detected by ultrasonography.
2. Age between 20 to 40 years
3. Alcohol consumption less than (40 gm/week)
4. Willing to participate in the study

Exclusion criteria

1. Final diagnosis other than NAFLD
2. Secondary causes of steatohepatitis and drug induced liver disease
3. Any case of chronic liver disease

Height, weight, waist and hip circumference and blood pressure of each subject were measured at the baseline visit. Enzyme linked Immunosorbent Assay (ELISAs) was used to measure the serum concentration of TNF-α and IL-1a, IL-4, IL-6, IL-10, IL-17a in the NAFLD and control subjects. Chemiluminescent assay was used to determine the serum levels of 25(OH)D. Liver ultrasonography (US) scanning was performed to assess the degree of steatosis. All US were performed by the same operator who was unaware of the aims of the study and blinded to laboratory values using a US apparatus equipped with a convex 3.5 MHz probe.

Where:
1. n = sample size
2. r = ratio of cases and controls (in our study of cases and controls being equal, r = 1)
3. \( Z_\alpha, 0.84 \) for power of the study at being 80%
4. \( Z_\alpha, 1.96 \) for level of significance at 0.05
5. \( S_1 = 9.2 \) (Standard deviation of case)
6. \( S_2 = 9.7 \) (Standard deviation of control)
7. \( d = \) Difference between means (20.5 – 14.8 = 5.7)^α

For power of the study at 80%, and level of significance taken at 0.05, \( Z_\alpha, 0.84 \) and \( Z_\alpha, 1.96 \), the required sample size was found to be 90. Finally, 94 subjects with NAFLD were included in the study as cases with a similar number of age, sex and demography matched healthy volunteers as control subjects.

SPSS version 20 statistical package was used to perform the analysis. Students T-test for continuous variables and \( \chi^2 \) test for categorical variables were used to compare mean values between two independent groups. 25(OH) Vitamin-D, TNF-α and IL-1a, IL-4, IL-6, IL-10, IL-17a were analyzed as continuous variables. Data is shown as mean ± standard X deviation. Receiver operator characteristic (ROC) curves were carried out to ascertain the usefulness of each of 25(OH) D, IL-6 and TNF-α as predictors of NAFLD in the whole study. Binomial logistics regressions were carried out to ascertain whether each of 25(OH) D, TNF-α and IL-1a, IL-4, IL-6, IL-10, IL-17a could independently predict the occurrence of NAFLD in the obese and non-obese subgroups. For all the above, a P-value <0.05 was considered statistically significant.

The study was carried out in the BRAM Teaching Hospital from November 2017 to October 2018. Of the 188 subjects who had enrolled in the study, maximum number (55/188, 29.3%) belonged to the age group between 36 to 40 years. The mean age of the study population was 33.23 years with a standard deviation of 6.916 years. Of the 188 subjects, 67 (35.6%) subjects were male whereas 121 (64.4%) subjects were female. 62.23% (117/188) subjects were obese while 37.77% (71/188) were non-obese. Of the obese subjects 68.38% (80/117) had fatty liver on ultrasonography whereas, of the non-obese subjects, only 19.72% (14/71) had fatty liver. Presence of obesity was significantly associated with presence of fatty liver (odds ratio: 8.80, 95% CI: 4.36 – 17.77; p < 0.001). There was a significant difference (Table 1) between the mean BMI of the cases and the controls (25.70 ± 2.93 kg/m² vs 23.09 ± 3.17 kg/m²; p < 0.001). 55.85% (105/188) subjects had subnormal levels of 25(OH) Vitamin D, either insufficiency (86/188, 45.74%) or deficiency (19/188, 10.11%). 44.15% (83/188) subjects had normal levels of 25(OH) Vitamin D. Of the 105 subjects with subnormal levels of 25(OH) Vitamin D, 76 (72.38%) had liver fat on ultrasonography where as,
There was a significant difference (p < 0.001) between the mean serum TNF-α levels of the cases and the controls (6.99 ± 2.81 Pg/ml vs 5.40 ± 3.08 Pg/ml; p < 0.001) (Figure 2B) of the cases and the controls.

There was a significant difference (p < 0.001) between the mean serum TNF-α levels of the cases and the controls (6.99 ± 2.81 Pg/ml vs 5.40 ± 3.08 Pg/ml; p < 0.001) (Figure 2B).

Analysis of ROC curve for 25(OH)D showed an AUROC curve in NAFLD group (AUC=0.790; 95% CI[0.724 – 0.846], p < 0.0001) (Figure 2D). The optimal cut-off value of 25(OH)D for NAFLD was 20.75 ng/ml below which NAFLD could be predicted with a sensitivity of 84.04% and a specificity of 68.09%. The results of the analysis of ROC curve for the rest of the parameters have been illustrated in Table 2.

Binominal logistic regressions showed that low serum 25(OH)D [OR: 0.87 (95% CI: 0.83 – 0.92), p = 0.0001] and high serum IL-1α [OR: 1.52 (95% CI: 1.26 – 1.84), p < 0.0001] were independently associated with the risk of NAFLD in the study population. Table 3 depicts the scenario.

Table 2: Results of receiver operator curves

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AUC</th>
<th>p Value</th>
<th>95% CI</th>
<th>Cut off value</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1α</td>
<td>0.833</td>
<td>&lt;0.0001</td>
<td>0.772 – 0.883</td>
<td>9.35 Pg/ml</td>
<td>74.47%</td>
<td>86.17%</td>
</tr>
<tr>
<td>IL-6</td>
<td>0.703</td>
<td>&lt;0.0001</td>
<td>0.632 – 0.767</td>
<td>2.08 Pg/ml</td>
<td>78.72%</td>
<td>58.5%</td>
</tr>
<tr>
<td>IL-10</td>
<td>0.634</td>
<td>&lt;0.0001</td>
<td>0.561 – 0.703</td>
<td>3.80 Pg/ml</td>
<td>81.91%</td>
<td>41.49%</td>
</tr>
<tr>
<td>IL-17</td>
<td>0.746</td>
<td>&lt;0.0001</td>
<td>0.678 – 0.807</td>
<td>3.60 Pg/ml</td>
<td>73.12%</td>
<td>75.53%</td>
</tr>
<tr>
<td>TNF-α</td>
<td>0.694</td>
<td>&lt;0.0001</td>
<td>0.623 – 0.759</td>
<td>5.50 Pg/ml</td>
<td>61.70%</td>
<td>74.19%</td>
</tr>
</tbody>
</table>

Discussion

The study sample was selected on a strict 1:1 pattern. While most of the other similar studies have not followed a 1:1 sampling, studies conducted by Jablonski et al10 and that conducted by Targher G et al11 have taken equal number of matched cases and controls.

Majority of the subjects (62.23%) subjects were obese and majority (68.38%) of the obese subjects had fatty liver on ultrasonography. Presence of obesity was significantly associated with presence of fatty liver. There was a significant difference between the mean BMI of the cases and the controls.

This study revealed a significant relationship between level of 25(OH) Vitamin D and fatty liver. The mean serum 25(OH)D levels in the cases was significantly lower than that found in the control subjects. The results were in unison with those seen in the studies conducted by Wang D et al,12 Zhai HL et al,13 Wang X et al,14 Kucukazman et al15 demonstrated that in contrast to the control group, the cases with NAFLD in their study had significantly lower levels of 25(OH)D (12.3 ± 8.9 ng/ml vs 20.0 ± 13.6 ng/ml, p<0.001). Hao Y et al,16 demonstrated similar results in their study where vitamin D levels were significantly lower in the NAFLD group.
and Black et al. 20 also showed similar results. A study conducted by Kumar et al. 22 found IL-6 significantly greater in the NAFLD group than in the non-NAFLD group. In another study, Mohamed AA et al. 23 found IL-6 to be higher in NAFLD than control though not significant (114.24 ± 22.32 Pg/ml vs 104.9 ± 19.98 Pg/ml). Taratino G et al. 24 found significantly higher IL-6 levels in NASH patients while Hasan K et al. 25 and Cosma M 26 also in their respective studies showed that low serum 25(OH)D was independently associated with NAFLD which was also the scenario in the present study. Studies conducted by Targher G et al. 11 made a mention of IL-6 to be increased in subjects with non-alcoholic fatty liver disease. However, in order to come to a definite conclusion, further studies involving larger number of subjects and long term follow ups are needed.

**Fig. 2:** (A) Box-plot showing relationship of IL-10 with NAFLD; (B) Box-plot showing relationship of IL-17a with NAFLD; (C) Box-plot showing relationship of TNF-α with NAFLD; (D) ROC for 25(OH) Vitamin D

The serum level of IL-1a was significantly higher in the cases as compared to the controls.

The serum levels of both IL-4 and IL-10 were surprisingly found to be higher amongst the subjects with fatty liver compared to the controls. A study by Das SK et al. found serum IL-4 level to be decreased and IL-10 level to remain unchanged amongst subjects with non-alcoholic fatty liver as compared to their healthy controls. 21

The level of serum IL-6 was significantly greater in the NAFLD group than in the non-NAFLD group. In a study conducted by Kumar et al. 22 IL-6 showed marked and selective increase only in the NAFLD patients. (p < 0.02). Mohamed AA et al. 23 found IL-6 to be higher in NAFLD than control though not significant (114.24 ± 22.32 Pg/ml vs 104.9 ± 19.98 Pg/ml). Taratino G et al. 24 found significantly higher IL-6 levels in NASH patients while Hasan K et al. 25 and Cosma M 26 also in their respective studies showed that low serum 25(OH)D was independently associated with NAFLD which was also the scenario in the present study. Studies conducted by Targher G et al. 11 made a mention of IL-6 to be increased in subjects with non-alcoholic fatty liver disease. However, in order to come to a definite conclusion, further studies involving larger number of subjects and long term follow ups are needed.

**Table 3:** Results of binomial logistic regression analysis

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>Co-efficient</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 (OH) Vitamin D</td>
<td>0.89</td>
<td>0.83 - 0.95</td>
<td>-0.12219</td>
<td>0.0003</td>
</tr>
<tr>
<td>IL-1a</td>
<td>1.52</td>
<td>1.26 – 1.84</td>
<td>0.42144</td>
<td>&lt; 0.0001</td>
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<tr>
<td>IL-6</td>
<td>1.44</td>
<td>0.99 – 2.06</td>
<td>0.36512</td>
<td>0.0501</td>
</tr>
<tr>
<td>IL-10</td>
<td>0.96</td>
<td>0.82 – 1.12</td>
<td>-0.04181</td>
<td>0.6068</td>
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<tr>
<td>IL-17</td>
<td>1.13</td>
<td>0.92 – 1.39</td>
<td>0.12267</td>
<td>0.2398</td>
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<tr>
<td>TNF-α</td>
<td>1.16</td>
<td>0.98 – 1.36</td>
<td>0.14435</td>
<td>0.0832</td>
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**Conclusion**

Thus this study has shown that 25(OH) Vitamin D deficiency and high levels of serum IL-1a were independently associated with the risk of development of NAFLD both in obese and non-obese individuals. Having done so it gives us values of serum 25(OH) Vitamin D, IL-1a and which can be used as cut offs for predicting the risk of development of NAFLD with reasonable sensitivity and specificity.

**Acknowledgements**

The study group is thankful to the Indian Council for Medical Research for the funding and Tripura Medical College and Dr. B. R. Ambedkar Memorial Teaching Hospital for providing the set up for conducting the study. The study group is also thankful to the Hepatitis Foundation of Tripura and Indian Medical Association, Tripura State Branch for their valuable support in reaching out to the far flung areas of the state for the purpose of collection of samples.

**References**


Risk Factors for Sputum Positive Pulmonary Tuberculosis Retreatment Cases and Factors Responsible for Treatment Outcome

KR Patel¹, Anand Patel²*, Narendra B Gadhiya³

Abstract

Background: Identification of the characteristics that confer higher risk of relapse, failure, or default and factors associate with treatment outcome in retreatment cases may help in planning country-specific prevention strategies.

Objective: To evaluate the risk factors for retreatment failure, default or relapse and factors responsible for the treatment outcome.

Methods: In this study sputum positive pulmonary TB retreatment cases were included. All patients were treated by eight months Revised National Tuberculosis Control Program (RNTCP) Cat II regimen. Outcome was recorded as Cured, Failure, Death or Defaulted.

Results: Patients having body weight ≥ 45 kgs had higher cure rates (94.74%). Poor outcome was significantly higher in patient with cavitory lesions on Chest X-ray (30.43% vs 7.14%) and in patients with bilateral lesions (28.57% vs 4.35%). Patients with initial sputum of 3 + grade was significantly associated with poor outcome than having sputum of scanty to 2 + grade (26.93% vs 8%).

Conclusion: Patients presenting for TB retreatment have distinct demographic and clinical characteristics, important difference in treatment outcomes in relation to different parameters. So, new country specific strategies are required to identify and address risk factor for retreatment cases and factors responsible for poor outcome of these cases.

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Received: 22.05.2018; Accepted: 06.06.2019
Introduction

Tuberculosis (TB) has reemerged as a major public health problem throughout the world. About one third of world’s population are infected with TB. Globally, TB accounted for 1.2-1.5 million deaths with 85% of this occurring in developing countries. Possible causes of reemergence are rapid increase in poverty, poor living conditions with overcrowding, malnutrition and nonadherence to programme policies. India is the highest TB burden country with an estimated incidence of 2.2 million cases out of global incidence of 8.7 million in 2011 and 394,431 retreatment cases.

According to the World Health Organization (WHO), TB cases are broadly classified into “new” or “retreatment” (Previously taken anti-TB drugs for ≥ 1 month) TB cases. Retreatment patients are further classified as “relapse”, “treatment after default”, “treatment after the loss to follow up (LTFU)” and others. Retreatment cases and others. Retreatment cases are rapid increase in poverty, poor living conditions with overcrowding, malnutrition and nonadherence to programme policies. India is the highest TB burden country with an estimated incidence of 2.2 million cases out of global incidence of 8.7 million in 2011 and 394,431 retreatment cases.

WHO have now recommended drug susceptibility testing (DST) in all retreatment TB cases. However, access to DST and to the second line anti TB drugs remains poor in high burden countries like India. Therefore identification of the characteristics that confer higher risk of relapse, failure, or default and factors associate with treatment outcome in retreatment cases may help in planning country-specific prevention strategies aiming to reduce the need for retreatment, reducing the risk of morbidity, drug resistance and transmission resulting in reduced financial burden.

Very few studies have identified characteristics of retreatment cases and factors that influence their treatment outcomes. Such information might allow program to identify the most vulnerable groups likely to interrupt treatment, fail or die, thereby allowing them to prioritize the patients. The present study was aimed to evaluate the risk factors for retreatment failure, default or relapse and factors responsible for the treatment outcome.

Materials and Methods

The present study was carried out in Respiratory Medicine Department of P. D. U. Medical College, Rajkot. In this prospective observational study sputum positive pulmonary TB retreatment cases aged 12 years or above of both the genders registered for Cat II under RNTCP program in District Tuberculosis Center, Rajkot during period from January 2008 to June 2008 were included. Ethical committee approval was not taken as it was not needed in our institute for prospective observational study during that period. A detail history and thorough physical examination was carried out. History of contact with active pulmonary tuberculosis were noted. Patients were divided according into upper, middle and lower socio-economic class (SEC) according to kuppuswamy classification. All patients were subjected to chest x-ray PA view and screening for HIV infections. Patients with seropositive for HIV were excluded from the study. Radiological lesions were classified as cavitary or non cavitary and unilateral or bilateral. Three sputum samples of two consecutive days were examined for AFB using Ziehl-Neelsen staining technique and positive smears were graded as per RNTCP guidelines. All patients were treated by eight months RNTCP Cat II regimen. In this study, the outcome of Category II patients under RNTCP was recorded as Cured, Failure, Death or Defaulted.

Results

In the present study total 72 patients were included. Among these 72 retreatment sputum positive PTB patients, 56 (77.78%) were males and 16 (22.22%) were females. Demographic and clinical characteristics of retreatment sputum positive pulmonary TB patients has been given in Table 1. Elderly patients were more likely to be defaulter (50%)
while younger patients had higher incidence of relapse (62.96%). Only four (5.56%) patients were alcoholics while 22 (30.56%) patients were smoker. Relapse was higher in smokers (72.73%) and alcoholics (75%). Most of the patients (81.94%) were of lower socio-economic class (SEC). Patients from lower SEC has slightly higher incidence of defaulter. Patient from urban areas had slightly higher occurrence of defaulter (57.5%) and relapse was slightly higher in patients from rural area (62.5%) while education level does not alter defaulter rate.

