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**Product information:**
- Tresiba  can be used in renal and hepatic impaired patients. Glucose monitoring is to be intensified and the dose should be adjusted based on the individual patient's needs.
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INSIGHTS (INSITES) on DPP 4 Inhibitors (Gliptins) for Diabetes Management in India

Mangesh Tiwaskar

The World Health Organisation places diabetes amongst the top 10 causes of death in the world.1 World Health Statistics (2018) affirmed that non-communicable diseases accounted for 71% of all deaths with diabetes being one amongst the top 4 causes with 1.6 million deaths.2 The global prevalence of diabetes has reached such massive proportions that, if all the diabetic individuals were gathered together in one country, it would be the third most populous country in the world with 415 million people.3 According to the latest diabetes atlas from the International Diabetes Federation (8th edition, 2017), India is home to the 2nd largest population of diabetic individuals in the world.4 Data from the Global Burden of Disease Study further showed that enhanced prevalence of overweight adults (across all Indian states) is a key contributing factor to this increase. Diabetes also contributed to 3.1% and 2.2% of the total deaths and total disability-adjusted life-years, respectively. India’s National Health Policy (2017) has hence targeted enhanced screening and treatment of diabetic individuals and has set its 2025 goal as 25% reduction in premature deaths due to diabetes.5

It is well-known that, in type 2 diabetes (T2D), 50% of β-cell function is lost at the time of diagnosis itself.6 Despite this, insulin sensitizers such as metformin continue to be the first choice for initiation of hypoglycaemic therapy in most patients as recommended by the 2019 guidelines from both the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/AEC).7,8 Though Sulphonylureas were the preferred drugs for several decades, the accompanying debatable issues like weight gain, hypoglycaemia, cardiovascular safety;9 especially with older sulphonylureas, has led over time to the search for better options for treatment. To this end, since monotherapy often does not ensure adequate control, in addition to Sulphonylureas, Thiazolidinediones and Basal Insulins, newer agents such as Dipeptidyl Peptidase 4 (DPP-4) inhibitors, Sodium–Glucose Cotransporter 2 (SGLT2) inhibitors and Glucagon-Like Peptide 1 Receptor Agonists (GLP-1 RA), have gained prominence in the treatment of T2D.7,8

DPP-4 inhibitors present with a novel mode of action (resulting in improved β cell health and suppression of glucagon, improving both fasting and post-prandial hyperglycaemia),10 are weight neutral, do not cause hypoglycaemia and are devoid of adverse cardiovascular effects (except Saxagliptin and Alogliptin-due to mild increase in heart failure risk). They are thus one of the preferred recommended medications for those who need to minimise hypoglycaemia and weight gain.2

There are several DPP-4 inhibitors available in India, with Sitagliptin being the oldest amongst them (approved in 2006).10 Sitagliptin has been extensively studied across several patient groups, both as monotherapy and in combination with other antidiabetic drugs. Its efficacy coupled with a good safety profile has made it a worthy addition to the armamentarium of diabetes management.11 DPP-4 inhibitors (Gliptins) have been used for more than 10 years in Indian diabetic patients.12 There is also evidence that DPP-4 inhibitors appear to work better in Asians, (particularly Indians and Koreans where, 1.4 to 1.5% reduction in HbA1c levels have been reported compared to Non-Asians where the HbA1c reduction is more modest, (0.5–0.8%).13-16 However, one limitation is their high cost. Since diabetes is a chronic condition, the financial burden on the patient could be substantial. Grover et al. found that the direct annual costs of antidiabetic treatment in India are in the range of 14,000 rupees out of which >60% is attributed to the cost of drugs. Indian families bear the brunt of this economic burden,17 hence, the therapeutic focus in diabetes should ideally hinge on affordability without compromising on efficacy. In this scenario, the recent entry of a more economical option amongst gliptins has come as a welcome respite to Indian patients. Teneligliptin, the latest agent, is available in India at a price which is considerably lower than other agents of the same class.12 Moreover, its unique metabolic profile has enabled its use across several patient groups without the need for dosage adjustment, unlike some of the other gliptins.7,18 Oral Teneligliptin therapy was efficacious in randomised placebo-controlled trials conducted in other Asian countries, both as monotherapy or in combination with other agents. It enhanced glycaemic control, was well tolerated19 and was found non-inferior to Sitagliptin as part of a triple therapy regimen.20

In this issue, a study by Mohan et al. compared the efficacy of two DPP-4 inhibitors in T2D patients who remained uncontrolled (HbA1c>7%) on Metformin and/or Sulphonylurea therapy. They compared Teneligliptin with Sitagliptin in A Prospective, OpeN-Label, Randomized Study Comparing Efficacy And Safety Of Teneligliptin Versus Sitagliptin In Indian Patients With Inadequately Controlled Type 2 Diabetes Mellitus (INSITES) Study.21 In India, diabetes has a younger age of onset (20-70 yrs) with overweight/obesity being one of the key risk factors22 which is in line with the T2D patients enrolled in this study (n=76; mean age 49.2 yrs; mean body mass index=27.5 kg/m²) making it a true representation
of the Indian diabetic population. The study subjects were treated with Teneligliptin and Sitagliptin in a 1:1 ratio. The primary outcome of mean change in HbA1c at the end of the study vs baseline was similar for both agents (±1%) with a greater proportion of patients achieving the HbA1c target of <7% with Teneligliptin (33.3%) vs Sitagliptin (19.4%; post-hoc analysis). Significant and equivalent reduction in fasting and postprandial glucose levels was also observed at week 12 with both the study drugs. The lipid parameters were minimally impacted and both drugs were well-tolerated with no incidence of hypoglycaemia with either agent. Lastly, no adverse changes in electrocardiographic (ECG) parameters were observed with both the study drugs, reaffirming their safety.21

In an era where the incidence of diabetes is reaching alarming proportions, this study is heartening evidence that cost-effective therapy can be obtained without compromising on efficacy. Though the open-label design, the small sample size and the short duration of this study may be viewed as shortcomings,21 it is a step in the right direction for a country like India where optimal diabetic management without its associated economic burden is the need of the hour.

After being first approved in Japan in 2012, Japanese and Korean studies of majorly 12 to 52-week duration currently underway.18 Long-term studies to accurately assess the efficacy and safety of Teneligliptin along with its impact on cardiovascular outcomes could enhance confidence in this agent and help generate data covering all aspects of its usage. Several small studies conducted in the Indian context have shown that Teneligliptin stands true on the two tenets of diabetic therapy – efficacy and economy.22 It must be emphasized that since U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) have mandated the need for Cardiovascular Outcomes Trials (CVOT) to establish their safety, longer trials on newer molecules like Teneligliptin need to be done. Since Teneligliptin has been recently introduced in India, this study can be considered a stepping stone for future longer-term trials which can further help cement its position as a good option for the treatment of T2D in our country.

References

The 47th national annual conference of RSSDI is being held at Jaipur from 7th to 10th November 2019. The eminent faculty from country and abroad in the field of diabetology has confirmed participation. Jaipur the pinkcity, awaits your participation. (visit rssdi2019.com)
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A ProspectIve, OpNE-Label, Randomized Study Comparing EffIcacy and Safety of Teneligliptin VErsus Sitagliptin in Indian Patients with Inadequately Controlled Type 2 Diabetes Mellitus: INSITES Study

V Mohan1*, M Ramu2, S Poongothai2, S Kasthuri2

Abstract

Background: Teneligliptin is widely prescribed dipeptidyl peptidase-4 inhibitor (DPP-4i) in India because of its economical pricing. However, there is no head-to-head trial comparing teneligliptin with any other DPP-4i in Indian setting. We evaluated the efficacy and safety of teneligliptin versus sitagliptin as add-on to metformin and/or sulfonylureas in patients with type 2 diabetes mellitus (T2DM).

Methods: This prospective, open-label, randomized, active-controlled study enrolled 76 patients (1:1) at 2 centres. Patients received teneligliptin 20 mg or sitagliptin 100 mg orally once daily for 12 weeks as add-on to ongoing metformin or sulfonylurea therapy. Primary endpoint was mean change in glycosylated hemoglobin (HbA1c) from baseline at week 12.

Results: Both arms were comparable (p>0.05) at baseline in terms of age, gender, metformin daily dose, sulfonylurea use, HbA1c, fasting and postprandial blood glucose (FBG and PPBG). At the end of 12 weeks, statistically significant reductions were observed in both teneligliptin and sitagliptin arms in HbA1c (−1.19 ± 1.16% p<0.0001 and -0.92 ± 0.95%, p<0.0001), in FBG (-28.3 ± 63.0 mg/dL, p= 0.01 and -22.9 ± 47.4 mg/dL, p=0.006) and PPBG (-41.3 ± 85.4 mg/dL, p=0.006 and -54.7 ± 85.6 mg/dL, p=0.005). The reductions in all glycemic parameters were similar between the arms. Both gliptins were well-tolerated with no difference in the number of adverse events. There was no change in QT/QTc intervals or other ECG parameters at week 12 in both arms. In post-hoc comparison, percentage of patients achieving target HbA1c <7% (as per American Diabetes Association guidelines) at week 12 favored teneligliptin arm over sitagliptin arm (33.3% vs. 19.4% patients).

Conclusion: Teneligliptin provided similar glycemic control as compared to sitagliptin and reduced HbA1c, FBG and PPBG values significantly within 12 weeks of treatment. Both gliptins were found to be safe and well-tolerated in Indian patients with T2DM.

Introduction

Type 2 diabetes mellitus (T2DM) had a global prevalence of 9.09% in 2017.1 In India, 8.8% of the adult population had diabetes in 2017; if the current trend continues, prevalence in India will increase to about 12.1% by 2040.2 Uncontrolled glycemia and reduced insulin sensitivity increases the risk of macrovascular and microvascular complications, including cardiovascular disease, renal disease and retinopathy.2,4

More than half of Indian patients fail to achieve the target glycemic control (glycosylated hemoglobin [HbA1c] <7%) recommended by most guidelines.5,6 The natural history of progressive decline in β-cell function limits the long-term use of metformin monotherapy. Hence, combination therapy with other oral anti-diabetic agents (OADs) is recommended for achieving and maintaining optimum glycemic control after failure of metformin monotherapy.7,8

Dipeptidyl peptidase-4 inhibitors (DPP-4i) are a promising class of OADs, which inhibit the endogenous glucagon-like peptide-1 (GLP-1) metabolism and thereby increase GLP-1 level in the physiological range. They act by regulating insulin and glucagon secretion. DPP-4i unlike sulfonylureas, meglitinides, or insulin are weight neutral.9 DPP-4i with metformin is associated with a lower risk of severe hypoglycemia, cardiovascular events, and all-cause mortality compared with metformin plus sulphonylurea.10 A recent study reported improvement of long-term survival in diabetic patients after first acute myocardial infarction, regardless of gender with use of DPP-4i.11 In a propensity score-matched T2DM patients (n=321,606), use of DPP-4i was associated with a reduced risk of heart failure hospitalization compared to GLP-1 agonists.12 The international guidelines advocate the use of DPP-4i as first line or second line agents in the treatment of T2DM.13 The Research Society for the Study of Diabetes in India (RSSDI) also advises the use of DPP-4i in patients who are non-responsive or contraindicated to metformin.14

Teneligliptin is a novel DPP-4i and has a unique J structure characterized by five consecutive rings; the interaction occurs between the phenyl ring on the pyrazole of teneligliptin and the S2 extensive subsite of DPP-4 enzyme. These unique properties

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and the 24 hours plasma half-life produces a potent, selective and long-lasting glucose-lowering effect.\textsuperscript{15} The pharmacokinetic properties, and the elimination route differs among DPP-4i and these differences are related to the need for dose adjustments in patients with renal or hepatic dysfunctions. However, present evidence suggests that linagliptin\textsuperscript{16} and teneligliptin\textsuperscript{17} can be used safely without dose adjustments in patients with renal impairment, including End Stage Renal Disease.

Teneligliptin was extensively evaluated for efficacy, safety and tolerability in Japanese and Korean patients with T2DM. A pooled analysis of two phase III trials has shown that teneligliptin as monotherapy or combination therapy has similar adverse event (AE) profile with lesser risk of hypoglycemia as compared to sulfonylurea for as long as 52 weeks.\textsuperscript{18} Teneligliptin monotherapy significantly reduced HbA1c by -0.94% in a 24-week placebo-controlled trial in Korea.\textsuperscript{19} Teneligliptin improved first phase of insulin secretion thus decreasing post meal glucose excursions in a 12-week study in drug-naive Japanese patients.\textsuperscript{20} Patients with mild, moderate, severe or end-stage renal diseases have been shown to tolerate teneligliptin, and dialysis did not affect the drug’s efficacy or safety.\textsuperscript{21} Recently, a post-marketing surveillance reported long-term safety of teneligliptin in T2DM patients with any stage of renal impairment.\textsuperscript{22} Moreover, no dose adjustment was required in hepatic impairment as the drug concentration was within FDA cut-off.\textsuperscript{23}

Sitagliptin is the first molecule launched in the class of DPP-4i. Sitagliptin monotherapy for 18 weeks was shown to significantly lower HbA1c as compared to placebo in Indian, Chinese and Korean patients.\textsuperscript{24} In a real world study, addition of sitagliptin was effective in lowering HbA1c by about 1% in patients who failed on sulfonylurea/ metformin.\textsuperscript{25} Teneligliptin has been introduced in India as an affordable and efficacious alternative gliptin. Teneligliptin can reduce the average pharmacotherapy cost by about 80% in India when compared to other DPP-4i.\textsuperscript{26} It was approved in India in 2015 based on data from a phase III clinical trial. Several individual studies have evaluated its efficacy and safety in Indian patients. However, no head-to-head trial has compared teneligliptin with any other DPP-4i in Indian setting. We conducted this study to evaluate the efficacy and safety of teneligliptin versus sitagliptin as an add-on to metformin and/or sulfonylureas in adult Indian patients with T2DM.

### Methodology

After obtaining approval from the Institutional Review Board of Madras Diabetes Research Foundation each, the study was conducted in compliance with the protocol and all applicable regulatory guidelines. Written informed consent was obtained from all patients prior to study participation. All study related data were recorded in a structured Case Record Form.

#### Study Population

Male and female patients aged 18-65 years with uncontrolled T2DM (HbA1c >7.5% and <10.0%) who were on a stable dose of metformin alone/ metformin plus sulfonylurea for past 4 weeks were included in the study. Patients with T1DM; history of hypersensitivity to study medication or its ingredients, any insulin use in past 6 weeks; history of administration of any other OADs except for metformin or sulphonylurea in past 4 weeks; history of serious infection/surgical procedure/severe trauma in past 4 weeks or planned surgery during the study period; history of repeated episodes of hypoglycemia or hyperglycemic events like hyperosmolar coma; history of concomitant medications such as corticosteroids, anti-epileptics, antipsychotics, and antiretroviral therapy; likely to go for ritual fasting or travel for longer duration; history or evidence of significant cardiovascular disorder such as heart failure, myocardial infarction or any conduction abnormality on electrocardiography (ECG) e.g. QT prolongation, arrhythmias; history or evidence of any significant hepatic, renal, gastro-intestinal, neurological or other endocrine disorder; history or risk of acute pancreatitis, chronic alcoholism or drug abuse; pregnant or lactating women were excluded. During study conduct, patients were planned to be withdrawn prematurely if blood glucose control worsened (fasting blood glucose [FBG] >180 mg/dL) and patient required additional anti-diabetic medication(s).

#### Study Design and Treatment

This was a prospective, randomized, open-label, active-controlled trial conducted at 2 sites in Chennai (Madras Diabetes Research Foundation (MDRF), Gopalapuram, Chennai and Dr Mohan’s Diabetes Specialties Centre, Tambaram, Chennai between November 2017 and October 2018. Patients were randomly assigned (1:1) on day 1 to receive either Teneligliptin (INOGLA® 20 mg marketed by Wockhardt Ltd.) or Sitagliptin (JANUVIA® 100 mg marketed by MSD Pharmaceuticals Pvt. Ltd.) once daily orally along with stable dose of metformin. The patients were instructed to bring all unused study drugs and empty blister packages to assess treatment compliance during scheduled follow-ups at week 6 and 12.

#### Study endpoints and assessment

The primary outcome measure was mean change in HbA1c from baseline at week 12. The secondary outcome measures included changes in FBG and postprandial blood glucose (PPBG) levels from baseline at week 6 and 12, and change in lipid profile from baseline at week 12. The safety endpoints included recording of type, incidence, severity, timing, seriousness, and relatedness of all AEs, adverse drug reactions, and serious adverse events (SAE). The ECG parameters examined included heart rate (HR), PR interval, QT interval and QT interval after correction for the change in HR (QTc) at week 6 and 12. Prolonged QTc was defined as any value above the cut-off point of 450 milliseconds (ms).

Baseline assessment included demographics, significant medical and surgical history, vital signs, anti-diabetic therapy, concomitant medications and a thorough physical examination. Investigations included HbA1c, FBG, PPBG, lipid profile, hemogram, SGOT (aspartate aminotransferase), SGPT (alanine aminotransferase), creatinine, amylase, lipase and ECG. At week 6, FBG, PPBG, and ECG were repeated. At week 12, patients underwent blood investigations (HbA1c, FBG, PPBG, lipid profile, hemogram, SGOT, SGPT and creatinine) along with ECG.

#### Statistical analyses

The study was planned to enroll 76 patients with T2DM considering maximum drop-out rate of 20% to get
Results

A total of 79 patients were screened of which 76 were randomized to treatment with teneligliptin (n=38) or sitagliptin (n=38). Patient disposition is presented in Figure 1; four patients discontinued the study prematurely and were excluded from the ITT population-efficacy. Baseline demographics and clinical characteristics were comparable between the treatment arms (Table 1). The mean ± SD age of patients was 49.4 ± 9.49 years with marginal female predominance (51.3%). The mean ± SD weight, BMI, and HbA1c at baseline were 68.7 ± 14.4 kgs, 27.5 ± 4.61 kg/m², and 8.7 ± 0.7%, respectively. At baseline, mean ± SD dose of metformin was 1104 ± 257 mg per day and 83% (n=63) patients were receiving sulphonylureas. None of the patients reported any prevalent co-morbidity such as hypertension or dyslipidemia.

Efficacy outcomes

Glycemic control

Treatment with both teneligliptin and sitagliptin showed a statistically significant reduction in mean HbA1c from baseline at week 12 (−1.19 ± 1.16% and -0.92 ± 0.95% respectively, p<0.0001) (Figure 2). By week 12, teneligliptin reduced the mean HbA1c from 8.82 ± 0.78% to 7.63 ± 1.09% and sitagliptin reduced HbA1c from 8.66 ± 0.69% to 7.74 ± 0.83%. The mean reduction in HbA1c was comparable between the two gliptins with inter-group difference being -0.16% (95% confidence interval [CI]: -0.61, 0.28; p=0.4675) with post-hoc construed 95% CI for the difference between two arms as per USFDA guidance indicating non-inferiority of teneligliptin vs. sitagliptin.

Table 2 presents change from baseline in primary and secondary efficacy endpoints. In post-hoc comparison of percentage of patients achieving target HbA1c <7% (target as per the American Diabetes Association [ADA] guidelines) by 12 weeks of treatment, the results favored teneligliptin treatment arm over sitagliptin treatment arm (33.3% vs. 19.4% patients).

Teneligliptin demonstrated a statistically significant reduction in mean FBG from baseline at week 12 (−28.3 ± 63.0 mg/dL, p=0.01). However, the reduction at week 6 was statistically not significant (−19.4 ± 68.8 mg/dL, p=0.10). The mean reduction in FBG with sitagliptin was statistically significant at both week 6 (−24.2 ± 38.9 mg/dL, p=0.0007) and week 12 (−22.9 ± 47.4 mg/dL, p=0.0064) (Table 2). The reductions in FBG at 6 and 12 weeks were comparable (p=0.05) between both gliptins. The inter-group difference was 6.9 mg/dL (95% CI: −15.6, 29.6) at 6 weeks and −3.6 mg/dL (95% CI: −27.0, 19.8) at 12 weeks.

Both teneligliptin and sitagliptin showed statistically significant reduction in PPBG levels at week 12 (−41.3 ± 85.4 mg/dL, p=0.006 and −54.7 ± 85.6 mg/dL, p=0.0005); change at week 6 was statistically significant for sitagliptin (−46.2 ± 69.3 mg/dL, p=0.0003) and not for teneligliptin (−25.6 ± 113.1 mg/dL, p=0.18). The reductions in PPBG at 6 and 12 weeks were comparable (p>0.05). The inter-group difference was 19.3 mg/dL (95% CI: −13.2, 51.7) at 6 weeks and 12 mg/dL (95% CI: −15.0, 39.0) at 12 weeks.

Table 1: Baseline characteristics of study groups

<table>
<thead>
<tr>
<th></th>
<th>Total (n=76)</th>
<th>Teneligliptin (n=38)</th>
<th>Sitagliptin (n=38)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), Mean (SD)</td>
<td>49.4 (9.49)</td>
<td>48.7 (9.46)</td>
<td>50.2 (9.58)</td>
<td>0.5020</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>39 (51.3)</td>
<td>22 (57.9)</td>
<td>17 (44.7)</td>
<td>0.5177</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>37 (48.7)</td>
<td>16 (42.1)</td>
<td>21 (55.3)</td>
<td></td>
</tr>
<tr>
<td>Weight (kg), Mean (SD)</td>
<td>68.7 (14.41)</td>
<td>70.4 (16.14)</td>
<td>66.9 (12.43)</td>
<td>0.3029</td>
</tr>
<tr>
<td>BMI (kg/m²), Mean (SD)</td>
<td>27.5 (4.61)</td>
<td>28.6 (5.20)</td>
<td>26.3 (3.65)</td>
<td>0.0287</td>
</tr>
<tr>
<td>Metformin Daily Dose</td>
<td>1104.6 (257.4)</td>
<td>1136.8 (308.8)</td>
<td>1072.4 (192.0)</td>
<td>0.2786</td>
</tr>
<tr>
<td>Sulfonlurea No, n (%)</td>
<td>13 (17.1)</td>
<td>8 (21.1)</td>
<td>5 (13.2)</td>
<td>0.6660</td>
</tr>
<tr>
<td>Yes, n (%)</td>
<td>63 (82.9)</td>
<td>30 (78.9)</td>
<td>33 (86.8)</td>
<td></td>
</tr>
<tr>
<td>FBG (mg/dL), Mean (SD)</td>
<td>174.2 (44.1)</td>
<td>177.8 (48.7)</td>
<td>170.6 (39.3)</td>
<td>0.4814</td>
</tr>
<tr>
<td>PPBG (mg/dL), Mean (SD)</td>
<td>284.5 (79.0)</td>
<td>286.0 (86.6)</td>
<td>283.0 (71.8)</td>
<td>0.8684</td>
</tr>
<tr>
<td>HbA1c (g%), Mean (SD)</td>
<td>8.7 (0.74)</td>
<td>8.8 (0.76)</td>
<td>8.7 (0.71)</td>
<td>0.3301</td>
</tr>
</tbody>
</table>
| BMI: body mass index; FBG: fasting blood glucose; HbA1c: glycosylated hemoglobin; PPBG: post-prandial blood glucose; SD: Standard deviation; Percentages are calculated based on total number of subjects in the respective treatment arm; n = Number of subjects in respective categories; N = Total number of subjects in the respective treatment arm/safety population; p-value compared the treatment groups using chi-square/fisher’s exact test for categorical parameters and independent t-test for continuous variables.
Mean Change in FBG and PPBG (mg/dl) from Baseline

Table 2: Primary and secondary efficacy endpoints at 6 and 12 weeks

<table>
<thead>
<tr>
<th>Parameters, mean (SD)</th>
<th>Teneligliptin (N=36)</th>
<th>Sitagliptin (N=36)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Week 6</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.82 (0.79)</td>
<td>7.63 (1.09)</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>FBG (mg/dL)</td>
<td>175.1 (46.4)</td>
<td>155.9 (57.7)</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-</td>
<td>-19.2 (68.8)</td>
</tr>
<tr>
<td>PPBG (mg/dL)</td>
<td>283.2 (82.6)</td>
<td>257.7 (79.1)</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-</td>
<td>-25.6 (113.1)</td>
</tr>
</tbody>
</table>

Lipid Profile

<table>
<thead>
<tr>
<th>Parameters, mean (SD)</th>
<th>Teneligliptin (N=36)</th>
<th>Sitagliptin (N=36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL-C (mg/dL)</td>
<td>38.22 (7.35)</td>
<td>38.03 (6.75)</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-</td>
<td>-0.19 (5.86)</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>110.97 (41.37)</td>
<td>98.72 (31.11)</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-</td>
<td>-13.00 (37.93)</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>180.42 (45.42)</td>
<td>164.78 (33.68)</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-</td>
<td>-15.64 (47.85)</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>169.19 (110.53)</td>
<td>141.33 (63.91)</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-</td>
<td>-27.86 (91.65)</td>
</tr>
<tr>
<td>VLDL (mg/dL)</td>
<td>29.56 (12.31)</td>
<td>28.25 (12.86)</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-</td>
<td>-1.85 (9.66)</td>
</tr>
</tbody>
</table>

Effect on Lipid Profile

Treatment with teneligliptin or sitagliptin for 12 weeks did not demonstrate a statistically significant change in any of the lipid parameters. Mean total cholesterol and low density lipoprotein cholesterol levels were numerically lower after 12 weeks of treatment with both DPP-4i; however, the changes were not statistically significant. Change in mean triglyceride was greater in teneligliptin arm than sitagliptin arm; however, difference was also not statistically significant (Table 2).

Safety and Tolerability

Of 76 enrolled patients, 9 patients experienced at least 1 AE. Of the total 11 AEs (8 in teneligliptin arm and 3 in sitagliptin arm), the most common AE was hypertension in teneligliptin arm (n=5, 13.2%). All the AEs were mild in severity, found to be ‘not related’ to either of the gliptins and recovered without sequelae. There was no difference in number of AEs reported between the two gliptins (p=0.48) (Table 3). No significant changes were reported in hepatic or renal parameters in both arms at week 6 and week 12. There were no reported hospitalizations or deaths during the study conduct.

At baseline, mean ± SD QTc interval and heart rate were 429.09 ± 24.05 ms (teneligliptin: 429.37 ± 18.12 ms and sitagliptin: 428.82 ± 29.04 ms) and 81.37 ± 11.93 beats per minute (teneligliptin: 82.97 ± 13.36 bpm and sitagliptin: 81.37 ± 11.93 bpm), respectively. ECG parameters (HR, PR interval and QT interval) did not change significantly during 12 weeks of treatment in both arms (Table 4). The QTc interval did
**Table 3: Summary of safety events**

<table>
<thead>
<tr>
<th>Body system/Preferred term</th>
<th>Teneligliptin n (%)</th>
<th>Sitagliptin n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n (%)</strong></td>
<td>(N=38)</td>
<td>(N=38)</td>
</tr>
</tbody>
</table>
| Number of patients with at least one AE  
  (N=38)                       | 6 (15.79)           | 3 (7.89)         |
| Blood and lymphatic system disorders | 0 (0.00)             | 1 (2.63)         |
| Eosinophilia                | 0 (0.00)             | 1 (2.63)         |
| Eye Disorders               | 1 (2.63)             | 1 (2.63)         |
| Diabetic Retinopathy        | 1 (2.63)             | 1 (2.63)         |
| Immune System Disorders     | 1 (2.63)             | 0 (0.00)         |
| Seasonal Allergy            | 1 (2.63)             | 0 (0.00)         |
| Metabolism And Nutrition Disorders | 1 (2.63)             | 0 (0.00)         |
| Hyperglycemia               | 1 (2.63)             | 0 (0.00)         |
| Vascular Disorders          | 5 (13.2)             | 1 (2.63)         |
| Hypertension                | 5 (13.2)             | 1 (2.63)         |

n = Number of subjects in respective categories; N = Total number of subjects in the respective treatment arm/safety population; percentages are calculated based on total number of patients in the respective treatment arm/safety population; p-value compared the treatment groups using chi-square/fisher’s exact test

*p-value: 0.4799

**Table 4: Summary of ECG at Week 6 and 12**

<table>
<thead>
<tr>
<th>Parameters, mean (SD)</th>
<th>Baseline Teneligliptin (N=38) Week 12</th>
<th>Baseline Sitagliptin (N=38) Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR interval (ms)</td>
<td>148.82 (21.14)</td>
<td>147.17 (19.77)</td>
</tr>
<tr>
<td>QTc interval (ms)</td>
<td>429.37 (18.12)</td>
<td>438.22 (33.49)</td>
</tr>
<tr>
<td>Heart Rate (bpm)</td>
<td>82.97 (13.36)</td>
<td>83.94 (11.02)</td>
</tr>
</tbody>
</table>

**Discussion**

To the best of our knowledge, this randomized, active-controlled study is the first to evaluate the efficacy and safety of teneligliptin in comparison with sitagliptin as an add-on therapy to metformin and/or sulfonylureas in Indian patients with T2DM. The findings of our study demonstrated that 3-month treatment with either teneligliptin or sitagliptin reduced HbA1c significantly by about 1%; where numerically higher reduction was observed with teneligliptin with post-hoc analysis indicating non-inferiority of teneligliptin vs. sitagliptin as well as numerically higher percentage of patients achieving target HbA1c levels (<7%) in teneligliptin arm. Additionally, there was a significant decrease in the fasting and postprandial glucose levels at week 12 with both DPP-4i. There was no change in metformin and sulfonylurea dosage during the study period which enabled ideal comparison of the study treatments. At study entry, patients were overweight (BMI: 27.5 ± 4.61 kg/m²) with uncontrolled glycaemia (HbA1c: 8.7 ± 0.7%) consuming about 1 gm of metformin per day and >80% of patients were receiving a second OAD (sulfonylurea). This represents the common clinical situation in India when gliptins are often considered as an add-on therapy.

The mean ± SD HbA1c level achieved after 12 weeks of teneligliptin and sitagliptin treatment was 7.6 ± 1.1% and 7.7 ± 0.8%, respectively; this is close to the target HbA1c level (<7.0%) recommended by the ADA. The mean reduction in HbA1c at week 12 was statistically significant and comparable between the treatment arms. Similarly, mean reductions in FBG and PPBG at week 6 and 12 were comparable between teneligliptin and sitagliptin. Recently, Kim et al. has reported similar reduction in mean HbA1c from baseline at 24 weeks (teneligliptin, −1.03 ± 0.10% and sitagliptin, −1.02 ± 0.10%) in Korean patients.27 The proportion of patients achieving HbA1c <7.0% at week 24 was 50.0% and 59.2% in the teneligliptin and sitagliptin arms, respectively. The change in FBG at week 12 reported in our study (teneligliptin, −28.3 ± 63.0 mg/dL and sitagliptin, −22.9 ± 47.4 mg/dL) were much greater than reported by Kim et al. (teneligliptin, −12 ± 3.4 mg/dL and sitagliptin, −14.4 ± 3.5 mg/dL). This greater decrease in FBG levels in our study population was most probably due to a higher baseline FBG (by about 20 mg/dL) in our study than the Korean study. The long-term 52-week pooled analysis of Japanese studies also demonstrated that the reductions in HbA1c were dependent on the baseline values: −1.0 ± 0.9% for HbA1c >8.0% at baseline.28 An Indian study reported a significant −0.55% change in HbA1c with teneligliptin monotherapy (p=0.0043) compared to placebo at week 16 in drug-naive T2DM patients (n=237).28 The real world data from TREAT-INDIA study (n=4305) also demonstrated significant HbA1c reduction with teneligliptin monotherapy (−1.0 ± 0.5%) and when used as add-on to metformin (−1.1 ± 0.8%) or add-on to metformin plus sulfonylurea combination (−1.46 ± 1.33%).29

We did not observe significant changes in any of the lipid parameters with either teneligliptin or sitagliptin in line with the finding reported by Kim et al.27 This shows that gliptins are perhaps neutral in terms of any effect on lipid profile.

Both teneligliptin and sitagliptin were well-tolerated with no difference in the number of AEs. QTc interval is an independent predictor of all-cause and CVD mortality in patients with T2DM.30 Sitagliptin shortened QT interval in Japanese patients with no significant difference in QTc interval.31 Teneligliptin (40 mg daily) does not cause QT prolongations, which is the maximal dose in usual clinical practice.32 In the present study, the QT interval did not increase significantly from baseline to week 12 with either of the two gliptins. There was no statistical difference between the two arms for changes in ECG parameters.