Treatment outcome in relation to patient’s characteristics has been shown in Table 2. Out of 72 patients, three (4.17%) was transferred out while 18 patients was defaulted (25%). Out of those 18 defaulter patients, nine (50%) was defaulter of previous treatment. Cure rate was higher among patients with 12 – 45 years of age group (85.71%). Body weight has some implication in treatment outcome. Patients having body weight ≥ 45 kgs have higher cure rates (94.74%). Poor outcome was significantly higher in patient with cavitary lesions on Chest X ray (30.43% vs 7.14%) and in patient with bilateral lesions (28.57% vs 4.35%). Patients with initial sputum of 3+ grade has significantly associated with poor outcome than having sputum of scanty to 2+ grade (26.93% vs 8%). One patient with retreatment subgroup of relapse was cured. Cure rate was slightly higher among relapse cases (84.85%) than defaulter cases (76.47%).

Discussion

Relapse cases formed the largest number of retreatment cases (59.72%) in this study followed by defaulter (37.5%). Other study from India has also show relapse cases formed highest number of retreatment cases (50%) followed by defaulter (32.43%). Loss to follow up during the initial treatment also comprise quite large number of patients. Some study have shown the loss to follow up formed the largest retreatment cases (48%). This may be due to a weak follow up system for new TB cases on treatment which indicates the need of strategies to strengthen this and thereby preventing retreatment cases.

In our study, treatment success differed among retreatment group, with highest cure rate in relapse cases which is similar to other studies. Risk factors for poor outcome are low body weight, cavitation and bilateral lesions on chest X-ray in present study. Other study have also shown poor outcome in patients with lower BMI, cavitary lesions and more than two zone involvement in chest X-ray. So, it is important to monitor body weight regularly along with proper counselling about the nutrition by health care provider and nutritional supplement should also be provided as far as possible particularly in patients with bilateral and cavitary lesions on Chest X-ray as majority of the patients are coming from lower SEC.

Loss to follow up was more common in patients with a prior history of loss to follow up during previous treatment in our study. Recent studies have also demonstrated that, in urban settings, adherence is linked to patient knowledge about TB and provision of disease specific education by health care provider to the patient. This suggest the need for different management strategies for different retreatment groups. Loss to follow up patients may require intensified case management and education rather than more intensive treatment. These results suggest that different group may benefit by different management strategies.

Conclusion

Preventing the need for the retreatment is the best strategy by strengthening the follow up system for new TB cases. Patients presenting for TB retreatment are often grouped together and treated with a standard Cat II regimen. However, these groups have distinct demographic and clinical characteristics, important difference in retreatment outcomes in relation to different parameters. So, new country specific strategies are required to identify and address risk factor for retreatment cases and factors responsible for poor outcome of these cases.

References

# REQUIREMENT (WALK IN INTERVIEW)

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Email: medicaldirector@klehospital.org  | hr@klehospital.org

DR. M.V. JALI  MD, FICP, FRCP (London)
MEDICAL DIRECTOR & CHIEF EXECUTIVE
Efficacy of DPP4i as the Fourth Drug in the Management of Type2 Diabetes Mellitus in Asian Indians Poorly Controlled by Use of at least 3 Oral Antidiabetic Drugs

Vijay Panikar1, Shashank Joshi1, Mangesh Tiwaskar2, Jimit Vadgama3, Nikhil Nasikkar3, Tejas Kamat3, Narayan Deogaonkar4, Sanhita Walawalkar5, Ishita Sachdev3, Chandani Jain1, Khushbu Modh3, Krish Panikar4, Pallavi Kulkarni3, Rahul Medidar3

Abstract
Aim: To evaluate the efficacy of DPP-4 inhibitors (DPP-4i) as the fourth drug in Asian Indian type2 DM patients uncontrolled in spite of using at least 3 oral anti diabetic drugs.

Methods: A retrospective analysis of 7858 T2DM patients, who received a DPP-4i (Sitagliptin, Vildagliptin, Teneligliptin, Linagliptin and Saxagliptin) as the fourth drug to achieve glycemic control was undertaken. Patients with inadequate glycemic control despite receiving optimum doses of at least any other three OADs were included in this analysis.

Results: Patients were subdivided into 5 groups, based on the DPP-4i used for treatment: Sitagliptin (n=4787), Vildagliptin (n=2205), Teneligliptin (n=775), Linagliptin (n=64) and Saxagliptin (n=27). The mean fasting blood glucose (FPG) was 160.9 ± 20.4 mg/dl and mean post prandial glucose (PPG) was 227.8 ± 26.3 mg/dl. The mean baseline HbA1c was 8.2 ± 1.5 %. The mean duration required to control diabetes with all DPP-4i was 8.2 weeks with significantly lesser time with Sitagliptin (6.8 weeks, p<0.001). 81.5% of the total cases responded to treatment with a DPP-4i (P <0.05). At the end of the monitoring period, there was significant reduction in mean FPG by-28.1 ± 16.1 mg/dL(P=0.001), mean PPG by -55.3 ± 17.0 mg/dL(P=0.001), and mean HbA1c by -1.2 ± 0.7 (P=0.001). There was no significant difference between the groups with respect to reduction in PPG and HbA1c.

Conclusion: DPP-4 inhibitors are effective in achieving desired glycaemic goals even when used as a fourth drug in patients with inadequate glycaemic control despite receiving an optimum dose of at least 3 OADs.

Introduction
The management of patients with type 2 diabetes mellitus (T2DM) remains a challenge due to the progressive nature of the disease and most patients inevitably require combination therapy in order to maintain a good glycaemic control. While tight glycaemic control minimizes long-term micro- and macro vascular complications, achieving glycosylated haemoglobin (HbA1c) goal is often difficult especially in patients who have had a longer duration of the disease. An interview and prescription medication data between 1999 and 2004, from the National Health and Nutrition Examination Survey (NHANES) suggests that only half of the adults with T2DM achieve HbA1c goal of <7% as recommended by the ADA guidelines. In India, recent data from the First Basal Insulin Evaluation (FINE) -Asia study showed that only 43.0% patients with T2DM reached target HbA1c levels of <7.0%.3

To overcome treatment failure and achieve targeted glycaemic control as well as to address different underlying patho-physiological defects of T2DM, a combined therapy of oral anti-diabetic agents (OADs) with complementary modes of action is usually considered. Indeed, the key to successful therapy of T2DM is the addition of agents to existing therapy over time due to progressive nature of the condition. The availability of diverse classes of OADs that act via different mechanisms to correct the underlying patho-physiological defects which characterize T2DM has greatly expanded the potential for combination therapy.

A significant change in diabetes therapy has been the introduction of drugs that act on the incretin axis like the dipeptidyl peptidase 4 inhibitors (DPP-4i). DPP-4i drugs are weight neutral and have very low incidence of hypoglycemia unlike sulfonylureas and insulin. Due to these beneficial qualities current guidelines prioritize DPP-4 inhibitors as part of early combination therapies.

Guidelines recommend, initiation of insulin therapy if glycaemic target is not achieved after 3 months of triple therapy. The current study was aimed to assess the efficacy of the commonly used DPP-4i as a fourth drug, in patients with T2DM uncontrolled on existing triple drug therapy with the objective of delaying insulin initiation.

Methods
This retrospective analysis was carried out in patients with T2DM uncontrolled on triple drug therapy and treated with DPP-4i (Sitagliptin...
Table 1: Comparison of mean duration (in Months) to control T2DM in patients treated with different DPP-4is

<table>
<thead>
<tr>
<th>Groups</th>
<th>Mean duration (months) (Mean ± SD)</th>
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<tr>
<td>Total (N = 7858)</td>
<td>1.99 ± 0.70</td>
</tr>
<tr>
<td>Vildagliptin (N = 2205)</td>
<td>2.10 ± 0.80</td>
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<td>Sitagliptin (N = 4787)</td>
<td>1.70 ± 0.60</td>
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<td>Teneligliptin (N = 0775)</td>
<td>2.40 ± 2.09</td>
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<td>Linagliptin (N = 0064)</td>
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<td>Saxagliptin (N = 0027)</td>
<td>1.85 ± 0.90</td>
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Table 2: Summary of demographics in 7858 patients treated with different dipeptidyl peptidase-4 (DPP-4i) inhibitors at Diabetes Specialty Clinic in Mumbai, India

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Sitagliptin (N = 4787)</th>
<th>Vildagliptin (N = 2205)</th>
<th>Teneligliptin (N = 0775)</th>
<th>Linagliptin (N = 64)</th>
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<tr>
<td>N</td>
<td>4787</td>
<td>2205</td>
<td>775</td>
<td>64</td>
<td>27</td>
<td>7858</td>
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<tr>
<td>Age in years (Mean ± SD)</td>
<td>54.82 ± 10.72</td>
<td>56.01 ± 10.65</td>
<td>53.04 ± 10.95</td>
<td>58.30 ± 9.90</td>
<td>57.30 ± 11.54</td>
<td>55.89 ± 10.71</td>
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<td>Age in years (%)</td>
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<tr>
<td>&lt; 55 years</td>
<td>2506 (52.4)</td>
<td>1033 (46.8)</td>
<td>427 (55.1)</td>
<td>0045 (70.3)</td>
<td>0017 (63.0)</td>
<td>4768 (62.1)</td>
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<tr>
<td>≥ 55 years</td>
<td>2281 (47.6)</td>
<td>1172 (53.2)</td>
<td>348 (44.9)</td>
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<td>Sex (%)</td>
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<td>Male</td>
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<td>1847 (38.6)</td>
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<td>≥ 5years</td>
<td>3277 (68.5)</td>
<td>1562 (70.8)</td>
<td>468 (60.4)</td>
<td>0044 (68.7)</td>
<td>0020 (74.1)</td>
<td>5371 (69.1)</td>
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</table>

Exclusion Criteria:
- Patients who have been previously on DPP4i.
- Patients who were on insulin or previously were on insulin.
- Patients in whom DPP4 inhibitor therapy was contraindicated due to:
  - History of pancreatitis.
  - History of MEN Syndrome/ Medullary thyroid Carcinoma

Inclusion Criteria:
- Patients who had records of 3 or more regular follow ups.
- Patients who had poor glycaemic control despite taking at least 3 OADs(metformin, sulphonylureas, pioglitazone or alpha-glucosidase inhibitors). (*poor glycaemic control was defined as fasting plasma glucose [FPG] ≥130 mg/dL, post-prandial plasma glucose [PPG] ≥180 mg/dL, and Hba1C 7%)
- Patients treated with any of the DPP-4i (Sitagliptin, Vildagliptin, Teneligliptin, Linagliptin or Saxagliptin)
- Doses of various DPP4i :- Sitagliptin -50 mg OD, Vildagliptin -50 mg BID, Teneligliptin-20 mg OD, Linagliptin- 5 mg OD, Saxagliptin- 5 mg OD

Results
Patients were divided into 5 subgroups based on the type of DPP-4i used for treatment: Sitagliptin (n=4787), Vildagliptin (n=2205), Teneligliptin (n=775), Linagliptin (n=64) and Saxagliptin (n=27). The average age of the patients included in this analysis was 55.89 years (SD ± 10.71). As shown in Table 1, 46.8% of the cases among Vildagliptin were in the age group < 55 years which was significantly less as compared to 52.4% of the cases among Sitagliptin and 55.1% of the cases among Teneligliptin groups. Also, number of patients in Linagliptin and Saxagliptin was significantly less than in Sitagliptin group (p<0.05). But average ages were comparable between the groups. Males comprised 62.1% of study population and 37.9% were females. 83.6%of patients had body mass index (BMI)>23.5kg/m² and 69.1% had T2DM for >5 years(Table 1).The mean duration of time required to introduce any DPP-4i was 119.59 months (~10 years) for the study population. The difference in mean duration of time to introduce different DPP4i was not statistically significant.

Time taken by various DPP4is to achieve glycaemic control
The mean duration required to achieve glycaemic control after introducing a DPP-4i was 8.2 weeks (1.99 ± 0.70 months). The mean duration required to control diabetes was 6.3 weeks among the Sitagliptin group which was significantly less as compared to 8.0 weeks among Vildagliptin and Teneligliptin group (Table 2).

Response rate
Out of total 7858 cases, 81.5% of the cases responded to the addition of a DPP-4i and were able to achieve FPG<130 mg/dL and PPG <180 mg/dL with significantly more responders in Teneligliptin group (86.3%) compared to Sitagliptin group (82%) and Vildagliptin group (79%), (P < 0.05) (Table 3).

Response according to Age, Sex, BMI and duration of diabetes
The response in age group <55 years
was 86.7%, whereas in >55 years, it was 76.1%. Males responded more (87.4%) compared to females (72.3%). Those with low BMI (<23.5 kg/m²) had higher response (89.8%) as compared to 79.7% with high BMI (23.5 kg/m²). In patients with a lesser duration of diabetes (<5 years), the response was better (89.5%) when compared to patients with a longer duration (≥5 years) of diabetes (77.8%).

Changes in mean fasting, post prandial blood glucose and HbA1c

Before starting DPP-4i, the mean baseline FPG and PPG was 160.9 ± 20.4 mg/dL and 227.8 ± 26.3 mg/dL respectively. After addition of DPP-4i, it decreased to 132.8 ± 12.2 mg/dL and 172.5 ± 18.2 mg/dL respectively. The mean reduction in FPG and PPG was 28.1±16.1 mg/dL and 55.3±17.0 mg/dL respectively. The change was statistically significant (P=0.001) (Table 4). Mean reduction in FPG was significantly higher in Teneligliptin (21.0%) group compared to Vildagliptin (15.2%, P=0.02) and Sitagliptin group (15.9%, P=0.001). Mean reduction in PPG was comparable in Teneligliptin (25.8%), Vildagliptin (24.2%) and Sitagliptin group (23.7%).

Overall, the mean HbA1C decreased from 8.2% at baseline to 7.0% at the end of treatment over three months. Reduction in mean HbA1C from baseline in all the groups was statistically significant (P<0.001). Mean reduction in HbA1C was comparable in Teneligliptin (1.2%), Vildagliptin (1.3%) and Sitagliptin group (1.2%) (Table 4).

Discussion

Despite wide structural heterogeneity among DPP-4i and differences in their pharmacokinetic profiles, the data available indicates similar glucose-lowering efficacy with DPP-4i in combination with other antidiabetic drugs, similar weight-neutral effects and comparable safety and tolerability profiles.

DPP-4i added to OADs with complementary mechanisms of action have been proven to be particularly effective in lowering all 3 glycaemic parameters (FBG, PPG and HbA1c) in multiple studies, regardless of age, gender, race/ethnicity, or body mass index.7,8 In metformin-treated patients, DPP-4is were associated with similar HbA1c reductions compared with a sulphonylurea (SU) and a thiazolidinedione (TZD). DPP-4i also exerts clinically relevant glucose-lowering effects as triple therapy with a good tolerability profile when added to a metformin–SU or pioglitazone–SU combination. With the use of three or more drugs, the risk of hypoglycemia increases significantly and the choice of drugs is therefore paramount in preventing this adverse event. DPP-4 inhibitors as fourth drug in patients failing on triple therapy may offer significant advantage of achieving glycaemic control.7,8

In this retrospective analysis, DPP4i were found to provide effective glycaemic control as observed by the significant decrease in all three glycaemic parameters (FBG, PPG and HbA1c). This benefit was observed when DPP-4is were used as a fourth drug to patients failing on triple therapy, thus providing effective glycaemic control.

We found differences in glycaemic control in these five agents studied. While these differences were statistically significant in this study, larger prospective, randomized, population based studies are needed to confirm the clinical advantage of one specific DPP-4 inhibitor over another. The strength of these data lies in the large number of patients evaluated and the consistency of the findings across various subsets, whereas the limitation of these data is the retrospective nature of the analysis. These findings warrant further prospective randomized clinical studies.

Conclusion

In T2DM patients, DPP4 inhibitors as a fourth drug, were found to be effective in achieving the desired glycaemic control within 8 weeks of initiation. These agents offer an important addition to the armamentarium of treatment options for patients with T2DM by providing another mechanism to address the multiple patho-physiologic defects present in this disease. Most diabetes treatment guidelines stress the fact that when 3 oral drugs fail to adequately control the blood glucose, insulin should be initiated. A vast majority of the patients would be pleased to avoid initiating insulin if given a choice. This data shows the efficacy of a four drug regime to effectively achieve glycaemic control and delay insulin initiation.

References

Skin Testing before Antibiotic Administration – Is there a Scientific basis?

Pradeep Narayan¹, Emmanuel Rupert²

Abstract
The practice of skin testing prior to administration of antibiotics in the absence of a history of allergy is non-existent in the western world. Reports on skin testing in the absence of known allergy are unheard of in the medical literature. The practice of giving a test dose prior to administration of the antibiotic is also practiced very sporadically and has no scientific basis. Despite this in India in most major institutions both in government and private hospitals, general practice set up and small and medium nursing homes, skin testing prior to administration of antibiotics remains extremely common and is even considered to be negligent if not practiced.

In this review the evidence for skin testing and test dose before antibiotic administration has been examined. Based on the evidence available skin testing should be restricted to patients with a history of prior penicillin allergy for whom penicillin or other B-lactam antibiotic is the drug of choice and there is no suitable alternative¹. There is no need to do skin testing without a history of penicillin allergy even if the drug is to be administered parenterally. Test dose administration does not protect patients from anaphylactic reactions and hence the practice has no scientific basis.

Introduction
Even though it has been recommended that skin testing should be restricted only to patients with a history of prior penicillin allergy for whom penicillin or other B-lactam antibiotic is the drug of choice and there is no suitable alternative¹ the practice of skin test has been deeply ingrained in the psyche of the health care providers including doctors as well as nursing staff. Currently in most hospital in India “Skin testing” refers to injecting a small amount of the antibiotic in question in varying dilution. There is no definite protocol for the dilution across institutions nor is there consensus about the injection being given intra-dermally or subcutaneously. Following the injection the area is examined for induration or features of systemic hypersensitivity reactions. The time one has to wait before confirming that the patient is not allergic to the antibiotic in question is also variable. There is no evidence in the literature that this practice is useful in reducing rates of anaphylactic reactions and the practice has been in vogue purely as part of the culture of administering antibiotics in institutions in our part of the world.

Test dose administration is often practiced by anaesthetists and other medical practitioners whereby a small amount of the antibiotic in question is administered intravenously and after a non-defined period of wait the remaining antibiotic is administered. The logic behind this practice is that by test dose administration even if the patient had hypersensitivity reaction the dose of antigenic challenge is limited therefore minimizing the chance of a full-blown anaphylaxis.

Scientific basis of Skin testing
At the outset it has to be clarified that skin testing in the patients with no history of previous allergic reaction to antibiotics and those with a positive history are two completely different scenarios. While clinically significant IgE-mediated penicillin allergy can be safely confirmed or refuted using skin testing with penicilloyl-poly-lysine and native penicillin G in presence of positive history of allergy,²,³ its utility as a screening tool in all patients without any history of allergic reaction is questionable.

There are two main arguments against skin test or test dose in patients with no previous history of allergy to penicillin or any other antibiotic. Firstly, anaphylaxis is a generalized hypersensitivity reaction which may be IgE or non-IgE mediated. Thus, the presentation can be within 1 hour (IgE mediated) or beyond 1 hour (non IgE mediated). So, the time we generally wait before giving the antibiotic after a skin test or a test dose does not assure that the patient is not allergic to the antibiotic in question and will not have a hypersensitivity reaction.

Secondly, hypersensitivity reactions are dose independent. Rawlins and Thompson classified adverse drug reactions into two types. Type A reactions which are dose dependent and are predictable and type B reactions which are dose independent and unpredictable. Hypersensitivity reactions to antibiotics belong to the type B of adverse drug reactions and thus are dose independent.⁴ This has been further confirmed by Wills and Brown who classified drug reactions into 9 types and suggested that hypersensitivity reactions are a type H reaction which are neither pharmacologically predictable, nor are they dose related.⁵

Moreover, while parenteral administration appears the most likely...
route to induce anaphylaxis; it has been reported to occur following parenteral, oral, topical, or inhalation routes.

Lastly, skin tests (in presence of penicillin allergy) have been well validated mainly for β-lactam but less well validated for other classes of antibiotics. Routine cephalosporin skin testing should be restricted to research settings. If skin test is negative, an oral amoxicillin challenge can be given. Acute tolerance of an oral therapeutic dose of a penicillin class antibiotic is the current gold standard test for a lack of clinically significant IgE-mediated penicillin allergy.

Pathology of Penicillin allergy

Adverse Drug Reactions (ADRs) account for 3% to 6% of all hospital admissions and occur in 10% to 15% of hospitalized patients. Drug allergy is relatively uncommon, accounting for less than 10% of all ADRs. Hypersensitivity reactions represent about one third of all adverse drug reactions.

The course of penicillin hypersensitivity is unpredictable with an individual tolerating penicillin earlier may show allergy on subsequent administration and those allergic earlier may not have problems on subsequent administration.

According to the World Allergy Organization drug allergies based on timing of symptoms can be classified into immediate and delayed. Immediate reactions occur within 1 hour after the drug administration and delayed reactions occur more than 1 hour after the last drug administration.

Immediate reactions can range from urticaria to anaphylactic shock and may be mediated by specific IgE-antibodies. Delayed reactions are usually manifested as a maculopapular rash and specific T lymphocytes may be involved in this type of reaction.

Antibiotics can be classified as β-lactam and non-β-lactam. The β-lactams share a 4-membered β-lactam ring and are consist of 2 major classes (penicillins and cephalosporins) and 4 minor ones ( carbapenems, monobactams, oxacephems, and clavams). Non-β-lactam antibiotics have different chemical structures and some of the commonly used non-β-lactam antibiotics include quinolones, macrolides, aminoglycosides, sulfonamides, rifamycins, and clindamycin.

IgE-mediated reactions involve drug allergens binding to IgE antibodies, which are attached to mast cells and basophils, resulting in IgE cross-linking, cell activation and release of preformed and newly formed mediators. Non–IgE-mediated drug allergy most commonly are T-cell-mediated reactions.

True incidence of Penicillin allergy

β-lactam are the most widely used antibiotic worldwide. It is also the most commonly reported cause of drug allergy, with a prevalence rate of 0.7 to 10% in adults and children. However it has been shown that 95% of patients with a history of penicillin allergy were considered not to be allergic in large scale follow up studies using various tests to confirm the diagnosis. Based on the recommendations of the European Network of Drug Allergy / European Academy of Allergy and Clinical Immunology; assessment of β-lactam hypersensitivity includes a detailed clinical history, in vitro quantification of specific IgE-antibodies, skin tests, and drug provocation test (DPT).

Those patients with non suggestive or unknown histories have a penicillin skin-test positivity rate of less than 2%. Among all patients labeled penicillin-allergic, the frequency of serious reactions to cephalosporin administration is less than 1%. Over diagnosis of drug allergy leads to the unnecessary use of broader spectrum and expensive antibiotics contributing to the emergence of multidrug resistant pathogens. Equally, underdiagnosis of antibiotic allergy can have serious and sometimes fatal consequences.

Tests to assess Penicillin allergy

A positive skin prick test (SPT) is defined as mean weal diameter greater than 3 mm (associated with a flare response) compared to the negative control after 15 to 20 minutes.

A positive intradermal test (IDT) while being more sensitive to the SPT it is also more prone to anaphylaxis. Similar to the SPT it is defined as an increase in the mean weal diameter of ≥3 mm compared to the baseline diameter for the negative control after 15 to 20 minutes. It is performed by injecting 0.02 to 0.05 mL of an allergen intradermally, raising a small bleb measuring 3 mm in diameter. Readings should be taken both after 15 to 20 minutes and after 24 and 72 hours for evaluation of non-immediate reactions.

Drug provocation tests (DPT) are used to objectively reproduce the patient’s symptoms and signs of hypersensitivity using the suspected agent. DPT involves administrating the drug using slow, incremental dose escalations and observing for the presence or absence of an objective reaction. However, a positive test does not confirm allergy (i.e. an immune-mediated reaction). It should be done only under strict supervision.

Anaphylaxis during general anaesthesia

Neuromuscular blocking agents account for over half of all cases of anaphylaxis. However anaphylaxis due to latex and antibiotics are on the rise. Anaphylaxis to fentanyl and neostigmine has also been reported. Researchers examining patients undergoing anaphylaxis during anesthesia have suggested that screening patients without a prior history of allergic drug reactions is not recommended because there is a discrepancy between skin pick test results and clinical outcomes.

Antibiotic hypersensitivity in children

Immediate hypersensitivity to as β-lactam is particularly rare in children, but identification of these patients is particularly important because these reactions can be life threatening. The decreased frequency of allergic drug reactions in children may be secondary to several factors, including fewer drug exposures, generally reduced allergic reactivity, less vigorous antibody response, and differences in drug metabolism.

Penicillin allergy in Cardiac Surgery

The Society of Thoracic Surgeons guidelines for prescribing antibiotics in presence of penicillin allergy recommend that “In patients with a history of an immunoglobulin-E (IgE)–mediated reaction to penicillin or cephalosporin (anaphylaxis, hives, or angioedema), vancomycin should be given preoperatively and for no more than 48 hours. Alternatively, skin testing may be performed in these patients and, if negative, a cephalosporin regimen administered (Class I, Level of Evidence A).” However for patients “with a history of a non-IgE
mediated reaction to penicillin (such as a simple rash) or an unclear history either vancomycin or a cephalosporin is recommended for prophylaxis with the understanding that these patients have a low incidence of significant allergic reactions to cephalosporins (Class I, Level of Evidence B).\(^\text{26}\)

**Desensitization**

This is a specialist area and has to be done by experts in the field. Oral route is the safest, however it can be performed by intravenous, or subcutaneous routes as well. Desensitisations have been performed safely even in pregnant women.\(^\text{29}\)

**Summary**

Over diagnosis of drug allergy leads to the unnecessary use of broader spectrum and expensive antibiotics and majority of patients with a history of penicillin allergy prove not to be allergic in large. Skin testing in the current form does not protect patients from anaphylaxis and there is no scientific basis for the practice.

**Recommended antibiotic administration protocol**

Based on the guideline the suggested protocol for antibiotic administration starts with a clinical history. A history of drug and antibiotic allergy has to be elicited. In the absence of history of allergy to antibiotics (usually penicillin group) no skin testing or test dose is required.

If the patient provides a history of allergy to penicillin then alternative appropriate antibiotic should be used.

The alternative antibiotics include - Cephalosporins and other non-penicillin beta-lactams. They have been used safely in individuals, even with confirmed penicillin allergy. Currently it is believed that there is little, if any, clinically significant immunologic cross-reactivity between penicillin and other beta-lactams.\(^\text{2}\)

Another safe option would be to use non-beta Lactams like Vancomycin.

In the unique situation of penicillin being the only drug of choice and the patient gives a history of penicillin allergy one has to seek specialist advice. A skin test and a course of desensitization vis. a vis. administration of penicillin or cephalosporin has to be taken based on the clinical condition of the patient and how convincing the history of allergy to penicillin is. It also has to be borne in mind that almost 85% patients previously allergic to penicillin may be able to tolerate the drug on re-administration, indicating the potential transient nature of the condition.\(^\text{3}\)

However, this has to be discussed with the patient, the family and other involved clinicians before reaching a consensus and has to be dealt with on a case to case basis.

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Supplemental Antioxidants: A Hype in Disease Prevention

Bhupinder Singh Kalra

Abstract

Supplemental antioxidants are being prescribed by medical practitioners without considering its ill effects at higher doses. Antioxidants dosing has not been standardized and optimum or recommended daily dose is inconsistent too. Literature and Cochrane database search for review and meta analysis for efficacy of preventing and treating chronic disorders like cardiovascular diseases, diabetes, cancer, infertility etc shows inconclusive or negative results. Despite lack of evidence these drugs are rampantely being prescribed without any specific indication. Antioxidants are extensively being marketed too and their over the counter availability is again is the reason for its inappropriate use by consumers. Need is to practice evidence based medicine, define recommended daily doses with upper intake levels and antioxidants should be prescribed only in profound deficiency states.

Antioxidants or free radical scavengers are believe to neutralize products of oxidation reaction happening in the body. Excess of free radical production is considered as deleterious for cells as it can damage DNA, protein components and membranes. Our body naturally possess some of these antioxidants(endogenous) and we also get them from diet. These dietary antioxidants are mainly betacarotene, lycopene, and vitamins A, C, and E (alpha-tocopherol). Fruits, vegetables and grains have numerous antioxidants.

Do we require supplemental antioxidants in the form of commercial vitamins, what for and how much? The answer to this question till date is not clear. As a result, hype is being created by pharmaceutical industry to cash upon this opportunity to promote sales of supplemental antioxidants. It has been observed that antioxidants are two edge sword, at high concentration it has destructive role and may also lead to cancer. Although, various animal studies have established role of antioxidants in prevention of certain disease conditions like cardiovascular disorders, diabetes, cancer prevention etc. but clinical evidence has been either inconclusive or negative.

The global antioxidants market is estimated at $377.1 million as of 2016 and is forecast to reach $485.17 million by 2021. Antioxidants are mainly categorized as natural or synthetic. Natural antioxidants are generally used for disease prevention and synthetic antioxidants are used as preservative in food and beverage industry to prolong shelf life. Natural antioxidants market has been categorized into four types-rosemary extract, vitamin A, vitamin C, and vitamin E; while synthetic antioxidants comprise three types-butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), and others. Our concern is growing natural antioxidant market wherein supplemental antioxidants are being marketed rampanty.

Consumers have been misguided by overemphasized advantages of consuming supplemental antioxidants by Pharmaceutical industry. Effect of antioxidants on ageing, cancer prevention, chronic disorders like Diabetes, Hypertension, congestive heart failure etc has not been substantiated by clinical evidence (Table 1). Unnecessary, hundreds of animals especially rodents are being killed to see the effect of antioxidants (herbal or synthetic) as a part of animal research. Is this research justified in lieu of lack of clinical evidence? Animal efficacy data with antioxidants is not being translated into human benefit.

Are medical practitioners aware of this fact? Since, patients will consume as they are being asked to take antioxidants by treating doctor. Role of treating physician is vital in this process. They should be made aware and practice of prescribing antioxidants without any indication or deficiency state should be curbed down. Evidence based medicine should be inculcated in routine practice. The other important flaw is lack of awareness on the part of consumer and availability of these antioxidants over the counter.

Large scale cohort studies or national surveys are needed to establish total antioxidant intake from diet and the percentage that comes from supplements. This holds the key in establishing a relationship between antioxidants and disease. Both inadequate and excess intakes of antioxidants impact vital body functions and are associated with increased morbidity and mortality. To begin with, need is to establish Recommended dietary allowance (RDA), average requirement (AR)/ adequacy intake (AI) and upper intake levels (UIL) of antioxidants in different geographic population. United States antioxidant intake data might not be relevant in Asian subcontinent.

In a study conducted in India, it was found that majority of the supplements contained vitamins and antioxidants in higher than recommended takes RDA, but many contained lower amounts or nutrients or other compounds that do not have recommended intakes. Since, retinol is the primary form of vitamin A in supplements, it is likely that the risk of excessive intakes is undesirably high for multivitamin users. In another study involving a multiethnic cohort in US, 10-15% of the participants had higher intakes of vitamin A. In a national survey in US,
it was observed that the labels of most preparations listed nutrients below the UIL. Amounts of vitamin B6, vitamin C and vitamin A were at or above the UIL.⁷

Antioxidants generally are not considered as drug rather they are regarded as dietary supplements. As a result the approval from Regulatory agencies for marketing is relatively easier process. Efficacy data is not mandatory or required for approval of antioxidants as they are considered as food supplement or nutraceuticals. This is again a flaw in the system leading to bulk manufacturing and marketing. The only beneficiary in this vicious cycle of supply and demand is the manufacturer of antioxidants.