None of the study patients reported any hypoglycemic event, while the incidence of hypoglycemia was 31.3% and 28.5% respectively in teneligliptin and sitagliptin arm in the Korean study.27 In another Japanese study in drug-naive patients, two episodes (14.3%) of hypoglycemia (<64 mg/dL) with teneligliptin (n=7) and one episode (7.2%) with sitagliptin (n=7) were reported using continuous
glucose monitoring. However, none of these episodes were associated with any hypoglycemic symptoms.33 Generally DPP-4i carry very low risk of hypoglycemia and the results of our study have confirmed the same. However, hypoglycemia has been reported in some other studies which call for vigilance and close monitoring while prescribing teneligliptin in patients who are prone to hypoglycemia.34

With increasing prevalence of T2DM in the Indian subcontinent, optimum pharmacotherapy is necessary to delay macro- and microvascular complications. Several of the OADs used as monotherapy, or in combinations are associated with AEs such as weight gain, hypoglycemia and gastrointestinal distress.35 Incretin-based therapies such as DPP-4i and GLP-1 agonists have emerged as preferred drugs in the past few years because of their efficacy and acceptable safety profile. DPP-4 inhibitors are less costly than GLP-1 agonists and have lower risk for hypoglycemia through unique glucagon dynamics. Sitagliptin requires dose adjustments in patients with renal and hepatic impairment which can be overcome by teneligliptin, which due to dual mode of excretion, offers a notable advantage in T2DM patients with hepatic and renal impairment, including patients on dialysis, without the need for dose reduction.

This study had few limitations mainly due to its open-label study design, shorter treatment duration of 12 weeks and smaller sample size. Despite these limitations, the study provided much needed insights about the comparative efficacy and safety of teneligliptin with the prototype DPP-4i, sitagliptin. However, future studies with large sample size and longer duration should be planned to provide further evidence in terms of long-term efficacy, safety and tolerability.

Conclusion

To conclude, teneligliptin provided similar glycemic control as compared to sitagliptin and reduced HbA1c, fasting and postprandial glucose values significantly within 12 weeks of treatment. No significant change was observed in the lipid profile with either of the two DPP-4i. Both teneligliptin and sitagliptin were found to be safe and well-tolerated. Teneligliptin can thus be used as an affordable add-on gliptin for treating T2DM patients who fail to achieve optimum glyemic control with metformin and/or sulfonylureas.

Acknowledgement

Authors would like to thank Medical Team of Wockhardt Pharmaceuticals for manuscript writing support.

Conflict of Interest

Study was sponsored by Wockhardt Pharmaceuticals Ltd.

References

Clinical Spectrum and Complications of Polycythemia, in Patients presenting at Tertiary Care Centre at Goa

Ramnath Nevrekar, Aparna Pai, Anar Khandeparkar

Abstract

Background: Polycythemia is characterized by rise in hemoglobin and hematocrit, either as a result of hematopoietic clonal expansion (Vera) or secondary to hypoxic stimuli (secondary polycythemia). It is of great importance to detect early and identify the type of polycythemia and also assess the thrombotic risk so that timely and appropriate treatment can be given. The present study aims to characterize the different presentations and complications of polycythemia, evaluate genetic factors and differences between the two categories of polycythemia in ethnic Goan subjects.

Aims and objectives:

1. To identify common presentations and etiologies of polycythemia
2. To evaluate and compare the differences in clinical features, hematological parameters and complications of polycythemia in primary (vera) and secondary polycythemia
3. To study the profile of JAK 2 V617F mutation in Goan patients with polycythemia Vera.

Materials and Methods: This was a retrospective observational cohort study, conducted at the Department of Internal Medicine, Goa Medical College, a tertiary care, teaching institute in the state of Goa. We analysed clinical and laboratory data of patients of polycythemia due to all causes (polycythemia Vera and secondary causes) previously admitted or following up at the hospital from January 2014 to December 2017. In each of these 2 groups, we studied the various clinical parameters including the age at presentation, sex, residence, symptomatology and clinical findings, presence of hypertension, as well as complications arising due to polycythemia (past and at present) hematological data including Hb, HCT, total WBC count, absolute neutrophil count, RBC and platelet count, ESR, rouleaux formation, EPO levels and JAK 2 V617F mutation analysis (done by real time PCR technique) and requirement of phlebotomies in the last 4 years. Commonest clinical presentations and complications arising due to polycythemia, in each group were analysed and compared.

Results: A total of 44 patients were included in the study out of which 33 were males. Polycythemia Vera was seen in 43.18% while secondary causes were seen in 56.8% patients. Patients with Vera were found to be more symptomatic with higher levels of mean Hb, HCT, cell counts and with a higher requirement of phlebotomy and more thrombotic complications. Amongst Vera group, patients having high WBC count, increased rouleau formation, and JAK2 positivity were found to be more prone for thrombosis. Hypertension was frequently seen to be associated with both groups. Obstructive sleep apnea followed by COPD was found to be the commonest causes of secondary polycythemia.

Conclusion: Our study revealed that patients with polycythemia Vera are more symptomatic and have a higher requirement of phlebotomy and a higher thrombotic tendency (arterial being more common than venous) as compared to the secondary polycythemia owing to a higher hyperviscosity in the former. Leukocytosis and JAK 2 617F positivity were found to be important predictors of thrombotic risk. Hypertension was found to be frequently associated with Vera as well as in secondary causes due to OSA.

Introduction

Polycythemia is characterized by an absolute increase in total body red cell volume (or mass) usually manifesting itself as high hemoglobin and or hematocrit (packed cell volume) levels. Polycythemia rubra Vera is a myeloproliferative neoplasm which involves clonal expansion of pluripotent hematopoietic stem cell and has to a varying degree the potential to transform into acute myeloid leukemia. It manifests as clinically as plethora with elevated levels of hemoglobin, hematocrit, RBC count with or without elevation in WBC and platelets. This disease has a variable course with risk of arterial and venous thrombotic tendency. The main aim of treatment is to reduce hyperviscosity of blood by periodic phlebotomies and in certain patient’s cytoreductive therapy to prevent thrombosis and disease progression. In 2005 mutation in JAK2 V617F leading to activation of tyrosine kinase pathway was identified as a causative factor for myeloproliferative disorders including polycythemia Vera. Its frequency varies worldwide, however in India very few studies have evaluated the association of this mutation with...
polycythemia vera. Presence of this mutation appears to be risk factor for development of thrombosis in patients with polycythemia vera, however it requires very sensitive allele specific PCR, pyrosequencing and quantitative real-time PCR for its detection. Alternative somatic mutations like EXON12 have also been implicated in JAK2 negative patients. The relative paucity of data on clinical features, hematological parameters, thrombotic tendency and most importantly JAK2 mutation profile in Goan subjects with polycythemia prompted us to undertake the above research.

Secondary polycythemia results from an increased erythropoietin drive either in presence or absence of tissue hypoxia. The common underlying disorders are congenital cyanotic heart diseases, high altitude, obstructive sleep apnea, COPD, chronic smoking, renal artery stenosis etc. The present study also aimed at identifying the differences in terms of symptomatology, clinical findings, associated complications, hematological parameters, erythropoietin (EPO) levels and requirement of phlebotomies between the two major subcategories of polycythemia.

**Aims and Objectives**

1. To identify common presentations and etiologies of polycythemia
2. To evaluate and compare the differences in clinical features, hematological parameters and complications of polycythemia in primary (vera) and secondary polycythemia
3. To study the profile of JAK2 V617F mutation in Goan patients with polycythemia Vera.

**Materials and Methods**

This was a retrospective observational cohort study conducted at the Department of Internal Medicine, Goa Medical College, a tertiary care hospital and teaching institute in the state of Goa. We retrospectively analysed clinical and laboratory data of patients of polycythemia due to all causes (polycythemia vera and secondary causes) previously admitted or following up at the hospital from January 2014 to December 2017. Data was obtained from patients clinical records, case papers in wards and OPD records. Approval of the Institutional Ethics Committee was taken.

Sample size: Data of total 44 patients of polycythemia (all causes) was obtained. All patients were classified into two groups

A. Polycythemia vera
B. Secondary polycythemia

**Inclusion criteria**

Polycythemia Vera: diagnosed as per revised who criteria 2016 which includes-

- Major criteria-
  1. Hb > 16.5 gm/dl or HCT > 49% (m)
  2. Bone marrow biopsy showing hypercellularity for age with trilineage growth including permanent erythroid, granulocytic and megakaryocytic proliferation with pleomorphic mature megakaryocytes

  3. Presence of JAK2V617F or JAK2 exon 12 mutation

- Minor criteria: subnormal serum Erythropoietin (EPO) levels

**Diagnosis requires meeting all 3 major criteria or first 2 major and minor criteria**

(Major criteria no 2 (bm biopsy) may not be required in patients with sustained absolute erythrocytosis Hb > 18.5gm/dl or Hct> 55.5% (males) Hb> 16.5gm/dl or Hct> 49.5% (females), if maturation criteria is present)

Secondary polycythemia diagnosed as Hb > 16.5 gm/dl or HCT > 49% (m) and Hb > 16 gm/dl or HCT > 48 % (f) with secondary underlying causes and not fitting into the diagnostic criteria for Vera. Various etiologies of secondary causes of polycythemia included COPD, obstructive sleep apnea syndrome, congenital cyanotic heart disease, smoking high altitude exposure etc.

In each of these 2 groups, we studied the various clinical parameters including the age at presentation, sex, residence, occupation, symptomatology and clinical findings, presence of hypertension, as well as complications arising due to polycythemia (past and at present) laboratory features, including Hb, PCV, total WBC count, absolute neutrophil count, RBC and platelet count, ESR, rouleaux formation, EPO levels and JAK2 V617F mutation analysis (done by real time PCR technique) and requirement of phlebotomies in the last 4 years. Commonest clinical presentations and complications arising due to polycythemia, in each group were analysed. Bone marrow aspiration reports of those patients in whom the procedure was done prior to diagnosis was obtained from their records. For patients of secondary polycythemia, data of specific investigations done to ascertain the etiology like echo, renal doppler, pulmonary function tests, polysomnography was also studied.

**Exclusion criteria**

1. Patients admitted with acute dehydration, sepsis, shock and other conditions leading to spurious polycythemia
2. Patients on diuretics

Statistical analysis was done using SPSS software. Quantitative data (like age) was expressed as mean ± standard deviation (SD) and compared between two groups using independent student t test. A two tailed p value < 0.05 was considered significant. Categorical data in both the groups was expressed as percentages (like percentage of hypertensive patients in each group) and compared using chi square test. ODDS ratio was used to see whether a significant association exist between sex and JAK2 mutation positivity. MS word and excel were used to generate tables and graphs.

**Results**

A total of 44 patients of polycythemia were included in our study, amongst whom 33 (75%) were males while 11 (25%) were females with a male: female ratio of 3:1. The polycythemia Vera group had total 19 patients amongst which 18 (94.7%) were males while only one was female. The mean age at presentation in Vera group was 46.7 years (SD 12) while it was 52.7 years (SD 18.8) in the secondary group. The sex distribution and the baseline...
A higher incidence of complications were found in the Vera group as compared to the secondary group (p=0.001). The occurrence of thrombotic complications in polycythemia vera were found to be more frequent in secondary group (p=0.001). Mean RBC count in vera group was significantly higher 5.96 lakhs/mm$^3$ (SD 1.32) while it was 3.25/mm$^3$ (SD 1.12) in the secondary group. ESR was significantly lower (p=0.001) while platelet count was significantly high in the vera group (p=0.001). Increased rouleaux formation was seen significantly higher in Vera group as compared to secondary causes. EPO levels were found to be lower in 68 % patients and normal in 31.6 % patients of Vera group while in secondary group 40 % patients had a normal and 32% patients had a high EPO levels.

JAK2 positivity was found in 9 out of 19 (47%) patients with Vera.

The mean Hb and PCV at the time of diagnosis were significantly higher in the vera group 19.7 gms/dl and 59.4 % respectively as compared to the secondary polycythemia group which had Hb and PCV of 18.3 gms/dl and 55.6 % respectively (p=0.015). The highest level of Hb in this group was seen in congenital cyanotic heart diseases.

Total WBC count and Absolute neutrophil count was significantly high in the vera group (12369/mm$^3$ and 9089/mm$^3$ respectively) as compared to 7650/mm$^3$ and 4904/mm$^3$ respectively in secondary group (p=0.001). Mean SBP and DBP being 135/mmHg and 86.6 mmHg respectively while 36% patients of secondary group (all cases of obstructive sleep apnea syndrome) were found to be hypertensives (stage II). However hypertension was not found to be statistically significant between the two groups (p=0.25).
patients with JAK 2 positivity, comorbid conditions, higher WBC count though these findings need to be confirmed on a larger sample size.

Overall polycythemia vera was seen in 19 (43%) of patients while the remaining 25 (56.81%) had underlying secondary causes for their polycythemia amongst which OSA (obstructive sleep apnea) was the leading cause, seen in 10 (23%) followed by COPD in 5 (12%). Cyanotic congenital heart diseases 4 (9%), chronic smoking 4 (9%), while one patient had fibroid uterus and one was a resident in high altitude (Table 4). Amongst the secondary causes highest HB and PCV was seen in patients with congenital cyanotic heart diseases.

Discussion

In our study, polycythemia was found to be more common in males as compared to females with M: F ratio of 3:1. In the Vera group 94.7% were males suggesting a male preponderance. Similar findings have been reported in previous Indian studies.7,8

The mean age at presentation for the vera group was 46.7 years, was similar to previous study by Bhattacharya et al11 (48 yrs) and lesser than that reported (53.19) by Sazawal et al.7 Patients in the vera group were found to be more symptomatic than those with secondary polycythemia, where 68% patients were asymptomatic. This is probably attributable to higher mean values of mean HB and PCV, a higher total WBC and RBC count resulting in a higher hyperviscosity in the former. The commonest symptoms being fatigue (52.6%), followed by erythromelalgia (42.1%), headache (31.5%), pruritus (31.5%), dizziness (26.3%). These were consistent with observations in the initial Polycythemia vera study group PVSG.1 Pruritus (aquagenic) is reported as a common symptom (almost 50% cases of Vera) in literature;6,10 was found to be less common symptom (31%).

Plethora was the commonest clinical sign observed in 18 (94%) while splenomegaly was detected in 14 (73.3%) in vera group which was similar to findings in the previous studies in Indian population.6,11 Absence of clinically palpable spleen or even on imaging, does not rule out polycythemia vera. However splenomegaly in a patient with polycythemia (with or without leukocytosis or thrombocytosis) should always arouse a suspicion of myeloproliferative neoplasm. Importantly, splenomegaly as a finding speaks against secondary disorders as a cause of polycythemia.

In our study, 57.9% patients of Vera group had hypertension (stage 1) with mean values of SBP 135 mmHg and DBP 87 mmHg. The occurrence of hypertension in Indian patients with Vera was found to be 25% in a long term follow up study at Delhi by J Bhattacharya et al.11 These findings suggest an association between polycythemia Vera and hypertension and highlight importance of looking for polycythemia in all hypertensives as both diseases independently predispose to cvs risk and timely phlebotomy in this strata of patients is crucial for reducing hyperviscosity and subsequent thrombotic events. Amongst the secondary polycythemia group, 36% (all of whom were having obstructive sleep apnea syndrome) were hypertensives (stage 2) and were on multiple antihypertensives. Though renal artery stenosis (RAS) is also an important cause of hypertension with secondary polycythemia, we did not get any such patients in our study. Again both these conditions (OSA and RAS) are an important cause of secondary hypertension and should be aggressively sought for in all hypertensives, particularly in patients with stage II, refractory cases, young, obese and in patients with malignant hypertension. Treatment of the underlying disorder often results in significant reduction of BP as well as associated polycythemia and associated CVS risk.

In our study, the mean Hb and PCV at diagnosis was significantly higher in the vera group as compared to secondary group. Amongst all secondary causes, highest values of Hb, HCT were noted in the congenital cyanotic heart diseases, reflecting the effect of a longer duration of hypoxia sustained by these patients. Interestingly 15 patients who were excluded from the study as their Hb was slightly less than the WHO cutoff level for diagnosing polycythemia vera (Hb >16.5 gm/dl or HCT > 49%) nor had any underlying secondary causes; did have clinically evident plethora with low ESR and hypertension and normal to low EPO values. The mean HB in them was 15.8 gm/dl. Though these patients were not included in the study, considering that the normal mean Hb level in general population of country like India may be lower than the western countries probably due to nutritional factors, the cut off level of Hb for defining polycythemia in India may be lesser than international standards and we require a nationwide survey to define the normal range of Hb, PCV in India. Ethnicity and genotypic factors of local subgroup may also influence the normal Hb range in a large country like India.

In our study, the mean Total WBC count was 12369/mm^3 (±3941.1), absolute neutrophil count 9089/mm^3 (±3401) and platelet count 5.51 lakhs/mm^3 (±1.11) were significantly higher in the vera group as compared to secondary polycythemia group (p=0.001). Similar values of Total WBC count were obtained in study by Bhattacharya et al11 while a much higher figure of 29900/mm^3 was reported in study by Sudha Sazawal et al.7

The higher cell counts in the Vera
group probably reflect the trilineage marrow hypercellularity, resulting in greater hyperviscosity and subsequent thrombotic complications, as seen in the present study. Previous studies have also implicated the role of leukocytosis in thrombotic tendency in polycythemia vera.12,13 Leukocytosis and thrombocytosis warrant the use of cytoreductive therapy in vera in addition to periodic phlebotomies to maintain Hb < 16 gm/dl for risk reduction.

Low EPO levels were found in 68% of vera patients and none amongst secondary causes (p = 0.001) while 31% of vera and 40% patients of secondary polycythemia had a normal erythropoietin levels thereby suggesting that normal levels do not correlate well with the type of polycythemia but low levels definitely favor vera.

In our study, Jak 2V617F positivity was seen in 47% patients of vera (p=0.005) while Exon 12 positivity was seen in only one patient. Males had a higher incidence of JAK 2 positivity as compared to females (odds ratio of 3 at 95% CI (0.1-83). In a study by Sazawal et al.,7 Jak2V617F was found positive in 82% patients with PV in Indian patients. Overall the frequency of JAK 2 mutations amongst Indian patients appears to be lower as compared to that reported in western literature (97%) Baxter et al.,3 (89%) James et al.,4 (65%) Kravolici et al.,5 (74%) Levine et al.6 and this could be attributable to ethnic variations in allele burden and also the type of molecular test used to detect the mutation. In our study the mean Hb and PCV, WBC count and also incidence of thrombotic complications were higher in PV with JAK 2 positivity.

The requirement of phlebotomy was higher in patients of PV as compared to secondary causes. Amongst patients with Vera the JAK 2 positive patients had a higher requirement of phlebotomy.

In the present study The incidence of complications arising due to polycythemia were higher in patients with PV as compared to those with secondary causes, this could be attributable to the higher hyperviscosity in the vera group on account of higher mean Hb and counts. Commonest complications were arterial thrombosis (IHD, ACS, TIA, CVA) followed by venous thrombosis (DVT, CTV and intraabdominal venous thrombosis). In the observations of polycythemia Vera study group (PVSG), the thrombosis was seen in 30% patients, more than 50% of these were arterial. In study by Thomas et al. in South India, thrombotic events were reported in 35% of study subjects of which 24% were arterial.

Amongst all patients of PV in the study the thrombotic complications were higher amongst those with JAK 2 positivity and a high total WBC count. Previous studies have mentioned leukocytosis, high mean Hb and HCT as risk factors for thrombosis in PV.2,12,13 JAK2 V617F homozygosity in Vera has been found to be associated with thrombosis.14

In current study, the commonest secondary cause of polycythemia was OSA, followed by COPD, cyanotic heart diseases, chronic smoking, high altitude and fibroid uterus. The mean HB PCV levels, counts, complications, requirement of phlebotomy were significantly lesser in these patients. Majority of the patients were asymptomatic for polycythemia amongst secondary etiologies. All this indicates that the hyperviscosity in secondary causes is less as compared to Vera.

Conclusions

In summary our study revealed that patients with polycythemia Vera are more symptomatic and have a higher requirement of phlebotomy as compared to the secondary polycythemia owing to a higher hyperviscosity in the former. Hypertension is frequently associated with polycythemia Vera as well as in secondary causes due to OSA. As compared to secondary causes, polycythemia Vera has a higher thrombotic risk (arterial being more common than venous) particularly in patients having leukocytosis and JAK 2 617F positivity. Also low ESR and increase in rouleaux formation in peripheral smears seen in polycythemia vera patients is a simple cost effective indicator of hyperviscosity. Splenomegaly and Low EPO levels correlates well with polycythemia Vera but its absence or normal EPO levels does not exclude vera and finally the mean Hb and PCV cut off for polycythemia in Indians may have to be redefined after doing a larger nationwide study so as to have a true estimate of the disease burden of this largely neglected hematological disease.

References

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Rural Set Up Experience of Viper Bite Treatment with Special Reference to FFP in Venom Induced Consumption Coagulopathy

Suvarna Patil1*, Amey Paranjape2, Netaji R Patil3, Harshal S Patil2, Rahul A Surve4, Maruti B Desai5

Abstract
Snake bite is one of the major public health problems in India. Venom induced consumption coagulopathy (VICC) is the commonest coagulopathy resulting from viper bites. Anti-snake venom (ASV) is the only mainstay therapy in the management of snake bite. Despite anti-venom being efficacious and bonding to multiple toxins in the venom, there are number of reasons it may not be effective. The most important being irreversible toxic effects cannot be reversed by anti-venom to toxin after damage has occurred, such as clotting factor deficiencies resulting from VICC.

This study was done to evaluate the efficacy of use of anti-snake venom and ASV with fresh frozen plasma (FFP) in haemotoxic snake bites in a tertiary care hospital. Total 500 patients admitted during period from January 2010- April 2017 with history of snake bite, vasculotoxic[278], neurotoxic[126], localtoxic[64] and nontoxic[32]. Overall outcome in term of time recovery, renal complications, and death better in ASV plus FFP group. The complications due to snake bite were minimum, if anti snake venom was administered within first 4 hours.

Introduction
Anti-snake venom is a double edged sword. It risks of anaphylactic reaction. It is also available and costly. For anti-venom to be effective against irreversible toxic effects, it must be administered early, so it can bind to toxin before they distribute their target sites and cause irreversible toxicity. Pro-coagulant toxins act in central compartment (circulation), making their onset of action relatively rapid. Once they have activated the clotting pathway and clotting factors have been consumed, this process is irreversible until further clotting factors can be re-synthesized. Administration of anti-venom will potentially bind the active pro-coagulant toxins, allowing the clotting factors to recover. Anti-venom will therefore be clinically effective in shortening the duration of VICC and reducing the risk of bleeding.[8] VICC is characterized by low or undetectable levels of one or more clotting factors, most commonly fibrinogen. Anti-venom will only stop the consumption process so once it has been given it still takes 24 to 48 hours for full recovery of clotting factors.[11] While the clotting factors are re-synthesized by liver there is a period of time during which patient remains at risk of hemorrhage. For this reason, clotting factor replacement has been suggested as an adjuvant treatment for VICC. The most commonly used factor replacement is FFP as it is widely available and contains fibrinogen, factor- V, factor- VIII, factor- X. Clotting factor replacement for VICC is controversial because of the concern that it may worsen VICC by providing more clotting factors for the pro-coagulant toxins.[1] However, it has been assumed that once anti-venom has been given and the toxins are bound, clotting factors replacement is likely to speed the rate of recovery. Full recovery of clotting function takes up to 48 hours, during which time patient potentially remains high risk of bleeding. Theoretically FFP administration should rapidly correct the coagulopathy in absence of ongoing venom induced clotting factor consumption. This has been shown for Australian elapid snake bite, but has not been investigated in viper envenoming.[3]

Methods
The information of 500 patients’ snake bite was collected retrospectively from BKL walawalkar rural medical college and hospital Dervan, Ratnagiri, Maharashtra throughout the years: January 2010- April 2017. Detail history, clinical examinations were noted. After identification of snake and those who had ptosis and respiratory paralysis were enrolled in neurotoxic group. Those who had prolong PT(INR) and 20 min’s whole blood clotting time (WBCT) with bleeding were selected for vasculotoxic group. Those who did not have systemic manifestations but has local cellulitis were included in locally toxic group. We have studied only vasculotoxic snake bites. This is an observational study to evaluate the efficacy of ASV versus ASV plus FFP group. Data is categorical, using statistical technique for Chi-square test and Z-test for proportion. Frequency and percentage is used for analysis.

All patients with snake bite underwent, 20min whole blood clotting time (WBCT).[4] Blood was investigated for hemogram, fibrinogen levels,[3] PT(INR), serum creatinine, urine. Those who had deranged PT(INR) and low fibrinogen levels and bleeding manifestations were selected for study and labeled as Venom induced consumption coagulopathy.[5] All patients were given 10 vials of ASV(polyvalent for India).[4] After 6 hours PT (INR) and 20 min WBCT was repeated.[5] PT(INR)> 2-3 min’s and bleeding patients were given FFP along with 10 vials of ASV. Dose of FFP was 10-15 mg/kg. In this way every

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Flow-chart: Showing study procedure

6 hourly coagulation parameters and clinical bleeding was assessed and FFP was given. Maximum ASV given were 30 vials.7 Urine output was measured and creatinine was repeated every 24 hours in oliguric patients. Those who developed acute renal failure were hemodialysed according to their serum creatinine levels and fluid status. FFP was used only after 6 hrs of treatment.

Results

Total 500 patients admitted during period of January 2010- April 2017 with history of snake bite. In our observation 278 (55.60%) were vasculotoxic, 126 (25.20%) were neurotoxic, 64 (12.80%) were locally toxic and 32 (6.40%) were non-toxic. Vasculotoxic and Neurotoxic deaths were 9 (3.59%) and 5 (3.17%) respectively.

Table 1 showed, ARF (11.16%), Hemodialysis (HD) (6.31%), mortality rate (4.85%), Hemorrhage (4.85%) , local bleeding (40.29%) was much more in ASV group than ARF (1.38%), HD (1.38%), Mortality rate(0%), local bleeding(0.50%) in ASV plus FFP group. Proportion of mortality rate in ASV was 0.485, 95% C.I [0.416-0.553] and ASV+FFP was 0; z=7.4 and p< 0.00001 i.e. statistically significant difference between mortality rate in ASV and ASV+FFP group.

Table 2 revealed that as time lapse increases, percentage of ARF, HD, mortality rate, hemorrhage was increased. If time lapsed more than 12 hours then complications are more compared to 4-12hours and less than 4 hours.

Figure 1, seasonal prevalence was comparatively very high in rainy season. Type of snake bite depends on season’s [P=0.00003] at 5% level of significance.

Discussion

As one vial neutralizes 6 mg, this would have neutralised 144 mg of venom. The range of venom injected is 5mg-147 mg. This is sufficient to inactivate unbound venom. Therefore further administration of ASV is of no use. Fibrinogen levels were low in all envenomated patients in our study. They were given FFP. It also helps to prevent complications in elderly patients with co morbidities like DM, Hypertension, IHD and those who are on antiplatelet drugs. Isbister et al in their study demonstrated that neither earlier administration of anti-venom nor higher doses of anti-venom reduced time to recovery of Venom-induced consumption coagulopathy. However, early administration of FFP was associated with faster recovery.9

For anti-venom to be effective against irreversible side effects, it must be administered early, so it can bind with toxins before they distribute to their target sites and cause irreversible toxicity. The current evidence would suggest that FFP should be administered in patients with acute bleeding and is more likely to be effective if given more than 6 hours after the bite. VICC is the most common indication for anti-venom administration in patients with Russell viper bites, although there is ongoing controversy over the dose of anti-venom (initial dose of 10-20 vials) repeat anti-venom dosing and use of factor replacement.

Maduwage et al have recently shown that recovery of coagulopathy occurs over a period of 24-48 hours in patients given 10 vials of anti-venom. Even so full recovery of clotting function takes up to 48 hours, during which patient potentially remains at risk of bleeding. Treatment usually includes antivenom and potentially, clotting factor replacement, but evidence to support their effectiveness in resolving VICC is limited, there are no placebo-controlled trials of antivenom, and only one of fresh frozen plasma. The majority of studies of FFP in VICC have been observational in nature. In a study of FFP in Australian elapid envenoming causing VICC, the administration of FFP sped up the recovery of coagulopathy, except when given < 6 hrs after snake bite.12

However, the etiology of VICC is different for Russell’s viper venom, which contains metallo- proteinase FX and FV activators, rather than a serine protease pro-thrombin activator. Coagulopathy from later develops rapidly and appears to resolve irrespective of anti-venom, where as
Russell’s viper VICC appears to be slower in onset and recovery is delayed unless anti-venom is administered. The failure of anti-venom for VICC in Australia and success of anti-venom from Echis spp; in Africa demonstrates that studies of one snake (and therefore one pro-coagulant toxin) can’t be generalized to other snakes. Studies are required for each major group of snakes and toxin from different parts of the world, although understanding the mechanism of pro-coagulant toxin should inform empirical studies of different anti-venoms.1

Conclusion
Administration of anti-venom will potentially bind the active pro-coagulant toxins, allowing the clotting factors to recover. Anti-venom will effectively shorten the duration of VICC and reduces the risk of bleeding. However, while the clotting factors are re-synthesized by liver there is a period of time during which patient remains at risk of hemorrhage. For this reason, clotting factor replacement (FFP) has been suggested as an adjuvant treatment for VICC. Studies are also required for efficacious use of FFP focusing on when to use, how much to use, for how much time it has to be given.

Acknowledgement
I express my deepest gratitude to Dr. David Warrell for his continuous support and guidance.

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A Descriptive Study to Find Possible Correlation between Pituitary Magnetic Resonance Image Findings and Abnormal Pituitary Hormones: A Retrospective Single Centre Study in Saudi Community Based Hospital

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Abstract

Background: Data on pituitary Magnetic Resonance Imaging (MRI) in patients with abnormal pituitary hormones in Saudi Arabia are very scarce.

Objective: To define the frequency of normal pituitary MRI in patients with abnormal pituitary hormones in a well-defined population

Design: Retrospective analysis of radiological and hormonal data of patients with pituitary MRI between January 2008 and December 2015.

Settings: Departments of Endocrinology and Radiology at King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia.

Patients: 459 patients with clinical, hormonal and radiological data.

Main outcome measures: The frequency of normal pituitary MRI in patients with abnormal pituitary hormones.

Results: Over the 7-year period, Out of 459 patients; 129 (28.1 %) were males and 330 (71.9 %) were females with mean age of 35.4 ± 13.7. Positive MRI compared to normal MRI were seen in 268 (58.4 %) and 191 (41.6 %) subjects respectively. Subjects with Positive MRI were significantly older, 36.8 ± 14.1 vs. 33.5 ± 12.9, p value=0.01. Hyperfunctioning pituitary hormones were significantly associated with positive MRI, 259 (63.2%) vs. 151 (36.8) where as hypofunctiong pituitary hormones were associate with normal MRI, 40 (81.6%) vs. 9 (18.4%), p value < 0.001. Females with hyperfunctioning pituitary hormones were significantly associated with positive MRI whereas males with hypofunctioning pituitary hormones were significantly associated with normal MRI. Three types of hyperfunctioning pituitary gland were seen such as hyperprolactinemia, somatotroph adenoma, and corticotroph adenoma were associated with more frequent positive MRI as to Five types of hypofunctioning pituitary gland were seen such as panhypopituitarism, secondary hypogonadism, growth hormone deficiency, central hypothyroidism and central adrenal insufficiency which were associated with more frequent normal MRI.

Conclusion: The current study indicates hyperfunctioning pituitary gland was significantly associated with positive MR whereas hypofunctioning pituitary gland was associate with normal MRI. In the absence of registry data, larger cooperative studies involving diverse population samples from multiple centers could help to provide further information on the true frequency nationally.

Limitations: Question of clustering of cases within the study region and limited study sample size.

Introduction

The procedure of choice in the evaluation of sellar masses is MR imaging using (3 mm) sagittal and coronal T1-weighted images with optional T2-weighted or fat-suppressed sequences.1,2 Histological analysis of autopsy specimens and radiologic (computed tomography [ CT ] and MRI) data from patients being treated or studied for conditions related and unrelated to pituitary disease are the two principal methods that have been used to estimate the population prevalence of PA. Many studies have been performed using this approach to estimate the prevalence of Pituitary adenoma (PA). Both methods have generated estimates ranging from 1% to 30%.3-9 In addition, intracranial tumors constitute 10-15% of PA in surgical specimen.

Typical hypersecretory syndromes constitute 65% of PA (48%prolactin,10% growth hormone, 6% corticotropin, and 1% thyrotropin).10,11 Nonfunctioning (or nonsecreting) PA constitute the remaining 35%.

The objective of this study, therefore, is to investigate a possible relationship between the frequency of normal MRI findings and different hormones abnormalities in a tightly defined geographical area in Jeddah, Saudi Arabia.