The reason for failure of antioxidants in clinical studies despite positive findings in invitro and invivo studies could be pharmacokinetic, optimal dose not known, negative results of invivo studies not being published or targeting wrong biomarkers. Any recommendation on antioxidants must be based on solid clinical evidence and patient-relevant outcomes rather than surrogate parameters.⁸ Approaches or substances which trigger endogenous antioxidant system might be more rewarding in clinical scenario.⁹

Need of the hour is to come up with guidelines or recommendations for optimal consumption of antioxidants.

| Table 1: Evidence for effect of supplemental antioxidants |
|----------------|---------------|----------------|-----------------|----------------|
| Title of study                                                                 |
| Antioxidant supplements for preventing gastrointestinal cancers | Meta analysis | 20 randomised trials (211,818 participants), assessing beta-carotene (12 trials), vitamin A (4 trials), vitamin C (8 trials), vitamin E (10 trials), and selenium (9 trials) | 1.Antioxidant supplements were without significant effects on gastrointestinal cancers (RR 0.94, 95% CI 0.83 to 1.06) | 9 |
| Antioxidant supplements for liver diseases | Meta analysis | Twenty randomised trials with 1225 participants. The trials assessed beta-carotene (3 trials), vitamin A (2 trials), vitamin C (9 trials), vitamin E (15 trials), and selenium (8 trials) | Antioxidant supplements had no significant effect on all-cause mortality (relative risk (RR) 0.84, 95% confidence interval [CI] 0.60 to 1.19, I(2) = 0%), or liver-related mortality (RR 0.89, 95% CI 0.39 to 2.05, I(2) = 37%) | 10 |
| A randomized factorial trial of vitamins C and E and beta carotene in the secondary prevention of cardiovascular events in women: results from the Women’s Antioxidant Cardiovascular Study | Randomized Controlled Trial | 1450 women experienced 1 or more CVD outcomes | No overall effect of ascorbic acid (relative risk (RR) 1.02; 95% CI 0.92-1.13 [P = .71]), vitamin E (RR, 0.94; 95% CI, 0.85-1.04 [P = .23]), or beta carotene (RR, 1.02; 95% CI, 0.92-1.13 [P = .71]) on the primary combined end point | 11 |
| Vitamins E and C in the prevention of prostate and total cancer in men | Randomized Controlled Trial | Total of 14,641 male physicians in the United States initially aged 50 years or older, including 1307 men with a history of prior cancer at randomization, were enrolled | Vitamin E had no effect on the incidence of prostate cancer [HR, 0.97; 95% CI], (9 trials) | 12 |
| Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT) | Randomized Controlled Trial | Total of 35,533 men from 427 study sites. Primary analysis included 34,887 men who were randomly assigned to 1 of 4 treatment groups: 8752 to receive selenium; 8737, vitamin E; 8702, both agents, and 8696, placebo | Compared with placebo, the absolute increase in risk of prostate cancer per 1000 person-years was 1.6 for vitamin E, 0.8 for selenium, and 0.4 for the combination. | 13 |
| Effects of vitamins C and E and beta-carotene on the risk of type 2 diabetes in women at high risk of cardiovascular disease | Randomized Controlled Trial | Total of 8171 female health professionals aged > or =40 y randomly assigned to receive vitamin C (ascorbic acid, 500 mg every day), vitamin E (RRR-alpha-tocopherol acetate, 600 IU every other day), beta-carotene (50 mg every other day), or their respective placebos. | Median follow-up of 9.2 y | 14 |
| The Effect of Vitamin E and Beta Carotene on the Incidence of Lung Cancer and Other Cancers in Male Smokers | Randomized Controlled Trial | Total of 29,133 male smokers randomly assigned to one of four regimens: alpha-tocopherol (50 mg per day) alone, beta carotene (20 mg per day) alone, both alpha-tocopherol and beta carotene, or placebo. Follow-up continued for five to eight years. | No reduction in incidence was observed among the men who received alpha-tocopherol (change in incidence compared with those who did not, -2 percent; 95 percent confidence interval, -14 to 12 percent). | 15 |
| Efficacy of vitamin and antioxidant supplements in prevention of cardiovascular disease | Meta analysis | 50 randomised controlled trials with 294478 participants (156663 in intervention groups and 137815 in control groups) | Supplementation with vitamins and antioxidants was not associated with reductions in the risk of major cardiovascular events (relative risk 1.00, 95% confidence interval 0.98 to 1.02; 12=42%) | 16 |
Regulatory authorities, academia and pharmaceuticals should jointly work upon this process to draft recommendations to enlighten and benefit consumers.

References


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Pacemaker Mediated Tachycardia

Rajeev Bhardwaj1, Someshwar Rao2, Naresh Gaur2

6 7 yrs male, a known case of dilated cardiomyopathy, was implanted dual chamber permanent pacemaker, two years back, for complete heart block. He presented with increased breathlessness and palpitation for two days. ECG showed wide QRS tachycardia (Figure 1, Figure 2, strip A). There was suggestion of pacing spike before the QRS complex. P waves were not identified. Since ventricular pacing was occurring at inappropriately higher rate, possibility of pacemaker mediated tachycardia (PMT)/endless loop tachycardia was kept. Magnet was kept over the generator, and the tachycardia was terminated (Figure 2, strip B). After this, post ventricular atrial refractory period (PVARP) was increased by programming the pacemaker and ECG showed atrial sensing with ventricular pacing (Figure 2, strip C).

Pacemaker-mediated tachycardia, also called endless-loop tachycardia, is used to refer to a form of a reentrant tachycardia and can occur in patients who have dual-chamber pacemakers. The pacemaker forms the anterograde (atrium to ventricle [A \rightarrow V]) limb of the circuit and the atroventricular (AV) node is the retrograde limb (ventricle to atrium [V \rightarrow A]) of the circuit.

The following is the most common scenario causing PMT. A dual-chamber pacemaker programmed DDD is implanted. The patient must have retrograde (V\rightarrow A) conduction with an atrial activation time that is longer than the programmed PVARP. A ventricular-paced beat or a properly timed premature ventricular contraction (PVC) conducts retrograde via the AV node (or an accessory pathway, if present) to the atrium. If the atrial depolarization occurs after the set PVARP, but before the next timed atrial-paced beat, ventricular pacing will be triggered at the programmed AV interval. PMT tends to occur at or near the programmed upper rate limit and depend upon the programmed AV delay and the PVARP. This generates an incessant reentrant arrhythmia circuit that persists as long as there is continuous VA conduction with atrial activation outside the PVARP. Ventricular pacing at or near the upper rate limit of the pacemaker is evident on ECG. The presence of a paced rhythm exactly at the upper rate limit with atrial sensing and exact A-V association warrants evaluation for pacemaker-mediated tachycardia (PMT). A magnet placed on the pacemaker will stop the tachycardia.

Treatment, prevention, and termination of pacemaker-mediated tachycardia (PMT) typically involves altering the pacemaker programming to prevent sensing of the retrograde P wave. This is most easily done by prolonging the PVARP. During the PVARP, the atrial lead does not sense any atrial activity; hence, ventricular pacing is not triggered. Carotid sinus massage or AV nodal blocking drugs such as adenosine, verapamil, or beta-blockers can block VA conduction (ie, retrograde conduction) directly and can terminate PMT.

Reprogramming a dual-chamber, dual-mode, dual pacing, dual-sensing (DDD) pacemaker to AAI, VVI, or DVI (DDI) abolishes the PMT reentrant circuit, thereby prohibiting PMT from occurring. These other programming modalities can lead to serious problems as DDD pacing may be necessary (consider the difficulty of AAI pacing in a patient with complete heart block).

Atrial sensitivity may be programmed so that sinus P waves are detected but not retrograde P waves (which can be smaller). The downside of this approach is that intrinsic P-wave amplitude can be lower at higher rates, which could potentially result in atrial undersensing. Making sure that atrial capture is adequate is also important. Attempting to adjust sensitivity is generally impractical. Most modern dual-chamber pacemakers are capable of detecting PMT and initiating PMT intervention by automatically prolonging the PVARP for the beat after a ventricular-sensed event that is not preceded by atrial pacing, ie, a PVC (PVARP extension).

References


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Prostate Cancer Presenting as Collet-Sicard syndrome

Mugundhan Krishnan¹, Balamurugan N², Thiruvarutchelvan K³, Sivakumar S⁴

60 year old male, non smoker, non alcoholic, not a known diabetic or hypertensive presented to us with dysphagia with nasal regurgitation, 6 months duration. On examination, the patient was conscious, oriented, Fundus examination was normal. Right side tongue atrophy was noted (Figure 1). Right side palatal palsy was present (Figure 2). wasting of sternomastoid (Rt) and Wasting of trapezius (Rt) was also present (Figures 3 and 4). There was no limb weakness. All deep tendon jerks were normal. Plantars were flexor. Sensory and cerebellar systems were normal. On rectal examination, hard prostatic mass was felt.

Blood investigations including blood biochemistry were normal. Serum alkaline phosphatase was 98U/l. Ultrasonogram of abdomen and pelvis showed enlargement of prostatic gland (4.3 x 4.6 cm). Serum prostatic specific antigen was 650 ng/ml. MRI Brain showed secondaries in clivus (Figure 5). MRI Dorsal spine showed multiple well defined hypointense sclerotic secondaries (Figure 6). Histopathological Examination (HPE) of prostatic gland biopsy showed irregular small round to oval glands lined by columnar cells with mild to moderate nuclear pleomorphism and hyperchromatism. There are other foci showing sheets of tumour cells with diffuse infiltration of stroma. These features were suggestive of adenocarcinoma of prostate.

Brain showed secondaries in clivus (Figure 5). MRI Dorsal spine showed multiple well defined hypointense sclerotic secondaries (Figure 6). Histopathological Examination (HPE) of prostatic gland biopsy showed irregular small round to oval glands.
Total Anomalous Pulmonary Venous Connection

Rajeev Bhardwaj¹, Sachin Sondhi², Shivani Rao², Vaishali Verma²

23 years female presented with breathlessness and palpitation for last 10 years. She also had marked kyphoscoliosis.

Her echocardiography showed dilated right atrium(RA) and right ventricle(RV). There was ASD secondum, of 13 mm in size. Pulmonary veins were not seen opening into left atrium. There was a large venous channel, in which all pulmonary veins drained and this channel was opening into RA near the opening of superior vena cava (Figures 1, 2). On contrast echocardiography, there was right to left shunt through ASD (Figure 3).

Total anomalous pulmonary venous connection (TAPVC) is a rare but heterogeneous anomaly, accounting for ≈1% to 3% of congenital heart disease cases.¹ Historically, TAPVC has led to a high mortality rate of ≈80% in the first year of life without intervention.² In 1959, Darling and associates proposed a classification, also based on the anatomy of the anomalous connection.³ Four types were identified: type 1, anomalous connection at the supracardiac level; type 2, anomalous connection at the cardiac level; type 3, anomalous connection at the infracardiac level; and type 4, anomalous connection at two or more of the above levels. Treatment is surgical correction. The goal of surgery is to redirect all pulmonary veins to the left atrium through wide and nonrestrictive connection.⁴

Our patient had type 2 TAPVC and underwent successful surgical repair.

References
3. Darling RC, Rothney WB, Craig JM. Total pulmonary venous drainage into the right side of the heart: report of 17 autopsied cases not associated with other major cardiovascular anomalies. Lab Invest 1957; 6:44–64.
Undiagnosed Fever in a TB Contact Patient: An Unusual Cause

Himanshu Narang¹, Animesh Ray¹, Surabhi Vyas², Madhavi Tripathi³, Nishikant Damle⁴, Ranveer Singh Jadon¹, Piyush Ranjan¹, Ved Prakash⁵, Naval Vikram¹

Abstract
IgG4-Related Disease (IgG4-RD) is a rare disease that can present with myriad clinical features. We report a tuberculosis contact case who presented with fever and constitutional complaints with imaging evidence of paravertebral and retroperitoneal soft tissue thickening. Further workup, including tissue biopsy ruled out tuberculosis and revealed diagnosis to be IgG4-related disease. Patient was started on oral steroids, which led to symptomatic improvement. In a TB endemic country such as ours, for a patient presenting with pleural and/or peritoneal fibrosis, a differential diagnosis of IgG4-RD must be kept.

The various causes of retroperitoneal fibrosis were reviewed and are elucidated in Table 1. Retroperitoneal fibrosis may be idiopathic or secondary. Idiopathic retroperitoneal fibrosis occurs in the 40-60 year age group with a 2:3:1 male predominance. It may be IgG4 related (70 % cases) or non-IgG4 related (30% cases). Retroperitoneal fibrosis due to IgG4 related disorder (IgG4 RD) is usually associated with involvement of other organs, including pancreas, salivary glands, lymph nodes, and mediastinal periaortitis. Radiologically, it can be classified into three types based on site of involvement: (1) periaortic, involving tissue around the abdominal aorta and its main branches; (2) periureteral; and (3) plaque-like mass that diffusely involves the retroperitoneum.

As the patient did not give any history of offending drug use, a differential diagnosis of tuberculosis, IgG4 related disease and malignancy were kept.

Table 1: Etiology of retroperitoneal fibrosis

<table>
<thead>
<tr>
<th>Idiopathic</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs</td>
<td></td>
</tr>
<tr>
<td>• Ergot derivatives – beta blockers, bromocriptine, methyldopa, hydralazine, methysergide</td>
<td></td>
</tr>
<tr>
<td>• Biologicals – Etanercept, infliximab</td>
<td></td>
</tr>
<tr>
<td>Isolated</td>
<td></td>
</tr>
<tr>
<td>Malignancy – carcinoid tumour, Hodgkin lymphoma, Non-hodgkin lymphoma, retroperitoneal sarcoma, ca colorectum, ca breast, ca prostate, ca bladder</td>
<td></td>
</tr>
<tr>
<td>Infections – tuberculosis, histoplasmosis, actinomycosis</td>
<td></td>
</tr>
<tr>
<td>Radiation therapy</td>
<td>Retroperitoneal hemorrhage</td>
</tr>
<tr>
<td>Secondary(AA) amyloidosis</td>
<td>Histiocytosis (Erdheim-Chester disease)</td>
</tr>
</tbody>
</table>

We present the case of a 64 year old gentleman, resident of Delhi, currently retired office worker who had developed low grade fever with constitutional symptoms of weight loss (6 kg over 1 month) and loss of appetite for 2 months. Fever was around 100 deg F, associated with bodyache and headache, but without chills or rigors. He also complained of generalized weakness and malaise. There was no history of night sweats, hospitalisations or similar complaints in past. The patient was a known hypertensive and had symptomatic benign prostatic hypertrophy. His wife had been diagnosed with pulmonary tuberculosis 8 years back and died 5 years back apparently due to a renal ailment.

Patient initially was empirically treated with IV antibiotics however, his low grade fever persisted for which he was referred to us after 2 months. His CECT chest and abdomen showed homogenously enhancing plaque like soft tissue thickening along the pleura in right paravertebral location extending from D6 to D11 vertebral levels without vertebral (bone) involvement. Right pleural thickening with mild pleural effusion was noted, without significant mediastinal lymphadenopathy. Similar soft tissue thickening was also present in the retroperitoneum and presacral region encasing the IVC, bilateral internal iliac and right external iliac arteries along with left distal ureter leading to mild proximal hydronephrosis (Figure 1). Suggestive of a fibrotic process involving the retroperitoneum, pleura and paravertebral area.

Fig. 1: Axial contrast enhanced CT images (A&B) show homogenously enhancing soft tissue thickening in the right paravertebral location and in the retroperitoneum around both common iliac arteries (*). Note the normal cortical outline of the dorsal vertebra (arrow)

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raised serum IgG4 levels. Although is often, but not always, associated with a dense lymphoplasmacytic infiltrate characterized by storiform fibrosis, and members. living without assistance from family able to perform all activities of daily on tapering doses of steroids. He is After 6 months follow up, patient is resolved and his appetite improved. Fever and malaise reported significant improvement (prednisolone 1 mg/ kg) initially. He decided to proceed with tissue biopsy. FDG Fluorodeoxyglucose positron emission tomography/CT (FDG-PET) was done to look for disease activity and detect other sites of involvement. It revealed metabolically active soft tissue thickening in the right thoracic paravertebral, region from D6-D11 level and in presacral region from L4-S2 with left internal mammary, left para-aortic and right perirectal lymph nodes (Figure 2).

A CT guided biopsy was done from the thoracic paravertebral soft tissue. Histopathology revealed fibrosis with increased plasma cells positive for IgG4 (Figure 3). Thus, a diagnosis of IgG4 related retroperitoneal and thoracic paravertebral fibrosis was made.

Patient was started on steroids (prednisolone 1 mg/ kg) initially. He reported significant improvement in his symptoms. Fever and malaise resolved and his appetite improved. After 6 months follow up, patient is on tapering doses of steroids. He is able to perform all activities of daily living without assistance from family members.