Methods

All MRI pituitary records were collected from the radiology department data base between January 2008 and December 2015 at King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia. MRI and clinical Records of patients were thoroughly analyzed. Out of the initial screening of 630 subjects, 93
Table 1: Gender and age in correlation to MRI findings

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Total</th>
<th>MRI findings</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Positive</td>
<td>Normal</td>
</tr>
<tr>
<td>Age (years)</td>
<td>459</td>
<td>268 (58.4)</td>
<td>191 (41.6)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>129 (28.1)</td>
<td>70 (26.1)</td>
<td>59 (30.9)</td>
</tr>
<tr>
<td>Female</td>
<td>330 (71.9)</td>
<td>198 (73.9)</td>
<td>132 (69.1)</td>
</tr>
</tbody>
</table>

Data are number (%) and mean ± standard deviation

Table 2: Pituitary hormones in correlation to MRI finding

<table>
<thead>
<tr>
<th>Associated pituitary abnormalities</th>
<th>Total</th>
<th>MRI findings</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Positive</td>
<td>Normal</td>
</tr>
<tr>
<td>Hyperfunctioning</td>
<td>410 (89.3)</td>
<td>259 (63.2)</td>
<td>151 (36.8)$</td>
</tr>
<tr>
<td>Hypopituitarism</td>
<td>49 (10.7)</td>
<td>9 (18.4)</td>
<td>40 (81.6)</td>
</tr>
<tr>
<td>Hyperprolactinemia</td>
<td>399 (86.9)</td>
<td>248 (62.2)</td>
<td>151 (37.8)</td>
</tr>
<tr>
<td>Acromegaly</td>
<td>10 (2.2)</td>
<td>10 (100)</td>
<td>0</td>
</tr>
<tr>
<td>Corticotroph adenoma</td>
<td>1 (0.2)</td>
<td>1 (100)</td>
<td>0</td>
</tr>
<tr>
<td>Panhypopituitarism</td>
<td>7 (1.5)</td>
<td>3 (42.9)</td>
<td>4 (57.1)</td>
</tr>
<tr>
<td>Secondary hypogonadism</td>
<td>24 (5.2)</td>
<td>2 (8.3)</td>
<td>22 (91.7)</td>
</tr>
<tr>
<td>Growth hormone deficiency</td>
<td>16 (3.5)</td>
<td>4 (25.0)</td>
<td>12 (75.0)</td>
</tr>
<tr>
<td>Central hypothyroidism</td>
<td>2 (0.4)</td>
<td>0</td>
<td>2 (100)</td>
</tr>
</tbody>
</table>

Data are number (%). $ = p value < 0.0001

Discussion

The preferred diagnostic imaging modality for evaluation of sellar and parasellar tumors, including adenomas is pituitary MRI. In particular, when functioning adenomas are suspected, a dynamic pituitary MRI, which obtains images within seconds after gadolinium contrast injection, may be more useful because it has higher sensitivity than other imaging modalities for detecting small microadenomas. Finding of small incidental lesions of little or no clinical significance on dynamic pituitary MRI may be misinterpreted as the pathological source of excess hormonal secretion during evaluation of patients for Cushing’s disease or acromegaly given lower specificity vs. conventional MRI. Because there are few conditions in which clinicians would obtain pathology results of the pituitary mass when a normal pituitary gland is reported on MRI, he calculation of the specificity of pituitary MRI is likely limited due to underestimation of true negative values.

PA are the most common intracranial neoplasm comprising approximately 5–20% of primary central nervous system tumors, which would translate into a relatively low prevalence. Epidemiologic studies are limited by their dependence on population-specific registries, which subject them to bias from regional influences such as diagnostic practices, reporting patterns, and case definitions. There are limited data on the prevalence of PA in spite of epidemiologic, postmortem, and radiologic studies have been used to estimate their prevalence. In general, the incidence of PA is higher in more recent than in older studies, probably due to improved endocrinological and radiological diagnosis, and increased neurosurgical interest in these lesions. In this sample, the mean age of patients was 35 years old. It should be taken into account that PA mostly affect young and economically active individuals in whom diagnostic delay translates into loss of productivity.
The clinical features of pituitary adenoma vary depending on the location and size of the tumor and its secretory capability. Pituitary adenomas typically appear during early adulthood, and no sex predilection is known. Approximately 65% of PA secrete a hormone causing typical hypersecretory syndromes. The remaining (35%) PA do not secrete a hormone and are thus referred to as nonfunctioning (or nonsecreting) adenomas. Due to compression of pituitary tissue, pituitary stalk and its vascular supply, partial or total hypopituitarism may occur, resulting in deficit of production of some or all pituitary hormones. There depends on the presenting symptoms diagnostic approach to a suspected PA variety depending on the adenoma the tumor produces. The tumors are related to the specific symptoms or hypopituitarism, though pituitary adenomas are usually small lesions limited in size and therefore may not be apparent in a mass reported in 69% of scans, the highest observed among all endocrinopathies which lower than our finding however the number of acromegaly cases in our study was small (10 patients with acromegaly). In contrast, 84% of MRI scans ordered for hypergonadism did not reveal a pituitary lesion which compatible with us. These results highlight that pituitary MRI is likely not helpful as a screening tool for patients with hypergonadism. Positive pituitary MRI scans observed with hypergonadotropic hypergonadism were typically observed in cases of severe testosterone deficiency in which total testosterone was less than 100 (normal 250-1000 ng/dl). Given the lack of definitive imaging changes in patients screened for hypergonadism, clinicians should use a higher judgment threshold before ordering pituitary imaging for these patients.

We aimed to identify the clinically apparent pituitary masses as screened by MRI scans, and this aim was reflective of the clinical setting because not all pituitary masses are formally diagnosed with histological confirmation. Furthermore, due to the retrospective nature of this study, the observed population reflects a selected yet comprehensive group of patients referred for pituitary MRI, rather than the general population as would be encountered in an autopsy series. Our study could be limited by the question of clustering of cases within the study region and the effect that might have on our estimates, in addition, the current study population may appear limited in size and therefore may underestimate the true prevalence of PA in the general population. In addition, the study shares the limitations of all retrospective studies.

In conclusion, the current study indicates hyperfunctioning pituitary hormones were significantly associated with positive MR whereas hypofunctioning pituitary hormones were associated with normal MRI. In the absence of registry data, larger cooperative studies involving diverse population samples from multiple centers could help to provide further information on the true frequency nationally.

Acknowledgement

The author would like to thank all colleagues from the Department of Endocrinology for helping in data collection.

References


**Association of Physicians of India**

**API Chapters / Branches Awards 2019**

1. Recommendations are invited from API Chairman / Secretaries of all State Chapters / City Branches for the following award:  

**Best State Chapter and Best City Branch Award**

The award is based on overall API/ICP/PRF activities by the State Chapter / City Branch from 1st January to 31st December. Selected City Branch and State Chapter will get the award of Silver Memento and a citation from API during Annual General Body meeting to be held on 15th December 2019.  
Chairman / Secretaries of all state Chapters / City Branches are requested to send the report of their activities for the year 2019 by 15th December 2019. All the above nomination should reach to Hon. General Secretary – API, Dr. Mangesh Tiwaskar of API, Unit No. 6 & 7, Turf Estate, Opp. Shakti Mill Compound, Off. Dr. E. Moses Road, Near Mahalaxmi Station West, Mumbai – 400 011

Dr. Mangesh Tiwaskar  
Hon. General Secretary

**Association of Physicians of India**

**Visiting Lectureship Award for 2020**

Recommendations are invited from members for the following assignment so as to reach, Hon. General Secretary – API, Dr. Mangesh Tiwaskar by 15th December 2019.

**Visiting Lectureships for 2020 is**

Boehringer-Knoll Junior Lectureship in Diabetes

The above lectureship is open to eminent persons from the discipline of Medicine and allied subjects such as Pharmacology, Biochemistry, Pathology and Physiology.

The selected candidate has to deliver his/her lecture at the Institution of his/her choice in the year 2020. The candidate has to get a notification in writing from the Institution that he / she has delivered the lecture.

Persons are selected from the recommendations received from members of the API. The orator in the discipline of Medicine should preferably be a member of API. The recommendations for the above assignments must be accompanied with reasons for recommending a particular person showing the value of his/her research and eight copies each of three of his/her best publications. All relevant papers in connection with the suggestions, such as the bio-data, list of publications etc., should be submitted in 8 sets by the proposer.

The members of the Governing Body of API and the Members of the Faculty Council of ICP are not eligible to receive any Oration, Lectureship or Award.

The prescribed nomination form for the above Lectureship are on the API website “apiindia.org”

The completed application forms for the above Orations / Lectureships should reach to Dr. Mangesh Tiwaskar, Hon. General Secretary of API, Unit No. 6 & 7, Turf Estate, Opp. Shakti Mill Compound, Off. Dr. E. Moses Road, Near Mahalaxmi Station West, Mumbai – 400 011 not later than 15th December 2019.

Dr. Mangesh Tiwaskar  
Hon. General Secretary
A Prospective Study of Thyroid Function Test in Geriatric Population and its Clinical Correlation

Natasha1, Raju Badiger1*

Abstract

Background and Objectives: Thyroid disorders in elderly population are of prime importance as it has emphasis on various metabolic activity and disease states. There is limited data regarding the prevalence of thyroid disorders in elderly from India. This study was an attempt to assess the thyroid function tests in elderly population and to correlate them with clinical symptoms.

Methodology: This one year hospital based prospective cross sectional study was done in outpatient Department, Department of General Medicine and Geriatric Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi on a total of 100 elderly patients who presented for regular checkups with clinical suspicion of thyroid disorders from January 2017 to December 2017. The selected patients were investigated for T3, T4, TSH and thyroid antibodies.

Results: Majority of the patients were females (67%), the male to female ratio was 1:2.03. The mean age was 67.69±7.21 years. The mean T3 levels were 1.32±0.88 ng/mL, the mean T4 levels were 7.69±4.13 µg/mL and mean TSH levels were 12.31±22.82 mcIU/mL. The mean TPO antibodies were noted as 95.97±211.82 IU/mL. Thyroid abnormalities were diagnosed in 28% of the patients. No association was found between thyroid abnormalities and sex (p=0.349) as well as age (p=0.946). Easy fatiguability (94%) and generalized weakness (93%) were the common clinical complaints and mild pallor was the common clinical sign noted in 26% of the patients followed by dry/coarse skin in 25% of the patients. Thyroid abnormalities were significantly associated with easy fatiguability, generalized weakness, swelling of limb/face, weight gain, constipation and with clinical signs of pallor, dry/coarse skin, hoarseness, ankle jerk and oedema. Family history of thyroid disorders was reported by 47% of the patients and it was significantly associated with of thyroid disorders (p=0.001).

Conclusion and Interpretation: There is higher incidence of thyroid abnormalities among elderly population in the study area and overt hypothyroidism is the common thyroid abnormality.

Introduction

Thyroid gland is unique among endocrine organs in the body and the first to develop in fetal life. Even after 100 years, thyroid gland has been the subject of intense research and considerable attention due to the vast array of developmental, inflammatory, hyperplastic and neoplastic disorders which are exceedingly common in clinical practice.1 However, aging changes occur in all body systems due to the decreased amount of hormones secreted or the decreased sensitivity of target organs.2 Thyroid disease is frequent in older individuals, and symptoms of hypothyroidism such as tiredness, fatigue, lack of concentration, or dry skin can be very similar to complaints associated to aging.3,4 Even for hyperthyroidism, clinical presentation in elderly people is much more silent when compared to middle-aged people.5

All over the world the elderly population is growing continuously. Ageing leads to number of medical problems, which could be attributed to various physiological changes occurring in all organs of the body.6,7 There has been long standing controversy about the thyroid function test results in the elderly.8 The levels of TSH, free T4 and free T3 hormone concentrations change with aging.9 Also, thyroid disorders increase morbidity and mortality in elders, so dictation of thyroid disorders in elderly become very important. Several thyroid function abnormalities are observed in the elderly.10 Hence, health care professionals should have awareness about the thyroid profile changes that distinguish older from younger patients. Epidemiologic studies have shown a remarkable increase in the incidence and prevalence of thyroid disorders in older populations.11

Furthermore, Subclinical hyperthyroidism appears to be a significant risk factor for all cause and cardiovascular mortality in subject aged from 55 to 60 years to the oldest old. Subclinical hypothyroidism might be also associated with increased mortality in middle-aged and young elderly.4 Considering these facts the present study was planned to assess the thyroid function tests in elderly population and to correlate clinical symptoms with abnormal thyroid function.

Methodology

This one year hospital based cross sectional study was undertaken in the Department of General Medicine and Geriatric Medicine, of a tertiary care teaching hospital situated in north Karnataka, India from January 2017 to December 2017. A total of 100 elderly patients (aged > 60 year) of either sex with clinical suspicion of thyroid disorders were enrolled. Critically
ill patients, patients with established thyroid disorders, on treatment with thyroid supplements and drugs known to alter the thyroid functions, who have undergone thyroid surgery and taken radioactive iodine therapy, on iodine deficiency, on iodine deficiency were excluded from the study. The ethical clearance was obtained from Jawaharlal Nehru Medical College, Belgaum prior to the commencement.

**Procedure**

Patients who were eligible were briefed about the nature of the study and a written informed consent was obtained. Patients were interviewed and demographic data like gender and age were noted. Patients were also briefed about the nature of the study and a written informed consent was obtained. Patients were interviewed and demographic data like gender and age were noted. Patients were also interviewed for the detailed history of associated medical conditions, surgical history if any, ongoing medical treatment if any, family history, diet pattern and personal history. A thorough general physical examination was conducted to assess vital parameters, anthropometry and clinical signs followed by systemic examination. All these findings were recorded on a predesigned and pretested proforma. The selected patients were subjected for the evaluation of thyroid function tests.

**Statistical analysis**

The data thus obtained was tabulated on Microsoft Excel spreadsheet. The categorical data was expressed as ratios and percentages. Chi-square test was used to find the association between thyroid abnormalities and clinical presentation. Continuous data was expressed as mean ± standard deviation (SD) and independent sample t test was used to compare the means. At 95% confidence interval (CI), a probability value ('p' value) of less than or equal to 0.050 was considered to be statistically significant.

**Results**

In the present study majority of the patients were females (67%) and 33% of the patients were males. The male to female ratio was 1:2.03. Most of the patients were aged between 60 to 65 years (56%).

Easy fatiguability (94%) and generalized weakness (93%) were the common clinical complaints. Mild pallor was the common clinical sign noted in 26% of the patients followed by dry/coarse skin in 25% of the patients. Further, 18% of the patients reported history of clinical complaints suggestive thyroid abnormalities in the past and most of them had treatment with multivitamins (38.89%). History of other associated medical conditions was present in 54% of the patients and hypertension was the most common comorbid condition (33.33%) followed by diabetes mellitus (22.22%).

The thyroid abnormalities were diagnosed in 28% of the patients and hypothyroidism was the most common thyroid abnormality noted in 12% of the patients while subclinical hypothyroidism was diagnosed in 10% of the patients. However, 4% and 2% of the patients were diagnosed to have subclinical hyperthyroidism and hyperthyroidism respectively. The mean T3, T4, TSH and TPO antibodies were statistically comparable among

### Table 1: Factors associated with thyroid abnormalities

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Findings</th>
<th>Thyroid abnormalities</th>
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<td></td>
<td>Present (n=28)</td>
<td>Absent (n=72)</td>
<td></td>
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</tr>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>21.21</td>
<td>26</td>
<td>78.79</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>31.34</td>
<td>46</td>
<td>68.66</td>
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<tr>
<td><strong>Easy fatiguability</strong></td>
<td>Present</td>
<td>23</td>
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</tr>
<tr>
<td></td>
<td>Absent</td>
<td>5</td>
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<tr>
<td><strong>Generalised weakness</strong></td>
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<td>22</td>
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<td>71</td>
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<tr>
<td></td>
<td>Absent</td>
<td>6</td>
<td>85.71</td>
<td>1</td>
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<tr>
<td><strong>Lethargy/Disinterest in daily activities</strong></td>
<td>Present</td>
<td>15</td>
<td>25</td>
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<tr>
<td></td>
<td>Absent</td>
<td>13</td>
<td>32.5</td>
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<tr>
<td><strong>Anorexia</strong></td>
<td>Present</td>
<td>12</td>
<td>31.58</td>
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</tr>
<tr>
<td></td>
<td>Absent</td>
<td>16</td>
<td>28.51</td>
<td>46</td>
</tr>
<tr>
<td><strong>Swelling of limb/face</strong></td>
<td>Present</td>
<td>13</td>
<td>68.42</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>15</td>
<td>18.52</td>
<td>66</td>
</tr>
<tr>
<td><strong>Weight gain</strong></td>
<td>Present</td>
<td>12</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>16</td>
<td>20</td>
<td>64</td>
</tr>
<tr>
<td><strong>Constipation</strong></td>
<td>Present</td>
<td>10</td>
<td>50</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>18</td>
<td>22.5</td>
<td>62</td>
</tr>
<tr>
<td><strong>Heat intolerance</strong></td>
<td>Present</td>
<td>2</td>
<td>18.18</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>26</td>
<td>29.21</td>
<td>63</td>
</tr>
<tr>
<td><strong>Sweating</strong></td>
<td>Present</td>
<td>3</td>
<td>21.43</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>25</td>
<td>29.07</td>
<td>61</td>
</tr>
<tr>
<td><strong>Palpitations</strong></td>
<td>Present</td>
<td>4</td>
<td>30.77</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>24</td>
<td>27.59</td>
<td>63</td>
</tr>
<tr>
<td><strong>Weight loss</strong></td>
<td>Present</td>
<td>2</td>
<td>15.38</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>26</td>
<td>29.89</td>
<td>61</td>
</tr>
<tr>
<td><strong>Increased appetite</strong></td>
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<td>4</td>
<td>28.57</td>
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</tr>
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<td></td>
<td>Absent</td>
<td>24</td>
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<tr>
<td><strong>Diarrhoea</strong></td>
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<td>0</td>
<td>1</td>
</tr>
<tr>
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<td>28</td>
<td>28.28</td>
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<tr>
<td><strong>Tremors</strong></td>
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<td>30.95</td>
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<tr>
<td><strong>Pallor</strong></td>
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<td>Absent</td>
<td>25</td>
<td>35.21</td>
<td>46</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>Present</td>
<td>6</td>
<td>66.67</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
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<td>24.19</td>
<td>69</td>
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<tr>
<td><strong>Dry/coarse skin</strong></td>
<td>Present</td>
<td>14</td>
<td>56</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>14</td>
<td>18.67</td>
<td>61</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>Present</td>
<td>4</td>
<td>66.67</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>22</td>
<td>23.08</td>
<td>70</td>
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<tr>
<td><strong>Oedema</strong></td>
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<td>7</td>
<td>77.78</td>
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<td></td>
<td>Absent</td>
<td>21</td>
<td>23.08</td>
<td>70</td>
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<tr>
<td><strong>Hoarseness</strong></td>
<td>Present</td>
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<td>10.13</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>28</td>
<td>28.28</td>
<td>72</td>
</tr>
</tbody>
</table>

The data was statistically compared among...
The incidence of thyroid abnormalities steadily increases with advancing age, predominantly due to a rising incidence of autoimmune thyroiditis. The frequency of thyroid abnormality noted in the present study (28%) was very high and it was in agreement with a recent study by Madhuvan HS et al. who found that 25% patients have thyroid disorders. The frequency of thyroid abnormality noted in the present study was low compared to a study by Laxminarayan GR et al. (2016) from Northern Kerala (15.99%), Cappola AR et al. (2006) (18.33%) and Iglesias, P. et al. (2009) (13.4%).

Western studies show a lower incidence compared to Indian series. Also a study from North Kerala also showed lower incidence. The peak frequency of thyroid disorders was observed in the present study compared to other studies may be due to the selection bias and varied sample size of the study population in other studies.

In the present study among the thyroid abnormalities, overt hypothyroidism was the common abnormality (12%) in the study area among elderly patients which was in agreement to the recent study by Madhuvan HS et al. who also noted overt hypothyroidism as common thyroid abnormality in 1% of the patients. Another study by Laxminarayan GR et al. also reported that, overt hypothyroidism as most common abnormality but with relatively lower frequency (5.81%). However, Iglesias, P. et al. (2009) reported lower rate of hypothyroidism (3.1%).

In the present study females (67%) outnumbered males (33%) with male to female ratio of 1:2.03. These findings suggest that the females are at high risk of thyroid disorders and the frequency of thyroid abnormalities is double in females as compared to males. Further out of 28 patients with thyroid abnormalities, higher frequency of thyroid abnormalities was noted in females (31.34%) compared to males (21.21%). Though these findings hypothesize four fold occurrence of thyroid abnormalities among females but the difference observed was statistically not significant (p=0.289). Hence the thyroid abnormalities are common in elderly irrespective of gender. Madhuvan HS et al. report was consistent with the present study. Madhuvan HS et al. also noted a higher prevalence of thyroid dysfunction in females. Similar observations were noted in a recent study by Laxminarayan GR et al. which can be explained by the autoimmune nature of the disease.

The present study was comprised of patients who belonged to seventh decade in life. But again the association was not significant between age and thyroid abnormalities (p=0.946). These findings suggest that thyroid abnormalities are common in geriatric population irrespective of age range. Madhuvan HS et al and Laxminarayana GR et al. noted that as the age advances the incidence of thyroid dysfunction increases (p value significant) findings consistent with the present study.

As noted in the presents study, easy fatigability and generalised weakness were the most predominant features noted in a study by Madhuvan HS et al. They also reported that, hyperthyroidism presented with features of weakness, fatigability, heat intolerance, increased sweating, although diarrhea was not seen in any patients. Though, the strong association observed between the clinical features cited above with thyroid abnormalities was the strength of the present study but prompts cautious interpretation due to several limitations. Earlier, Bemben et al. (1994) reported that there were no significant differences (P > 0.05) in the frequencies of any of the clinical sign and symptoms of hypothyroidism between euthyroidism and hypothyroid patients. They concluded that thyroid status could not be predicted from clinical sign and symptoms in the elderly community dwelling patients.

In the present study most of the patients (41%) had body mass index between 25 to 29.99 Kg/m². These findings suggest that, most of the patients in the present study were overweight. However, no association was found between thyroid abnormalities and body mass index. These finding propose lack of association between thyroid abnormalities and obesity. In contrast to these observations a recent study by Kumar H. et al. reported positive association between TSH and body mass index that is, 50% cases of high level of TSH patients had >30 BMI. Due to the methodological differences the findings of the present study could not be compared with the study by Kumar H. et al.

Overall in the nutshell, the present study showed that, there is higher incidence of thyroid abnormalities among elderly population in the study area with overt hypothyroidism being the common abnormality. Furthermore, thyroid abnormalities are common among females and in those who present during seventh decade of life. Furthermore, family history of thyroid disorders is also strongly associated with thyroid abnormalities in elderly. However these finding require further validation due to the potential limitations of the study that
Efficacy and Safety of Canagliflozin in Patients with Type II Diabetes Mellitus Inadequately Controlled on Triple Drug Therapy

Deepak Bhosle1*, Zubair Quazi2, Snehal Chavan2, Huzaif Shaikh2

Abstract

Objective: Canagliflozin, a sodium glucose co-transporter 2 (SGLT2) inhibitor, has been associated with HbA1c reduction and weight loss in a broad range of patients with type 2 diabetes mellitus (T2DM). This analysis evaluated changes in HbA1c and body weight in patients who were inadequately responding to maximum dose of three oral hypoglycemic agents and reluctant to take insulin therapy.

Methods: In this open label intervention single arm study, patients aged 18 to 65 years (N=118) received Canagliflozin 100 mg for in addition to an ongoing triple drug oral hypoglycemic agents (OHA) regimen for a period of 12 weeks. The said population was inadequately responding to maximum dose of three oral hypoglycemic agents and was reluctant to take insulin therapy. Percent change from baseline in HbA1c and body weight was evaluated in the study.

Results: Canagliflozin 100 mg additional dose above a triple OHA provided significant HbA1c reduction by 1.9% and weight reduction by 3.01 kg over 12 weeks from baseline. Canagliflozin was generally well tolerated with 2.54% of the patient population reporting Urinary tract infection (UTI) who were withdrawn from study and given appropriate treatment.

Conclusions: Canagliflozin 100 mg (One tablet) administered to patients in addition to the inadequately controlled triple drug OHAs who were reluctant for an insulin therapy provided a significant reduction in HbA1c and body weight over 12 weeks. Canagliflozin a SGLT 2 inhibitor is a promising new drug in patients with T2DM in patients who are inadequately controlled on triple therapy and are reluctant to insulin therapy. A result of defective insulin secretion and is frequently associated with obesity-related insulin resistance. Glucose-lowering agents are regularly implemented to manage hyperglycemia when lifestyle modifications (eg, diet and exercise) are insufficient. The disease progression leads to treatment intensification with combination therapy, and ultimately insulin therapy is often initiated which again may be inadequate in managing hyperglycaemia in some patients. Some oral hypoglycaemic agents (OHAs) are associated with weight gain (e.g. sulfonylurea, insulin, thiazolidinediones, glinides), which can make it difficult for patients with T2DM to achieve and maintain weight loss.

Canagliflozin is a novel oral antidiabetic agent belonging to the class of sodium–glucose co-transporter 2 (SGLT2) inhibitors provides glycemic control along with clinically meaningful weight loss, in a broad range of patients with T2DM who were on various

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic disease that develops as

References

At 12 weeks and BMI > 25 kg/m². Newly diagnosed inadequate response, HbA1c > 8.5% on maximum dose of three OHA with patients of either sex (male or female) test. Inclusion criteria was T2DM HbA1c, body weight and renal function were screened at first visit for fasting patients fulfilling eligibility criteria Type 2 Diabetes Mellitus (T2DM). controlled on triple drug therapy for years (N=118) who were inadequately study done at Deogiri Diabetes Centre, single arm, interventional, clinical end point was change in HbA1c (%) from baseline up to 12 weeks. Safety assessment was performed by general and systemic examination and as per ADR reported by patients.

**Materials and Methods**

**Study Design**

A 12 weeks, open label, single centre, single arm, intervention clinical study done at Deogiri Diabetes Centre, Aurangabad, patients aged 18 to 65 years (N=118) who were inadequately controlled on triple drug therapy for Type 2 Diabetes Mellitus (T2DM). Patients fulfilling eligibility criteria were screened at first visit for fasting blood sugar, post prandial glucose, HbA1c, body weight and renal function test. Inclusion criteria was T2DM patients of either sex (male or female) on maximum dose of three OHA with inadequate response, HbA1c > 8.5% and BMI > 25 kg/m². Newly diagnosed T2DM patients, type 1 diabetes mellitus, gestational diabetes, patients with eGFR value less than 45 ml/min/1.73 m² calculated by MDRD formula, patients on insulin therapy, patients with recurrent UTI and patients with history of diabetic ketoacidosis or other co-morbid cardiac, hepatic and renal diseases were excluded.

Canagliflozin 100 mg (1 tablet) once daily was administered as an add-on therapy to triple drug treatment to be taken in morning with ample amount of water at the initial visit of the study. Fasting blood sugar and post prandial sugar measurements with safety assessment was performed during the intermediate visit at 6 weeks. At 12 weeks, the end of the study patients were assessed for fasting and post prandial blood glucose levels, HbA1c, body weight, and renal function test.

Primary end point was change in HbA1c (%) from baseline up to 12 weeks. Secondary end point was change in body weight from baseline up to 12 weeks. Safety assessment was performed by general and systemic examination and as per ADR reported by patients.

**Statistics**

The study was performed on 118 patients of which 76 were male and 42 were female. Data was collected at the baseline and at 12 weeks for HbA1c value and Body weight. Paired t test was applied to this data and result was derived by using SPSS v.22.

**Result**

Among 118 patients recruited, 114 patients completed the study (96.61%), 3 were withdrawn due to ADR (2.54%) and there was 1 drop out (0.8%). After 12 weeks of study, 1.9% reduction in HbA1c was observed from baseline (Figure 1) and 3.01 kg reduction in body weight was recorded (Figure 2). P value= 0.001. 3 out of 118 patients (2.54%) reported UTI and were withdrawn from study. All the three patients were female and treatment for UTI was provided as required.

**Discussion**

In healthy individuals, about 180g of glucose is filtered and reabsorbed daily through the kidneys and maximal transport rate (Tmax) is 300mg/min. This rate is about 20% higher i.e. 352 mg/min (19.5mmol/l/min) to 419mg/min (23.3mmol/l/min) in patients with poorly controlled T2DM. This pertains to the increased expression of SGLT2s in persons with diabetes which represents a physiological response to increased glucose delivery to the nephrons that is ultimately maladaptive. Antagonizing these transporters with SGLT2 inhibitors is an insulin-independent mechanism that offers a considerable advantage of increasing urinary glucose excretion without inducing hypoglycaemia and promoting weight loss due to loss of 300–400 kcal/day.

Canagliflozin is the first SGLT2 inhibitor approved for reducing the risk of 3 point MACE in patients of type II diabetes with established cardiovascular diseases on basis of the CANVAS trial. The CANVAS program, was composed of 2 double-blind, randomized, placebo-controlled trials, Canagliflozin Cardiovascular Assessment Study (CANVAS) and CANVAS-R, analyzed jointly to address CV safety and renal outcomes. It involved 10,142 patients with T2DM and high CV risk with a median follow-up time of 126.1 weeks. Significantly fewer participants in the canagliflozin group than in the placebo group had a primary outcome event (the composite of death from CV causes, nonfatal myocardial infarction (MI), or nonfatal stroke). The results also showed that patients treated with Canagliflozin had a lower risk of hospitalization for heart failure, progression of albuminuria, and substantive loss of kidney function than patients who received placebo.

Based on the positive CV outcome of the CANVAS Program in September 2018 European Commission, granted approval to update the canagliflozin labelling to include data on the reduction in MACE events in patients with T2DM who had either a history of CV disease or at least two CV risk factors. Also, Canada health and USFDA have approved the label update and indication update respectively which includes reduction in MACE in patients with established CV event. According Canagliflozin becomes the only Oral anti-glycemic agent to receive a approval for 3 point MACE reduction and as well as in both Primary prevention and secondary prevention cohort.

In this study, at week 12, Canagliflozin 100 mg provided significant reductions in HbA1c from baseline (p<0.001). Differences in mean changes in HbA1c were −1.94 with Canagliflozin 100 mg given additionally with three drug combination therapy (Table 1).
Subgroup analyses based on baseline HbA1c showed that HbA1c reductions with Canagliflozin were greater in the higher baseline HbA1c group; however, sizeable reductions were also seen in with the lowest baseline HbA1c.

In study done by Stenlof et al14 a 26-week, randomized, double-blind, placebo-controlled, phase 3 trial, subjects (N=584) received canagliflozin 100 or 300 mg or placebo once daily. At week 26, HbA1c was significantly reduced from baseline with canagliflozin 100 and 300 mg compared with placebo (−0.77,−1.03 and −0.94%, respectively; p<0.001 for both).

Significant dose-related reductions from baseline in body weight were observed at week 12 (p<0.001) with canagliflozin 100mg. Canagliflozin 100 mg provided LS mean changes of −3.01 kg from baseline. Weight loss with canagliflozin 100mg occurred rapidly through week 6; a progressive decrease in weight loss over the remaining treatment period was seen.

In study done by J.P.H. Wilding et.al.15 on 469 Patients (N = 469) received canagliflozin 100 or 300 mg or placebo once daily during a 26-week core period and a 26-week extension. At week 26, canagliflozin 100 and 300 mg significantly reduced body weight from baseline compared with placebo, with LS mean percent changes relative to placebo of −1.4% (−1.1 kg) and −2.0% (−1.7 kg), respectively (p < 0.001 for both canagliflozin doses); Reductions in body weight with canagliflozin 100 and 300 mg compared with placebo were sustained over 12 weeks of treatment with differences in LS mean percent changes (95% CI) vs. placebo of −1.3% (−2.1, −0.5) and −2.2% (−3.0, −1.4) for canagliflozin 100 and 300 mg, respectively, at week 52. Weight loss occurred most rapidly with both canagliflozin doses through week 12, with a continued gradual decrease through week 52 with canagliflozin 300 mg and minimal further reduction observed with canagliflozin 100 mg.

In this study done on 118 patients of T2DM inadequately controlled on triple drug therapy, we observed that Canagliflozin 100 mg reduces HbA1c by 1.9% and body weight by 3.01 kg in 12 weeks. Three patients suffered ADR of urinary tract infection and were withdrawn from study. 114 patients tolerated Canagliflozin 100 mg once daily well. This is the only study done by adding Canagliflozin to triple drug therapy till now, but our results correlate with studies done on T2DM patients who were administered Canagliflozin 100 mg or 300 mg as monotherapy, or other regimens like with metformin, other two OHA and insulin.

In conclusion, Canagliflozin 100 mg (one tablet) administered to patients in addition to the inadequately controlled triple drug OHAs who were reluctant for an insulin therapy provided a significant reduction in HbA1c and body weight over 12 weeks. Canagliflozin a SGLT 2 inhibitor is a promising new drug in patients with T2DM in patients who are inadequately controlled on triple therapy and are reluctant to insulin therapy.

References

Factors Differentiating Acute Hepatitis B from Acute Exacerbation of Chronic Hepatitis B in Prospective-retrospective Cohort

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Abstract
Introduction and Aim: It is difficult to distinguish acute hepatitis B (AVH-B) from chronic hepatitis B with an acute exacerbation (CHB-AE) in patients whose prior history of HBV infection is unknown. The present study aimed to screen laboratory parameters at presentation to discriminate between these two conditions.

Materials and Methods: A prospective study was conducted in patients presenting clinically as AVH-B without known previous chronic hepatitis B status. Patients were divided into AVH-B and CHB-AE at end of six months follow up. Clinical and laboratory profiles were compared between these two groups at presentation.

Results: There was no significant difference in clinical presentation and risk factors profile in patients of both the groups. Mean age of presentation in AVH-B was 31.8 ± 14.9 years while, 47.2 ±17.3 years in CHB-AE group (p=0.005). Mean IgM anti-HBc levels were higher in AVH-B than in the CHB-AE group (p=0.001). Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of IgM anti-HBc [>12.14 S/CO (Sample/Cut-off)] for diagnosis of AVH-B was 76.9%, 71.4%, 76.9% and 71.4 % respectively. Quantitative HBV DNA levels were significantly higher in CHB-AE than in AVH-B group (p=0.015). Sensitivity, specificity, PPV and NPV of HBV DNA ( > 15390 IU/ml) for diagnosis of CHB-AE was 78.6%, 46.2%, 44% and 80% respectively

Conclusions: A high percentage of patients with apparent AVH-B might be cases of CHB-AE. Elderly patient (mean 47.2 years), high titers of HBV DNA (>15390 IU/mL) and low IgM anti-HBc titer (<12.14 S/CO) favours CHB-AE over AVH-B.

Introduction
Hepatitis B virus (HBV) infection is a global health problem. Cirrhosis and/or hepatocellular carcinoma (HCC) are found in 25%-40% of patients with chronic hepatitis B (CHB) infection.1,2 Natural history of HBV infection is a dynamic state of interactions between HBV, hepatocytes, and immunity of the host.

Acute viral hepatitis B (AVH-B) resolves completely in 90–95% of the adult patients. Persistence of hepatitis B surface antigen (HBsAg) beyond 6 months is considered as chronic hepatitis which develops in about 1-5% of the adult patients who had presented with AVH-B.3,4 Chronic hepatitis B with exacerbation (CHB-AE) is defined as “Abrupt elevation of serum ALT to >5 ULN (Upper limit of normal) or a greater than 3-fold increase in baseline ALT, whichever is higher” in known hepatitis B carrier.5,6 Acute exacerbations are due to spontaneous viral activation (immune clearance) in 50-90 % patients, the remaining being due to super-infection by non-B hepatitis virus.7,8 Reactivation following immunosuppression is characterized by the initial phase of enhanced viral replication during the immune suppression followed by immune-mediated destruction of HBV infected hepatocytes, resulting in hepatitis when immunosuppression is withdrawn.9,10 In 40–50% of hepatitis B e antigen (HBeAg) positive patients, CHB-AE can occur during the immune-clearance phase; it can be repeated when there is an unsuccessful clearance of HBeAg.11 In HBeAg-negative patients, reactivation occurs in 15–30% cases and is occasionally associated with HBeAg seroreversion.12

Endemicity for chronic hepatitis B is defined as, high (>8%), intermediate (2-7%) and low (<2%) according to the percentage of population positive for HBsAg.13 In countries with intermediate and high endemicity, the possibility of exacerbation of chronic HBV infection is high. It may be the first presentation of chronic hepatitis B or compensated cirrhosis, which was asymptomatic before exacerbation. Hence, a possibility exists that a proportion of patients with suspected AVH-B might actually be suffering from CHB-AE. At the first presentation, it is difficult to differentiate between these two conditions especially when the chronic hepatitis status is not known.

This study was undertaken to assess the clinical, biochemical, and virological characteristics of patients presenting clinically as AVH-B and to find features that could differentiate them from patients having the first episode of symptomatic CHB-AE.

Materials and Methods
Study design
This was a prospective-retrospective...
An observational study of patients presenting with features of AVH-B admitted at a tertiary health care centre in the gastroenterology department during August 2016 till July 2018. The study was approved by the institutional ethics committee.

**Patient selection**

Patients presenting clinically with acute viral hepatitis with HBsAg positive status were assessed for eligibility. Data was collected on a predesigned proforma. History of previous episodes of jaundice, known chronic hepatitis B, contact with chronic HBV infected patient, blood transfusion, surgery, dental procedures, tattooing, high-risk sexual behavior, and intravenous drug abuse were noted. Information was obtained regarding the onset of symptoms, altered sleep pattern, and the presence of ascites. Detailed physical examination was performed and the presence of pallor, icterus, pedal edema, hepatomegaly, splenomegaly, ascites, and flaps was noted. All routine investigations were performed like complete blood count, renal function tests and serum electrolytes. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, direct bilirubin, total protein, albumin, prothrombin time and an international normalized ratio (INR) were done in all patients.

Serological tests for HBV like HBsAg, hepatitis B e-antigen (HBeAg), quantitative hepatitis B virus DNA (HBV DNA), and hepatitis B core antibody titers (IgM anti-HBc) were requested in all cases. Blood samples for antibodies to hepatitis A virus (IgM anti-HAV), hepatitis E virus (IgM anti-HEV), and hepatitis C virus antibody (Anti-HCV) were also collected. Serological tests were done using the enzyme-linked immunosorbent assay (ELISA) technique. Serum IgM anti-HBc was done using the fully automated chemiluminescent microparticle immunoassay, measured as a sample to the cut-off ratio (S/CO). Serum HBV DNA was done using the real-time polymerase chain reaction (PCR). All the patients underwent an abdominal ultrasound examination performed by a single observer with Xario 100, platinum series, Canon medical system USA. Esophagogastroduodenoscopy (EGD) was done with (GIF Q150 Olympus, Japan) in all patients.

**Inclusion criteria**

Patients with clinical features of acute viral hepatitis and HBsAg positive status, presenting within four weeks of the onset of symptoms and completing at least 6-months of follow-up were included in the present analysis. All the patients included were above 18 years of age.

**Exclusion criteria**

Patients with antibodies against hepatitis A, C or E virus, superimposed alcoholic liver disease, clinical, radiologic or endoscopic evidence of chronic liver disease at presentation were excluded from the study. HIV patients and pregnant females were also excluded from the study.

**Follow-up**

Patients were followed up after the initial diagnosis of acute hepatitis for at least 6 months. Data were obtained suggesting the clearance or persistence of HBsAg and development of clinical, radiologic and endoscopic evidence of chronic liver disease. At 6 months follow-up, all the patients underwent ultrasound abdomen and fibroscan (Fibroscan, echosens Abbott India Limited) and EGD scopy.

**Study groups**

The diagnosis of acute hepatitis B was made on the basis of clinical features, compatible liver function tests and exclusion of other causes of jaundice. Patients were divided into 2 groups. Group 1 included patients, who on follow-up lost HBsAg antigen and did not develop evidence of chronic liver disease on ultrasound abdomen, fibroscan or EGD scopy. These patients were considered as AVH-B. Group 2 patients included those who on follow-up remained HBsAg-positive for at least 6 months and developed clinical, biochemical, radiologic, or endoscopic evidence of chronic liver disease. These patients were considered to be having CHB-AE. Laboratory parameters at the time of first presentation analysed retrospectively between these two groups. Out of the 53 patients presenting as acute icteric viral hepatitis B, 40 fulfilled the inclusion criteria. Thirteen patients were excluded from the study: 3 had
Out of 53 patients, 13 were excluded from the study because they failed to fulfill the inclusion criteria (Figure 1). Out of the 40 patients available for final analysis who underwent investigations at 6 months, 25 (62.5%) patients had negative HBsAg, 1 (2.5%) patient had positive HBsAg with a normal abdominal ultrasound examination, normal EGD scope and normal fibroscan were defined as AVH-B patients. Fourteen (35%) patients had positive HBsAg and abnormal abdominal ultrasound and/or EGD scope and/or fibroscan were defined as CHB-AE. Laboratory parameters at the time of first presentation analysed retrospectively between these two groups.

Demographic characteristics

Mean age of presentation in AVH-B group was 31.8 ± 14.9 years and 47.2 ±17.3 years in CHB-AE group. Age of presentation was significantly higher in the CHB-AE group (p=0.005). Male to female ratio was 1:1.1 in AVH-B and CHB-AE group respectively. Baseline clinical features and risk factor profile for acquiring hepatitis B infection were comparable in both study groups (Table 1).

Biochemical parameters at the time of admission

Among the biochemical parameters at the time of admission, platelet count, AST, ALT, total bilirubin, direct bilirubin, and INR were not significantly different in both groups. Mean serum albumin levels in AVH-B (3.63 ±0.44 gm/dl) was significantly higher than CHB-AE (3.01 ± 0.5 gm/dl) group (p=0.001) (Table 2).

Virus serology at the time of admission

Four (15.3%) out of 26 patients of the AVH-B group and 3 (21.4%) out of 14 in CHB-AE group were HBeAg positive. HBeAg positivity was not statistically different between the two groups (p=0.65).

Mean IgM anti-Hbc levels in the AVH-B group was 21.4 ± 10.78 whereas 10.48 ± 4.75 in the CHB-AE group (Figure 2). IgM anti-Hbc levels were significantly higher in the AVH-B group (p-0.001) as compared to CHB-AE. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of IgM anti-Hbc (>12.14 S/CO) for diagnosis of AVH-B was 76.9%, 71.4%, 76.9%, and 71.4 % respectively. Receiver operating characteristics curve (ROC) of IgM anti-Hbc is shown in (Figure 3). The area under the curve was 0.82.

Mean quantitative HBV DNA levels were 119723.69 ± 212067.18 in the AVH-B group, while 1200572.14 ± 2158872.79 in the CHB-AE group (Figure 4). Quantitative HBV DNA levels were significantly higher in the CHB-AE group than in the AVH-B group (p-0.015). Sensitivity, specificity, PPV and NPV of HBV DNA (cut-off > 15390 IU/ml) for diagnosis of AVH-B was 76.8%, 71.4%, 76.8%, and 71.4 % respectively. ROC of HBV DNA is shown in (Figure 5).

EGD, Ultrasound abdomen and Fibroscan at 6 months

Ultrasound abdomen at 6 months was normal in all patients of the AVH-B group. Six (42.8%) out of the 14 patients in the CHB-AE group showed signs of chronic liver disease on ultrasound examination. (Four (28.5%) patients had coarse echotexture and dilated portal vein > 13 mm and 2 (14.3 %) had coarse echotexture and mild ascites (p=0.008)). EGD scope was normal in
all 26 patients of the AVH-B group with no evidence of esophageal varices while four (28.5%) out of 14 patients in the CHB-AE group had esophageal varices (p=0.04). On fibroscan examination, mean of median stiffness of liver in the AVH-B group was 5.5 ± 1.1 Kpa, while in CHB-AE group it was 8.8Kpa ± 2.6 (p=0.0003).

Discussion

Differentiation between AVH-B and CHB-AE has always been a task for the hepatologists.

Management in these two conditions differs considerably. Acute hepatitis B is usually a spontaneously recovering disease and does not require antiviral treatment except patients with ‘severe acute hepatitis B’ who have a protracted severe disease characterized by bilirubin >5 mg/dl plus INR >1.5, for >4 weeks or acute liver failure (ALF). However, antiviral treatment is required for CHB-AE which can present as hepatitis, ALF, decompensated liver disease or acute on chronic liver failure (ACLF).17

In high prevalent areas for chronic HBV infection, the cases of CHB-AE might account for an appreciable percentage of cases presenting clinically as AVH-B. Kumar et al reported an occurrence of CHB-AE in 37.9% of all clinical acute presentations.8 Chu et al found 63% of CHB-AE actually presenting as acute hepatitis.19 In the present study, 35% of the patients presenting as apparent AVH-B, actually had CHB-AE.

Hepatitis B is a ‘stealth virus’, does not activate the innate immune system which recognizes pathogen-associated molecular patterns (PAMPs) and results in clearance of the pathogen.19 Instead of that adaptive immunity comes into play in the form of high levels of circulatory CD 8 cells which react with HBV antigens and eliminate the virus by destroying infected hepatocytes. Control of the infection during the incubation phase leads to a marked fall in virus load before the onset of clinically evident disease in humans who were identified before acute icteric hepatitis B. On the other hand, in patients with exacerbation, the on-going liver injury is due to the increased level of HBV DNA.20 Non-cytolytic processes could contribute to the elimination of the virus from the hepatocyte during acute infection of hepatitis B.21

Our study emphasizes the importance of HBV DNA in differentiating patients with AVH-B from CHB-AE. In the CHB-AE group, HBV DNA levels were high in 10 out of 14 (71.5%) patients with cut off of 15390 IU/mL. The sensitivity and specificity of HBV DNA levels (>15390 IU/mL) in the diagnosis of CHB-AE were 78.6% and 48.2% respectively. Higher levels of HBV DNA at admission predicted persistence of HBsAg antigen and development of chronic liver disease on follow-up. Close follow up and early introduction of potent antivirals could prevent the progression of liver disease in these patients. The study by Kumar et al showed high HBV DNA levels (> 0.5 pg/mL = 28751 IU/mL) had sensitivity and specificity of 86.6%, 95.9% respectively for diagnosis of CHB-AE.8 Han et al demonstrated HBV DNA (<105 copies/ml = 17857 IU/mL) had 75.4% sensitivity and 79.2% specificity for the diagnosis of AVH-B.22 Park et al showed HBV DNA <5.5 log10 IU/mL had a sensitivity of 81.1% and specificity of 72.4% for the diagnosis of AVH-B.23 Rising viral load in CHB-AE becomes detectable in the serum during spontaneous reactivation of chronic hepatitis B infection.24 Dao et al found a low or undetectable IgM anti-HBc level, with elevated HBV DNA to >5 log10 IU/mL, in a patient with ALF due to underlying chronic hepatitis B rather than acute infection.25

Our results demonstrated the importance of the titre of IgM anti-HBc. Around 76.9% of patients in the AVH-B group had high IgM anti-HBc titre (>12.14 S/CO). On the other hand, low IgM anti-HBc titre (<12.14 S/CO) was seen in the majority (71.4%) of the patients in the CHB-AE group. The study by Kumar et al have found an incidence of high IgM anti-HBc titre (>1:1000) in 77.5% patients of AVH-B and low IgM anti-HBc titre (<1:1000) in 70% patients of CHB-AE group [8]. Han et al reported an incidence of high IgM anti-HBc titre (>1:10,000) in 96.2% patients of AVH-B and low IgM anti-HBc titre in 76.9% patients with CHB-AE group.22 Park et al showed cut-off values for IgM anti-HBc as >8 S/CO which had sensitivity and specificity of 96.2% and 89.7% respectively for diagnosis of AVH-B.23 Importance of IgM anti-HBc in the diagnosis of acute hepatitis has been well reported by Papaevangelov et al in 1984.26

Serum alpha-fetoprotein (AFP) levels are usually raised in around 45-60% patients of CHB-AE. Peak elevation of AFP is usually seen after 1-2 weeks of elevation of serum aminotransferases and normalizes over 3-12 months. Han et al reported, lower cut off of serum AFP (< 5 times of normal) minimally improve the diagnostic accuracy of IgM anti-HBc for diagnosis of AVH-B.22,27

Liver biopsies during hepatitis B flares invariably show unevenly distributed lobular necro-inflammatory changes, occasionally it may be so

![Fig. 3: ROC curve of IgM Anti-HBc for diagnosis of AVH-B](image)

![Fig. 4: Difference between mean HBV DNA in both groups](image)

![Fig. 5: ROC curve of HBV DNA for diagnosis of CHB-AE](image)
extensive that bridging hepatic necrosis (BHN) might occur. Liaw et al showed that BHN is present in more than 80% of the patients with AFP >100 ng/ml during hepatitis B exacerbation.11

Age of presentation was a unique finding in our study, which has not been reported in the previous studies.3,12,23 Elderly age of presentation (mean 47.2 years) possibly represents CHB-AE presenting clinically as acute hepatitis (Mean age was 31.8 years in the AVH-B group).

Conclusion
A high percentage of patients with apparent AVH-B might be cases of CHB-AE in intermediate and high endemicity areas. Elderly age of presentation (mean 47.2 years), high titre of HBV DNA (>15390 IU/mL) and low IgM anti-HBe titre (<12.14 S/CO) favors CHB-AE over AVH-B. Exacerbation of chronic hepatitis in underlying cirrhotic patients always requires immediate antiviral therapy. Non-cirrhotic patients with decreasing HBV DNA trend may be followed for 3-6 months for real indication of antiviral therapy.6

Limitations of the study
Quantitative HBsAg (qHBsAg), Quantitative HBeAg (qHBeAg), Anti-HBeAg and serum AFP levels which were used in previous studies could not be done due to logistic problems. Liver biopsies were not performed in CHB-AE patients owing to ethical concerns. We recommend prospective studies and longer follow-up trials for better differentiation between AVH-B and CHB-AE.

References
17. Garg H, Sarin SK, Kumar M, Garg V, Sharma BC, Kumar Tenofovir improves the outcome in patients with spontaneous reactivation of hepatitis B presenting as acute-
Determinants of Expenditure on Diabetes Care: A Community Based Longitudinal Study in a Resettlement Colony of Delhi

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Abstract

Introduction: Diabetes is one of the expensive diseases due to its chronic nature and gradual involvement of multiple organs. Moreover loss of economic productivity further enhances the cost of care. Several factors were reported to have impact on overall economic burden in diabetic patients. So, the present study aims to determine influence of various socio-demographic and clinical factors on expenditure of diabetes care among patients residing in resettlement colony of East Delhi.

Methodology: A community based one year longitudinal study was conducted in Kalyanpuri area of East Delhi. All the diabetes patients aged 25 years and who were the permanent residents of Kalyanpuri, attending the Diabetic Clinic of a government hospital in November-December 2014 were selected for the study. A pre-tested semi-structured interview schedule was used as study tool. Each subject was followed up 3 monthly from January to December 2015.

Results: Data of 150 study subjects was analyzed. Out of 150 subjects 45(30 %) were male and 105 (70%) female. Overall mean age of study subjects was 53 ± 10 years Among socio-demographic factors, Expenditure on diabetes care showed significant association with male gender and among clinical factors, longer duration since diagnosis, use of Insulin with Oral Hypoglycemic drugs, hospitalization and utilization of private care has shown positive association with expenditure on diabetes care.

Conclusions: The present study concludes that there is need of better provisioning of services for diabetes care in government health facilities to cater needs of growing diabetic population..

Introduction

Diabetes is one of the major lifestyle diseases in the world. Globally around 382 million people at a prevalence of 8.3% suffered from diabetes recently and this number is expected to reach 592 million in less than 25 years.¹ In India too, the rising trend of diabetes is a big concern with more than 65.1 million people lived with diabetes in the year 2013 and will possibly reach 109 million by the year 2035.²

Diabetes is one of the expensive diseases in the world.³ It poses heavy economic burden on national economies and healthcare systems, especially in developing countries. Moreover the spending on diabetes by the countries is not evenly distributed as only 20% of global health expenditure on diabetes is made in low- and middle-income countries whereas 80 % of diabetic population live.³ Studies in India estimated that for a low income Indian family with an adult with diabetes, as much as 25% of family income may be devoted to diabetic care as compared to 10% in USA.⁴

Cost of care is high because diabetes is a chronic disease, needs lifelong care and if not controlled often leads to multi organ involvement with various complications. Loss of economic productivity is another important attribute that has made diabetes highly expensive disease. Several factors were reported to have impact on overall economic burden in diabetic patients. Studies showed that cost of diabetes are affected by various demographic and clinical factors like age, gender, duration of disease, presence of complication and occurrence of hospitalization.

There is scarcity of valid data in India to estimate per capita annual expenditure on diabetes care and its determinants. Moreover, the available studies rarely addressed the issues in the setting of developing countries. An analysis of the socio-demographic and clinical factors that affect expenditure on diabetes care will help better understand the increasing medical cost of diabetes and better planning and implementation of health services for diabetes patients, especially in developing countries like India. The present study is a part of larger study⁵ aims to determine influence of various socio-economic and clinical factors on expenditure of diabetes care among patients residing in resettlement colony of East Delhi.

Methodology

Study design and data collection

The study was done at Kalyanpuri, a resettlement colony of East Delhi in the year 2014-15. It was a community based longitudinal study. The study was carried out from November 2014 to December 2015. During first two months enlisting and enrolment of the study subjects were done from the records of Diabetic Clinic of a local Government Hospital. All the diabetes patients (consecutive sampling) aged more than 25 years and who were permanent resident of Kalyanpuri, attending the Diabetic Clinic in November-December 2014 were selected for the study. Patients of gestational diabetes and those who did not give consent for study were excluded. After obtaining

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the personal details of the patients from the diabetic clinic house visits were made for the selected subjects. Based on inclusion criteria, 153 subjects were enrolled. A semi structured interview schedule was used after doing adequate pretesting for collection of data. Data was collected by house to house visits to residence of diabetic patients. Each subject was followed up 3 monthly from January 2015-December 2015. In the first visit a small diary was provided to the subjects to record the relevant information in terms of cost of medicine, hospitalization, investigation etc associated to diabetes. The subjects were also told to keep record of all prescription and bills made during the study period. The details of expenditure on diabetes care incurred every quarterly by the subjects were recorded.

Data about Direct and indirect expenditure were collected. Direct expenditure included the cost of medicine, doctor's fees, investigation, inpatient care (in case of hospitalization) and treatment of complications like cataract operation, laser, dialysis etc). Cost of transportation and diet modification were also included in direct expenditure. Loss of wages for visiting the doctor, illness or premature loss of work was considered as indirect expenditure. Besides expenditure, information on various socio demographic factors like, age, gender, education, occupation, total monthly family income and socioeconomic status was collected. Clinical details of patients were also taken like type of disease, duration since diagnosis, place of care, number of visits, type of medications, presence of history of any hospitalization due to cause related to diabetes or its complications in preceding 3 months of each visit. Details of complications were collected from medical records and in some case self reported history was also taken.

**Statistical analysis**

SPSS version 16 was used for entering and analyzing the data. Mean, median and standard deviation were calculated for quantitative data. Proportions were calculated for qualitative data. Due to skewness of data, test of normality was used to see Gaussian pattern of data in different group and based on that parametric and non-parametric test applied where applicable. Unpaired t test, Mann whitney U test and Kruskal wallis test were used to compare mean expenditure among various socio-demographic and clinical factors and p value <0.05 has been considered statistically significant.

**Ethical approval**

Ethical approval was taken from ethical body of Lady Hardinge Medical college. Permission was granted from the Government Hospital for enrolment of diabetes patients. Written consent from literate and thumb impression from illiterate subjects were taken after informing them the purpose of study.

**Results**

Out of 153 subjects initially enrolled, 2 migrated and 1 died during the course of study. Hence 150 subjects were analysed at the end of study. Out of 150 subjects 45(30 %) were male and 105 (70%) female. More than half of study participant i.e.63.5% belonged to age group 45-65 years. Overall mean age of study subjects was 53 ± 10 years. The mean age for men was 53 ±11 years and for women 53 ± 9 years.

Almost half of study subjects i.e. 49.2% were illiterate. Illiteracy rate was more in female (64.8%) as compared to male (13.3%) (x² 40.28, p value <0.001). Maximum study subjects i.e. 73(48.7%) belonged to upper lower socio economic status followed by middle i.e. 71(47.3%) whereas 6(4 %) study subjects belonged to upper socioeconomic class. None of the subjects were from lower socioeconomic status.

In the study almost all subjects 149 (99.3%) were type 2 diabetes except one case of type 1 diabetes. So, data related to type 1 diabetes could not be analyzed separately.

The pattern of expenditure has already been explained in our previous work. Here we tried to find out the association of expenditure pattern with demographic and clinical profile of diabetics.

The mean annual expenditure was found significantly higher in male as compared to female (Rs. 11,815 vs Rs.7, 733) (p< 0.05). Other factors like age, education and socioeconomic status were not significantly associated with diabetes expenditure (Table 1).

There were significant positive association of mean annual expenditure with (longer) duration of diabetes (p value <0.013), receiving of both insulin and oral hypoglycemic drugs (OHA) (p value < 0.003), history of hospitalization during study period (p value<0.001) and utilizing private care facilities(<0.05) have been found in our study. Though annual expenditure was higher for diabetics with complications but results were not found statistically significant. (Details about co morbidities and complications has been put in another yet unpublished paper) (Table 2).

**Discussion and Recommendations**

There are very limited studies on assessment of diabetes expenditure and its determinants especially in India. Most of available studies are cross sectional which might not give exact pattern of annual expenditure and so, difficult to comment on determinants also. The present study is a sincere effort to overcome such limitation. Also all the patients were enrolled specifically from a tertiary care government hospital in a resettlement colony of East Delhi where majority are from lower and lower middle socioeconomic status. So, this study helps us to know the

<table>
<thead>
<tr>
<th>Sociodemographic factors</th>
<th>Total expenditure (in Rs) (%)</th>
<th>Mean ±2SD</th>
<th>Median</th>
<th>Range</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (in years)</td>
<td>25-65 (n=124) 11,01,209 (82.0)</td>
<td>8,880± 11,337</td>
<td>5,094</td>
<td>200-65,280</td>
<td>&lt;0.202*</td>
</tr>
<tr>
<td>&gt;= 65 (n=26)</td>
<td>2,42,501 (18.0)</td>
<td>9,326± 13,560</td>
<td>3,206</td>
<td>00-51,556</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>Male (n=45) 5,31,689 (39.6)</td>
<td>11,815±14,415</td>
<td>5400</td>
<td>00-59,460</td>
<td>&lt;0.049**</td>
</tr>
<tr>
<td>Female (n=105)</td>
<td>8,122,021 (60.4)</td>
<td>7,733±10,016</td>
<td>3268</td>
<td>00-59,460</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td>Illiterate (n=74) 5,89,415 (43.9)</td>
<td>7,965±9,326</td>
<td>3726</td>
<td>200-43,280</td>
<td>&lt;0.948***</td>
</tr>
<tr>
<td>Primary and middle school</td>
<td>n=64)</td>
<td>6,31,316 (46.9)</td>
<td>9,864±13,792</td>
<td>4980</td>
<td>00-65,280</td>
</tr>
<tr>
<td>Socio economic status</td>
<td>Upper (n=6) 39,635 (2.9)</td>
<td>6,605± 4,592</td>
<td>6822</td>
<td>1,280-13,890</td>
<td></td>
</tr>
</tbody>
</table>

*Mann Whitney U test, **Unpaired t-test, *** Kruskal Wallis test
Table 2: Comparison of annual expenditure on the basis of clinical feature

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Total expenditure (in Rs.) (%)</th>
<th>Mean±2SD</th>
<th>Median</th>
<th>Range</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration (in years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤10(n=118)</td>
<td>9,12,910 (67.9)</td>
<td>7,736±10,005</td>
<td>3,955</td>
<td>00-59,460</td>
<td>&lt;0.013*</td>
</tr>
<tr>
<td>&gt;10(n=32)</td>
<td>4,30,800 (32.1)</td>
<td>13,462±15,937</td>
<td>7,517</td>
<td>00-65,280</td>
<td></td>
</tr>
<tr>
<td>Type of anti-diabetes medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OHA+insulin(n=12)</td>
<td>10,98,606 (81.8)</td>
<td>8,196±11,157</td>
<td>3,726</td>
<td>00-65,280</td>
<td>&lt;0.003**</td>
</tr>
<tr>
<td>Insulin only(n=4)</td>
<td>37,135 (2.8)</td>
<td>9,283±3,677</td>
<td>10,798</td>
<td>3,818-00-11,720</td>
<td></td>
</tr>
<tr>
<td>Complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present(n=67)</td>
<td>7,01,767 (52.2)</td>
<td>10,474±13,589</td>
<td>5,445</td>
<td>00-65,280</td>
<td>&lt;0.15*</td>
</tr>
<tr>
<td>Absent(n=83)</td>
<td>6,41,943 (47.8)</td>
<td>7,734±9,844</td>
<td>3,540</td>
<td>00-65,280</td>
<td></td>
</tr>
<tr>
<td>History of hospital admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present(n=41)</td>
<td>6,36,779 (47.4)</td>
<td>15,531±16,639</td>
<td>10,560</td>
<td>650-65,280</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Absent(n=109)</td>
<td>7,06,931 (52.6)</td>
<td>6,485±7,993</td>
<td>3,650</td>
<td>00-49,275</td>
<td></td>
</tr>
<tr>
<td>Place of care</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exclusively government</td>
<td>9,330 (0.7)</td>
<td>3,110 ± 3,491</td>
<td>1,200</td>
<td>990-7,140</td>
<td>&lt;0.05**</td>
</tr>
<tr>
<td>Predominantly</td>
<td>2,91,059 (21.6)</td>
<td>7,276±12,042</td>
<td>2,900</td>
<td>00.0- 51,556</td>
<td></td>
</tr>
<tr>
<td>Predominantly private</td>
<td>9,43,090 (70.2)</td>
<td>9,245±10,797</td>
<td>5,250</td>
<td>200.0-65,280</td>
<td></td>
</tr>
<tr>
<td>Exclusively private</td>
<td>1,00,231 (7.5)</td>
<td>20,046±23,017</td>
<td>8,692</td>
<td>3,330-0.59,460</td>
<td></td>
</tr>
</tbody>
</table>

*Unpaired t-test, **Kruskalwallis test

Determinants of diabetes expenditure in such population taking treatment from a government hospital where it is expected that most of services will be free of cost.

In our study, annual per capita expenditure was found significantly higher in males as compared to females (p value<0.049). The same finding has been reported by Akari et al, Rayappa et al and many foreign studies. The higher indirect expenditure in terms of wage loss may be the possible justification for this difference as most of male diabetics were daily wage earner and the females in majority were homemakers. Also, better heath seeking behavior could be another reason for higher expenditure among male.

Expenditure on diabetes care significantly increased with duration of diabetes(p value< 0.013) and same has been echoed by Akari et al,6 Ramachandran et al, Kumar et al,8 Rayappa et al and also by some foreign studies conducted in Thailand, China and Singapore. Complications increase with duration of diabetes, resulting in additional cost on medication, monitoring and hospitalization. In this study also, complication was present in 87.5% patients with duration more than 10 years as compared to only 34.7% of patients with duration of disease less than 10 years.

In present study annual mean per capita expenditure was significantly high (p value <0.033) among subjects on insulin injections and oral hypoglycemic agents (OHA) as compared to subjects on OHA only. This association has also been reported by various Indian and foreign studies. The higher cost is not only attributed by the cost of insulin itself (if not available free of cost) but also the cost of syringes. Type 2 diabetics become insulin dependent in later stages of their life after a long duration of disease.

We found that the cost of care significantly increased among study subjects with history of hospitalization despite presence of a well functional government hospital in the study area (p value <0.001). As much as 42.9% of all diabetes related hospitalisations in our study was made in private hospitals which is a matter of challenge for Government health policies. Akari et al, Rayappa et al and some global studies have also reported the inpatient treatment as one of the strong determinant of expenditure on diabetes care.

Cost of care was also higher in subjects aged more than 65 years which is coherent with the fact that diabetes related complications increased with age and duration of disease. However, we feel that the expenditure is underestimated as awareness of complications of diabetes is likely to be low in an under privileged community.

Though not statistically significant, the mean per capita annual expenditure was higher in subjects belonging to lower socioeconomic status than the well-off subjects. The low literacy level and lack of awareness are likely to be associated with under-privileged section which may lead to delay in diagnosis, poor health seeking, non-compliance and complication.

Our study concludes that expenditure on diabetes care was significantly higher among male patients, those who had longer duration of disease since diagnosis, those who taking both Oral hypoglycaemic drugs and insulin, had history of hospitalisation and taking treatment from private care facilities. Preventive measure to maintain controlled blood sugar level in diabetes patients has to be strictly taken which would decrease dependence on insulin, rate of complications and number of hospitalization. There can be various community based innovations like Self Help groups of diabetes, to improve compliance to treatment and also risk pooling would definitely help the patient in financial crisis as well as in prevention of complications.

Also, there should be better provision of services for both acute and chronic complications of diabetes in Government health facilities so that preference to private facilities can be reduced. We also recommend similar large scale studies for estimation of cost on diabetes.

References

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Abstract

Although there is much information about T2DM, there are still many misconceptions. The mechanism of the disease is not clearly understood. Therefore, a coordinated approach is necessary to improve the treatment of T2DM. The present study suggested that T2DM patients should be treated with a combination of conventional and complementary medicines. The study was conducted in a hospital setting and was approved by the institutional review board.

Conclusion

The study concluded that the current treatment strategy for T2DM should be supplemented with complementary medicines. The study also suggested that further research is needed to identify the specific mechanisms of action of the complementary medicines used. The findings of the study can help to improve the treatment of T2DM and reduce the burden of the disease.
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Association of Coronary Heart Disease and CRP – as a Noble Marker of Inflammation - A Case Control Study

Narayan Chandra Sarkar¹, Piyabi Sarkar²*, Pubali Sarkar³, Suranjita Das⁴

Abstract

Background: Attention has increasingly turned towards the role of factors, such as inflammation in the development of atherosclerosis and CHD. C-reactive protein (CRP) has emerged as one of the most important novel inflammatory marker. Subsequent risk modification and treatment strategies of CHD keeping on pointer towards inflammation may be the appropriate approach.