IgG4 related disease (IgG4 RD) is a fibroinflammatory condition that is characterized by storiform fibrosis, and a dense lymphoplasmacytic infiltrate rich in IgG4 positive plasma cells, that is often, but not always, associated with raised serum IgG4 levels. Although single organ involvement with the characteristic tissue involvement (e.g. Miculicz’s disease, Reidel’s thyroiditis) have been known for more than a century now, it was only in 2010 that the disease name was finally coined “IgG4 Related Disease”. It was the result of series of findings that led to understanding the pathophysiology of the disease, as well as association with raised serum IgG4 levels and multiple tissue involvement. Currently, IgG4 RD is known to involve virtually any organ system including retroperitoneal soft tissue, pulmonary and mediastinal, lymph nodes, salivary and lacrimal glands, orbit, liver, gall bladder, pancreas, etc.

However, despite the varied organ involvement, the histopathological features are characteristically similar. In this regard, the disease has often been compared to sarcoidosis, another systemic disease with multiple organ involvement, but characteristic histological findings.

The diagnostic criteria of IgG4 RD were formulated in 2011 require histopathological presence of dense lymphoplasmacytic infiltrate with increased IgG4 positive plasma cells (at least > 10/ high power field (HPF) and/or increased IgG4/IgG ratio (usually >40%), storiform fibrosis and obliterative phlebitis (Figure 4). Other common histological findings include tissue eosinophilia, obliterative arteritis and inflammatory infiltrate rich in B and T lymphocytes.

Clinical presentation of IgG4 RD is subacute, and majority of patients do not have fever or constitutional symptoms. The condition is often detected incidentally in CT scan/ MRI done for another disorder, or pathological tissue specimens. Patients usually present with a single organ involvement with or without subclinical involvement of other organ systems. Thus presenting symptoms are organ specific as shown in Table 3.

Our patient predominantly presented with fever and non specific symptoms of generalized weakness and malaise with no localizing features. This is not a typical presentation of the disease thus the disease was not kept in the initial differential diagnosis.

### Table 2: Disorders with increased serum IgG4 levels

<table>
<thead>
<tr>
<th>Autoimmune disorders</th>
<th>– ankylosing spondylitis, rheumatoid arthritis, myositis, Granulomatosis with polyangiitis (Wegener’s), polyarteritis nodosa, eosinophilic granulomatosis with polyangiitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1 diseases</td>
<td>– sclerosing cholangitis, cirrhosis</td>
</tr>
<tr>
<td>Hematological diseases</td>
<td>– AML, multiple myeloma, lymphoma, castleman disease</td>
</tr>
<tr>
<td>Infectious diseases</td>
<td>– Filariasis, strongyloidosis, herpes virus group (HSV, EBV), nocardia</td>
</tr>
<tr>
<td>Respiratory disorders</td>
<td>– asthma, bronchiectasis, idiopathic pulmonary fibrosis, sarcoidosis</td>
</tr>
<tr>
<td>Solid organ malignancy</td>
<td>– Ca lung, ca gall bladder, cholangiocarcinoma, ca colorectum, ca stomach, ca pancreas, sarcoma</td>
</tr>
</tbody>
</table>

![Fig. 2: F-18 FDG-PET imaging showed (A) FDG avid right paravertebral, prevertebral and presacral soft tissue thickening showing contrast enhancement from D6-D11 and L4-S2 vertebral level (sagittal view); (B) FDG avid prevertebral and presacral soft tissue (axial view); (C) FDG avid right paravertebral soft tissue thickening (axial view)](image)
of considering this condition in patients presenting with non-specific constitutional symptoms where routine workup has been unrevealing. In a tuberculosis endemic country IgG4 RD disease might closely mimic the manifestations of the common malady.

**References**

Behcets Syndrome with a Rare Manifestation

Nirmal Taparia¹, Vitthal Dhadke ²

Abstract
We report a case of a 25 year old patient with history of recurrent oral aphthous ulcers and genital ulcers and phylectenular conjunctivitis presenting to us with sudden onset of cough and difficulty in breathing diagnosed as Behcets disease with pulmonary embolism. A rapid and precise diagnosis and treatment of this patient led to good recovery of this patient. Pulmonary thromboembolism is a rare complication of Behcets disease.

Introduction
Behcets disease is a chronic, relapsing inflammatory disease characterized by recurrent oral and genital ulcers as well as lesions affecting the eyes, skin, nervous system, joints and vessels.² It is classified among vasculitides.¹⁰

The diagnostic criteria are clinical and based on the Internationally agreed diagnostic criteria described in Table 1.¹

It is a rare immune mediated small vessel systemic vasculitis. It is named after the Turkish dermatologist Hulusi Behcet who described the triple symptom complex in 1937. The specific etiology of Behcets disease remains elusive and it could be auto inflammatory or auto immune in origin. Behcets disease is a sporadic disease but carriers of HLA B51/HLA B5 have an increased risk of developing this disease than non carriers.² Recent research has shown that multiple genes in the interleukin 23 signalling pathway contribute to this disorder. Polymorphism of JAK2 and STAT3 are associated with these disorders.³

Males and females are equally affected but males often have a more serious disease. Sex prevalence varies by country. Turkey has the highest prevalence of Behcets disease with 420 cases/1,00,000 population.⁴

Here, we present a case of Behcets in a young male patient presenting in OPD with recurrent oral and genital ulcers and an episode of severe dyspnea and hemoptysis.

Case Report
A 25 years old male patient came in OPD with c/o oral ulcers and severe breathlessness and cough since 2 days. It was of sudden onset with no fever, chest pain, or trauma. He had no such past history. Patient gave a prior h/o recurrent oral (Figure 1) and genital ulcers (Figure 2) with conjunctivitis (Figure 3) and imaging studies a diagnosis of pulmonary embolism with Behcets disease was made. Pulmonary function test and ulcer biopsy were not done.

Based on his clinical features of recurrent oral and genital ulcers and conjunctivitis, Pathergy test (Figures 6 and 7) and imaging studies a diagnosis of pulmonary embolism with Behcets disease was made. Pulmonary function test and ulcer biopsy were not done.

Patient was admitted on 21/03/2016 in civil hospital and followed. Pt was conscious, tachypneic with a Respiratory rate of 35/min, Spo2 of 88% on room air, tachycardic with Heart Rate of 116/min, Blood Pressure of 110/80 mm of Hg.

He was evaluated and investigated. His laboratory evaluation were as showed in table 2 below. X-ray of chest showed wedge shaped ground glass opacity in left lower zone. So CT chest and Pulmonary angiogram was done which showed thrombus in subsegmental branch of pulmonary artery with consolidation and minimal left pleural effusion (Figures 3, 4 and 5).

ECG was normal. 2DEcho was normal.

Sputum examination showed no pathogen and AFB was –ve.

Sputum culture reports later were negative.

USG Colour Doppler for both lower limbs were normal, arterial as well as venous.

Blood parameters Patients value Normal range
Hemoglobin (gm/dl) 11.0 12.0-15.0
WBC (x10³/ul) 9.5 4-10
Platelets (x10³/ul) 30 150-400
Biochemistry
blood urea (mg/dl) 28 7-40
Sr. creatinine (mg/dl) 1.0 0.6-1.2
BSI R (mg/dl) 91 65-95
Sr.Na (meq/l) 141 136-146
Sr. K (meq/l) 4.2 3.5-5.0
Sr. bilirubin (mg/dl) total 0.6 0.3-1.3
Direct bilirubin 0.3 0.1-0.4
Indirect bilirubin 0.3 0.2-0.9
AST (U/L) 29 14-36
ALT (U/L) 28 9-52
Coagulation profile
Bleeding time 4min 55sec <7.1 min
Clotting time 5min 18sec <7.1 min
Prothrombin time 13 sec 12.4-15.7 sec
INR 1.15 0.8-1.2

Case was treated with IV fluids, Oxygen by nasal prongs to maintain Spo2 > 90%. IV steroids Methylprednisolone at a dose of 250mg twice daily for 5 days, Inj Low molecular weight heparin was given subcutaneously at a dose of 2500u twice a day for 5 days along with oral anti platelet agent aspirin 75 mg daily. Prophylactic antibiotic Inj. Cefotaxime 1 gm was given iv twice daily for 5 days.

Table 1: Diagnostic Criteria for Behcets syndrome
Recurrent oral ulceration plus two of the following
Recurrent genital ulceration
Eye lesion
Skin lesion
Pathergy test

Table 2: Laboratory Investigations of the patient

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For oral ulcers local steroids and vitamin B complex tablets were given. Patient responded well to above line of treatment and was discharged on 29/3/2016 with oral anticoagulation acitrom 1 mg/d and wysolone 0.5 mg/kg of body weight and advised to f/u in opd regularly.

**Discussion**

Behcets disease is a benign condition with mucocutaneous and ocular manifestations of disease. There are 4 major case series in the world, Turkey with 2147 patients, Korea with 1155 patients, Morocco with 1034 patients, and UK with 419 patients.10

Recurrent aphthous ulcers are a sine qua non for the diagnosis. The ulcers are usually painful, shallow or deep with a central yellowish necrotic base and are located anywhere in the oral cavity with 1 to 10 mm in diameter. They subside without leaving scars and are seen in 85% of patients.2 The localization in the order of frequency is lips, cheeks, tongue, gingival, palate, tonsils and pharynx.10

Non specific skin reaction to intradermal saline injections (pathergy test) or scratches is observed in 50% of patients.2

Genital ulcers are less common, in 73%, more specific, painful, do not affect the glans penis or urethra and produce scrotal scars. As shown in the figure in this case.

Eye involvement with bilateral panuveitis is the most dreaded complication. Eye disease occurring in 50% of patients may develop in few years as it did in our patient. Iritis, posterior uveitis, optic neuritis and retinal vein occlusion all can be seen.2

Non deforming arthritis or arthralgias are seen in 50% of patients and affect the knees and ankles.2 Neurological involvement seen in (7.3%) of cases classically manifests as meningoencephalitis, and GI cases (9%) presenting as ulceration of the ileo-cecal region, also occur.10

Pulmonary artery aneurysms (PAAs) are the most common pulmonary lesions in Behcets disease and these are almost always associated with hemoptysis. Upto 78% patients with aneurysms have concomitant extrapulmonary venous thrombi or thrombophlebitis. Underlying pathology is pulmonary vasculitis which may result in thrombosis, infarction, hemorrhage or PAA formation.6,7 Immunosuppression is the mainstay therapy for treatment.8

Pulmonary disease can be divided into subtypes depending upon involvement viz9

1. PAA
2. Pulmonary parenchymal changes.
4. Radiologic abnormalities
5. Infection, immunosuppressive related presentation
6. Abnormal pulmonary function finding or COAD.

Pulmonary emboli are a rare complication seen in 0.5% of cases of Behcets disease.9 Pulmonary artery vasculitis presenting with dyspnea, cough, chest pain, hemoptysis and infiltrates on chest x ray have been reported in 5% of patients.5

Our patient showed a thrombus in subsegmental branch of right pulmonary artery. The differential diagnosis could be acute coronary syndromes, acute pericarditis or pleuritis, pneumonia, hypersensitivity pneumonitis,
Tetany in an Extensively Drug Resistant Tuberculosis (XDR-TB) Patient Treated with Capreomycin

Man Mohan Puri1, Anil Kumar2, Pooja Aneja3, Rajnish Gupta4, Lokender Kumar4, Rohit Sarin5

Abstract
Gross electrolytes disturbances including hypokalemia, hypomagnesemia, and hypocalcaemia have been reported in tuberculosis patients who have been treated with capreomycin.1-3 Capreomycin is recommended in the treatment of M. tuberculosis isolates resistant to kanamycin at baseline in multi drug resistant tuberculosis (MDR-TB) and treatment of extensively drug resistant tuberculosis (XDR-TB) under programmatic management of drug resistant tuberculosis (PMDT) in India.4 We report a case of tetany in a extensively drug resistant tuberculosis (XDR-TB) patient treated with capreomycin. She developed hypokalemia after 7 weeks of administration of injection capreomycin intramuscularly daily in dose of 750 mg. Hypokalemia was refractory to intravenous potassium replacement therapy. At 12 weeks during the treatment she developed tetany and hypocalcaemia. Hypomagnesemia was also associated with hypocalcaemia and hypokalemia. Normal level of serum potassium and calcium were achieved with correction of hypomagnesemia.

Introduction
The national guidelines for programmatic management of drug resistant tuberculosis (PMDT) in India offer an integrated drug resistant treatment algorithm with standard treatment regimen for multi-drug resistant (MDR-TB) and extensively drug resistant tuberculosis (XDR-TB). The algorithm also offers scope for modifying the standard regimen for MDR-TB in cases with additional resistance to fluoroquinolones (FQ) or second line injectables (SLI). Although the proportion is small, the number of persons with MDR TB is sizeable in numbers. 1-3% of new and around 12% re-treatment tuberculosis patients are MDR TB4. On an average, an estimated 9.7% of patients With...
and/or ototoxic drugs. Electrolyte disturbances are reported rarely with capreomycin. Here, we report a case of dyselectrolytemia presenting as tetany in a young female patient of XDR-TB without prior renal disease treated with capreomycin.

**Case Report**

A 21- year, female was admitted in ward on 10th June 2015 as case of extensively drug resistant (XDR) pulmonary tuberculosis (TB), for treatment initiation under programmatic management of drug resistant tuberculosis (PMDT) with Category –V (CAT- V) XDR regimen. She was on treatment for multi-drug resistant (MDR) pulmonary tuberculosis since 2-10- 2014 under PMDT. At the start of MDR TB treatment her sputum test was positive for Mycobacteria tuberculosis complex resistant to Isoniazid and Rifampicin by line probe assay test (LPA), which was resistant to ofloxacin and sensitive to second line injectable drugs (Kanamycin, Amikacin, Capreomycin). 6th month follow – up sputum M. tuberculosis culture was resistant to ofloxacin and second line injectable drugs (Kanamycin, Amikacin). Her treatment was switched over to XDR TB treatment regimen on 17-6- 2015. The following drugs were included in Category-V XDR tuberculosis treatment regimen: Capreomycin, Linezolid, Moxifloxacin, Amoxicillin-clavulanic acid, clofazimine, high dose Isoniazid and Para Amino-salicylic acid after pre evaluation with complete blood count (CBC), liver function test (LFT), Kidney function test (KFT) and serum electrolytes. She tolerated anti-tuberculosis treatment (ATT) well for first 1.5 months but developed tingling sensation of lower extremities after 7 weeks of start of XDR treatment regimen. There was no complaint of vertigo, giddiness or tinnitus. She had no history of vomiting, diarrhea or oliguria. Blood examination revealed hyponatremia (Na+ 130 mmol/L) and hypokalemia (K + 2.9 mmol/L). Normal value for serum sodium and potassium as per the laboratory is 133-145 mmol/L and 3.8 -5.5 mmol/L respectively. She was given intravenous injection Potassium chloride (KCL) with normal saline to correct the deficit (Figure 1). Hyponatremia was improved but hypokalemia persisted. After 5 weeks, MDR TB have XDR TB. As per PMDT guidelines, kanamycin is substituted by capreomycin if drug susceptibility testing results of M. tuberculosis isolates is resistant to kanamycin at baseline or patient is intolerant to same. MDR tuberculosis patient on follow - up, if diagnosed as XDR TB on M. tuberculosis culture report, will also be switched to XDR - TB regimen4.

The intensive phase of XDR –TB regimen consist of 7 drugs including injection capreomycin for 6-12 months. Capreomycin is a nephrotoxic drug and monitoring of renal function tests and serum electrolytes is required for prolonged use. Nephrotoxicity is most likely to occur in patients with renal impairment, in geriatric patients and in patients receiving other nephrotoxic
she complained of severe abdominal pain and carpopedal spasm (tetany). Serum calcium was 5.05 mg/dl and serum magnesium was 1.19 mEq/l (Figure 2). Normal value for serum calcium and magnesium as per the laboratory is 8.5 – 11.0 mg/dl and 1.3 - 2.50 mEq/L respectively. Inj Magnesium sulphate was given at the rate of 1mEq/kg over 24 hours followed by 0.5mEq/kg over 24 hours for next 4 days. Hypokalemia was also corrected with injection potassium chloride infusion. Injection calcium gluconate 200mg in 100 ml normal saline was given intravenously over 10 minutes and continued at the rate of 1-2mg/kg/hour for next 10 days till the normalization of calcium level and symptomatic relief. Kidney function tests and liver function tests were within normal limits. Injection Capreomycin was also withheld as a part of treatment for dyselectrolytemia because of reported side effect and there was no other cause for present electrolyte dysfunctions. Injection capreomycin was substituted with injection imipenem and cilastatin with other drugs of CAT- V XDR TB treatment regimen. Serum phosphate was within normal limits and vitamin D3 levels were low. Gradually patient recovered from dyselectrolytemia with normal serum potassium and serum magnesium levels (Figures 1, 2). Later on, oral Calcium was continued along with Vitamin D3 supplementation. No attempt was made to re-introduce injection capreomycin.