Aim: The aim of this study was to determine the association of CHD with CRP, a sensitive marker of inflammation.

Material and Methods: This is a case control study amongst 300 subjects (150 cases and 150 controls), conducted in the Department of Cardiology at Sri Aurobindo Medical College and P.G Institute, Indore, M.P. Subjects with definite diagnosis of CHD established by coronary angiography (CAG) was taken as cases, subjects matched with age, gender with no conventional risk factor and past history of CHD from the relatives and accompanying persons were enlisted as controls.

Results: Estimation of CRP reveals ≥0.6 mg/dl in 88(58.7%) subjects out of 150, compared to 26 (17.3%) control subjects out of 150 which is statistically significant (p value<0.0001) (OR=6.7).

Conclusion: CRP as a noble marker of inflammation was significantly higher in subjects of CHD and thus supported adequately the hypothesis of an activation of inflammatory cascade for coronary atheromatous plaque formation and causation of CHD.

Introduction

Coronary heart disease (CHD) is one of the leading causes of death and disease burden throughout the world. Communicable diseases have been concurred by various preventive measures such as adequate public health care, immunization and invention of various antibiotics but metabolic diseases especially CHD is the major concern which is yet to be concurred adequately and uniformly worldwide. Current global death toll due to CHD is 17.3 million per year.¹,²

It is apprehended that death toll will be mounted to 33.6 million by 2030 of which 20% deaths will be shared by high income group countries, 8% by upper middle income group of countries, 37% by lower middle income countries and 35% by low income group of countries including India. In India CHD is in the form of epidemic.³

There are 30 million CHD patients in India in the term of absolute number. Acute myocardial infarction (AMI) death toll is 31.7% all death and enhancement of death rate from 2% in the year 1970 to 4.5% in the year 2000.CHD is a major health and economical burden in the developing country like India. According to the recent epidemiological studies, it is apprehended that Indian subcontinent will have to bear more than half of the burden of risk and eventuality of CHD in the coming days.³,⁴

During the past decades much knowledge has been achieved regarding the risk factors and pathophysiology of CHD but exact mechanism underlying development of CHD still remains to be fully evaluated. Multiple risk factors such as hypertension, diabetes mellitus (Type II DM), dyslipidemia, tobacco smoking, obesity and physical inactivity have been identified. However despite identification of risk factors, about half of all events of CHD reported to occur in apparently healthy individuals who have a few or none of the traditional risk factors. Now attention has been increasingly turned to the roll of other factors such as inflammation, in the development of atherosclerosis and CHD.⁵,⁶

Atherosclerotic plaque refers to a variable combination of changes of the intima of coronary arteries consisting of a focal accumulation of lipids, complex carbohydrates, blood and blood products, fibrous tissue, calcium deposits and associated medial changes. Coronary atherosclerotic plaque formation is the underlying pathology responsible for CHD which is considered as an inflammatory disease. Recent studies suggested that the atherosclerotic process is characterized by low grade inflammation altering the endothelium of coronary arteries and is manifested with an increased level of marker of inflammation such as CRP and other cytokines.

The atheromatous plaque fissuring and rupture is the primary event of AMI.⁶ Plaque disruption exposes the underlying sub endothelial matrix to formed elements of circulating blood leading to activation of platelets, thrombin generation and clot formation. This process of blockage of coronary

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artery deprived the heart muscle of oxygen and nutrients subsequently AMI. 6  

During the last 15 years compelling experimental and clinical evidence have demonstrated that both systemic and local inflammation might play a prominent role in the pathogenesis of atherosclerosis and it’s clinical consequence. 7  

Among the inflammatory biomarkers, CRP is an important bio marker of inflammatory process which has been considered as a causal factor and predictor of CHD in many studies. CRP levels are stable over long periods and have no diurnal variation and can be measured accurately. CRP reduces the expression of nitric oxide (NO) synthetase and prostacyclin synthetase and binds low density Lipoprotein (LDL-C) and promotes its uptake by macrophages, a key process in the genesis of atherosclerosis. It also regulates the expression of adhesion molecule on endothelial cells. All these phenomena are associated with atheromatous plaque formation.  

Material and Methods  

This was a case control study to determine the possible association of CRP a noble marker of inflammation in the pathophysiology of atheromatous plaque formation in the coronary arteries leading to the causation of CHD. This study was conducted at Department of Cardiology, Sri Aurobindo Medical College and P.G. institute, Indore, M.P from June 2013-December 2016. This is a tertiary care hospital which drains patient from urban, and rural areas of adjoining districts of M.P from all classes of socio economical section of the society.  

A round figure of 300 patients were enlisted for this study (150 cases and 150 controls). Subject aged 40-60 years of both genders diagnosed as CHD by CAG were considered as Cases. Subjects with no history of CHD from the close relatives of same locality matched with age, gender and socio economical status were taken as controls. Patients having Type 2 DM, Hypertension, Rheumatoid arthritis, dyslipidemia, asthma, acute infections, co-morbid diseases and malignancy were excluded from the study. Blood samples were collected from the study subjects for both cases and control to estimate CRP, lipid profile and blood sugar level.  

The CRP values were recorded as per manufacturer’s guidelines – Quanta (CRP) by Tulip diagnostics (p) ltd. The CRP measured value ≥0.6 mg/dl was considered as significant.  

Ethical approval for the study was obtained from Institutional review board of Sri Aurobindo Institute of Medical Sciences, Indore (M.P). Permission was obtained from Department of Cardiology, Sri Aurobindo Institute of Medical Sciences, Indore (M.P). Written informed consent was obtained from all the subjects before conducting the study.  

Results  

Table 1 shows a total of 300 subjects were examined among which 69 (46%) cases were in the age group of 40-50 years followed by 46 (30.7%) cases in the age group of 51-60 years and 35 (23.3%) cases were there in the 61 years and above category. Among the controls 72 (48%) subjects were in the age group of 40-50 years followed by 42 (28%) subjects in the category of 51-60 years and 36 (24%) in the category of 61 years and above. No significant difference was observed between cases and controls with respect to the distribution according to age group.  

Among the controls 72 (48%) subjects were in the age group of 40-50 years followed by 42 (28%) subjects in the category of 51-60 years and 36 (24%) in the category of 61 years and above. No significant difference was observed between cases and controls with respect to the distribution according to age group.  

Table 2 reveals case group comprised of 111 (74%) males and 39 (26.0%) females. The control group had 112 (74.2%) males and 38 (25.3%) females. The frequency distribution of study subjects was similar with respect to gender (p-value = 0.895).  

Table 3 shows the subjects among the case group were in the pre obese category (64.7%). Only 1.3% and 34% were in obese class 1 and normal category respectively. Among the controls 53.3% were in the normal category and 46.7% were in the pre obese category. A significant difference was seen in the frequency distribution of BMI among the cases and controls. (P value=0.002*)  

Table 4 shows the distribution of family history of CHD amongst the study participants. 14 % cases had a family history of coronary heart disease while 87.3% reported no history of coronary heart disease while 8.6% reported no history of coronary heart disease. While control group had family history of CHD in 19% and no history of CHD in 87.3%. No statistical significance was found.  

Table 5 shows the distribution of CRP in two categories (≥0.6 mg/dl was taken as significant). The CRP level (≥0.6 mg/dl) was significantly higher among the cases (58.7%) compared to controls 17.3%. Amongst the cases CRP level <0.6 mg/dl was 41.3% and in controls it was 82.7%. which is statistically significant (p value <0.0001**)  

Discussion  

Coronary heart disease (CHD) is a multifactorial disease. Various risk factors such as age, gender, family history of heart disease, smoking habit, alcohol intake, Type 2 DM, sedentary habit, obesity, and high blood pressure play a major role in the pathogenesis of CHD 8. However, despite identification of modifiable risk factors, CHD remains the leading cause of death worldwide. Upto half of all events associated with CHD are reported to occur in apparently healthy individuals who have few or none of the traditional risk factors. As a result, attention has increasingly turned to the roll of other factors, such as inflammation, in the
Atherosclerosis is a complex multifactorial pathophysiology. Recently there has been a wide acceptance of the role of inflammation in the pathogenesis of atherosclerosis and destabilization of coronary artery plaque though the first description of the role of inflammation in coronary artery sclerosis 200 years back. Russell Ross who described first that atherosclerosis is an inflammatory disease.\(^{6,9}\) Inflammation in the vessel wall plays an essential part in the initiation, progression, atheromatous plaque formation, destabilization and rupture. Atheromatous lesions obtained at autopsy have demonstrated the presence of inflammatory mononuclear cells monocytes, macrophages and T lymphocytes in the arterial wall. Endothelial dysfunction and injury triggers a cascade of events that modulates the inflammatory response leading to the recruitment of white blood cells into the vessel wall formation, of foam cell and initiate the development of atherosclerotic lesion.\(^8\)

In view of the importance of role of inflammatory process in the plaque formation and destabilization recent interest has been focused on whether biomarker of inflammation may help to improve risk stratification and identification of patients who may be benefited from particular treatment strategies. Among the inflammatory bio markers (CRP), a prototype marker of inflammatory process has drawn much attention both as a causal factor and in the pre condition of CHD.\(^9\)

Multiple prospective cohort studies revealed increased CRP level with wide age range, in both genders with increased CHD risks in primary as well as secondary prevention setting. This findings have been prevalent in different populations with diverse ethnic background and in diverse clinical settings. They also predicted the risk of a variety of cardiovascular outcome such as acute myocardial infarction (AMI), sudden cardiac death and peripheral arterial disease.


Assessment of Prognostic Factors and Natural History of Idiopathic Pulmonary Arterial Hypertension in Eastern India

Manish Vinayak\textsuperscript{1*}, Anupam Sharma\textsuperscript{2}, Dhurjati Prasad Sinha\textsuperscript{3}

Abstract

Background and objectives: Idiopathic pulmonary arterial hypertension (IPAH) is a rare disorder of unknown aetiology associated with poor survival. Disease severity assessment by various prognostic factors play important role in management of these patients. The aim of our study was to assess various factors and their natural history and course of disease in Indian population.

Material and Methods: We followed 27 patients of IPAH after complete work up of exclusion of other causes of pulmonary hypertension and analysed various demographic, echocardiographic and haemodynamic parameters and their correlation with mortality.

Results: A total of 27 patients (14 new and 13 previously diagnosed) were followed for mean duration of 18 months. At time of data analysis, 11 patients were alive and 16 patients died with overall mortality rate of 59.25%. Among various factors, presence of pericardial effusion (p=0.005), pulmonary artery acceleration time (PAAT) (p = 0.005), tricuspid Annular Plane Systolic Excursion (TAPSE) (p = 0.0004), heart rate (p=0.031), mean blood pressure (p =0.017), right atrial pressure (p=0.045), mean pulmonary artery pressure (PAP) (p =0.039) and six minute walk distance (p= 0.0002) were significantly associated with mortality. On multivariate cox proportional hazard analysis, PAAT (p =0.034), TAPSE (p=0.003) and six minute walk distance (p=0.002) remained significant predictors of mortality.

Conclusion: Idiopathic pulmonary arterial hypertension is associated with poor prognosis and survival despite advancements of disease specific therapies. Higher mortality in our study is due to delayed presentation and diagnosis. Also lack of availability of prostacyclins and lung transplantation in advanced stages of disease contribute to higher mortality in Indian setup. Non-invasive echocardiographic factors and six minute walk distance are important prognostic factors that help in disease severity stratification to identify patients in need of intensive medical management.

Introduction

Idiopathic pulmonary arterial hypertension (IPAH) is a rare disorder of unknown aetiology and poor survival. Pathophysiologically it is characterized by obliterative vasculopathy. Various invasive and non-invasive parameters (clinical, echocardiographic, cardiac catheterization) have been identified as markers of prognosis in previous studies. Also recent studies have shown improved survival with advancement of specific therapies and lung transplantation. Due to paucity of data in Indian population, this study was done to assess various prognostic factors and their impact on natural history and course of the disease in Indian population.

Methods

Patients

This study included 27 patients (14 newly diagnosed and 13 known prevalent cases of IPAH). The study had the approval of the ethics committee of our institution. All the patients were informed about the study in their vernacular language with written consent.

IPAH was diagnosed by a complete workup, including clinical history, physical examination, laboratory tests, chest radiography, electrocardiogram, pulmonary function tests, echocardiography, HRCT Chest, CT pulmonary angiography and cardiac catheterization. Criteria used to establish the diagnosis of IPAH included a mean pulmonary arterial pressure (mPAP) of more than 25 mmHg at rest with normal pulmonary capillary wedge pressure (PCWP) and absence of other disease known to cause or to be associated with secondary pulmonary hypertension.

Study Protocol

Following variables were assessed in our study protocol:

1. Demographic data: Age, Sex
2. Symptoms and Duration of symptoms
3. World Health Organization (WHO) Functional Class at presentation and during follow up (stable or worsening).
4. Echocardiography: Following echocardiographic variables were analysed using a predefined imaging protocol: Right ventricular end-diastolic area (RVEDA), Right ventricular systolic function as estimated by the right ventricular percent change in area, Right atrial area, Eccentricity index, presence of pericardial effusion, Severity of Tricuspid Regurgitation, Tricuspid regurgitation peak pressure gradient, Pulmonary Artery Acceleration Time (PAAT), Tricuspid Annular Plane Systolic Excursion (TAPSE), Inferior
Fig. 1: Kaplan-Meir Survival curve of the study population

Table 1: Patient characteristics at inclusion

<table>
<thead>
<tr>
<th>Age</th>
<th>36.9±14.1 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Female 19 (70.37%), Male 8 (29.62%)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>27 (100%)</td>
</tr>
<tr>
<td>Palpitation</td>
<td>16 (59.26%)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>7 (25.93%)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>7 (25.93%)</td>
</tr>
<tr>
<td>Syncope</td>
<td>2 (7.41%)</td>
</tr>
<tr>
<td>WHO Functional Class I</td>
<td>2 (7.41%)</td>
</tr>
<tr>
<td>WHO Functional Class II</td>
<td>9 (33.33%)</td>
</tr>
<tr>
<td>WHO Functional Class III</td>
<td>11 (40.74%)</td>
</tr>
<tr>
<td>WHO Functional Class IV</td>
<td>5 (18.5%)</td>
</tr>
</tbody>
</table>

Table 2: Echocardiographic variables at inclusion

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median</th>
<th>Lower Quartile</th>
<th>Upper Quartile</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVEDA</td>
<td>21.2</td>
<td>17.8</td>
<td>29.1</td>
</tr>
<tr>
<td>RV area change %</td>
<td>22.4</td>
<td>19.14</td>
<td>26.1</td>
</tr>
<tr>
<td>RA area</td>
<td>18.4</td>
<td>15.6</td>
<td>22.2</td>
</tr>
<tr>
<td>Systolic Eccentricity Index</td>
<td>1.72</td>
<td>1.56</td>
<td>2.07</td>
</tr>
<tr>
<td>Diastolic Eccentricity Index</td>
<td>1.59</td>
<td>1.4</td>
<td>1.74</td>
</tr>
<tr>
<td>TR max pressure gradient</td>
<td>68</td>
<td>58</td>
<td>77</td>
</tr>
<tr>
<td>PAAT</td>
<td>65</td>
<td>42</td>
<td>70</td>
</tr>
<tr>
<td>TAPSE</td>
<td>12</td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td>MEA ratio</td>
<td>0.84</td>
<td>0.63</td>
<td>1.26</td>
</tr>
<tr>
<td>LVEF</td>
<td>66</td>
<td>60</td>
<td>74</td>
</tr>
</tbody>
</table>

Table 3: Echocardiographic variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>N(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pericardial Effusion</td>
<td>76.19%</td>
</tr>
<tr>
<td>Tricuspid Regurgitation (Severe)</td>
<td>51.85%</td>
</tr>
<tr>
<td>Tricuspid Regurgitation (Moderate)</td>
<td>48.14%</td>
</tr>
<tr>
<td>IVC diameter &gt;20mm and &lt;50% collapsibility</td>
<td>33.33%</td>
</tr>
</tbody>
</table>

Table 4: Cardiac catheterization parameters at inclusion

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median</th>
<th>Lower Quartile</th>
<th>Upper Quartile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Rate</td>
<td>83</td>
<td>75</td>
<td>99</td>
</tr>
<tr>
<td>Mean BP</td>
<td>90</td>
<td>82</td>
<td>100</td>
</tr>
<tr>
<td>RA Pressure</td>
<td>10</td>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td>Mean PAP</td>
<td>58</td>
<td>45</td>
<td>70</td>
</tr>
<tr>
<td>PCWP</td>
<td>5</td>
<td>4</td>
<td>6</td>
</tr>
</tbody>
</table>

Table 5: Univariate analysis of quantitative variables among survivors and non-survivors

<table>
<thead>
<tr>
<th>Label</th>
<th>Cohort = Survivors, N=11</th>
<th>Cohort = Non-Survivors, N=16</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE</td>
<td>29</td>
<td>18</td>
<td>45</td>
</tr>
<tr>
<td>Symptom duration</td>
<td>24</td>
<td>15</td>
<td>28</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>13</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>FVC%</td>
<td>84</td>
<td>77</td>
<td>87</td>
</tr>
<tr>
<td>FEV1%</td>
<td>88</td>
<td>81</td>
<td>89</td>
</tr>
<tr>
<td>RVEDA</td>
<td>19.2</td>
<td>18.1</td>
<td>26.8</td>
</tr>
<tr>
<td>RV area change %</td>
<td>23</td>
<td>20.98</td>
<td>28.4</td>
</tr>
<tr>
<td>RA area</td>
<td>18.5</td>
<td>15.6</td>
<td>24.3</td>
</tr>
<tr>
<td>Systolic Eccentricity Index</td>
<td>1.72</td>
<td>1.6</td>
<td>2.07</td>
</tr>
<tr>
<td>Diastolic Eccentricity Index</td>
<td>1.59</td>
<td>1.5</td>
<td>1.8</td>
</tr>
<tr>
<td>TR max pressure gradient</td>
<td>72</td>
<td>54</td>
<td>77</td>
</tr>
<tr>
<td>PAAT</td>
<td>68</td>
<td>64</td>
<td>90</td>
</tr>
<tr>
<td>TAPSE</td>
<td>19</td>
<td>17</td>
<td>21</td>
</tr>
<tr>
<td>LVEF</td>
<td>68</td>
<td>59</td>
<td>74</td>
</tr>
<tr>
<td>Heart Rate</td>
<td>78</td>
<td>66</td>
<td>84</td>
</tr>
<tr>
<td>Mean BP</td>
<td>100</td>
<td>92</td>
<td>106</td>
</tr>
<tr>
<td>RA Pressure</td>
<td>7</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>Mean PAP</td>
<td>45</td>
<td>40</td>
<td>58</td>
</tr>
<tr>
<td>PCWP</td>
<td>4</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

Six minute walk distance  966 832 1100 385 155 437 0.0002

5. Cardiac catheterization: Right heart catheterization was performed during the study after informed consents. Hemodynamic measurements included heart rate, mean arterial pressure, right atrial pressure, mean pulmonary artery pressure and mean pulmonary capillary wedge pressure. Pulmonary vasoreactivity testing was not done.

6. An unencouraged 6-min walk test was performed as an assessment of exercise capacity.

All patients were treated with vasodilators and oral anticoagulants; and therapy for heart failure as per guidelines directed was given to patients with clinical evidence of right heart failure. Long term follow up was done by regular 6 weekly outpatient clinic visits and by telephone contact.

Statistical analysis

Both descriptive and inferential statistical analysis were done. In descriptive statistical analysis results on continuous measurements were presented on Mean ± Standard deviation or Median (with interquartile range) depending on the distribution of data. The normality of the study variables was tested through Shapiro-Wilk and Anderson Darling test. The results on categorical measurements were presented in number (%). P value <0.05 was considered as statistically significant.

Inferential statistical analysis

Statistical analysis was performed...
Table 7: Multivariate Cox Proportional Hazard model for Identifying Predictors (continuous variables) of Mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter Estimate</th>
<th>Standard Error</th>
<th>Chi-Square</th>
<th>p</th>
<th>Hazard ratio for mortality</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAAT</td>
<td>-0.06881</td>
<td>0.0326</td>
<td>4.4567</td>
<td>0.034</td>
<td>0.93</td>
<td>0.89-0.96</td>
</tr>
<tr>
<td>TAPSE</td>
<td>-0.82066</td>
<td>0.28084</td>
<td>8.539</td>
<td>0.003</td>
<td>0.44</td>
<td>0.18 - 0.72</td>
</tr>
<tr>
<td>Heart rate</td>
<td>-0.10268</td>
<td>0.05087</td>
<td>4.0741</td>
<td>0.053</td>
<td>0.90</td>
<td>0.83 - 1.01</td>
</tr>
<tr>
<td>Mean BP</td>
<td>-0.08549</td>
<td>0.05477</td>
<td>2.4362</td>
<td>0.1188</td>
<td>0.91</td>
<td>0.36 - 1.44</td>
</tr>
<tr>
<td>RA pressure</td>
<td>-0.02893</td>
<td>0.07263</td>
<td>0.1586</td>
<td>0.690</td>
<td>0.97</td>
<td>0.33 - 1.62</td>
</tr>
<tr>
<td>Mean PAP</td>
<td>0.04143</td>
<td>0.03672</td>
<td>1.2727</td>
<td>0.042</td>
<td>1.042</td>
<td>0.96 - 1.076</td>
</tr>
<tr>
<td>Six minute walk distance</td>
<td>-0.175</td>
<td>.576</td>
<td>12.503</td>
<td>0.002</td>
<td>0.98</td>
<td>0.97-0.99</td>
</tr>
</tbody>
</table>

on SAS statistical software (version 9.2, SAS Institute, Cary, NC, USA) and SPSS version 15.0 (Chicago, IL, USA). The study endpoint was mortality. Qualitative variables were first compared between deceased and surviving patients using chi-squared and Fisher’s exact tests. A non-parametric Wilcoxon’s test was used to compare distribution of quantitative variables between deceased and surviving patients. Kaplan–Meier survival curve was drawn for study population.

Results

Patient Characteristics

This study included 27 patients (14 incident and 13 prevalent) who were followed for 18 months. The mean age of the study population was 36.9±14.1 years and female predominant (Females 70.37% and males 29.62%).

The symptoms and functional status of patients at inclusion according to WHO classification are shown in Table 1, echocardiographic findings at inclusion in table 2 and 3, right heart catheterization findings in table 4 respectively.

Of the 27 patients enrolled in the study, 11 patients were alive at the time of data analysis and 16 patients died of their disease with mortality rate of 59.25% (Figure 1). Mean duration of follow up in survivors was 13.94±3.61 months. Mean duration of survival in non survivors was 3.76±3.63 months.

Demographic, echocardiographic, cardiac catheterization parameters were assessed as predictors of mortality as shown in Table 5 and 6 respectively.

Presence of pericardial effusion (p=0.005), PAAT (p = 0.005), TAPSE (p = 0.0004), Heart rate (p=0.031), mean Blood pressure (p =0.017), Right atrial pressure (p=0.045), mean PAP (p=0.039) and six minute walk distance (p=0.0002) were significantly associated with mortality.

As illustrated in Table 7, PAAT, TAPSE and six minute walk distance were significant predictors of mortality in multivariate cox proportional hazard analysis.

Discussion

Pulmonary hypertension (PH) is defined as an increase in mean pulmonary arterial pressure (mPAP) ≥25 mmHg at rest as assessed by right heart catheterization (RHC). Pulmonary arterial hypertension (PAH) is defined as PH with normal left sided filling pressure (i.e., pulmonary capillary wedge pressure (PCWP) <15 mm Hg and an increased pulmonary vascular resistance (PVR).

Term IPAH corresponds to subgroup of PAH patients, without any familial history of PAH or known associated risk/trIGGERING factor. Term ‘PH on exercise’ is no longer used due to insufficient data to define that which levels of exercise-induced changes in mPAP or PVR have prognostic implications.

IPAH is a progressive disease with a poor long term prognosis. Evaluation of disease severity and prognostic factors is important both for diagnosis and for therapeutic management. There is limited data and lack of consensus on prognostic factors. The reason behind this is that IPAH is fatal and a rare disease.

In our study of 27 patients, cumulative mortality rate was 59.25%. The mean survival duration of non-survivors was 3.76±3.63 months. Higher mortality and lower survival in our study was similar to as reported by Eysmann et al who reported mean survival rate of 4.8±8.0 months. However, the National Institutes of Health (NIH) registry reported estimated median survival rate of 2.8 years, with 1 year, 3 years and 5 years survival rates of 68%, 48% and 34% respectively. Lower survival rate in our study was probably due to higher functional class of patients during inclusion in study, lack of availability and use of prostacyclins and transplantation in WHO Class IV patients due to lower socioeconomic profile as compared to Western population.

At inclusion, the mean age of study population was 36.9±14.1 years with female predominance (female/male ratio: 2.3:1). Our findings are similar to as reported in literature and various previous registries, that women in third decade of life is the group with highest disease frequency.

The mean symptom duration of the patients included in the study was 24.74±26.2 months. This long symptom duration suggests that patient already have advanced disease when they presents because symptoms (fatigue, chest discomfort) in early stages are difficult to recognize and are often ignored.

Demographic characteristics i.e. age, sex distribution and symptom duration were statistically similar between survivors and non-survivors.

Among the presenting symptoms, exertional dyspnea was most common (100%) followed by palpitation (59.26%), chest pain (25.93%), peripheral edema (25.93%) and syncope (7.41%). Dyspnea occurs due to reduced oxygen delivery during physical activity as a result of an inability to increase cardiac output in response to increased demand.

On comparison among survivors and non survivors, Peripheral edema had statistically significant association with all-cause mortality on both univariate (p value 0.021) and multivariate analysis (p value 0.010), while there was no significant association with dyspnea, palpitation, chest pain and syncope. Peripheral edema is a sign of right ventricle failure and hence is more likely to be associated with advanced pulmonary vascular disease.

The functional status of patients during inclusion in the study according to WHO classification was as follows: 7.41% of the patients were in WHO Class I, 33.33% were in WHO Class II, 40.74% were in WHO Class III and 18.52% were in WHO Class IV. Most of the patients are in WHO Class II and III at the time of presentation. Relative
paucity of patients in WHO Class I may be due to difficulty in recognizing mild degree of symptoms and WHO Class IV due to higher mortality and poor survival in advanced disease. Although WHO functional class is a good indicator of disease severity, still it is a subjective measure and is confounded by other associated comorbidities such as obesity and age, coexisting diseases and exercise capacity.

Echocardiogram has been an important tool both in the term of diagnosis and prognosis. Among the above variables assessed, presence of pericardial effusion (p value=0.005), TAPSE (p value=0.0004), PAAT (p value=0.005), had a statistically significant association with mortality. On multivariate analysis, presence of pericardial effusion (p value=0.005), TAPSE (p value=0.003) and PAAT (p value=0.034) remained statistically significant.

Pericardial effusion occurs because of impaired lymphatic drainage because of raised right atrial pressure. Normally, myocardial lymph drains into right atrium, so raised atrial pressure will impair lymphatic drainage. Our study support the relation between severity of pericardial effusion and elevation of RA pressure, both of which are significantly associated with survival.

TAPSE was a prognostic factor for mortality on both univariate (p value 0.0004) and multivariate analysis (p value=0.003) in our study. TAPSE is a relatively simple assessment of the longitudinal movement of the lateral tricuspid annulus towards the right ventricle apex and has been shown to correlate with right ventricular systolic function. Forfia et al found cut-off value of 18 mm and TAPSE< 18 mm correlated with greater degrees of RV dysfunction.6

Pulmonary artery acceleration time (PAAT) was associated with mortality on both univariate (p value 0.005) and multivariate analysis (p value 0.034) with a HR=0.93, 95% CI=0.89-0.96. Studies have shown strong association between PAAT and pulmonary pressures, because PAAT assess maximum acceleration of blood flow which occurs earlier with elevated right ventricle ejection impedance due to pulmonary vascular disease.4

Right ventricular end diastolic area, Right ventricular % area change, Right atrial area were found not to be significantly associated with mortality. This could be because assessment of above variables are operator dependent and vary significantly dependent on patient’s body habitus. Also in diseased hearts, ventricular cavity shapes are distorted and getting true area on echocardiogram in sometimes difficult.

In our study, the eccentricity index, whether end diastolic or end systolic, did not appear to be a prognostic factor for mortality, which was statistically significant prognostic factor in analysis by Raymond et al.7 This may be due to difficulty of measurement of true diameters of distorted cavities, as qualitatively it is very easy to see an abnormal septal curve leading to D-shaped left ventricle cavity.

Severity of tricuspid regurgitation and Estimated Systolic PAP from maximum peak tricuspid regurgitation pressure gradient also did not correlate with mortality. This was in agreement in findings with earlier series by Yeo et al.8 This is because towards the advanced stages of disease, when right ventricle fails, severity and pressure gradient of tricuspid regurgitation starts decreasing. So assessment of pulmonary vascular disease based only on severity and pressure gradient of regurgitant jet may underestimate severity of the disease.

Among the cardiac catheterization parameters, heart rate (p value=0.031), mean blood pressure (p value=0.017), mean RA pressure (p value=0.045) and mean PA pressure (p value=0.039) correlated significantly with survival. Higher mean RA pressure and high mean PAP among non-survivors are predictive of more advanced pulmonary vascular disease. Higher heart rate and lower blood pressure among non-survivors also indicates right ventricle failure and fixed cardiac output.

There is large supportive data on haemodynamic and cardiac catheterization parameters. In NIH registry, three measured haemodynamic variables were associated with increased risk of death by univariate analysis: increased mPAP (odds ratio:1.16, CI=1.05-1.28); increased mRAP (odds ratio:1.99, CI=1.47-2.69); and decreased Cardiac Index (odds ratio:0.62, CI=0.46-0.82). In fact, a regression equation was formulated from data of NIH registry in which these three haemodynamic variables were used to estimate survival.5

Exercise capacity of our patients was measured with six minute walk distance due to its ease of administration and reproducibility. The mean value of six minute walk distance in our study was 580±362 m; while REVEAL registry reported mean value of 370±127 m.

Six minute walk distance had a high statistically significant association with mortality on comparison among survivors and non-survivors with non-parametric Wilcoxon test (p value=0.0002). It remained statistically significant on multivariate analysis (p value=0.002). Our findings are supported by previous reported series that prognosticate six minute walk distance as predictive factor of mortality.9,10

Limitations

It was a single centre study with small sample size of 27 patients (14 incident and 13 prevalent cases) with limited duration of follow up (mean follow up of 13.94±3.61 months). Small sample size could not be avoided because of rarity of disease and short mean survival due to advanced progressive nature of disease.

Genetic testing for identifying Heritable PAH which forms 6-10% of patients with PAH was not done in our set up due to lack of availability. As the term IPAH is reserved for patients without a family history and without an identified genetic abnormality.

Pulmonary vasoreactivity testing to detect patients responsive to high dose of calcium channel blockers was not done.

As all the patients were on anticoagulants, phosphodiesterase 5 inhibitors (PDE 5 inhibitors) and endothelin receptor antagonists, further sub group analysis to study the effect of treatment on mortality could not be done.

Lack of use of prostacyclins and lung transplantation in WHO FC IV patients because of poor affordability due to low socioeconomic profile and lack of easy availability of transplantation was the reason of high mortality rate (59.25%) seen in our study on Indian population as compared to previous data.

Further large multicenter study including large pool of patients with
increased duration of follow up with newer echocardiographic tools is necessary in Indian population.

Conclusion

Idiopathic pulmonary arterial hypertension is a rare disease with a short mean survival time. Females of third decade are most commonly affected. By the time of presentation, patients usually are in WHO functional class II or III. Various factors can be used to assess the disease prognosis so that early diagnosis and therapy escalation can be done. Among symptoms, presence of peripheral oedema is associated with worse survival suggestive of right ventricle failure. Echocardiography can be used as a tool to assess prognosis. Presence of pericardial effusion, lower TAPSE and PAAT are all indicators of advanced disease and poor survival. Hence, non-invasive methods like echocardiography may be used to evaluate prognosis when diagnosis of IPAH has been made and invasive testing is unavailable or risky. These characteristics may help identify patients appropriate for more intensive medical therapy.

Higher mortality in Indian population as compared to previous data indicates that further work needs to be done on both early diagnosis as well as therapeutic management (availability of prostacyclins and lung transplantation) of advanced disease.