**Discussion**

Aminoglycosides and capreomycin cause renal wasting of electrolytes, including potassium, magnesium, and calcium.\(^1\) Nephrotoxicity of capreomycin is most likely to occur in patients with renal impairment, in geriatric patients and in patients receiving other nephrotoxic and/or ototoxic drugs. Electrolyte disturbances resembling Bartter’s syndrome are reported rarely with capreomycin. The electrolyte disturbances may not be from the toxic levels, but an adaptive immune response to therapy. Autopsy finding of hydropic changes in the epithelial lining of the distal tubules was reported in a patient of electrolyte disturbances suspected due to capreomycin.\(^2\) Caroline bell reported zebra bodies limited to tubules on renal biopsy in a patient of XDR tuberculosis of lymph node due to capreomycin induced acute kidney injury with hypokalemia, hypomagnesaemia and tetany.\(^3\) Zebra bodies are commonly seen with Anderson- Fabry disease, a lysosomal storage disorder of glycosphingolipid catabolism caused by deficiency of a galactosidase. These bodies are lysosomes containing broad transversely stacked myelinoid membranes and also seen in iatrogenic interstitial phospholipidosis (PL) from various pharmacological agents including aminoglycosides.\(^4,5\) Drug-induced phospholipidosis is characterized by intracellular accumulation of phospholipids with lamellar bodies, most likely from an impaired phospholipid metabolism of the lysosome. The iatrogenic interstitial phospholipidosis (PL) effects may result from retention of a small, but significant (approx 5%) proportion of administered dose in the epithelial cells of proximal tubules,\(^9\) mainly in endosomal and lysosomal vacuoles.\(^10,11\) This results in accumulation of phospholipids in and enlargement of, the lysosomes with inhibition of lysosomal phospholipases. Each cationic, amphiphilic drug (CAD) induces its own phospholipid composition and selectively targets different organs.\(^12\)

Gross electrolytes disturbances including hypokalemia, hypomagnesaemia and hypocalcaemia have been reported in tuberculosis patients who have been treated with capreomycin. Hypokalemia is reported in 4 to 15% of patients receiving capreomycin therapy for 6 to 26 months.\(^5,14-17\) In a large cohort of MDR-TB patients receiving an injectable agent (i.e., streptomycin, amikacin, kanamycin, or capreomycin), forty of the 115 patients (34.8%) were found to have an electrolyte disturbance during the course of therapy.\(^14\) The average potassium was 2.85 mEq/L on presentation, with a nadir of 2.65 mEq/L occurring approximately 6 weeks after diagnosis of hypokalemia.\(^14\) Hypomagnesaemia often accompanied hypokalemia.\(^14\) In our patient, hypokalemia reached at nadir of 1.7 mmol/l after 42 days of diagnosis of hypokalemia. Shin et.al reported fourteen patients (12.2%) of MDR-TB who had both low potassium and magnesium while receiving an injectable agent.\(^14\) The mean duration of therapy at the time of diagnosis of hypokalemia was 5.1 ± 4.0 months.\(^14\) Our patient was switched to capreomycin for treatment of XDR TB after 8 months treatment with kanamycin for MDR TB. She developed hypokalemia in seventh week of capreomycin therapy. Electrolyte disturbances did not appear to be related to preexisting renal disease.\(^3\) Her renal functions were within normal limits before starting treatment with capreomycin and even with development of electrolyte disturbances she had normal renal functions. Capreomycin and low initial body weight were significantly associated with an increased likelihood of occurrence of hypokalemia.\(^14\) Our patient too had low initial body weight 39 Kg (BMI = 15.6 Kg/m²). Use of streptomycin as the choice of injectable was associated with lower rates of hypokalemia in comparison with capreomycin.\(^14\) In our patient, M. tuberculosis isolate was also resistant to streptomycin.

Normalization of electrolyte values may take up to four months after cessation of the offending agent.\(^16\) Approximately 86% of those with hypokalemia went on to normalize, with a mean duration of potassium disturbance of 6.6 ± 3.9 months.\(^14\) Hypokalemia may be refractory to treatment if hypomagnesaemia is present and not addressed. In a multivariable model; factors associated with earlier time to hypokalemia resolution were male gender and absence of hypomagnesaemia.\(^14\) Magnesium serves as a cofactor in the adenosine Triphosphatase dependent mechanism for active transport of sodium and potassium across the cell membrane, further potassium wasting occurs as a consequence of resultant intracellular magnesium deficiency. Decreased cell magnesium may open potassium channels in the luminal membrane of the loop of Henle and increase in membrane permeability may lead to potassium leakage out of the cells and increase potassium excretion.\(^18-19\) Spironolactone (100 to 300 mg/day) may also aid in the normalization of serum potassium and magnesium.\(^5,20\) However the use of potassium-sparing diuretics (spironolactone, triamterene, or amiloride) was not associated with resolution of hypokalemia in a cohort of MDR TB patients receiving treatment\(^14\). Caution should be used...
when potassium-sparing diuretics are administered in conjunction with potassium supplements, since hyperkalemia or orthostasis can result. 

In our patient hypokalemia was refractory to potassium replacement therapy till hypomagnesaemia was corrected. (Figure 1). Aquinas et al reported recurrence of hypokalemia on resuming capreomycin in two patients with resolution on discontinuation of the injectable. We did not try to re-introduce capreomycin in our patient; however Caroline had re-introduced capreomycin successfully at a lower drug dose.

**Hypomagnesemia, though infrequently looked for, is present in up to 12 % of hospitalized patients.** Few studies have documented the association of hypomagnesaemia in patients with tuberculosis and is multifactorial in origin such as malnutrition, malabsorption, and therapy induced renal loss. There is also evidence of renal loss. Fewer patients have hypokalemia associated with hypomagnesaemia. Hypomagnesemia is believed to cause impaired synthesis or secretion of parathyroid hormone which results in decrease serum calcium levels. Hypomagnesemia is associated with aminoglycoside therapy. Although capreomycin induces iatrogenic interstitial phospholipidosis (PL) results from retention of small but significant (approx 5%) proportion of administered dose in the epithelial cells of proximal tubules with cationic, amphiphilic drug (CAD). There are few reports of capreomycin induced iatrogenic interstitial phospholipidosis presenting as hypokalemia, hypocalcemia and hypomagnesemia. Our patient developed hypokalemia after 7 weeks of therapy of capreomycin. The hypokalemia was refractory to intravenous potassium replacement therapy. On presentation of tetany at 12 weeks she was diagnosed to have hypokalemia associated with hypocalcemia and hypomagnesemia. Normal level of serum potassium and calcium were achieved with correction of hypomagnesemia. A high level of suspicion of hypomagnesemia is warranted in patient developing hypokalemia on prolonged therapy with capreomycin. Serum magnesium and calcium levels may be checked in hypokalemic and/or symptomatic individuals.

**Conclusion**

**Iatrogenic interstitial phospholipidosis (PL)** results from retention of small but significant (approx 5%) proportion of administered dose in the epithelial cells of proximal tubules with cationic, amphiphilic drug (CAD). There are few reports of capreomycin induced iatrogenic interstitial phospholipidosis presenting as hypokalemia, hypocalcemia and hypomagnesemia. Our patient developed hypokalemia after 7 weeks of therapy of capreomycin. The hypokalemia was refractory to intravenous potassium replacement therapy. On presentation of tetany at 12 weeks she was diagnosed to have hypokalemia associated with hypocalcemia and hypomagnesemia. Normal level of serum potassium and calcium were achieved with correction of hypomagnesemia. A high level of suspicion of hypomagnesemia is warranted in patient developing hypokalemia on prolonged therapy with capreomycin. Serum magnesium and calcium levels may be checked in hypokalemic and/or symptomatic individuals.

**References**

Inflammatory Myositis—Secondary to SLE

Sreejith V Ravi1, CJ Selvakumar2, M Sacrates3, Shobhana2, Arjunan Mahesh3

Abstract

Inflammatory myositis involving the proximal muscles has been reported to occur in 5% to 11% of SLE patients and may develop at any time during the course of the disease. It can be secondary to internal malignancies also. We report one such patient who presented with generalised muscle weakness for 7 months. Erythematous hyperpigmented scaly patches were present over the scalp, face, trunk, upper limbs. We discuss the inflammatory myopathies secondary to SLE and internal malignancies. Most cases respond to low-dose corticosteroid treatment.

Introduction

In SLE, generalized myalgia and muscle tenderness are common, especially during disease exacerbations. As per the Kelley’s Textbook of Rheumatology, 8th ed; Inflammatory myositis involving the proximal muscles has been reported to occur in 5% to 11% of patients and may develop at any time during the course of the disease. There have been many associations between the inflammatory myopathies and the presence of malignancy, but the etiology of the association is controversial. Here we report a lady who presented with inflammatory myositis, secondary to SLE, and discuss the possible causes of such a presentation.

Table 1: Suggested classification for inflammatory myopathies

<table>
<thead>
<tr>
<th>Descriptions</th>
<th>Pure Dermatomyositis (DM)</th>
<th>Pure Polymyositis (PM)</th>
<th>Cancer-associated myositis (CAM): clinical paraneoplastic features without an overlap autoantibody or anti-Mi-2</th>
<th>Overlap myositis (OM): myositis with at least one clinical overlap feature or an overlap autoantibody</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>5. Electromyographic triad of short, small, polyphasic motor unit potentials; fibrillations, positive sharp waves, and insertional irritability; and bizarre, high-frequency repetitive discharges</td>
<td></td>
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<tr>
<td>Probable myositis: 3 criteria (without the rash) for PM; 2 criteria (plus the rash) for DM</td>
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<tr>
<td>Definite myositis: 4 criteria (without the rash) for PM; 3 or 4 criteria (plus the rash) for DM</td>
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Case Report

A 44 year old housewife, mother of two children, presented with c/o progressively increasing symmetrical weakness of all four limbs and neck muscles for 7 months, for which she consulted primary care physicians and received symptomatic treatment without a proper diagnosis (Details not available). There was no history of diabetes, hypertension and cardiovascular disease. She had history of hysterectomy eight years back for fibroid uterus. On examination erythematous hyperpigmented scaly patches were present over the scalp, face, trunk, upper limbs (Figures 1-3). She had multiple small joint arthritis (Figures 4-5). She also had bilateral hallus valgus which was an incidental finding (Figure 6). There were no cutaneous markers suggestive of Dermatomyositis. CNS examination showed generalised wasting, hypotonia in all four limbs, symmetrical weakness (Proximal>Distal) of all four limbs and neck muscles. All deep tendon reflexes were sluggish. There were no signs of involvement of sensory system and cranial nerves. Other systems were within normal limits.

Routine full blood count and biochemical analysis including thyroid function tests were normal. Chest X-ray, Electrocardiogram, USG Abdomen and CECT Abdomen were also normal. ESR was 20 mm/hr. She was negative for HIV test. We investigated her for muscle disorders secondary to autoimmune and neoplastic causes: CPK-10,730. LDH - 298. pANCA and cANCA- negative. CEA and CA-125 were Negative, USG B/L Breast was Normal study, Stool occult blood—negative. Rheumatoid factor was negative. Colonoscopy and Upper GI Endoscopy were normal.

Muscle Biopsy (Left vastus lateralis) showed perifascicular interstitial inflammation with perifascicular atrophy, ATPase enzyme histochemistry showed atrophic Type two fibres: Inflammatory myopathy—consistent with polymyositis and possible vasculitis. There were no histopathological features of dermatomyositis. Decreased fibre density with a few regenerating fibres on myelin stain and Mild to moderate chronic axonopathy was there in Left Sural nerve biopsy which can be secondary to SLE. NCS was suggestive of sensory motor axonal neuropathy. EMG was suggestive of neuropathic pattern of weakness. ANA was positive. ANA profile was (Anti U1 RNP, Anti Sm, Anti Ro, Anti SSA, Anti SSB, Anti Jo-1 and Anti ScI-70 autoantibodies) negative, except that Anti ds DNA was positive. (The pattern is attached).

She was diagnosed to have inflammatory polymyositis secondary to SLE: was managed conservatively with dexamethasone 8 mg iv, as she had gastritis at admission which later changed to prednisolone at a dose of 0.5 mg/kg/day and azathioprine 50 mg/day1 and physiotherapy and is on follow up for internal malignancy. Her weakness was improving with treatment.

Discussion

Myositis

Polymyositis (PM), Dermatomyositis (DM), and inclusion body myositis (IBM) are the classic idiopathic inflammatory myopathies (IIMs) (Table 1), yet the same clinical picture and

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investigational findings may be found in patients with SLE, scleroderma, MCTD, and Sjögren’s syndrome. Inflammatory myositis involving the proximal muscles has been reported to occur in 5% to 11% of SLE patients and may develop at any time during the course of the disease.

**Inflammatory Myopathies**

The inflammatory myopathies in adult populations encompass a group of illnesses characterized by an idiopathic immune-mediated attack on skeletal muscle that results in muscle weakness. There have been many associations between the inflammatory myopathies and the presence of malignancy, but the etiology of the association is controversial. Dermatomyositis has classically been associated with occult malignancies, whereas the associations between polymyositis and inclusion body myositis are less clear. A further issue is whether the inflammatory myopathy predates the malignancy and can be considered a primary rheumatic disease with known risks of developing malignancy, or whether it simply represents a manifestation of a paraneoplastic process.

On average, the prevalence of malignancy in association with the inflammatory myopathies has been approximately 25.3 The frequency of malignancy has ranged, however, from 6% to 60% in patients with dermatomyositis and from 0 to 28% in patients with polymyositis. Other estimates have placed the incidence of cancer in patients with inflammatory myopathies at five to seven times that of the general population. In polymyositis, the relative risk for developing internal malignancies seems to be lower than that for dermatomyositis, but it is consistently increased over that expected in the general population. Studies have found a 14% to 30% prevalence of cancer among patients with polymyositis.

Studies have suggested that imaging of the chest, abdomen, and pelvis may increase the potential for discovery of underlying malignancy. Other studies have suggested the use of serum tumor markers (CA125 and CA19-9) to augment detection of patients with dermatomyositis or polymyositis at highest risk for associated malignancy. Malignancies associated with inflammatory myopathies have been known to develop many years after the diagnosis of muscle disease, so continued vigilance and repeated screening for malignancy are warranted. Although the pathogenesis is unknown, the types of malignancy associated with the inflammatory myopathies have been varied, including adenocarcinomas of the breast, ovaries, and stomach.

**SLE with Myositis**

Generalized myalgia and muscle tenderness are common, especially...
During disease exacerbations. Inflammatory myositis involving the proximal muscles has been reported to occur in 5% to 11% of patients and may develop at any time during the course of the disease. The differential diagnosis of proximal muscle weakness in SLE includes a drug-related myopathy secondary to corticosteroid, antimalarial, or statin medications use. Concurrent hypothyroidism also can cause an increase in creatine phosphokinase and proximal myopathy. Muscle biopsy, electromyographic studies, and elevation of the serum creatine phosphokinase value help to differentiate between inflammatory and drug-related myopathy. The histologic features of myositis in SLE may be less striking than in idiopathic polymyositis. Histologic features include muscle atrophy, microtubular inclusions, and a mononuclear cell infiltrate. Fiber necrosis is an uncommon finding, but immunoglobulin deposition is almost always present despite the rarity of concurrent inflammation. A low serum creatine phosphokinase value can be found in patients with connective tissue disease including SLE; a normal creatine phosphokinase value in the presence of symptoms and signs of myositis should not dissuade the physician from a diagnosis of myopathy. The skin lesions of dermatomyositis also can appear in patients with SLE. Chest pain or discomfort secondary to costochondritis has been reported in SLE, and other conditions, such as angina pectoris, pericarditis, and esophageal spasm, must be ruled out first.