References


Socio-demographic Profile of MDR-TB and XDR-TB Patients Admitted in DR-TB Centre, North India

Om Prakash Giri1, Vishal Prakash Giri2*, Nishant Nikhil3

Abstract

Background: As per WHO Global TB report (2018), 10.0 million people developed TB in 2017. India accounted for 20 % of world cases. Globally, 3.5 % of new cases and 18% of previously treated cases had MDR-TB. Corresponding figures for India are 2.8 % and 12 %. Among cases of MDR-TB in 2017, 8.5% were estimated to have XDR-TB. Drug resistant TB cases are on rise and needs planning and research for its treatment and control.

Materials and Methods: A retrospective study was conducted on MDR-TB and XDR-TB patients to evaluate social and demographic profile of these patients in Bihar.

Results: A total of 700 (530 males and 170 females) MDR-TB and 51 (40 males and 11 females) XDR-TB patients were analyzed, which revealed 293 (41.86 %) patients of MDR-TB and 23 (45.10 %) patients of XDR-TB in the age group of 15 to 25 years. Mean age of MDR-TB patients in this age group was 20.52 years and for XDR-TB 21.17 years.

Conclusion: Drug Resistant Tuberculosis Control Programme should focus adequately on youth in state of Bihar, India.

Introduction

Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis. It typically affects lungs (pulmonary TB) but can also affect other sites (extrapulmonary TB).1 A patient of TB, whose biological specimen is resistant to both Isoniazid (H) and Rifampicin (R), with or without resistance to other first-line anti-tuberculosis drugs is called Multi Drug Resistant Tuberculosis (MDR-TB). MDR-TB patients may also have additional resistance to any/all Fluoroquinolone (FQ) or any/all Second-line injectable (SLI) anti-TB drugs. Shorter MDR-TB regimen [(4-6) Mfx6 km Eto Ciz Z ] is recommended for pulmonary and extra-pulmonary (pleural effusion and lymphnode) MDR-TB patients sensitive to both FQ and SLID. Patients who are not considered eligible for shorter MDR-TB regimen are recommended Conventional MDR-TB regimen. Pulmonary MDR-TB patients

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(aged >18 years), with additional resistance to FQ/SLI are prescribed, Bedaquiline / Delamanid containing regimen, provided they meet inclusion criteria. Delamanid, additionally, can be prescribed to 6 - 17 years age group patients wherein, Bedaquiline is currently not permissible. MDR-TB patients not suitable for Bedaquiline / Delamanid are prescribed Modified MDR-TB regimen.² ²⁺⁵ MDR-TB patient whose biological specimen is additionally resistant to at least a FQ (Ofx, Lfx, Mfx) and a SLI (Km, Am, Cm) is called Extensive Drug Resistant TB (XDR-TB). XDR-TB regimen also comprises of with /without new drug (Bedaquiline /Delamanid).⁶

The present study was planned with the aim to assess distribution of MDR-TB and XDR-TB among patients of DR-TB of different age groups, genders, weight bands, communities and districts in North Bihar.

Materials and Methods

The present retrospective record based study was conducted on patients admitted in DR-TB centre, Darbhanga, which attached with Department of Pulmonary Medicine, Darbhanga Medical College and Hospital, Darbhanga, between 15 June 2014 to 31 December 2016.

Patients of all age groups (children and adults) and genders (male and female) suffering from MDR-TB and XRD-TB were studied. Rapid molecular diagnostic tests (CBNAAT and LPA) were done in RNTCP certified Demian Foundation India Trust (DFIT) laboratory, situated in State TB Training and Demonstration Centre (STDC), Darbhanga and LC-DST was done at National Reference Laboratory (NRL) National Institute of Tuberculosis and Respiratory Diseases (NITRD), Delhi.

DR-TB Centre, Darbhanga admits MDR-TB and XDR-TB patients of six districts of Bihar: Darbhanga, Madhubani, Samastipur, Saharsa, Supaul, and Madhepura.

Data entered in the DR-TB Centre computer were analyzed using appropriate statistical software, SPSS version 20. Frequencies (number and percentage) were obtained using descriptive statistics.

Results

Total 700 patients of MDR-TB were admitted in DR-TB Centre, out of which 589 (84.14 %) were noted to be in the age group of 15 to 45 years and 89 (12.71 %) in age group 46 to 65 years. Patients aged less than 15 years and more than 65 years were least affected, 14 (2.0 %) and 8 (1.14 %) patients were observed in the corresponding age groups respectively (Table 1).

230 (32.85 %) patients of MDR-TB in the age group of 15 to 25 were noted to be males, while in the same age group the females comprised of 63 (9.0 %) patients. Similar was situation in the age group of 26 to 45 years, where males 210 (30 %) again outnumbered females 86 (12.28 %). Females were recorded to be minimally affected in the age group of 56 to 65 years, while males were so in the age group of less than 15 years. Females were not observed to be affected with MDR-TB in the age group of more than 65 years. Total 530 (75.71 %) patients of MDR-TB were males and 170 (24.28 %) females, thus male to female ratio was noted to be 3.11 : 1 (Table 1) (Figure 1).

Total 51 patients of XDR-TB were admitted in DR-TB centre, out of which 48 (94.11 %) were observed to be in the age group of 15 to 45 years and 3 (5.88 %) belonged to the age group of 46 to 65 years. XDR-TB was not observed in the age groups of less than 15 years and more than 65 years (Table 2) (Figure 2).

18 (35.29 %) patients of XDR-TB in the age group of 15 to 25 years were noted to be males, while in the same age group females comprised of 5 (9.80 %) patients. Similar was situation in the age group of 26 to 35 years, where males 17(33.33 %) again outnumbered females 3 (5.88 %). Male and females were least affected in age group of 36 to 65 years, the corresponding figures

---

Table 1: Age group and gender distribution of MDR-TB patients admitted in DR-TB centre

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>2014 Male n (%)</th>
<th>2015 Male n (%)</th>
<th>2016 Male n (%)</th>
<th>Total Male n (%)</th>
<th>2014 Female n (%)</th>
<th>2015 Female n (%)</th>
<th>2016 Female n (%)</th>
<th>Total Female n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-14</td>
<td>1 (1.2)</td>
<td>1 (0.5)</td>
<td>2 (0.7)</td>
<td>4 (0.57)</td>
<td>2 (6.9)</td>
<td>1 (2.1)</td>
<td>7 (7.4)</td>
<td>14 (2.0)</td>
</tr>
<tr>
<td>15-25</td>
<td>39 (47.0)</td>
<td>67 (37.8)</td>
<td>124 (45.9)</td>
<td>230 (32.85)</td>
<td>67 (37.8)</td>
<td>124 (45.9)</td>
<td>230 (32.85)</td>
<td>230 (32.85)</td>
</tr>
<tr>
<td>26-35</td>
<td>18 (21.7)</td>
<td>60 (34.0)</td>
<td>68 (25.2)</td>
<td>98 (14.0)</td>
<td>11 (37.9)</td>
<td>21 (44.7)</td>
<td>33 (35.1)</td>
<td>230 (32.85)</td>
</tr>
<tr>
<td>36-45</td>
<td>13 (15.7)</td>
<td>23 (13.0)</td>
<td>28 (10.4)</td>
<td>64 (9.1)</td>
<td>5 (17.2)</td>
<td>6 (12.8)</td>
<td>11 (11.7)</td>
<td>85 (12.1)</td>
</tr>
<tr>
<td>46-55</td>
<td>7 (8.4)</td>
<td>14 (8.0)</td>
<td>18 (6.7)</td>
<td>39 (5.57)</td>
<td>2 (6.9)</td>
<td>1 (2.1)</td>
<td>3 (3.2)</td>
<td>45 (6.4)</td>
</tr>
<tr>
<td>56-65</td>
<td>3 (3.6)</td>
<td>11 (6.2)</td>
<td>25 (9.2)</td>
<td>41 (5.86)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>41 (5.86)</td>
</tr>
<tr>
<td>65-75</td>
<td>2 (2.4)</td>
<td>1 (0.5)</td>
<td>5 (1.8)</td>
<td>8 (1.14)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>8 (1.14)</td>
</tr>
<tr>
<td>Total</td>
<td>83(100.0)</td>
<td>177(100.0)</td>
<td>270(100.0)</td>
<td>530 (75.71)</td>
<td>589 (84.14)</td>
<td>270 (38.57)</td>
<td>230 (32.85)</td>
<td>700 (100)</td>
</tr>
</tbody>
</table>

Males=530 (75.71 %), Females= 170 (24.28 %), Total cases=700. Pulmonary MDR-TB=692/ 700 (98.85 %), Extra-Pulmonary MDR-TB=8/700 (1.14 %). STR for MDR-TB was started on 12 June 2014 in Darbhanga, DR-TB centre.
Figures in parenthesis are percentage

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Male</th>
<th>Female</th>
<th>Total n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-25</td>
<td>10 (45.5)</td>
<td>8 (44.4)</td>
<td>5 (71.4)</td>
</tr>
<tr>
<td>26-35</td>
<td>9 (40.9)</td>
<td>9 (44.4)</td>
<td>20 (39.2)</td>
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<tr>
<td>36-45</td>
<td>2 (9.1)</td>
<td>1 (5.5)</td>
<td>1 (5.9)</td>
</tr>
<tr>
<td>46-55</td>
<td>1 (4.5)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>56-65</td>
<td>0 (0.0)</td>
<td>1 (5.5)</td>
<td>1 (2.0)</td>
</tr>
</tbody>
</table>

XDR-TB 36 (4.79) 15 (1.99) 51 (6.79)

Table 2: Age group and Gender distribution among XDR-TB Patients admitted in DR-TB centre

MDR-TB 509 (67.79) 191(25.43) 700 (93.20)

495 (70.71 %) and 191 (27.28 %) patients MDR-TB cases revealed that 14 (2 %), as paediatric (Tables 1 and 2).

Females were affected by MDR-TB at up to 14 years age group were classified paediatric XDR-TB cases were not.

Extra-pulmonary paediatric XDR-TB cases were not observed in 8/700 (1.14%) cases. Distribution revealed, (A) Community - Hindu(6), and Muslims (2 ) ; (B) Gender- Males (7) and Female (1); (C)

Site-Spinal TB with cold abscess (3), Sternal tuberculosis with cold abscess (1), Intracranial tuberculoma (1), Tuberculous empyema (2) and Cervical lymphnode TB with cold abscess (1) ; (D) Age group- 15 to 25 years (4), 26 to 35 years (2), 56 to 65 years (2) ; (E) District- Darbhanga (4), Madhubani (1), Samastipur (2) and Saharsa (1) case; (F) Division- Darbhanga to Kosi division case ratio of 7: 1. (G) HIV status- One patient was HIV positive.

Discussion

The present study conducted on DR-TB (MDR-TB and XDR-TB) patients observed 316/ 751 (42.07 %) patients in the age group of 15 to 25 years. Males comprised of 570/ 751 (75.89 %) patients and females 181/ 751 (24.10 %). Male to female ratio observed was 3.14 :1. Minimum age of male and female MDR-TB patients noted in the present study was 14 and 10 years and maximum 76 and 66 years respectively. The minimum age of male and female XDR-TB patients observed was 15 and 19 years. Maximum age of XDR-TB in both genders was 60 years.

The present study observation is consistent with similar study conducted by Dholakia et al, Javia et al, Mukati et al who also reported DR-TB common in young people but is not consistent with them as regards to age group affected. We observed DR-TB most prevalent in comparatively lower age group (15 to 25 years) than reported by Dholakia et al (15 to 35 years), Javia et al (18 to 35 years), Mukati et al (31 to 40 years), Mukherjee et al (21 to 30 years), Gupta et al (21 to 40 years) and Munje et al (25 to 34 years). The present study is comparable with studies conducted by Javia et al (M:F=3:2), Mukati et al (2.33:1), Mukherjee et al (1.60:1), Kapadia et al (1.73:1), Gupta et al (1.67:1), Datta et al (1.26:1) and Munje et

Table 3: Weight distribution among 751 DR-TB patients admitted in DR-TB centre

<table>
<thead>
<tr>
<th>Weight band distribution of DR-TB patients number</th>
<th>&lt; 45 kg</th>
<th>&gt;45 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDR-TB cases</td>
<td>206/ 751 (27.43 %)</td>
<td>751 (100.0)</td>
</tr>
<tr>
<td>XDR-TB cases</td>
<td>206/ 751 (27.43 %)</td>
<td>751 (100.0)</td>
</tr>
<tr>
<td>Total cases</td>
<td>206/ 751 (27.43 %)</td>
<td>751 (100.0)</td>
</tr>
</tbody>
</table>

Figures in parenthesis are percentage

Table 4: District wise distribution of MDR-TB and XDR-TB patients during 2014-2016

<table>
<thead>
<tr>
<th>District</th>
<th>MDR-TB</th>
<th>XDR-TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darbhanga</td>
<td>2015</td>
<td>2016</td>
</tr>
<tr>
<td>Madhubani</td>
<td>2015</td>
<td>2016</td>
</tr>
<tr>
<td>Samastipur</td>
<td>2015</td>
<td>2016</td>
</tr>
<tr>
<td>Saharsa</td>
<td>2015</td>
<td>2016</td>
</tr>
<tr>
<td>Supaul</td>
<td>2015</td>
<td>2016</td>
</tr>
<tr>
<td>Madhepura</td>
<td>2015</td>
<td>2016</td>
</tr>
<tr>
<td>Total</td>
<td>2015</td>
<td>2016</td>
</tr>
</tbody>
</table>

Hindu to Muslim ratio= 2.42 :1.
al (2.44:1) who have also reported males dominance but we have observed a comparatively higher (M:F=3:10:1) male dominance than previous published reports. The present study is not in line with study conducted by Dholakia et al, where gender distribution equality (M:F=1:1) has been reported among DR-TB patients. Males have been observed in the present study to be more affected than females in adult age groups. This finding is not consistent with similar studies conducted by Mukati et al, Mukherjee et al and Prakash et al where DR-TB affected females have been observed to be significantly younger than males.7-13

2.28 % of MDR-TB were noted to be co-infected with HIV infection. This figure is lower than reported by Dholakia et al (8.82%), Javia et al (5.2%), Mukherjee et al (2.9%) and higher than Mukati et al (1.5%) and Datta et al (1.9%).7-10

Young age group is developing, has highest social interaction and is productive. Their involvement with DR-TB is challenging because they act as source of spread of infection and their involvement also leads to damage of potential work force. Adolescent Friendly Health Services (AFHC) Clinic can include TB in its curriculum as it is already dealing with reproductive health care services, testing of HIV and other sexually transmitted diseases and mental health care services in adolescents. Adolescents could be provided professional assistance and guidance and referred back to TB health care system for needful.

Conclusion

The present study was conducted to know the population affected by DR-TB, so that more concentration could be directed towards the target and observed 293/700 (41.86%) MDR-TB and 23/51 (45.10%) XDR-TB patients in the age group of 15 to 25 years.

Present study concludes that high percentage of youth affected by DR-TB in North Bihar is a matter of concern for all of us and should be addressed. It reflects change in pattern of age group involvement in DR-TB towards lower side. We recommend RNTCP PMDT to concentrate on youth and take it as challenge in delivery of DR-TB treatment services in this zone of Bihar state, India.

Percentage of Muslims among DR-TB cases is higher (29%) compared to Muslim population percentage (19%) in North Bihar. Either incidence of DR-TB is high in Muslims or Muslims are more conscious in taking treatment, this needs exploration. We suggest DR-TB prevention and control approach should focus adequately on Muslims.

Further, Darbhanga division of Bihar state (comprising three districts : Darbhanga, Madhubani and Samastipur) had maximum 672/751 (89.48%) DR-TB patients, while Kosi division (comprising three districts Supaul, Madhepura and Saharsa) had minimum 79/751 (10.51%) DR-TB patients, this finding also needs exploration and research. We recommend strengthening of TB care system in Kosi division of Bihar state, India.

Acknowledgement

Authors are thankful to Mr. Manohar Kumar Mishra, Statistical Assistant, MDR-TB centre, Darbhanga for his contribution in data analysis.

References

Chellaram Diabetes Institute

4th International Diabetes Summit-2020, Pune

6th – 8th March, 2020 – (Friday – Sunday)

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- Karolinska Institute, Sweden
- Mayo Clinic, USA
- Imperial College, London
- University of Leicester, UK
- University of Newcastle, UK
- Dusseldorf University, Germany
- University of Virginia, USA

Highlights – 3rd International Diabetes Summit - 2019

- 50 National and 10 Best In Class International Speakers from USA, UK and Europe.
- 2000 delegate registrations from all over India and abroad.
- Omi / Poster presentations by 45 young researchers.
- Pre-conference Workshops on Management of Diabetic Neuropathy, NAFLD, Symposiums, Scientific CME on Digital Diabetology and the Scientific Sessions on Diabetes Complications and Management.
- Chellaram Foundation Diabetes Research Award - 2019 of Rs. 1,00,000/- given for the outstanding research.
- Chellaram Foundation also announced one gived prizes of Rs. 10,000 and Rs. 5,000 for the 2 best papers in Clinical science presentation.
- The Maharashtra Medical Council awarded 10 Credit Points to the program.

REGISTRATION FORM

First Name: ___________________________ Surname: ___________________________ Gender M/F: ______
MAC/Other Council No.: ___________________________
Hospital/Institution: ____________________________________________
Qualification: ___________________________ Specialty: ____________________________
Address for Communication: ____________________________________________
City: ___________________________ Pincode: ___________________________ State/Country: ___________________________
Mobile Number/Contact No (with area code): ___________________________ Email Id: ___________________________

PAYMENT DETAILS

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<th>9th Mar 2020</th>
<th>10th Mar 2020</th>
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<td>3. ECP &amp; HCP</td>
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*Includes PHY/CEN course participation
- Pre-conference Workshops on Management of Diabetic Neuropathy, NAFLD, Symposiums, Scientific CME on Digital Diabetology and the Scientific Sessions on Diabetes Complications and Management.
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**Anti-diabetic Agent and Cancer**

Krishna Kumar Pareek¹, Girish Mathur², GD Ramchandani³

**Introduction**

Diabetes is a chronic disease in which multiple organs and systems are affected, likewise cardiovascular system, renal system, nervous system and vision etc. Proper glycemic control is the best prevention that slows down the progression of disease and development of associated complications. Diabetes effective treatment has become possible since the discovery of insulin in the 1920s for type 1 diabetes and after that numerous oral glucose lowering agents are developed which are now mainstay of type 2 diabetes management, but when oral drugs are not sufficient or in some particular conditions such as pregnancy, peri-surgical time or acute states, e.g. myocardial infarction; insulin is added to oral agents. Several groups of drugs are used in monotherapy or in polytherapy of diabetes, including insulin and insulin analogs, insulin secretagogues (sulfonylureas, meglitinides, GLP-1 agonists, DPP-4 inhibitors), insulin sensitizers (biguanides, thiazolidinediones), and drugs with other mechanisms of action (alpha-glucosidase inhibitors, SGLT2 inhibitors). Although they help to maintain proper blood glucose level, their side effects may limit the use of those drugs. Numerous epidemiological research and meta-analyses based on both comparative and cohort studies indicate the association between diabetes and the incidence and mortality due to cancer.¹,²

**Table 1: Possible risks to develop cancer by anti-diabetic agents**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug</th>
<th>Risk of cancer</th>
<th>Cancer site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>Human insulin</td>
<td>Not elevated</td>
<td>Overall</td>
</tr>
<tr>
<td></td>
<td>Insulin</td>
<td>Increased</td>
<td>Liver, colorectum, pancreas</td>
</tr>
<tr>
<td></td>
<td>Lispro</td>
<td>Not elevated vs insulin</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Aspart</td>
<td>Not elevated vs insulin</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Glulisine*</td>
<td>Not elevated vs insulin</td>
<td>Breast</td>
</tr>
<tr>
<td>Insulin secretagogues</td>
<td>Glargine</td>
<td>Increased</td>
<td>Breast</td>
</tr>
<tr>
<td></td>
<td>In general</td>
<td>Increased</td>
<td>Overall, pancreas</td>
</tr>
<tr>
<td></td>
<td>Glibenclamide</td>
<td>Increased</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Glipizide</td>
<td>Reduced</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Gliclazide</td>
<td>Reduced</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Meglitinides</td>
<td>Reduced (in vitro)</td>
<td>Breast, hepatic, cervical carcinoma cells</td>
</tr>
<tr>
<td></td>
<td>Repaglinide</td>
<td>Reduced (in vitro)</td>
<td>Breast, hepatic, cervical carcinoma cells</td>
</tr>
<tr>
<td>GLP-1 agonists</td>
<td>Exenatide</td>
<td>Not elevated</td>
<td>Intestine</td>
</tr>
<tr>
<td></td>
<td>Liraglutide</td>
<td>Not elevated</td>
<td>Intestine, pancreas</td>
</tr>
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<td>DPP-4 inhibitors</td>
<td>Sitagliptin</td>
<td>Not elevated</td>
<td>Intestine</td>
</tr>
<tr>
<td></td>
<td>Metformin</td>
<td>Reduced</td>
<td>Pancreas, breast, lung, prostate, colorectum, liver</td>
</tr>
<tr>
<td>TZDs</td>
<td>In general</td>
<td>Reduced</td>
<td>Lung</td>
</tr>
<tr>
<td></td>
<td>Pioglitazone</td>
<td>Reduced</td>
<td>Lung, bladder, breast, colon, prostate</td>
</tr>
<tr>
<td></td>
<td>Rosiglitazone</td>
<td>Reduced</td>
<td>Liver</td>
</tr>
<tr>
<td></td>
<td>Troglitazone</td>
<td>Reduced</td>
<td>Liver, colorectum</td>
</tr>
<tr>
<td>Others</td>
<td>Alpha-glucosidase</td>
<td>Decreased</td>
<td>Lung</td>
</tr>
<tr>
<td></td>
<td>inhibitors</td>
<td>Not elevated</td>
<td>Thyroid</td>
</tr>
<tr>
<td></td>
<td>Acarbose</td>
<td>Not elevated</td>
<td>Kidney, bladder, breast</td>
</tr>
<tr>
<td></td>
<td>SGLT2 inhibitors</td>
<td>Not elevated</td>
<td>Bladder</td>
</tr>
</tbody>
</table>

Elevated cancer risk in type 2 diabetes refers to liver, pancreatic, colorectal, kidney, endometrial and breast cancers. Australian researchers examined the risk of site-specific cancer among people with diabetes (type 1 and type 2) compared with the general population and they observed significantly elevated standardized incidence ration (SIRs) for brain, thyroid, esophageal, stomach, colorectal, pancreatic, liver, lung, endometrial and ovarian cancers, and for melanoma in type 1 diabetes while type 2 diabetes was linked with significantly increased SIRs for almost all site specific cancers (with the highest SIR observed for pancreas and liver) and decreased risks for melanoma and prostate cancer. Elevated cancer risk was observed throughout all follow-up time, but was notably high in 3-month-period after registration.³ Moreover, coexistence of cancer and diabetes is related to the elevated risk of all-cause mortality by 41%, compared to the presence of cancer without diabetes.⁴ However, in recent time there is a need to find out the possible mechanism for developing cancer in diabetes. More specifically, it is a need to confirm that is it because of diabetes disease or anti-diabetic medications? Table 1 is showing possible risk of anti-diabetic medications for development of cancer at various site is our body.⁵

**Insulin and its analogs**

Insulin is treatment of choice for type 1 diabetes and some cases of type 2 diabetes when adequate control on glucose level is needed with lifestyle changes and oral antidiabetic drugs or in other conditions such as pregnancy, peri-surgical time or sudden acute medical states, e.g. myocardial infarction. The insulin molecule is a polypeptide, consisting of two chains...
The Insulin-like growth factor 1 (IGF-1) receptor (IGF-1R) is connected to cancer risk. A study conducted by Currie et al. confirmed this relationship (adjusted RR = 2.16, p = 0.001). In another study, the overall risk of cancer in insulin users (n = 5135) compared to non-insulin users (n = 3639) and the non-diabetic type 2 patients, were observed. In 2009, one study published, showing an effect of anti-diabetic drugs on pancreatic cancer. In diabetic patients who had ever used insulin and who ever used sulfonylureas, there was by 4.99 and 2.52 times greater risk of pancreatic cancer compared to diabetic patients who had never used such drugs. The latest meta-analysis of 18 sulfonylurea studies showed that sulfonylurea use in T2DM was linked with an increase in overall cancer risk in cohort studies (RR = 1.55, 95% CI = 1.48–1.63), though, the results from randomized control trials (RR = 1.17, 95% CI = 0.95–1.45) and case-control studies (OR = 1.02, 95% CI = 0.93–1.13) proved no statistically significant effect. Bo et al. among 1277 T2DM patients treated with sulphonylureas in the retrospective cohort study with 14 years of the followup, was observed that Gliclazide and tolbutamide were associated with a significantly lower cancer mortality comparing with glibenclamide (HR = 0.30, 95% CI = 0.16–0.55, and HR = 0.48, 95% CI = 0.29–0.79, respectively). Cancer mortality was markedly reduced in patients treated with gliclazide and tolbutamide. In recent time glipizide, gliclazide and glibizide and gliquidone (the second generation of sulfonylurea) are in common use due to the improvement of glycemic control and the reduction of side effects, particularly, long episodes of hypoglycemia. In several studies, an increased risk of cancer or cancer mortality among patients treated with sulfonylurea was observed. In 2009, one study published, showing an effect of anti-diabetic drugs on pancreatic cancer. In diabetic patients who had ever used insulin and who ever used sulfonylureas, there was by 4.99 and 2.52 times greater risk of pancreatic cancer compared to diabetic patients who had never used such drugs. The latest meta-analysis of 18 sulfonylurea studies showed that sulfonylurea use in T2DM was linked with an increase in overall cancer risk in cohort studies (RR = 1.55, 95% CI = 1.48–1.63), though, the results from randomized control trials (RR = 1.17, 95% CI = 0.95–1.45) and case-control studies (OR = 1.02, 95% CI = 0.93–1.13) proved no statistically significant effect. Bo et al. study, among 1277 T2DM patients treated with sulphonylureas in the retrospective cohort study with 14 years of the followup, was observed that Gliclazide and tolbutamide were associated with a significantly lower cancer mortality comparing with glibenclamide (HR = 0.30, 95% CI = 0.16–0.55, and HR = 0.48, 95% CI = 0.29–0.79, respectively). Cancer mortality was markedly reduced in patients treated with gliclazide and tolbutamide. According to the retrospective study conducted by Currie et al., combined therapy with sulfonylurea and metformin declined the increased risk of cancer caused by insulin secretagogues (HR = 1.08, 95% CI = 0.96–1.21 for sulfonylurea with metformin and HR = 1.36, 95% CI = 1.19–1.54 for sulfonylurea monotherapy). Nevertheless, sulfonylurea, increasing insulin secretion, can promote oncogenesis directly or indirectly by increasing IGF-1 activity, resulting in pathological stimulation of multiple cellular signaling cascades, facilitating the growth factor-dependent cell proliferation and affecting cell

**Fig. 1: Anti-diabetic drugs and role in cancer disease**

- Insulin
- Sulfonylureas
- GLP-1 agonists
- TZDs
- Metformin
- Caspase 3 reduction
- AMPK dependant mTORC1
- AMPK independant RagGTPase; ROS

**Carcinogenic activity**
- Anti-cancer activity

**Anti cancer drugs**
- Insulin
- Sulfonylureas
- GLP-1 agonists
- TZDs
- Metformin
metabolism.

**Meglitinides**

These group of drugs have similar mode of action like SUs and release more amount of Insulin. But there clinical impact on cancer disease is not evaluated comprehensively, because of limited usage and short duration of action.

**Incretin Mimetics**

These group of drugs usage is continuously increasing, specially of GLP-1 receptor agonist (GLP-1RA) like Exenatide, Liraglutide, Dulaglutide etc. and DPP4 inhibitors like Sitagliptin, Vildagliptin, Linagliptin, Teneligliptin etc. Major advantages of these drugs are better hypoglycemic control with body weight loss and avoidance of hypoglycemia. GLP-1 works through its receptor coupled with G protein and second messenger-cyclic adenosine monophosphate (cAMP) and the molecules of protein kinase A (PKA), and guanine nucleotide exchange factors (GNEFs). GLP-1 regulates differentiation and proliferation of alpha cells and beta cells by increasing insulin synthesis through stimulating transcription of insulin promoter factor (Pdx-1, pancreatic and duodenal homeobox 1) [37]. GLP-1 agonists both increase beta cell mass by cellular expansion (Pdx1) and cause the inhibition of apoptosis (reduced caspase 3). Funch et al. evaluated the relationship between pancreatic lesions and liraglutide after 15 therapy. The incidence ratio for acute pancreatitis for liraglutide was higher than for all non-GLP-1-based therapies (adjusted RR = 1.10, 95% CI = 0.81– 1.49). The IR for pancreatic cancer was lower for Liraglutide compared with non-GLP-1-based therapies (IR = 19.9 vs IR = 33.0, adjusted RR = 0.65; 95% CI = 0.26–1.60). No excess risk of pancreatic cancer was observed with Liraglutide. Similarly, saxagliptin- a DPP-inhibitors, was examined whether it has an impact on pancreatitis and pancreatic cancer incidence in the SAVOR-TIMI 53 trial. A total of 16,492 patients, 40 years old, diabetics 2 type with cardiovascular disease or its risk factors were randomly assigned to saxagliptin or placebo and observed for 2.1 years. The study showed no significant difference in the pancreatitis and cancer incidence between both groups. To date there is no sufficient evidence to show significant coexistence between Incretin mimetics and cancer. There is a need a long term study to evaluate distant effect of these group of drugs on cancer related disease.

**Insulin Sensitizers**

**Biguanides**

Metformin (Dimethylbiguanide) is the first choice of medicine for type 2 DM, to lower glucose level by enhancing cells response to endogenous and exogenous insulin. Moreover, the large cohort studies have demonstrated that in diabetic patients taking metformin the mortality rate from cancer is lower than in those treated with insulin and sulfonylurea. Possible mechanism is believed to be associated with stimulation of protein kinase activated by adenosine monophosphate (AMPK), which inhibits tumor growth (Figure 1). Hosono K et al. reported that nondiabetic patients randomized to the group with 1-month-use of metformin in low dose (250 mg/day) had significantly less rectal aberrant crypt foci (ACF) and significant decrease in the proliferating cell nuclear antigen index. No adverse effect of the drug used was reported. Numerous studies were devoted to a preventive role of metformin against cancer. A review article published in 2013 described the pharmacological factors and complex pathways crucial for the metformin action. They found gap points in the knowledge about the role of drug transporters in normal and malignant tissues or about drug-drug interactions. Pharmacological factors may be the key to the patient response to metformin used in cancer prevention.

**Thiazolidinediones (TZDs)**

TZDs are peroxisome proliferated activated receptor – gamma (PPARγ) agonist and maintain glucose level by increasing glucose protein transport activity and cellular uptake of glucose. Currently only Pioglitazone from this group is available in market, while rosiglitazone and troglitazone are withdrawn because of increase incidences of MI and drug induced liver injury respectively. TZD have also anticancer activities, providing extensive cell growth stop signal, preventing cell differentiation and cancer cell spread through inhibition of the proteasome system (ubiquitin) and the kinase signaling pathway. Chang et al. conducted a case-control study in which there were 606,583 type 2 diabetes patients using rosiglitazone and pioglitazone had a significantly lower risk of hepatic cancer incidence and that was cumulative dose dependent effect of both drugs. In that trial, TZDs were not related to lung or bladder cancer incidence. Additionally, TZDs also promote apoptosis by increasing proapoptotic p53 and reducing anti-apoptotic Bcl-2. Mutations of loss-of-function type of PPARγ have been found in numerous cancer types, e.g. lung, breast, colon, liver, prostate and thyroid cancer. PPARγ-dependent effects of TZDs were observed in preclinical models of hepatic cell cancer (HCC). In the light of the inhibitory role of PPARγ in tumor growth and metastasis, TZDs can be a new target in HCC treatment. The retrospective cohort study was carried out among patients with type 2 diabetes mellitus treated with TZD (n = 18,459 patients) or sulfonylurea (n = 41,396 patients), and it was observed that there was an increased risk of bladder cancer among patients with 5-year-use of TZD vs sulfonylurea therapy (HR = 3.25, 95% CI = 1.08–9.71). The latest reports of USFDA and EMA suggested no overall elevated risk of bladder cancer associated with TZD use but an increased risk of bladder cancer was noted among patients with the highest cumulative dose and the longest exposure to pioglitazone, which may be minimized by the appropriate patient selection and exclusion criteria. Using these medicines in patients with current bladder cancer history or macroscopic hematuria of unknown origin should be avoided. It is advised to assess risk factors for every patient while starting pioglitazone treatment. In general, thiazolidinediones have not been found to increase cancer risk in meta-analyses. However, their association with bladder cancer is currently being assessed in cohort study.