Definition of clinical Paraneoplastic Features

Cancer within 3 yr of myositis diagnosis, plus absence of multiple clinical overlap features; plus, if cancer was cured, myositis was cured as well

References


Congenitally Absent Left Circumflex Artery

Rajneesh Calton1, Amit Gulati2, Cinosh Mathew3, Sakshi Khurana4

Abstract

Congenital coronary anomalies are uncommon with rarest being absent left circumflex artery (LCX) having prevalence of 0.003%. We report a case of a 68 year old male having acute coronary syndrome and left ventricular dysfunction whose coronary angiogram showed an absent LCX with super dominant right coronary artery (RCA). Precise morphological evaluation is needed for best suited management strategy.

Introduction

Congenital coronary anomalies have an uncommon occurrence with the incidence of approximately 0.1–2%. Majority of coronary anomalies (80%) are asymptomatic and clinically silent, which are detected incidentally, while approximately 20% of them have been reported to have a clinical presentation. One of the rarest vascular anomaly is congenitally absent left circumflex artery (LCX) with a prevalence of 0.003% where LCX artery is not seen to develop in the left atiroventricular groove. While commonly being detected incidentally on various imaging studies, congenital absence of LCX artery has been seen to be associated with myocardial infarction, vasospastic angina and systolic click syndrome. We hereby describe a case of 68 year old male who presented with recent worsening of breathlessness with a dilated left ventricle and poor left ventricular ejection fraction on echocardiography. Coronary angiography showed a long segment of disease involving the left anterior descending (LAD) artery with absent LCX artery and a large super dominant right coronary artery (RCA). Aortic root injection did not show any

Fig. 1: Coronary angiogram image depicting left main artery continuing as left anterior descending artery with absent left circumflex artery (arrow)

Fig. 2: Coronary angiogram image on right coronary injection showing the superdominant right coronary artery (arrow) supplying the vascular territory of left circumflex artery

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anomalous origin of LCX artery. MDCT angiography further confirmed the absence of LCX artery. Acute coronary syndrome, left ventricular dysfunction and coronary artery disease in association with congenital absence of LCX artery is rarely described.

Case Report

A 68 year old gentleman with diabetes presented with history of breathlessness for 2 months which worsened over one week before presentation. He had no history of palpitations or chest pain in the past. Physical examination revealed an average built male with a pulse rate of 110 beats per minute and a blood pressure of 160/90 mm Hg. Peripheral pulses were palpable and normal. Routine investigations were within normal limits. Systemic examination revealed bilateral basal crepitations while on cardiac auscultation S3 was audible in addition to the normal heart sounds. Chest radiograph showed borderline cardiomegaly with mild pulmonary oedema. A 12 lead electrocardiogram showed normal sinus rhythm with T wave inversions and a super dominant RCA was seen in anterior leads suggestive of anterior sinus rhythm with T wave inversions. Echocardiography was performed via the femoral approach. On angiography.

Aortic root injection further confirmed the absence of any anomalous origin of left circumflex artery.

On the following day, 128 slice MDCT angiography was performed which showed the absence of LCX. No anomalous LCX artery was visualised. LAD showed a long segment of stenosis while a super dominant RCA was seen with no discrete stenosis (Figures 3 and 4).

Discussion

Though varying from mild to life threatening presentation, anomalous coronary arteries are a rare occurrence. Most commonly seen coronary anomaly is LAD and LCX arising separately from left sinus of valsalva. Failure of development of LCX in the left atrioventricular groove leading to an absent LCX is an extremely rare anomaly with a reported incidence of 0.003%.3

There are many schools of thoughts for the congenital absence of LCX artery. Some believe that this condition is not a real congenital anomaly, and that it is the anomalous origin of the LCX artery from distal RCA.4 Recently the new acronym, congenital ostial stenosis or atresia (COSA) has been coined. Most of the times, this anomaly is a benign condition. However, it can cause chest pain, particularly on exertion. Our, patient also complaint of occasional chest pain, but his main complaints were that of breathlessness.

Ueyama et al. have previously reported an anomalous origin of LCX where the vessel was seen arising from the right sinus of valsalva or from the RCA.5 When following a normal origin and course, LCX runs around the atroioventricular groove along with RCA and forms a circle. RCA thereby compensates for the absence of LCX by perfusing its territories. This compensatory mechanism leads to a benign outcome is majority of cases.

Mievis et al. have reported myocardial infarction in a 31 year old male where on coronary angiography no significant stenosis could be seen involving the coronaries, but it showed an absent LCX.6 As seen by Mohsen et al.7 in our case too, a super dominant RCA perfused a large area extending to the left ventricle.

Though conventional angiography is well known for its ability to detect coronary anomalies but MDCT being a non invasive modality with a three dimensional imaging and reconstruction is well suited for defining coronary arterial anatomy and their course. At times, there may be difficulty in differentiating between congenital absence of an artery or an ostial stenosis. A detailed angiographic evaluation is must to understand the course of each coronary artery and its relationship with various clinical presentations so that the best treat treatment modality can be selected.

References

An Access to Androgen Excess: The Ovary Unregulated

Neha Agrawal1, Saumik Datta2, Puranjoy Chakrabarty1, Veronica Arora3, Salil Kumar Pal4

Abstract
Hirsutism is excess terminal hair that commonly appears in a male pattern in women. It is associated with hyperandrogenemia. Ferriman-Gallwey scoring system is the most popular scoring system for evaluation, treatment and monitoring the response to therapy. Causes include PCOS, Cushing syndrome, glucocorticoid resistance, drugs, fetal aromatase deficiency, idiopathic hyperandrogenism and idiopathic hirsutism, more serious conditions like androgen secreting tumour from ovary in a 30-yr-old lady. This case emphasizes on the spectrum of manifestations that PCOS can come with and the importance of trans vaginal ultrasonography in diagnosing ovarian conditions and its superiority over conventional trans abdominal USG or CT scan.

Introduction
Hirsutism is the presence of terminal hair that commonly appears in a male pattern in women, often jeopardising her personal, social and sexual life. Ferriman-Gallwey scoring system is the most popular scoring system which helps in evaluation, treatment and monitoring the response to therapy. It can be due to both benign and malignant conditions. Causes include PCOS, cushing syndrome, glucocorticoid resistance, drugs, fetal aromatase deficiency, idiopathic hyperandrogenism and idiopathic hirsutism, more serious conditions like androgen secreting tumour from ovary or the adrenal, hyperthecosis ovarii and luteoma of pregnancy.

PCOS is the most common form of chronic anovulation associated with hyperandrogenism; affecting 5% to 10% of reproductive-age women. It leads to reproductive morbidity as well as increased metabolic and cardiovascular risk linked to insulin resistance. However, insulin resistance also occurs in lean PCOS. It is inherited in a polygenic fashion with a strong family history.

Table 1: Routine tests

<table>
<thead>
<tr>
<th>Labs</th>
<th>Results</th>
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<tbody>
<tr>
<td>Hb</td>
<td>10.3 gm%, normocytic, normochromic</td>
</tr>
<tr>
<td>FBS,PPBS</td>
<td>93mg/dl,136mg/dl</td>
</tr>
<tr>
<td>LFT</td>
<td>Within normal limit</td>
</tr>
<tr>
<td>Urea,Cr,Na,K</td>
<td>Within normal limit</td>
</tr>
<tr>
<td>Lipid Profile</td>
<td>Total cholesterol-209,LDL-112,Triglyceride-222,HDL-42</td>
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Here, we are sharing our experience and obstacles we faced in clinching the diagnosis and treating a hirsute Indian female.

Case Report
A 30-year-old female born of a consanguinous marriage was evaluated for irregular menstrual cycles with 3 years oligomenorrhoea and excessive facial hair for last 6-7 months. She attained menarche at 13 years with uneventful puberty and got married at 17 years of age. Her obstetric history: P1, T1; last child birth 11 years back; a spontaneous abortion at 6 weeks of gestational age, 8 years back followed by secondary subfertility for 3 years. She noticed increased hair growth over cheek, upper lip, chin, middle of the chest, lower back and inner side of thigh which was insidious in onset and progressive modestly over last 5-6 months causing lot of emotional distress. She also noticed breast atrophy, increased seborrhea and acne for last 1 month. However, she had no complaints of deepening of voice. She removed hair by threading every 2-3 weeks. She did not make any complaint of galactorrhea, headache, unconsciousness, convulsion, blurring of vision, abdominal pain or dyspareunia. We did not find her to use any drugs causing hirsutism. Family history for subfertility/hirsutism was absent. She was on Levothyroxine for last 3 years. She had BMI of 26.2 Kg/m², normotensive, FG score 17 with temporal loss of hair. Goiter was present. Striae or proximal muscle weakness was absent. Tongue and hands were not enlarged, but acanthosis nigricans was seen. She suffered from clitoromegaly (clitoral length and width measured 1.3 cm, 0.9 cm).

Laboratory data (Tables 1 and 2) showed a normal complete hemogram, blood sugar, liver and renal function tests. The serum lipid profile showed elevated total cholesterol at 209 mg/dl, LDL at 112 mg/dl, TG at 222 mg/dl and normal HDL 42 mg/dl. TSH was 6.49 µIU/ml (0.30-5.5 µIU/ml) and free T4 was 6.3 µg/dl (5.2-14.2). Serum Prolactin was 12.8 ng/ml, Serum total Testosterone (9 AM) elevated at 187 ng/dl, Serum DHEAS was 109.6 mcg/dl, 17 OH Progesterone (Day 3) 182.22 ng/dl.

Trans abdominal USG showed normal size uterus with endometrial thickness of 2 mm. Right ovary 4.2 X 1.5 cms, Left ovary 2.9 X 1.8 cms; containing multiple small cystic follicles in the periphery. One hypoechoic SOL (1.3 X 1.8 cms) was noted in left ovary and adnexal region, suggestive of cystic lesion. Contrast enhanced CT abdomen (Figure 1) revealed bilateral ovarian mass. Trans vaginal USG showed uterus of normal size and shape with regular outline. Cervical canal was normal. Both ovaries showed few small peripheral cysts of diameter 0.6 to 0.7 cm – suggestive of polycystic ovaries. Right ovary was 1.9 x 2.6cms and Left ovary was 2.6 x 3.3cms.TVS negates transabdominal and CECT pelvis findings.

Table 2: Hormonal profile

<table>
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<tr>
<th>Hormonal Study</th>
<th>Results</th>
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<tr>
<td>TSH,FT4</td>
<td>6.49 µIU/ml,63 µg/dl</td>
</tr>
<tr>
<td>Prolactin</td>
<td>12.8 ng/ml</td>
</tr>
<tr>
<td>Total testosterone</td>
<td>187 ng/dl</td>
</tr>
<tr>
<td>DHEAS</td>
<td>109.6 mcg/dl</td>
</tr>
<tr>
<td>17-OHP</td>
<td>182.22 ng/dl</td>
</tr>
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Discussion

This young lady presented with initial regular cycles followed by successful pregnancy which is not usual to PCOS. The presence of Non Classic Congenital Adrenal Hyperplasia and hyperprolactinemia were ruled out by the normal values of 17-OHP and Serum prolactin, respectively. On the other hand, recent onset hirsutism moderately progressing to the extent of temporal loss of hair over last few months favoured for the strong possibility of androgen secreting tumor of ovary or adrenal gland. This possibility was also increased by serum Testosterone level which was more than three times elevated. USG finding of thinner endometrium (2 mm) also suggested a major change in estradiol and testosterone ratio. However, androgen secreting tumors of adrenal origin was a remote possibility as serum DHEAS was not elevated. DHEAS is exclusively secreted from adrenal gland. So, at this juncture, we were more in favour of androgen secreting tumor of ovary. This was supported by initial imaging. Trans abdominal USG showed one hypoechoic SOL (1.3 X 1.8 cms) in left ovary and adnexal region and Contrast enhanced CT abdomen revealed bilateral ovarian mass. But, TV-USG ruled out the possibility of Androgen secreting ovarian tumor and was in favour of PCOS. There was a satisfaction mixed with wonder that the diagnosis was made but still we started the treatment of PCOS rather skeptically for we were not convinced with the turn of events. We started oral contraceptives. She responded well after 3 months with regular cycles, better FG score and elevated mood.

Hence, proving the superiority of trans vaginal sonogram over all other modalities of investigation for imaging of the ovaries and adnexa. The need for the presence of this facility at all contact points for physicians dealing with such patients cannot be overemphasized. We failed to do it initially as the patient was not convinced.

So, it might be a case of severe PCOS (hyperthecosis ovarii) which presented at the end of third decade mimicking androgen secreting ovarian tumor and responding to OCP for the time being. It is surprising as it rarely responds to conservative management and more commonly to surgically done wedge resection of ovaries. Hyperthecosis ovarii is a unique problem in gynecological practice. It is rarely encountered in some cases of infertility associated with polycystic ovarian syndrome (PCO). The actual incidence of this problem in cases of infertility and PCOS is not known, as a degree of similar histopathological hyperthecotic changes are commonly encountered in PCO which is known to occur in 10% of cases of infertility.

Conclusion

The patient has improved in terms of hirsutism, but the issue of secondary subfertility is yet to be answered. Encounter with this situation led us realize about the spectrum of manifestations that PCOS can come with and how often investigations can trick us into believing something else. Strong clinical intuition is nevertheless indispensable in most situations. Also the importance of a TVS in diagnosing ovarian conditions and its superiority over conventional trans abdominal USG or CT scan was proven again.

References

Podophyllin Toxicity with Systemic Manifestations in a Young Male

Manish Jha¹, Shivanshu Raj Goyal², Subhash Chander Sharma³

Abstract
Podophyllin poisoning is a rare but a fatal poisoning with a long term systemic and neurological sequela. There has been no case report reported in an adult in India. We present a 28-year-old young male with podophyllin poisoning. This report confirms the transient central neurotoxicity of podophyllin and persistent peripheral neurotoxicity of podophyllin.

Case Report
A 28-year-old gentleman presented to the ED (Emergency Department) with a 2 days history of deteriorating sensorium. Two days ago he was found unconscious alongside road with a leaflet of PODOWART PAINT (Podophyllin resin paint 20% + Benzoin + Aloes and Salicylic acid solution) inside his pocket. With this background he underwent gastric lavage at a nearby hospital and was referred to our center. There was no history of previous psychiatric disorder, head trauma, drug or alcohol abuse, or other toxin exposure. He is a known case of hypothyroidism on tablet Eltroxin 25 mcg once a day with no other co-morbidities.

On examination, his blood pressure was 110/70 mm of Hg, temperature 38.0 degree Celsius, heart rate 100 BPM and regular, respiratory rate of 18 BPM with SpO2 of 94% on room air. His GCS (Glasgow Coma Scale) was 110/70 mm of Hg, temperature 38.0 degree Celsius, heart rate 100 BPM and regular, respiratory rate of 18 BPM with SpO2 of 94% on room air. His GCS (Glasgow Coma Scale) being 38.0 degree Celsius, heart rate 100 BPM and regular, respiratory rate of 18 BPM with SpO2 of 94% on room air.

Further, upper GI endoscopy, performed to rule out any evidence of corrosive injury, was normal. He was managed in intensive care unit (ICU).

With this kind of acute presentation our working differentials were of a Toxic encephalopathy and a possibility of Infective etiology or cerebrovascular accident. His initial relevant investigations as shown in Table 1, revealed Thromocytopenia (75,000), deranged liver functions (SGPT - 91, SGOT - 196), arterial ammonia of 56. Immature platelet fraction (IPF) value was 15.9% pointing towards peripheral destruction of platelets. Brain MRI and EEG were performed which revealed subtle area of hyper intensity in left frontal white matter and moderate to severe cerebral dysfunction respectively. CSF analysis and all cultures were noncontributory.

Hence, a diagnosis of acute Podophyllin toxicity secondary to PODOWART PAINT ingestion was made, on the basis of history and examination. Further, upper GI endoscopy, performed to rule out any evidence of corrosive injury, was normal.

He was weaned off the ventilator by day 8 with GCS of E4VTM3. At this stage, his Nerve Conduction Velocity (NCV) study was performed which pointed towards a distal symmetrical large fibre sensorimotor axonal polyneuropathy involving both lower and upper limbs. Subsequently a percutaneous endoscopic gastrostomy (PEG) was performed upon him to aid in long term feeding and he was shifted to floor once he was able to maintain himself on room air.