**Other anti-diabetic drugs**

**SGLT2 inhibitors**

Sodium glucose co-transporter 2 (SGLT2 inhibitors) agents promote urinary glucose excretion in an insulin-independent manner to reduce hyperglycemia. SGLT2 is a protein responsible for glucose reabsorption in kidneys. The location of SGLT2 is the proximal tubule of the kidney, which makes this group of drugs relatively safe. The advantages, associated with
SGLT2 inhibition, are low risk of hypoglycemia, urinary caloric-related weight loss, blood pressure decrease due to diuresis and a potentially good effect on the cardiovascular system. Lately, there has been a suspicion of some adverse effects including hypoglycemia, urinary and genital tract infections. According to the FDA, among patients receiving dapagliflozin, there were nine cases of bladder cancer per 5478 patients comparing 1 case per 3136 control patients. Similarly, there were nine cases of breast cancer per 2223 patients taking dapagliflozin compared to one case in 1053 controls. Dapagliflozin demonstrates a similar safety profile in preclinical in vitro, in vivo and in clinical trials in humans due to its simple mechanism of action.

**Alfa-Glucosidase inhibitors**

Alpha glucosidase inhibitors restrain the enzymatic cleavage of oligo- and disaccharides by the enzyme glucosidase in the brush border of the small intestine. Currently there is no any strong evidence to prove Acarbose or voglibose adverse effect on oncological disease.

**Conclusion**

As per this review article discussion among glucose-lowering medications, insulin and insulin secretagogues can be distinguished as drugs that may possibly increase cancer risk. Their mechanisms of action include IR and IGF-1R signaling which enhances proliferation and cancerogenesis. Based on the studies mentioned in this paper, it is suggested that breast, pancreas, liver and colorectal cancer risk may be increased by insulin and insulin secretagogues. On the contrary, insulin sensitizers (metformin, TZD) seem to exert cancer protective effect due to promoting AMPK, PPARg and Egr-1 regulation pathway. Interestingly, the risk of breast, lung and prostate, stomach as well as pancreas, liver and colorectal cancers may be reduced by insulin sensitizers. Cancer incidences in diabetes may be due to metabolic changes, which are done in liver, muscle and fatty tissues. To date there is no any large scale clinical study available to establish long term impact of anti-diabetic agents in cancer disease; whether it is pro-cancer or anti-cancer effect.

**References**

When are we Going to Settle the Diagnostic Criteria of Gestational Diabetes Mellitus?

Veeraswamy Seshiah¹, Sidharth N Shah², Vijayam Balaji³, C Anjalakshi⁴, Rajesh Jain⁵

Abstract

Guidelines to diagnose Gestational Diabetes Mellitus (GDM) have changed a number of times from O’Sullivan & Mahan, Carpenter & Coustan, World Health Organization, American Diabetes Association to that of International Association of Diabetes in Pregnancy Study Group (IADPSG). The IADPSG guideline was based on Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study which was performed in caucasian population only and thus literally cannot be considered as international. Recently a study commented that this guideline needs revision for standardization of this strategy for diagnosing GDM. Based on a prospective study, Diabetes in Pregnancy Study Group India (DIPSI) recommended a single step procedure of diagnosing GDM with 2hr PG > 140 mg/dl after 75g of oral glucose administered irrespective of the last meal timing. This guideline has been approved by the Ministry of Health Government of India, WHO, IDF and Federation of Gynaecologists and Obstetricians Society (FIGO). National Institute of Clinical Excellence (NICE) also recognises cut off value, 2hr PG > 140 mg/dl based on a study in multi ethnic population of UK. Hence, we can safely conclude, A Single Step procedure has settled the criteria for diagnosing GDM.

Introduction

Gestational Diabetes Mellitus (GDM) has been included in the classification of diabetes mellitus, yet there is no global uniformity in the guidelines to diagnose GDM. O’Sullivan first used the terminology gestational diabetes in 1961, following the term meta-gestational diabetes used by Dr Jp Hoet in 1954. Historically, initially the diagnostic criteria was suggested by O’Sullivan and Mahan followed by Carpenter and Couston

Table 1: IADPSG Methodology to derive at the cumulative proportion of GDM

<table>
<thead>
<tr>
<th>FPG 92 mg/dl</th>
<th>136</th>
<th>9.30%</th>
</tr>
</thead>
<tbody>
<tr>
<td>2hPG 140 mg/dl</td>
<td>98</td>
<td>6.70%</td>
</tr>
<tr>
<td>2hPG 153 mg/dl</td>
<td>299</td>
<td>20.40%</td>
</tr>
</tbody>
</table>

Table 2: Prevalence of GDM not adhering to IADPSG methodology (OR= 1.75)

<table>
<thead>
<tr>
<th>FPG ≥ 92 mg/dl</th>
<th>136</th>
<th>9.30%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1hPG ≥ 180 mg/dl</td>
<td>65</td>
<td>4.40%</td>
</tr>
<tr>
<td>2hPG ≥ 153 mg/dl</td>
<td>299</td>
<td>20.40%</td>
</tr>
</tbody>
</table>

Table 3: If IADPSG had accepted OR = 1.5 the prevalence would be the same for FPG, 1 hr and 2 hr

<table>
<thead>
<tr>
<th>FPG ≥ 90 mg/dl</th>
<th>183</th>
<th>12.50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1hPG ≥ 160 mg/dl</td>
<td>190</td>
<td>13.40%</td>
</tr>
<tr>
<td>2hPG ≥ 140 mg/dl</td>
<td>196</td>
<td>13.40%</td>
</tr>
</tbody>
</table>

Where is the problem and what is the problem for not universally accepting IADPSG guidelines?

In the city of Pasadena (USA) in 2008 a consensus meeting of IADPSG group was held. Most of the delegates voted for OR=1.75 for diagnosing GDM. A few countries including India opted for OR=1.5. Based on the Hyperglycaemia and adverse pregnancy outcome (HAPO) study performed in Caucasian population, IADPSG suggested that the diagnosis of GDM can be made when any of the following plasma glucose value meets or exceeds: Fasting:5.1 mmol/L (92 mg/dl), 1- hour:10.0 mmol/L (180 mg/dl), 2-hour: 8.5 mmol/L (153 mg/dl) with 75 OGTT which corresponds to an OR=1.75. IADPSG methodology to derive cumulative prevalence of GDM is by measuring FPG alone, adding measurement of 1-hour plasma glucose identified additional prevalence and finally adding the 2-hour plasma glucose measurement.

Table 4: Comparison between IADPSG and DIPSI criteria on GDM prevalence

<table>
<thead>
<tr>
<th>IADPSG and DIPSI Criteria</th>
<th>n = 1,463</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criteria</td>
<td>Prevalence of GDM</td>
</tr>
<tr>
<td>IADPSG (3 test – F, 1 hr and 2h)</td>
<td>216 (14.6%)</td>
</tr>
<tr>
<td>DIPSI (1 test – 2 hr only)</td>
<td>196 (13.4%)</td>
</tr>
<tr>
<td>Difference</td>
<td>2.2%</td>
</tr>
</tbody>
</table>

¹Distinguished Professor, The Tamil Nadu Dr. M.G.R. Medical University, Chennai, Tamil Nadu; ²Chairman, ³Honorary Secretary, Diabetes in Pregnancy Study Group, India; ⁴Prof. and HOD, Dept. of Obstetrics & Gynaecology, Madha Medical College and Research Institute, Kundrathur, Chennai, Tamil Nadu; ⁵National Health Mission with the World Diabetes Foundation

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With this background, we analysed our data of 1463 pregnant women who underwent OGTT with 75g oral glucose. In this cohort the cumulative prevalence of GDM was 14.60% based on IADPSG methodology (Table 1).

Sacks et al mentioned that, centre to centre differences occur in GDM frequency and relative diagnostic importance of fasting, 1-hour and 2-hour glucose levels. This may impact strategies used for the diagnosis of GDM. If centres follow as observed by Sacks et al, the prevalence would vary depending on the centres which give importance to FPG, 1-hour or 2-hour and the cumulative prevalence will be 20.40% (Table 2). This anomaly could be the reason why in a recent publication, Annunziata Lapolla et al commented even at centres, that accepted IADPSG recommendation, the approach varies and needs revision for standardization of the strategy for diagnosing GDM. Further, many do not follow or may not be aware of the cumulative prevalence suggested by IAPDSG.

**Performance of WHO (2013) and DIPSI criteria are same in outcome**

<table>
<thead>
<tr>
<th>Test</th>
<th>Testing protocol</th>
<th>Number of women with GDM detected and requiring treatment</th>
<th>Number of women with GDM missed</th>
<th>Number of LGA infants in women with detected GDM</th>
<th>Number of LGA infants prevented in women with GDM with treatment</th>
<th>Number of LGA infants in women without GDM or without detected GDM</th>
<th>Number (%) of women requiring an OGTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>IADPSG</td>
<td>75 g OGTT</td>
<td>100</td>
<td>Nil</td>
<td>18</td>
<td>9</td>
<td>76</td>
<td>1000 (100%)</td>
</tr>
<tr>
<td>2013 WHO Criteria</td>
<td>75 g OGTT</td>
<td>100</td>
<td>Nil</td>
<td>18</td>
<td>9</td>
<td>76</td>
<td>1000 (100%)</td>
</tr>
<tr>
<td>FPG only</td>
<td>FPG</td>
<td>52</td>
<td>48</td>
<td>10</td>
<td>5</td>
<td>84</td>
<td>Nil</td>
</tr>
<tr>
<td>*Non-fasting 75 g OGTT</td>
<td>RGT ± 75g OGTT</td>
<td>100</td>
<td>Nil</td>
<td>18</td>
<td>9</td>
<td>76</td>
<td>1000 (100%)</td>
</tr>
<tr>
<td>*DIPSI Criteria</td>
<td>Diagnostic Non-fasting 75 g OGTT</td>
<td>100</td>
<td>Nil</td>
<td>18</td>
<td>9</td>
<td>76</td>
<td>1000 (100%)</td>
</tr>
<tr>
<td>Glucose challenge test</td>
<td>Screening 1-h 50 gGCT ± 75 g OGTT</td>
<td>75</td>
<td>25</td>
<td>14</td>
<td>7</td>
<td>78</td>
<td>220* (22%)</td>
</tr>
</tbody>
</table>

**Fig. 1: Comparison of testing scenarios of GDM-varying diagnostic criteria and outcome**

The methodology of working out cumulative prevalence by applying OR=1.5 which few countries suggested during Pasadena meeting

IADPSG recommended that GDM can be diagnosed if any one value is abnormal in OGTT. This is possible only if OR=1.5 is implemented to diagnose GDM that is, FPG 90 mg/dl (5 mmol/l), 1-hour 160 mg/dl (8.8 mmol/l) or 2-hour 140 mg/dl (7.8 mmol/l) (Table 3).

**A Single Step Procedure**

Diabetes in Pregnancy Study Group India recommends a 2 hr PG ≥ 140 mg/dl (7.8 mmol/dl) with 75g oral glucose administered to a pregnant woman in the fasting or non-fasting state, irrespective of the last meal timing is able to identify women with GDM. Diagnosis of GDM with 2-h PG ≥ 140 mg/dl (7.8 mmol/l) and treatment are worthwhile with a decreased macrosomia rate, fewer emergency caesarean section, serious perinatal morbidity and may also improve the women’s health-related quality of life.

It is interesting, that properly worked out cumulative prevalence of GDM suggested by IAPDSG procedure and DIPSI procedure is almost same with no statistically difference. Using the DIPSI criterion of 2-h PG ≥ 7.8 mmol/l, n= 196 (13.4%) women were diagnosed as GDM. By applying IADPSG recommendation the prevalence of GDM observed was n=214 (14.6%). We found that there was no significant difference (P>0.05) in the discordant pair of diagnosing GDM by the two criteria which in turn implies, that the disagreement in diagnosing GDM by both criteria was not significant (P = 0.21).

Yet another important observation was IADPSG criteria (2013 WHO criteria) and Non-fasting 75g OGTT, (DIPSI criteria) the performance was same (Figure 1).

**Summary**

The comparison of prevalence of GDM by IAPDSG and DIPSI procedures revealed no statistical difference provided proper methodology is applied. DIPSI criteria has been approved by the Ministry of Health Govt of India and International Societies, WHO, IDF and FIGO. DIPSI guideline is also being followed in South Asian counties. In relation to
FPG, there is a considerable variability between countries noted in the HAPO study with FPG diagnosing only 22% of GDM in women in Bangkok and Hong Kong compared with up to 71% in some US centers. A low diagnostic rate of FPG has also been reported in the Asian Indians with a fasting plasma glucose 5.1 mmol/l diagnosing only 22% as GDM. There is no high-quality evidence that women and their fetuses benefit from treatment if only the fasting value is abnormal. RCT shows benefit of treating GDM women identified primarily by post load values. Hence DIPSI prefers 2-hour post glucose of 7.8 mmol/l to diagnose GDM.

Annunziata Lapolla et al. observation mentioned earlier, that even at centers that accepted IADPSG recommendation, the approach varies and needs revision for standardization of the strategy for diagnosing GDM. Even if revised, the glycemic cut off to diagnose GDM in Caucasian women may not be suitable for other ethnic populations due to their anthropometric parameters.

Boyd Metzer et al. suggested, in future clinical practice, simpler and more cost-effective strategies that do not require performing an OGTT on most pregnant women may be developed. DIPSI procedure fits in here. This procedure requires one blood sample drawn at 2hr after 75g oral glucose load for estimating plasma glucose. Even if the test is to be repeated in each trimester, the cost in performing this procedure will be 66% less than the cost of performing IADPSG recommended procedure.

GDM is an important public health problem at all levels of economic development, but immediate and pragmatic considerations, may limit the resources devoted to this issue in developing countries. Thus, DIPSI procedure is feasible, sustainable, evidence based cost-effective and high impact best buy for less resource settings at present. We hasten to add as stated by David Macintyre that for GDM diagnosis, “one size does not fit all.” where possible, diagnostic thresholds should be adapted using local data.

References

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Abbreviated prescribing information: NovoMix™ 30 biphasic insulin aspart LPA 30/70. Presentation: NovoMix™ 30 FlexPen, NovoMix™ 30 Normal. All presentations contain soluble insulin aspart (insulin aspart 100 unit/ml in the ratio of 30:70, produced by recombinant DNA technology) in such physiologically preferred pharmaceutical forms. For further information on the formulation, see section 2.4. Indications: Treatment of patients with diabetes mellitus requiring insulin therapy. NovoMix™ 30 FlexPen is indicated for the treatment of patients with type 1 diabetes, type 2 diabetes, and as an alternative to conventional basal insulin. NovoMix™ 30 Normal is indicated for the treatment of patients with type 1 diabetes in cases when more frequent injections are desirable. NovoMix™ 30 Normal is not intended for use in patients with type 2 diabetes, type 1 diabetes, or as an alternative to conventional basal insulin. Landmark studies have shown that NovoMix™ 30 Normal can provide better glycemic control and lower hypoglycemia risk compared to conventional basal analogues. NovoMix™ 30 Normal has been shown to improve glycemic control and reduce hypoglycemia risk in patients with type 2 diabetes compared to conventional basal analogues.

References:

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Epilepsy with Single Small CT Scan Enhancing Lesion in India-Do we Know all the Answers Yet?

Prahlad K Sethi¹, Nitin K Sethi²

So do we know all the answers when it comes to epilepsy with single small CT enhancing lesion (SSCTEL)? The answer is an emphatic no. In 1985, we were the first to draw attention to these lesions in a publication titled “Appearing and disappearing CT abnormalities and seizures”.¹ Our small series of 11 patients aroused considerable interest nationally and internationally in these lesions. The patient reported were treated with no specific medicines except anticonvulsants and in all these, lesions disappeared spontaneously after a variable periods of 2-3 months. Prior to our publication, due to high incidence of tuberculosis in our population and response of these lesions to anti-tubercular therapy (ATT) it was widely believed that these lesions were tuberculomas. In absence of any biopsy in our series, by a process of exclusion, we thought that these lesions represented some sort of spontaneously resolving infection, peculiar to the Indian subcontinent and referred to it as a “focal encephalitis”. In hindsight the choice of our word was inappropriate and a better term would have been “focal encephalitides”.² Following our publication others reported presumptive diagnoses of these lesions as tuberculoma, cysticercosis, sarcoidosis, larva migrans, transient viral encephalitis, microabscess, post ictal enhancement and even vascular lesions. Rajshekhar documented stereotactic biopsy findings in 6 such cases. In all cases the biopsy was reported as “non specific chronic inflammatory lesions” or “focal encephalitides”.² Five of these lesions were followed up with anticonvulsant therapy and in all of them the lesion reportedly disappeared in three months. The authors disagreed with policy regarding starting these patients on ATT preferring to treat only with anti-convulsants as advised by us. A subsequent paper published in 1991 which included stereotactic biopsy in some of the cases, it was concluded that in Indian epileptic patients with SSECTL, cysticercosis is the commonest etiology. A critical analysis of Chandy’s and Rajshekhar’s paper reveals that in a significant number of their patients, the lesion disappeared or turned into calcific dots with no specific therapy. The authors concluded that disappearing lesions are nothing but a manifestation of a “very benign form of neurocysticercosis”.³ While the disappearance or death and calcification of these parasites in the brain is a natural event in the evolution of most types of benign cerebral cysticercosis, the process can take anywhere from 18 months to 10 years from the time of manifestation. The rapid resolution of the granulomas (disappearance in 4 to 6 weeks) in some patients and the long duration of symptoms in others is difficult to explain except by postulating that this is determined by the individual host immune status and the host-parasite reaction. A point to ponder here is that why in cases reported from the Indian subcontinent 60 to 80% of SSECTL lesions disappear while in South America, where neurocysticercosis is rampant, disappearing lesions have not been commonly reported. How do we explain this paradox?

Currently in India when it comes to SSCTEL pendulum has swung from tuberculosis to cysticercosis. In-fact SSCTEL lesion has become synonymous with cysticercosis. This is unfortunate since many things remain unexplained. No critical analysis of published case series has been carried out. In many cases biopsies were not done to confirm or refute the diagnosis of NCC. Neither was immunoblot assay for cysticercosis antibodies carried out. ELISA was done which has a poor sensitivity. Should we treat these patients with anticonvulsants alone or anticonvulsants along with albendazole? Which patients should be treated with anti-tubercular therapy (ATT)?

We want to stress that SSCTEL is not synonymous with cysticercosis. It is a mixed bag. Lesions suggestive of NCC on CT, in patient with compatible clinical picture residing in endemic areas are and should usually be diagnosed as NCC. Differentiating NCC from tuberculosis though remains a diagnostic challenge. On CT scan or MRI unless you have a scolex, etiology at best is an educated guess. Ancillary investigations such as ESR, Mantoux test (PPD), lymphadenopathy on X-ray or CT chest may help to identify a small group of patients. Serology is not usually helpful. In SSCTEL with negative initial ancillary investigation for tuberculosis the lesion in 60-80% may disappear with no other treatment except anticonvulsants. Either this is a non-specific infection or a very benign form of cysticercosis. Lesion may persist in 20-30%. In these cases we advise to repeat ancillary investigations. Of note some lesions may disappear further in 3-6 months. Albendazole may be tried. If lesion does not disappear or patient clinically worsens, ATT should be initiated. Prognosis is excellent in the large number of cases in which the lesion spontaneously disappears, needing no specific treatment other than AED and is thus aptly described as the “syndrome of disappearing CT lesions”. Question though remains when to do stereotactic biopsy for definitive diagnosis.

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SSCTEL is mainly confined to the Indian subcontinent, age group affected is mostly children or young adults and type of epilepsy is mostly focal (partial). Severity of epilepsy is benign responding usually to one AED. The diagnosis is retrospective and made when the lesion disappears and etiology is nonspecific infection vs. benign form of cysticercosis. When one encounters a case with seizure and SSCTEL, there is no way to predict whether the lesion will disappear on its own or not. Disappearing lesions do not require any other treatment except AED which can be stopped after 1 to 3 months of disappearance of lesion. There is no role of albendazole in such a lesion. Addition of steroids may theoretically reduce edema but exposes the patient to risk of having flare up of tuberculosis, if it turns out to be tuberculosis. Why some lesions do not disappear and persist is not known. Other questions remain unanswered. Is the etiology of disappearing lesion same as that of persistent lesion? Why some lesions heal clean, why others get calcified? In patients with seizure and calcified lesion how long should we administer AED? Do we operate on these lesions or not?

We conclude that the mystery of epilepsy with SSCTEL is far from solved, be it etiopathogenesis, diagnosis, treatment or prognosis. Unfortunately, interest in solving this mystery is already waning. We need large consecutive biopsy studies to answer some of these questions. This a problem unique to our country and one of commonest cause of symptomatic epilepsy in children and young adults. If we do not solve it, no one will. The battle is far from over, in fact it has just begun. We need to have reappearing interest in disappearing lesions.

References


New Drugs and Clinical Trial Rules 2019, What is New? Our Views from Ethical Perspective

Shivapraakash G1, Pallavi LC2

Abstract

A good quality research requires the incorporation of good ethical practices throughout the conduct of the study. An efficient Ethics Committee will facilitate such a research at the site, and can achieve the major objective of ICH-GCP (International Conference on Harmonisation -Good Clinical Practice) guidelines. Awareness of the changing rules among the stakeholders of clinical studies will ensure good clinical practice by safeguarding and protecting the rights, safety and well-being of the research participants. The draft of the New Drugs and Clinical Trials Rules was published in the Gazette of India by central government on March 19, 2019. Keeping abreast of the latest rules are essential for the uninterrupted conduct of clinical studies. We sought to give a summary of important changes in the new rules and to assess those rules from ethical perspective.

Background

Ministry of Health and Family Welfare (MoHFW), Government of India has announced New Drugs and Clinical Trials Rules, 2019, on March 19. New rules have made changes in the roles and responsibilities, functioning of all the stake holders involved in the conduct of the clinical trials. 1 We present here, the critical review of these rules in Ethics Committee (EC) functioning and whether these rules upholds the interest of participants in clinical studies.

What is new?

Ethics Committee for Clinical Trial, Bioavailability And Bioequivalence Study in Chapter III in the gazette mentions about the changes in the EC constitution and training of ethical members. As per the rule atleast 50% of the members should be non-affiliated and all the EC members should undergo timely mandatory training to continue as committee members. This is a welcome move as it empowers non-affiliated members in EC deliberations. The non-affiliated members in the EC are lay person and chairperson exclusively, but it can be any members in the committee like legal expert, social scientist/philosopher/ethicist/theologian, basic medical scientist and clinician. This is important because it facilitates a fairer and unbiased decision making in EC meetings. The increasing pressure from the higher hierarchy and ‘publish or perish’ attitude of many of the institutes/organization may influence the affiliated members to approve studies. Fixing the number of non-affiliated members may balance the discussion in the meetings. The rule also makes it mandatory that every member of EC should have training in Good Clinical Practice (GCP) and participate in the developmental programs timely as specified by the central Licensing authority (CLA). This will certainly update the members with latest changes in the guidelines and provide adequate confidence in

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decision making.

Ethics Committee for Biomedical and Health Research in Chapter IV mentions about a separate EC for research involving basic, applied, operational or clinical research (Biomedical and health research). The institutes/organization should have a separate EC to be registered under the authority designated by the central government in the Ministry of Health and Family Welfare. It also mentions about the functioning and proceedings of such an EC should be in accordance with the National Ethical Guidelines for Biomedical and Health Research Involving Human Participants. This formation of a separate EC from EC’s involved in new drug or investigational new drug studies, will certainly eases the work load and enhances efficiency of EC functioning.

Clinical Trial, Bioavailability and Bioequivalence Study of New Drugs and Investigational New Drugs in Chapter V gives clarification regarding the conduct of research studies at a site which do not have ethics committee. If the site is not having the ethics committee of its own, the study can still be conducted at such sites after obtaining EC approval from another site, provided that such approving EC shall be responsible for the study at the trial site and it is located within 50 km radius from the clinical trial site. This is a welcome move as it ensures to an extent that the members from local ethnic community, who represents the actual population of the region are represented as members and they will be reviewing the studies. This also eases the EC to competently monitor the study at the site regularly.

Another incessant and highly debatable component in any study protocol is compensation. Newer rule in chapter VI emphasize on SAE and its compensation. It has significantly shortened the timeline of lengthy regulatory process involved in SAE. The timeline of independent expert committee to give its recommendation with respect to the cause of SAE and quantum of compensation to Central Licensing Authority is sixty days of receipt of SAE report. Earlier, it was 105 days for death as SAE and there was no clarity on time for SAE’s other than death. It has also set the timeline for decision making by Central licensing Authority (CLA). The CLA should pass the order to the sponsor regarding the SAE by 90 days (earlier 150 days) of receipt of SAE report both in case of death or SAE’s other than death. By this way the lengthy process of compensation path is shortened, which to some extent gives respite to the grief-stricken family.

Import or Manufacture of New Drug for Sale or for Distribution in Chapter X mentions about waiver of local clinical trials if a person or pharmaceutical company intends to sell the new drug approved and marketed in the list of countries specified from time to time in rule 104. We welcome this rule, though some are critical about it.\(^2\)\(^3\) The rule explicitly specifies the type of studies which do not require repetition of clinical studies locally. However, the applicant in such cases must give an undertaking to CLA to conduct phase IV clinical trial to establish the safety and efficacy of such new drug. This rule is certainly praiseworthy from participants and sponsors perspective as it not only avoids unnecessary exposure of participants into study risks but also evades needless usage of resources.

Second schedule in the gazette provides provision for Accelerated approval to a new drug if it is intended for the treatment of a serious or life-threatening condition or disease, where treatment in such cases is not addressed adequately by the available therapy. The efficacy observed in phase II for the investigational new drug may be considered for granting the marketing approval. This will encourage the sponsors to take-up more of such studies and enables early care of such needy patients in serious or life-threatening conditions with promising drugs, without having to wait for long regulatory process.

Conclusion

Overall, the newer rules have made more clearer on the roles and functioning of EC’s and has tried to frame rules carefully without relegating the interests of participants involved in the clinical studies.

References

Coexisting Cerebral Venous Sinus Thrombosis and Posterior Reversible Encephalopathy Syndrome in a Pre-Eclamptic Female

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A 25-year-old woman, G1 P0, at 35 weeks and 3 days of gestation, presented with severe headache for two days duration. She had no history of use

Fig. 1: (a), (b) and (c) Axial T2 weighted MRI sequence shows hyperintense signal changes in cortical-subcortical areas of bilateral parietal and occipital lobes which appear hypointense on T1 weighted sequence (e). (d) Apparent diffusion coefficient map shows no evidence of any restriction of diffusion compatible with vasogenic oedema. (f) MR venogram shows poor visualization of right transverse and sigmoid sinus suggestive of venous sinus thrombosis

Fig. 2: Follow up MRI brain with venography was performed 1 month later which shows (a) and (b) no obvious signal alteration in parietal and occipital lobes on T1 and T2 weighted images which suggest almost complete resolution of the abnormality. (c) MR venogram also shows recanalization of previously thrombosed right transverse and sigmoid sinuses
of oral contraceptives. At presentation her blood pressure and heart rate were 180/120 mmHg and 85 b/m respectively. She was hospitalized at our institute for evaluation of severe pre-eclampsia. Ultrasonographic examination detected a growth restricted fetus corresponding to 30 weeks 0 day gestational age. Fetal heart rate monitoring showed absence of fetal heart rate variability. Two doses of betamethasone 12 mg each were given intramuscularly 24 hours apart for fetal lung maturation. Antihypertensive treatment with 10 mg sublingual nifedipine was started and repeated after 30 minutes. Single live male baby was delivered by cesarean section. Mother’s complete blood counts, renal and liver function tests were within normal limits.

Prophylactic intravenous MgSO4 (1g/h) treatment was started due to prodromal symptoms of headache and visual disturbance and continued 24 h after delivery. On postoperative day 2, patient was consulted with Neurology Clinic since patient’s headache worsened and she had blurring of vision. On neurologic examination papilloedema was detected.

MRI brain with venography was performed which were consistent with posterior reversible encephalopathy syndrome (PRES) and cerebral venous sinus thrombosis (CVT) (Figure 1).

All laboratory tests to detect coagulation abnormalities were within normal range.

Under intensive care setting, Anticoagulation was started with low molecular weight heparin (LMWH) and patient was discharged on postoperative day 7. LMWH was continued for four weeks followed by oral warfarin. After 4 weeks, MRI brain with venogram was performed which was normal (Figure 2).

CVT and PRES are two different diseases with almost similar clinical presentation but different treatment protocols. Both have pregnancy and preeclampsia as common predisposing factors. MRI brain with venogram should be performed to confirm the diagnosis.1,2

It is important for both radiologist and treating physician to recognize the conditions and treat accordingly.

References

Malignant Melanoma Masquerading as Diabetic Gangrene

Prabhat Agarwal¹, Ashish Gautam¹, Manish Bansal¹, Rosmy Jose², Shalini Upadhyay²

A 60 year old male with type 2 DM presented to the outdoors with complaints of blackening of fingers & non healing ulcer on his right thumb for past 6 months. He presented to our OPD for his routine follow-up examination with complaints of a progressively worsening infected right thumb ulcer for over six months (Figure 1). Patient also admitted to having pain and foul smelling discharge from the ulcer. Patient denied any tobacco or alcohol use. Physical examination was unremarkable except for an ulcer on the thumb of his right hand measuring 2 cm*3 cm with an ulcerated area at the base PIP of the thumb. The ulcer was necrotic, black with bleeding and minimal purulent drainage. The patient was started on oral antibiotics with local wound care and surgical consultation obtained. Outpatient surgical evaluation revealed a black eschar with punctuate areas of bleeding after the removal of the eschar. The patient was admitted to the hospital for surgical debridement of the presumptive diabetic necrotic ulcer. Laboratory studies including C-reactive protein (CRP) were within normal limits. Patient is a known case of type II DM for last 6-7 years with good glycemic control on OHA.

Fasting blood sugar was 92 mg/dl &

Fig. 1: Nodular pigmented lesion with ulceration on the left thumb

Fig. 2: X-ray thumb showing bony involvement

Fig. 3: Histology showing Nodular Melanoma Clarke stage IV

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post prandial was 156 mg/dl. Liver and kidney functions were normal. Viral markers were negative. CXR and ultrasound abdomen were within normal limits. His HbA1C was 6.3% indicating excellent control of his diabetes. Radiographic studies of the hand showed soft tissue and bony involvement, however there were no signs of osteomyelitis. In the operating room under careful examination, the edges of the lesion were irregular with hyperpigmentation highly suggestive of a malignancy. An excision biopsy with 2 mm margin was sent for frozen section and pathology evaluation. Pathologic diagnosis was nodular malignant melanoma. The tumor had an ulcerated surface that permeated the papillary and reticular dermis with permeation of subcutaneous tissue. A definitive procedure was subsequently performed that included en bloc amputation and wide excision of the previously excised melanoma along with sentinel lymph node biopsy after localizing the node with radioscntigraphy. Patient’s sentinel lymph node biopsy was positive for lymph node metastasis.

Nodular melanoma is an invasive form of melanoma. Melanoma is a potentially serious skin cancer that arises from pigment cells (melanocytes). In nodular melanoma, malignant melanoma cells proliferate downwards through the skin – this is known as vertical growth. The lesion presents as a nodule (lump) that has been rapidly enlarging over the previous weeks to months. It can arise de novo in normal-appearing skin, or within an existing melanoma of other type. A nodular melanoma can penetrate deeply within the skin within a few months of its first appearance. Nodular melanoma accounts for about 15% of melanoma in Australia and New Zealand. Although more common in very fair skin, it may also occur in those who tan quite easily, and occasionally in brown or black skin. Nodular melanoma is more common in males than females. Most are over the age of 50 when it is diagnosed. The main risk factors for nodular melanoma are: Increasing age, Previous invasive melanoma or melanoma in situ, Many melanocytic naevi (moles), Multiple (>5) atypical naevi (funny-looking moles), Fair skin that burns easily. Nodular melanoma may arise on any site, but is most common on exposed areas of the head and neck. Nodular melanoma presents as a rapidly enlarging lump (over several weeks to months). The characteristics of nodular melanoma include: A) Larger size than most moles – >6 mm and often a centimetre or more in diameter at diagnosis B) Dome-shaped, often symmetrical firm lump C) Single colour or variable pigmentation – most often black, red or skin coloured D) Smooth, rough, crusted or warty surface E) Ulceration or bleeding F) Itching or stinging. One-third of nodular melanomas are not pigmented. They lack the ABCD melanoma warning signs. (Asymmetry, Border irregularity, Colour variation, large diameter.)

References

Introduction

Dengue has become one of the most dreaded tropical infections over the last decade. Apart from the typical manifestations - classical febrile episode, hemorrhagic fever with shock syndromes, various uncommon and severe clinical manifestations are now reported. These include encephalopathy, myocarditis and others. Acute disseminated encephalomyelitis (ADEM) is the most feared neurological complication and its diagnosis and successful management in a young individual.