Discussion
Podophyllin, used for topical treatment of external genital warts caused by human papillomavirus (HPV), and other warts, is a resin mixture obtained from the dried Rhizome and roots of Podophyllin peltatum (North America) and Podophyllin emodi (India). This resin contains at least 16 chemicals including podophyllotoxin, alpha and beta peltatin, desoxypodophyllotoxin and quer cetin. Of these, the toxic agent is thought to be Podophyllotoxin, a lipid soluble compound that crosses cell membranes with ease, fatal dose of podophyllin resin for humans has been estimated to be 0.3g to 0.6g, or as little as one half teaspoon of 25% podophyllin resin in benzoin tincture.

Systemic toxicity may result from either topical exposure or ingestion of this alkaloid. According to the CDC, podophyllum is no longer recommended as a treatment of external genital warts because of safer alternative options. Podophyllotoxin and its derivatives bind to the enzyme topoisomerase II.
during the late S and early G2 stage and arrests mitosis to produce its cytotoxic effects. Neurotoxicity, in addition, may be due to direct nonspecific effects on the neurons and glial cells. Multi organ dysfunction after podophyllin ingestion manifests as Bone marrow suppression (thrombocytopenia and leucopenia; early features), Gastrointestinal irritation (in form of nausea, vomiting, abdominal pain and diarrhea), Renal and hepatic failure (electrolyte disturbances, including hypokalemia and hypoglycemia). Neurotoxicity is the most severe effect of podophyllin poisoning. CNS presentation varies from altered sensorium, confusion, hallucinations, stupor, seizures to coma, and ultimately death. Peripheral neuropathies usually appear late in the course of illness, but can appear early with motor (hypotonia, hyporeflexia), sensory (paraesthesia, glove and stocking loss of light touch and proprioception) and Autonomic deficits (paralytic ileus, autonomic dysreflexia, urinary retention and apnea). The central nervous system toxicity is usually transient and reversible over a period of up to ten days, but deep coma leading to a fatal outcome or severe encephalopathy characterized by irreversible cognitive dysfunction may also occur. The course of the neuropathy is chronic and the recovery is delayed, sometimes improvement being minimal.

Management of podophylline toxicity is mainly supportive, no specific antidote exists. Activated charcoal is recommended for gastric lavage after recent ingestion. If topical contact occurs, wash with soap and water. Intensive management of ventilation and circulation, accompanied by monitoring for above mentioned complications is required. Haemoperfusion should be used for severe systemic poisoning since it has been shown to be effective in reducing the plasma fraction of podophyllum toxin and other active metabolites.

The first fatal case after oral administration was reported in 1890. The last known reported case in India was a pediatric patient in India in 2002 and a 3-year-old child in South Africa in 2015. A fatal case relating to topical application was reported in 1954. The initial manifestations exhibited by our patient, headache, nausea, diarrhea, and altered sensorium with hepatic impairment are among those previously described. Periphal destruction of platelets has not been described earlier. Later in the course, our patient showed features of paralytic ileus and peripheral neuropathy, all known complications of the toxicity.

Ethical approval. Informed consent for the publication of this case report was obtained from the father of the patient.

References

Acute Fulminant Uremic Neuropathy Following Coronary Angiography Mimicking Guillain Barre Syndrome

Kumari Priti1, Bhanwar Lal Ranwa2

Abstract
A 55 yr old diabetic lady suffered a posterior wall STEMI. She developed Contrast induced nephropathy following coronary angiography. Acute fulminant uremic neuropathy was precipitated which initially mimicked Guillain Barre Syndrome, hence reported.

Introduction
Uremic neuropathy is predominantly a distal symmetrical sensorimotor polyneuropathy, most often affecting the lower limbs. It characteristically progresses over the course of months, but can occasionally take a faster course, whereby, Guillain Barre Syndrome (GBS) and vasculitic neuropathy are its close differentials.

Case Report
A 55 year old lady presented with complaints of chest pain for 6 hours associated with profuse sweating. She had past history of...
diabetes and hypertension for past 12 years, controlled on drugs. Her general physical examination and cardiovascular system examination was normal except for presence of left ventricular fourth heart sound. 12-lead electrocardiography showed posterior wall ST elevation myocardial infarction. 2D echocardiography revealed inferior, inferolateral and anterolateral wall hypokinesia, mild mitral regurgitation and moderate left ventricular systolic dysfunction with left ventricular ejection fraction of 39%. Her laboratory parameters were Hb=11.8gm%, TC=11000/mm³, random blood sugar-265mg%, blood urea=50 meq/L, serum creatinine=1.3mg% (Cr Cl 54 ml/min), CKMB= 40 IU/L, serum sodium=140meq/L and serum potassium= 4meq/L. She was managed with thrombolytic therapy and guideline directed medical treatment. Coronary angiography showed triple vessel disease. Despite adequate glycemic control and adequate intravenous hydration pre and post coronary angiography, patient developed contrast nephropathy. Her urine output decreased along with rise in serum creatinine to 2.5mg% at 24 hours. Patient was kept under observation and i.v. hydration was continued. But she noted slight weakness over her both lower limbs below the ankle joint. Weakness progressed gradually and 2 days later, she was not able to move her lower limbs at all. Following day she felt paresthesia over her both upper limb associated with weakness. On examination, both the lower limbs were flaccid and power was zero. Deep tendon and plantar reflexes were absent bilaterally in lower limbs. Upper limbs also were hypotonic with power of 2/5 of both distal and proximal muscles. There was vibratory and pressure sensory loss in lower limbs below the knee and patchy sensory loss in upper limb. Higher mental functions were normal and Cranial nerves were intact. There was no involvement of bowel or bladder. Respiratory muscles were not involved. Of note, the patient did neither have any clinical signs of vasculitis such as rash, arthritis, or ocular involvement nor had a history of antecedent respiratory or gastrointestinal tract infection. ESR was 76 mm/hr and CRP was 68 mg/L. Cerebrospinal fluid examination revealed a normal cell count and elevated protein concentration. Nerve conduction studies showed very low amplitude potentials in the nerves of both the lower and upper limbs with prolonged distal latencies. Electromyographic examination showed evidence of acute partial active denervation over proximal and distal muscles examined with no evidence of demyelination. On day 6, her serum creatinine started decreasing with associated improvement of neuropathy. After 15 days, serum creatinine declined to 1.5 mg% and power in both upper and lower limbs improved to 4/5 but patchy sensory loss persisted and patient was discharged from the hospital with a diagnosis of resolving acute uremic neuropathy. The clinical picture though mimicked Guillain Barre Syndrome (GBS), an acute inflammatory demyelinating polyradiculoneuropathy.

**Discussion**

Peripheral neuropathy is a commonly encountered condition in clinical practice. Though, diabetes mellitus and excessive alcohol use coupled with a poor diet are the most common causes of peripheral neuropathy, onset is insidious and progression is slow in these conditions. The most common cause of acute muscle weakness associated with peripheral neuropathy in adults is Guillain-Barre syndrome. 1 The diagnosis of GBS is made by recognizing the pattern of rapidly evolving paralysis with areflexia, absence of fever or other systemic symptoms, and characteristic antecedent events. Rapidly progressing acute peripheral neuropathy in our patient favored GBS but coexistence of preexisting chronic kidney disease (CKD) with superimposed contrast induced neuropathy (CIN) and acute uremia point towards alternative diagnosis of acute uremic neuropathy. Although most commonly uremic polyneuropathy evolves over months, there have been reports of severe fulminant motor neuropathies, sometimes associated with sepsis. 2-5 CSF protein levels are usually normal but may be elevated in patients with severe uremic polyneuropathy. The most significant abnormality on electrophysiologic study is a reduction in the amplitude of compound motor and sensory action potential. Both motor and sensory conduction velocities are reduced and late reflexes (H reflex and F wave) become abnormally prolonged, more commonly in lower extremities. There is a high correlation between declining creatinine clearance and reduction in conduction velocities. Polyneuropathy is not seen in new onset acute renal failure, but when present systemic vasculitis is the underlying mechanism. Recovery often occurs in two phases, initial rapid improvement over days to weeks and then more protracted improvement over period of months. 4

Our patient harboured CKD and suffered acute kidney injury following coronary angiography due to risk factors like diabetes, poor left ventricular function and preexisting CKD. The acute worsening of renal function led to fulminant polyneuropathy which improved in concordance with the renal parameters. Acute polyneuropathy following coronary angiography is rare and clinical picture can mimic GBS, so diagnosis should be made cautiously as the management of the two entities is entirely different.

**References**

Rene Favaloro (1923-2000) was one of the most preeminent cardiovascular surgeon in the second half of 20th Century, a great innovator and a pioneer in the field. Denton Cooley said about him “surgeon we should credit with introducing CABG into the clinical arena. Indeed, Dr. Favaloro’s pioneering contribution to cardiovascular surgery will be an enduring legacy to his homeland Argentina and humanity”.

Favaloro was compassionate and selfless. He never forgot his country and its roots. A son of a carpenter from a small town in Argentina, he was influenced by his maternal uncle, who was a general practitioner. He grew up with love for land and nature, and graduated in 1949 from the Medical Science Faculty of La Plata University. His interest in thoracic surgery grew from his surgical teacher Dr. Mainette. Favaloro began a successful career as a surgeon at La Plata. However, he resigned due his differences in intellectual principles with Peron’s Party. He started general practice as a country doctor in a small town La Pampa in central Argentina. There he treated patients with minor surgeries as well as an internist, pediatrician, and obstetrician. His house became a clinic with a laboratory, radiology equipment and beds to hospitalize patients. As the facilities grew he even performed major surgeries such as colectomies and gastrectomies, He taught his poor patients preventive medicine and rules of hygiene, and also set up mobile blood banks.

After ten years of country practice, his interest in thoracic surgery still remained keen. Favaloro then traveled to Cleveland Clinic to join the Department of Thoracic and Cardiovascular surgery, where he became assistant to Donald Effler. During this period he developed lasting friendship with Mason Sones- father of coronary cine-angiography. His post operative results could be evaluated with cine-angiography.

Coronary artery bypass grafting (CABG) is a commonplace surgical procedure today for patients with proper indications. It was different in early 60s; concept of early myocardial salvage and revascularization was only a hope. At the Cleveland clinic Favaloro considered the possibility of saphenous vein to bypass diseased coronary artery in order to deliver blood flow distally. He put his ideas in practice in May 1967, on a stabilized patient with total occlusion of proximal third of his right coronary artery with success. Favaloro had performed the first documented “aorto-coronary bypass”. By November the same year he performed the first bypass for acute myocardial infarction. Standardization of his technique called bypass or myocardial revascularization surgery became fundamental work of his career. His ground breaking surgical and technical contribution has dramatically improved the quality of life of many more patients with IHD. For many it was the only hope at that time, since Coronary angioplasty and stents arrived only a decade later.

He returned to his native country in 1971 and established Favaloro Foundation for education, research and clinical activities. The Foundation was in debt due to economic depression of 1998 and political crisis. Argentine government never responded to his request for financial aid. Rene Favaloro was frustrated and committed suicide by shooting himself in the chest, in July 2000.

Apart from being a great innovator and pioneer in the field of myocardial revascularization surgery Rene Favaloro will be remembered, as a man with love for his country, a passion for his work and a strong sense of social responsibilities.
Methemoglobinemia: Challenges in Diagnosis and Management

Kamal Kant Sahu, Ajay Mishra
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Sir,

Methemoglobinemia is one of the most rewarding medical emergencies if promptly approached. We congratulate Krishna et al for their excellent work in saving lives of two patients suffering from methemoglobinemia.1 Through this correspondence, we wish to convey other relevant information to JAPI readers regarding methemoglobinemia based on our previous experiences.2-5

Importance of History

First step in diagnosis is suspicion. Knowledge of most common potential drugs is essential to consider methemoglobinemia. Krishna et al mentioned about EMLA cream and oral dapsone in their report. It is prudent for readers to know that even topical dapsone can cause methemoglobinemia.6 Also, apart from medication history, asking about any family members suffering from similar illness can sometimes help in diagnosing familial methemoglobinemia.3

Bedside Tests in community health centres

At peripheral medical centres, confirmatory tests like co-oximetry devices may not be available. For those places simple bedside tests can be fruitful. A semiquantitative test using “methaemoglobin colour chart” can be used to have an approximate idea of severity of methemoglobinemia. This test was originally developed by Shihana et al from Sri Lanka which was published in WHO bulletin (14 June 2016) as well and subsequently incorporated in the Sri Lankan national guidelines and management of poisoning.7

Diagnost ic pitfall while interpreting G6PD test

Krishna et al very well said that methylene blue is contraindicated in G6PD positive cases. One pitfall which internists should be aware of is the false negativity of G6PD test during active haemolysis as the newly circulating reticulocytes tend to have higher percentage of G6PD enzyme thereby negating the actual deficiency in an individual during testing for G6PD.8 Also, just a word of caution that co-oximetry may not be useful in monitoring percentage of MethHb in congenital cases.9

Treatment challenges

Apart from being detrimental to use in G6PD individuals, methylene blue can cause serotonin syndrome in psychiatric patients using SSRIs. This is due to the MAO-A inhibiting property of methylene blue. Interestingly, cimetidine has been found to be useful in dapsone induced methemoglobinemia. It acts by inhibiting the mandatory step “dapsone N hydroxylation” needed for formation of methemoglobin in body.10,11

In summary, we believe that with the help of above discussion, doctors especially ER physicians and internists would be able to diagnose more quickly the cases of methemoglobinemia and treat them promptly.

References


Letter to Editor - Spectrum of Cerebral Venous Thrombosis

Radhakrishna Hari
Consultant Neurologist, Care Hospitals, Nampally, Hyderabad, Telangana

Sir,

I read the original article “Spectrum of cerebral venous thrombosis in Uttarakhand” by Sunil Jee Bhat and Priyanka Vikas Kashyap in July 2018 issue of JAPI, with interest.1 It was a good article bringing out their observations in septic and aseptic types of cerebral venous thrombosis (CVT). Though I agree with some conclusions there are many with which I disagree and suggest a change in the approach to this not uncommon problem.

The same condition is referred to as CVT and CVS in different parts of the same article. I think it was probably an editorial error and was not intentional. If not so, each term needs to be elaborated as to what it means.

All the references in the index article are before 2006 except one. The scenario of CVT is changing. Now-a-days we are seeing more number of male patients affected by the condition unlike what the statistics in the article show.2,3 And some such patients are alcoholics. There was no mention of alcoholic CVT in the article. In a prospective study done from our department including 50 patients of CVT (unpublished data), there were more number of male patients (62%) with CVT and nearly 10% of them were alcohol related.

Many articles in the references are about septic cavernous sinus thrombosis, and the discussion in the article also is mostly about treatment of that condition. In clinical practice and also in their own article (22:8) the authors noted that nonseptic cases are more common. Septic cases are less common and are often treated by critical care specialists, while nonseptic cases are treated by neurologists and physicians.

According to literature, among the female patients, oral contraceptive pill consumption is a commoner cause of CVT when compared to postpartum CVT,4 unlike in the index article where the postpartum CVT cases outnumber contraceptive pill related cases. It was
not mentioned in the article how and when the prothrombogenic disorder profile was obtained. While evaluating such patients one must take care not to order such tests while the patient is on anticoagulants. Otherwise there can false results defeating purpose. I would order such tests when the patient had taken 3-6 months of oral anticoagulants, and stopped them for at least 10-15 days.

_Corticosteroids cannot be recommended routinely in CVT patients to reduce vasogenic edema, and they may even promote thrombosis._

The authors suggested that ‘anticoagulants have to be continued till clinical or radiological evidence of complete resolution’. They themselves mentioned that the role of anticoagulants is controversial in septic CVT cases. In nonseptic cases, it is common knowledge that clinical resolution will be complete in 10-15 days. Radiologically, the MR venogram will not be completely normal even after one year. Hence the authors’ suggestion about the duration of treatment is ambiguous.

_In our department we had performed mechanical thrombectomy for refractory CVT in 4% cases and intrasinus thrombolysis in another 4% cases with good outcomes. The proper cases selection is important. Whenever the patient is not responding to adequate anticoagulation and the sensorium or the lesion size is/worsening within the first 10 days after onset, intervention needs to be considered. There were no cases of deep venous system involvement in their series. Such cases are difficult to diagnose, are associated with more mortality and morbidity and may present in a comatose state._

### References

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<th>Selenium (100 mcg)</th>
<th>Lycopene (5 mg)</th>
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<td>VIT B5 (3.0 mcg)</td>
<td>VIT B6 (15 mcg)</td>
<td>Polycyclic (1.5 mcg)</td>
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