Case Report

A 24-year-old male, resident of Nagaland, India has been in Delhi for 14 days. He was having high grade fever with chills for past 5 days, found in a state of generalized body movement and altered sensorium(post ictal phase) when bought to our emergency department by relative (sister). Patient was febrile (100°F) with tachycardia (pulse rate-110/min) on initial evaluation with low Glasgow coma score (GCS) of E2V1M2. In view of poor sensorium he was kept on mechanical ventilation, intensive care and steroids eventually leading to successful clinical outcome.

Abstract

Dengue is the most common arboviral disease affecting many countries worldwide. With endemicity of the disease and huge burden, atypical clinical presentations occur posing high diagnostic and therapeutic dilemma. Emerging neurological complications in dengue fever are reported in recent past. Acute disseminated encephalomyelitis (ADEM) is an immune mediated acute demyelinating disorder of the central nervous system following recent infection or vaccination and characterized by multifocal white matter involvement. Early suspicion and diagnosis of such complication is clinical dilemma and it further complicates the clinical scenario. This case report highlights occurrence of such uncommon manifestation of ADEM in commonly occurring dengue fever along with its diagnosis and successful management in a young individual.

Table 1: Routine laboratory investigations

<table>
<thead>
<tr>
<th>Clinical variable</th>
<th>Value (standard units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>10.0 g/dl</td>
</tr>
<tr>
<td>RBC</td>
<td>3.0 lakhs/cumm</td>
</tr>
<tr>
<td>TLC</td>
<td>18,000/cumm</td>
</tr>
<tr>
<td>Platelet</td>
<td>72,000/cumm</td>
</tr>
<tr>
<td>Urea</td>
<td>23 mg/dl</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.6 mg/dl</td>
</tr>
<tr>
<td>Uric acid</td>
<td>3.4 mg/dl</td>
</tr>
<tr>
<td>Sodium</td>
<td>136 mEq/L</td>
</tr>
<tr>
<td>Potassium</td>
<td>4.5 Eq/L</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.9 g/dl</td>
</tr>
<tr>
<td>SGOT</td>
<td>1432 IU/L</td>
</tr>
<tr>
<td>SGPT</td>
<td>1200 IU/L</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>0.9 mg/dl</td>
</tr>
<tr>
<td>PT</td>
<td>13 s</td>
</tr>
<tr>
<td>APTT</td>
<td>40 s</td>
</tr>
<tr>
<td>INR</td>
<td>1.1</td>
</tr>
</tbody>
</table>

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**Table 2: Investigations for infective etiology**

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood for culture</td>
<td>Negative</td>
</tr>
<tr>
<td>Urine for culture</td>
<td>Negative</td>
</tr>
<tr>
<td>Procalcitonin</td>
<td>0.29 pg/ml</td>
</tr>
<tr>
<td>Dengue IgM antibodies</td>
<td>Positive</td>
</tr>
<tr>
<td>Chikungunya IgM</td>
<td>Negative</td>
</tr>
<tr>
<td>Scrub typhus IgM</td>
<td>Negative</td>
</tr>
<tr>
<td>Leptospirosis IgM</td>
<td>Negative</td>
</tr>
<tr>
<td>Malaria peripheral smear and RDT</td>
<td>Negative</td>
</tr>
</tbody>
</table>

**Table 3: CSF examination**

<table>
<thead>
<tr>
<th>Colour</th>
<th>Transparent</th>
<th>Cells</th>
<th>Protein</th>
<th>Glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dengue PCR</td>
<td>Positive</td>
<td>Nil</td>
<td>49 mg/dl</td>
<td>94 mg/dl</td>
</tr>
<tr>
<td>Herpes simplexvirus (PCR)</td>
<td>Negative</td>
<td>Japanese Encephalitis (ELISA) and chikangunya (PCR)</td>
<td>Negative</td>
<td></td>
</tr>
</tbody>
</table>

Bilateral white matter changes were suggestive of demyelination and a diagnosis of acute disseminated encephalomyelitis secondary to dengue fever was provisionally made in view of clinical and radiological findings. (Figure 2). With high grade of suspicion, CSF sample (previously done was preserved) was subjected to Dengue PCR which turned out to be positive in CSF (Table 3).

In view of persisting altered sensorium, and MR imaging suggestive of ADEM, he was started on steroids—methylprednisolone pulse at a dose of 1gm per day followed by oral steroids tapering. The sensorium improved from E1VtM3 to E3VtM5 in 72 hours. Patient was weaned off the ventilator by third day after pulse steroid. He was afebrile after day 5 of admission, however thrombocytopenia (platelet count <1 lakhs) was observed till day 16th of illness which was attributed to dengue illness. He had full recovery with no residual neurological deficits.

**Discussion**

Dengue fever with atypical neurological complications poses serious diagnostic and clinical challenge to clinicians. The neurological complications in dengue have various pathogenic attributes: a) direct viral invasion, b) systemic metabolic complications and c) post infectious immune-mediated acute disseminated encephalomyelitis (ADEM).

Acute Disseminated Encephalomyelitis (ADEM) is a monophasic, immune mediated acute inflammation and demyelination of central nervous system following recent infection or vaccination. Prevalence of ADEM in dengue reported to be 0.4–0.8/100,000/year. With paucity of reports highlighting ADEM in dengue
especially in our settings, to the best of our knowledge, this is one of the initial case reports from India describing ADEM following dengue febrile illness with detection of virus from the cerebrospinal fluid and associated with successful clinical recovery. ADEM in dengue occur during the acute phase or post-infectious phase of dengue (3-19 days) and it involves transient autoimmune response directed at myelin or other self-antigens, possibly by molecular mimicry leading to acute demyelination of the white matter of the brain, spinal cord or both. It is typically a polysymptomatic, multifocal, and monophasic disease with clinical spectrum comprising altered mental status, partial or generalized seizures and focal neurological deficits as also witnessed in this case.

Diagnosis of ADEM is very challenging and vigilant suspicion with early imaging are essential and life saving modalities. Brain imaging through MRI has become the most important test in the early diagnosis of ADEM. Three distinct categories of disease can be classified using MRI criteria. (a) multifocal lesions in the white matter with or without basal ganglia involvement, (b) single or multifocal lesions only in the grey matter and (c) localized lesions in the brain stem, basal ganglia, or cerebellum. Cranial MRI findings in our patient fall into the first category with multifocal white matter involvement. The CSF study is non-contributory in the majority of the cases, but before diagnosing ADEM, infection needs to be excluded by CSF analysis.

We also attained specific microbiological diagnosis of etiological agent in our case through specific dengue virus nucleic acid detection both in blood and CSF using polymerase chain reaction which are specific (100%) and sensitive (85-90%) in early acute phase (retrospectively). Furthermore in due course of clinical illness, the detection of “dengue-specific” IgM antibody was also performed, which has sensitivity and specificity of 90% and 98% respectively after fifth day of illness.

Once the presence of an acute and severe infection has been reasonably excluded after specific microbiological diagnosis, IV methylprednisolone, 25–30 mg/kg/day for 3–5 days, is the most common therapeutic medication administered in clinical practice, based on anecdotal evidence from case reports and clinical series. Our patient also received methylprednisolone for 4 days with remarkable clinical recovery. Intravenous immunoglobulin may be an effective alternative, especially in refractory or relapsing cases of ADEM. Plasmapheresis is another alternative for the steroid non responders. The prognosis, after an acute attack of ADEM, is usually excellent if timely treatment with steroids is instituted as also observed in this case. A close follow up with clinical and radiological monitoring is required to prevent relapses and recurrences.

Conclusion

High index of clinical suspicion is required to warrant attention for uncommon manifestations of a common disease - neurological manifestation in classical dengue fever. Rapid and efficient diagnosis with timely management and close monitoring of such fatal post infectious complications is sine qua non to curb further potential clinical complications and to achieve best possible clinical outcome.

References

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Diarrhoea, Hyperpigmentation and Hamartomatous Polyposis Syndrome

Shubham Jain¹, Ravi Thanage¹, Pravin M Rathi², Suhas Udgirkar¹, Prasanta Debnath¹, Qais Contractor³

Abstract
Cronkhite-Canada syndrome (CCS) is a rare non-hereditary hamartomatous polyposis syndrome of unknown aetiology. It is characterized by diffuse gastrointestinal polypos, dystrophic nail changes, alopecia, cutaneous hyperpigmentation, chronic diarrhea, anorexia and hypogusia. It is associated with a high incidence of gastrointestinal malignancies, mortality and morbidity. Early clinical suspicion and treatment is important. We report an elderly male with CCS who showed clinical and endoscopic improvement with long term corticosteroid therapy.

Introduction
Cronkhite and Canada first described this syndrome in 1955.¹ It is a rare, nonfamilial disorder associated with gastrointestinal polypos mostly hamartomatous, chronic diarrhea, cutaneous hyperpigmentation, alopecia, onychodystrophy and weight loss. Etiology is still unknown but may be immune-mediated since it responds to immunosuppressive therapy.² It has a high morbidity and mortality. Treatment includes nutritional support, glucocorticoids, azathioprine, acid suppression and antibiotics, but there is no consistently recommended therapy.

Case Report
A 56 year old, farmer was symptomatic since 1 year for repeated episodes of watery diarrhea, (voluminous, around 10 - 12 times per day), progressive hyperpigmentation of face, extremities and trunk, associated with loss of appetite and weight. There was no significant past history or family history. Physical examination revealed hyperpigmentation all over the body with no mucosal involvement. He had frontal alopecia, loss of eye brows & axillary hair, and dystrophic changes of nails (Figure 1). Laboratory parameters were normal except a low serum albumin of 2.8 gm/dl. C-reactive protein was also normal. Esophagogastroduodenoscopy (EGDscopy) showed normal oesophagus, thickened nodular gastric folds with multiple sessile polyps in the duodenum. There were multiple sessile polyps from caecum to rectum on colonoscopy, largest measuring around 1 x 1 cm in the caecum (Figure 2). On histopathology, gastric, duodenal and colonic biopsies revealed hamartomatous polypos showing villi flattening and cystic dilatation of glands. Lamina propria was edematous and filled with mixed inflammatory infiltrate predominantly eosinophils (Figure 3). On the basis of clinical features and histopathological findings of hamartomatous polyps in the gastrointestinal tract, a diagnosis of Cronkhite Canada syndrome was made. Patient was started on nutritional support and oral prednisolone 40 mg daily which was to be tapered slowly over 1 year. Patient had symptomatic improvement in diarrhea, reduced hyperpigmentation and no further worsening in dystrophic nails and hair at 2 month follow up. He unfortunately stopped treatment and was lost to follow up. Six months later he presented again with similar complaints. He was restarted on nutritional support and steroid therapy on which he showed improvement within 3 months but has not followed up thereafter.

Discussion
Until now more than 500 cases of CCS have been reported worldwide. Reports have been from Europe or Asia (mainly Japan) and the incidence of CCS is one per million.³,⁴ It is a hamartomatous polyposis syndrome of undefined etiology characterized by disturbances in epithelia of gastrointestinal tract and epidermis. Patients present in fifth to sixth decades of life and male to female ratio is 1.8:1.⁵ An underlying immune mechanism is a possibility as the syndrome is associated with other autoimmune diseases, ANA may be positive and presence of IgG4 antibody in the polyps with response to immuno-suppressants has been reported.² Physical exertion and mental stress may trigger this syndrome.³ Familial predisposition is unlikely and there is only one report of CCS in a father and son of Indian origin.⁶

It is characterized by diffuse gastrointestinal polyps, chronic diarrhea, and protein losing enteropathy with dystrophic skin and nail changes. Goto has divided this disease into five types based on the onset of clinical features: Type I: diarrhea as initial symptom (35.4%); Type II: dysguesia (40.9%); Type III: dominated by dry mouth (6.4%); Type IV: hair loss and nail atrophy (9.1%); and Type V: loss of appetite and malaise, followed by nail atrophy, hair loss but no diarrhea (8.2%).¹ Our patient presented as Type I CCS. Polyposis is seen in 52 to 96% of patients and they are distributed in the entire gastrointestinal tract. In contrast to prior reports the
oesophagus was involved in 12.3% of the cases. 15 Hamartomatous polyps are the most common but inflammatory, adenomatous and hyperplastic polyps can also be seen. 7 Mucosa in between the hamartomatous polyps shows features of inflammation. Adenomatous epithelium foci can lead to malignancy. Risk of gastric carcinoma is 5% and colorectal carcinoma is 9% with sigmoid colon and rectum being the common sites. 8,9 Endoscopic surveillance annually is recommended in these patients. 10 Because polyps have malignant potential, some experts suggest resection of all polyps that are >1 cm in diameter. 11 Similar to our case thickened hypertrophic gastric folds mimicking Menetrier’s disease with polypoid lesions has been reported. 12 Hyperpigmentation is usually found in neck, face, palms and soles. The cutaneous features are attributed to malnutrition or immune mediated and they may precede the gastrointestinal symptoms. Diagnostic ectodermal findings suggest increased IgG4 plasma cells.

Fig. 1: Clinical Findings: Cutaneous hyperpigmentation of (A) hand and (B) feet with dystrophic changes of all nails

Fig. 2: Endoscopy findings: Upper gastrointestinal endoscopy (A) Antrum showing edematous, erythematous mucosa with thickened gastric folds; (B) Duodenum showing multiple sessile polyps; colonoscopy (C) Caecum showing sessile polyp

Fig. 3: Histopathology Findings in low and high power field: (A) Antrum (B) Duodenum (C) Caecum biopsy showing changes of Hamartomatous polyp

Treatment regimens reported in the literature are variable. Corticosteroid, Anabolic steroids, various antibiotics, dietary supplementation, Ranitidine, Cromolyn sodium, Mesalazine or 5-aminosalicylic acid and symptomatic treatment have all been used. 2,13-15 Steroid therapy and nutritional support are the mainstays of medical treatment. The currently recommended high-dose prednisolone ≥ 40 mg/day is optimal for active CCS. 16 Average duration for clinical improvement and polyp regression is around 12 months. 11 Steroids should be tapered after endoscopic confirmation of polyp regression. Rapid steroid reduction can cause early relapse. Sustained endoscopic remission has been associated with reduced cancer risk. 5 Steroid-sparing therapies such as Azathioprine, cyclosporine, anti-TNF-alpha agent, can be used in steroid-resistant cases in order to induce or maintain clinical remission. 17,18 Surgery is reserved for bowel complications, such as severe protein-losing enteropathy, persistent haematochezia, malignant transformation and for reducing polyp burden. Mortality rate is up to 55%, frequently due to complications like anemia, gastrointestinal bleeding, congestive heart failure, septicaemia, intussusception and osteoporotic fractures. 3,19

Conclusion
Clinicians should be vigilant about CCS in patients with unexplained diarrhoea, gastrointestinal polyposis and ectodermal abnormalities.

References
‘Gym Tonic’ and Quadriparesis

Himmatrao S Bawaskar¹, Parag H Bawaskar², Pramodini H Bawaskar¹

Abstract
We report a case of acute onset quadriparesis which occurred after consumption of some drugs which were illicitly prescribed to our young patient by his gym instructor. The deadly concoction of so-called gym-thon (Cyproheptadine and dexamethasone) led to hypokalaemic paralysis in our patient.

Introduction
Intensive and aggressive body-building by regular gym routines has become a passion in youngsters. Even educated people put their lives at risk by blindly surrendering to the demands and advice of sharks that run the fitness industry. It is easy to fall prey to the tactics employed by underqualified fitness or wellness coaches who lure potential clients with dubious weight-loss or weight-gain remedies. Often, the victims have to pay a heavy price for this, at times at the cost of their lives.

Case
A 33 years male reported with complaints of sudden onset weakness in all four limbs in the form of inability to stand from squatting position, inability to button his shirt or hold the tea cup since one day. On the previous day, he developed sudden onset weakness of all four limbs, which were total at onset and non-progressive. He was unable to stand up from the floor bed or walk without support. The weakness had not improved with the medications dispensed by his family physician. He denied any history of preceding febrile illness or vaccination. There was no history of similar episodes in the past. He informed us that, in order to gain weight, he had enrolled in a gym 13 months ago. But at that point he denied consumption of any herbal, ayurvedic or diuretic drugs. He admitted that he had gained 15 kilograms weight in the past year after enrolling in the gym. After repeated grilling about illicit drug intake, his wife revealed that he had been taking some medicines on the advice of his gym instructor for the past thirteen months. She was immediately advised by us to make the tablets available for scrutiny.

On examination of the young male, we recorded stable vital parameters except for tachypnoea. On nervous system examination, higher functions and cranial nerves were normal. We found MRC grade 3 power in distal muscle and grade 2 power in proximal muscles of both upper and lower limbs. Tendon reflexes were not elicited even with reinforcement. No sensory or autonomic abnormalities were detected.

His ECG showed heart rate of 70 beats per minute, prolonged QT interval (QTc= 504 ms), widened QRS complexes (0.12 seconds) and prominent U waves in anterior leads (Figure 1 A) Blood sugar was 112 mg/dl, Thyroid function was normal. Serum potassium levels were remarkably low i.e. 1.9 meq (normal 3.5 to 5.6 meq/dl). He was admitted in the intensive care unit and under cardiac monitoring, potassium chloride infusion in Mannitol was started by intravenous route. At the end of six hour of admission power in all limbs had returned to Grade 5. Serum potassium level was 3.9 mEq/dl. The electrocardiogram showed regression of U waves and normalization of QRS duration (0.10 seconds) (Figure 1B and 1C). By then, the offending tablets were made available and found to be containing Cyproheptadine 4 mg and Dexamethasone 0.5 mg (Figure 2). This was corroborated on the next day by the gymnasium trainer as well. The patient was counseled about avoidance of such quick-fix remedies in the future. On follow-up, he is found to be in good health without any residual weakness.

Discussion
Steroid induced hyperinsulinemia leads to an increased NA+/K+-ATPase pool in the skeletal muscle. This exacerbates hypokalemia by promoting the renal excretion of potassium, resulting in muscle weakness. Dexamethasone which doesn’t have minercorticoid effects may cause paralysis by this method. At times hypokalemia may be the clue for diagnosis of chronic steroid consumption. Dexamethasone improves well being and appetite and redistribution of body fat result in Cushing syndrome. Weight gain in present case is because of excessive appetite stimulation by Cyproheptadine. Cyproheptadine is a H1 blocker. It directly inhibits serotonin stimulation by Cyproheptadine. Cyproheptadine is a H1 blocker. It directly inhibits serotonin stimulation by Cyproheptadine. Dexamethasone improves well being and appetite and redistribution of body fat result in Cushing syndrome. Weight gain in present case is because of excessive appetite stimulation by Cyproheptadine. Cyproheptadine is a H1 blocker. It directly inhibits serotonin stimulation by Cyproheptadine.

Fig. 1: ECG on admission (A) showing widened QRS duration and prominent U waves in V1-V6. ECGs (B and C) 6 hours and 24 hours respectively showing regression of U wave and reduction in widened QRS

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antagonist could have antagonized the dexamethasone action and prevented the development of Cushing’s syndrome in our patient.3

Conclusion
Our case highlights the importance of rigorous and thorough history-taking for there-in lies the clues to diagnosis. This case should also serve an eye-opener for fitness-seekers who blindly entrust their health in the hands of unqualified ‘wellness coaches’.

References

Plasmodium vivax Malaria Presenting with Acute Systemic Capillary Leak Syndrome

BK Das¹, Niraja Agasti², YK Sushma Singh², Ayan Midya²

Abstract
Systemic capillary leak syndrome (SCLS) is a very rare disorder characterized by hypotension with hemococoncentration, hypoalbuminemia without albuminuria and generalized edema, the etiology of which are snake bites, viral hemorraghic fever, drugs, sepsis, upper respiratory tract infection, Hanta virus and West Nile virus infection and serum paraproteinemias. Typically, the syndrome manifests in two phases: initial capillary leak phase characterized by edema, serous effusion, hypotension which is followed by phase of volume overload or recruitment phase. Treatment is in the form of fluid replacement, inotropic support and vasopressor therapy during capillary leak phase and diuretics during volume overload phase. Prognosis of this disease is very poor. Here we are presenting a rare case of plasmodium vivax with SCLS.

Introduction
Systemic capillary leak syndrome was first described by Clarkson in 1960. Thus, it is also known as Clarkson’s syndrome.¹ It is characterized by hemoconcentration, hypoalbuminemia and generalized edema. This syndrome is due to capillary hyperpermeability with massive extravasation of plasma containing macromolecules smaller than 200kD and sometimes up to 900kD. It has two phases: capillary leak phase and volume overload phase. Capillary leak may occur as a part of SCLS or secondary to systemic inflammatory response syndrome. This syndrome is observed in patients who demonstrate a state of generalized leaky capillaries following toxemias, shock syndromes, poisoning and ischemia-reperfusion injuries. It can lead to generalized edema and multiple organ failure. Volume overload state is characterized by flash pulmonary edema as sudden relocation of the extravasated plasma. There are two causes of SCLS: primary or idiopathic SCLS caused by serum paraproteinemias in 90% of cases and secondary SCLS caused by drugs (interleukin-2, gemcitabane), snake bite, viral hemorrhagic fever, toxins (abrin, ricin, sanguinarine), hypothyroidism, diabetes mellitus, sepsis related, viral infections like Dengue, Hanta, West Nile. We report a rare case of acute systemic capillary leak syndrome (SCLS) due to plasmodium vivax malaria infection.

Case Report
A 38 years male developed bilateral pedal edema (Figure 1) after second day of intermittent high temperature with chills and rigor. In next 4-5 days he noticed gradual distension of abdomen alongwith heaviness of chest and shortness of breath. He consulted a local doctor and was referred to us in a state of shock on 10th day of fever. There was no history of nausea, vomiting, headache, diarrhea or abdominal pain. Urine output and bowel motions were normal during this period. There was no past history of oliguria, facial puffiness, pedal edema or respiratory distress. He had normal built and he was restless. His BP was 90/60 mm of Hg and pulse was 116/min, low in volume. Respiratory rate was 28/min and there was bilateral pedal edema. JVP was not elevated. Abdomen was soft, distended with mild ascites and splenomegaly and no other organomegaly or tenderness. Breath sounds were diminished in both lower lung fields with features of pleural effusion. Cardiovascular examination was normal. His blood sugar at admission was 109 mg/dl. He was treated with antibiotic ceftriaxone, inotropic agent i.e. dopamine and fluid replacement keeping in mind that he might be suffering from sepsicemia. Blood parameters revealed Hemoglobin-10.5 gm %, hematocrit-39, Total leukocyte count-8,700/cu mm, Platelets count-110,000/cu mm, ESR-32 mm. Blood slide as well as malarial antigen was positive for Plasmodium vivax malaria. Serum urea-27 mg/dl, creatinine-0.8 mg/dl, Ca⁺⁺-8.3, Na⁺-128,
K+ -3.8. Liver function test showed normal bilirubin level (1.0 mg%), total serum protein-5.4 gm%, albumin-2.5 gm%, SGPT-20 IU/L, SGOT-38 IU/L, alkaline phosphatase-322 IU/L. Urine examination showed no obvious abnormality and Albumin: creatinine ratio was 2:1 mg/mmol. Blood cultures for both aerobic and non-aerobic bacteria were negative. X-ray chest showed normal cardiothoracic ratio with blunted costophrenic angles (Figure 2). USG revealed mild ascites, splenomegaly and bilateral pleural effusion. Aspiration revealed exudative pleural effusion and AFB stain was negative. Echocardiography with color Doppler shows good left ventricular function with ejection fraction of 60%. Patient was started with chloroquine 300 mg base, 2 tabs stat and then 1 tab after 12 hr, 24 hr and 36 hr of initial dose along with other supportive treatments. Patient showed signs of recovery from shock and edema and on 6th day after treatment his respiratory distress resolved within 1 to 4 days at which time patients are at increased risk for death from flash pulmonary edema due to rapid fluid remobilization. In addition to the acute form, a few cases of chronic SCLS have also been reported with history of progressive generalized edema with pericardial and pleural effusions, associated with a serum paraproteinemia. Diagnosis is made clinically and by exclusion of other diseases that cause similar signs and symptoms, most notably sepsis, anaphylaxis, angioedema and common causes of generalized edema like congestive heart failure, kidney failure, liver failure and nephrotic syndrome. The diagnosis should be suspected in patients with unexplained edema, increased hematocrit, hypoalbuminemia and hypotension. In absence of definite sepsis, cardiovascular, renal and hepatic dysfunction a diagnosis of acute systemic capillary leak syndrome was made in our case.

The pathophysiology of SCLS is still unclear but influenced by hemodynamic forces, cytokines and inflammatory mediators. Components from the serum of patients with acute SCLS in contrast to healthy subject mediate early and extensive endothelial apoptosis in vitro is associated with oxidation injury. So oxidation injury mediated endothelial apoptosis might be a mechanism of development of SCLS. Though SCLS is associated with monoclonal gammopathy in 90% of cases, absence does not rule out its diagnosis and an infection and inflammatory response could be a triggering factor.5,6

Conclusion

SCLS is a very rare clinically diagnosed disorder with poor prognosis as it can cause death both in capillary leak phase and volume overload phase. In absence of definite diagnostic test it can be easily missed as it shares many of its signs and symptoms with more common causes of edema and respiratory distress. High degree of suspicion and early diagnosis can save the patient and malarial fever to be kept in mind as a treatable cause of SCLS specially in tropical countries like us.

References

Scrub Meningitis Complicated by Multiple Cranial Nerve Palsies and Cerebellitis

Pratibha Himral¹, Kailash Nath Sharma², Susheel Kudial³, Surinder Himral⁴

Abstract
Meningitis or meningoencephalitis is a known complication of scrub typhus. Focal neurological deficits are rarely reported including hemiparesis, quadriplegia and isolated cranial nerve palsies. Here we are reporting a 24 years female who presented with fever, headache, ptosis, diplopia, facial deviation and unsteadiness of gait due to scrub typhus. Scrub typhus can present as acute or subacute meningitis complicated by multiple cranial palsies and cerebellitis. Hence it needs to be differentiated from acute bacterial meningitis and tubercular meningitis as delay in diagnosis and treatment will affect the morbidity and mortality.

Introduction
After its re-emergence, scrub typhus has become an important cause of morbidity and mortality in patients presenting with febrile illness during monsoon and post-monsoon season. This zoonotic disease is caused by Orientia tsutsugamushi mainly targeting the endothelial cells. Majority of sequelae due to scrub typhus are the outcome of ‘Rickettsial vasculitis’. Clinical manifestation include fever, headache, muscle pain, gastrointestinal symptoms, maculopapular rash, eschar and regional lymphadenopathy. Complications appear from second week onwards in form of multiorgan dysfunction. Central nervous system involvement is a known complication of scrub typhus and manifestations include aseptic meningitis, meningoencephalitis, acute disseminated encephalomyelitis, cerebral infarction, cerebellitis, subdural haemorrhage and isolated cranial nerve palsies but focal neurological deficit is rarely seen.¹ Here we are presenting a case of scrub meningitis complicated by cerebellitis and multiple cranial nerve palsies in early part of illness. To the best of our knowledge, no such case has been reported.

Case History
A 24 years female was admitted with five days history of fever associated with chills followed by diffuse and severe headache on day three of illness. On the morning of day four, she noticed sudden onset drooping of left eyelid, diplopia and deviation of angle of mouth along with unsteadiness of gait with tendency to fall towards left. There was no history of vomiting, convulsions, altered consciousness, any other cranial nerve involvement or weakness of any part of the body. There was no respiratory, abdominal or urinary complaint. On examination, she was febrile with a temperature of 102.3°F and haemodynamically stable. There was an eschar over the left axilla (Figure 1 Eschar).

On neurological examination, there were infra-nuclear palsies of oculomotor nerve with pupillary sparing, glossophyaryngeal nerve, vagus nerve and hypoglossal nerve and supra-nuclear paralysis of facial nerve on the left side. Cerebellar signs such as gait ataxia, dysmetria and dysdiadochokinesia were present on the left side. Examination of motor and sensory system was normal. Rest of the systemic examination was normal. On investigations she had leukocytosis (13600/mm³) with neutrophilia (90%), normal platelet count (2,50,000) and erythrocyte sedimentation rate was 40 mm in 1st hour. Her liver function tests (LFTs) showed total serum protein-7.1gm/dl, serum albumin-3.8 gm/dl, total serum bilirubin-1.66mg/dl, direct bilirubin-1.0mg/dl, aspartate aminotransferase-196 U/litre, alanine aminotransferase 98 U/litre. Renal functions were normal. Weil-Felix test was positive (OXK-1:320). Her IgM ELISA (inBios International, Inc. USA) was positive for scrub typhus. Blood and urine cultures were sterile. Chest X-ray, Widal agglutination test, peripheral blood film for malarial parasite were normal. Results of cerebrospinal fluid examination are shown in Table 1.

Non contrast cranial computed tomography on day of admission showed multiple white matter hypodensities in both the cerebellar hemispheres. Postcontrast gadolinium MRI brain done on third day of admission revealed multiple hyper-intensities in right frontoparietotemporal region, right thalamus, left temporal lobe and bilateral cerebellar hemispheres with focal meningeal enhancement on T2 and fluid attenuated inversion recovery images with evidence of restricted diffusion and corresponding low ADC values (Figure 2 MRI of patient obtained 3 days after admission showing hyper intensities in right

Table 1: Results of cerebrospinal fluid analysis

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Results</th>
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<tr>
<td>White cell count (per mm³)</td>
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<tr>
<td>Differential count (%)</td>
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<td>Lymphocytes</td>
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<td>Proteins (mg/dl)</td>
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<td>Sugar (mg/dl)</td>
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<tr>
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<td>ADA (IU/L)</td>
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</tr>
<tr>
<td>PCR for tuberculosis</td>
<td>Negative</td>
</tr>
<tr>
<td>PCR for Herpes simplex virus</td>
<td>Negative</td>
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frontotemporoparietal region and left cerebellar hemisphere on T2 weighted fluid attenuated inversion recovery and diffusion weighted images (A-C) and Figure 3 T1 weighted postgadolinium MRI showing focal meningeal enhancement in left cerebellar hemisphere. Furthermore, there was swelling of gyral spaces in frontoparietotemporal region. No enhancement was evident on post gadolinium scan (Figure 3). Patient was given doxycycline 100 mg twice a day. She became afebrile on day three of therapy and her total leukocyte count and LFTs were repeated on day seven of admission and were normal. Ninth, tenth and twelfth cranial nerve palsies improved during hospital stay. Third and seventh nerve palsies resolved completely when patient was seen in follow up after one month. Follow up non-contrast cranial computed tomography done on 13th day of admission showed decrease in the size of the hypodensities.

**Discussion**

Neurological involvement in scrub typhus may be attributed to *O. tsutsugamushi* being an intracellular obligate parasite of professional and non-professional phagocytes that invade the central nervous system as a part of systemic infection.² Pathologically, mononuclear cell meningitis, typhus nodule, perivascular cuffing of arteries, focal haemorrhages in parenchyma and meninges and degeneration of ganglion cells may be present.³ Meningitis or meningoencephalitis is the most common manifestation reported in 15%-50% patients with scrub typhus in different studies. Common symptoms include fever (100%, mean duration of fever 7.0±3.5 days to 8.4±3.5 days), headache (76-100%), meningism, altered sensorium (4-50%). Seizures, motor weakness, and cranial nerve deficit are also present.²³⁶ CSF findings of scrub typhus include mild lymphocytic pleocytosis (<250 cells/µL) with mononuclear predominance, raised proteins and normal sugar. Similar CSF findings may be seen in viral encephalitis, tubercular meningitis and leptospirosis.² Our patient had fever, headache and CSF findings were consistent with scrub meningitis. Presence of *O. tsutsugamushi* in CSF was demonstrated by Pai et al by nested PCR and Karp and Boryong genotypes were isolated from CSF.⁴ An equal proportion of Karp (27%) and Keto (27%) genotypes has been reported from our state.⁴ Meningeal enhancement may be seen in neuroimaging studies. In our patient, clinical cerebral involvement was present on the left side though in neuroimaging studies bilateral cerebellar lesions were seen. Involvement of cerebellum in scrub typhus occurs rarely. Cranial nerve involvement is seen in ~25% of patients with symptomatic involvement of abducent, facial and vestibulocochlear nerve with or without meningitis.³ Besides eighth nerve, ischemia of the glial part and mononuclear infiltrations of other cranial nerve including trochlear, facial, oculomotor, abducent, vago-glossopharyngeal complex and spinal nerve was documented by Noad et al.⁹ Two mechanisms have been proposed for cranial nerve involvement in scrub typhus though exact mechanism is not known. These mechanisms involve either direct invasion of central nervous system by *Orientia tsutsugamushi* leading to acute stage vasculitis or secondary immune mechanism causing vasculitis of vasa vasonum of nerve.¹⁰ In our patient involvement of third, seventh, ninth, tenth and twelfth cranial nerves was seen in early part of illness and deficit improved completely during convalescent period. If the patient of scrub meningitis is presenting during first week of illness with cranial nerve involvement then it poses a diagnostic dilemma as similar clinical presentation is seen in acute bacterial meningitis.

Presences of eschar, multiorgan dysfunction, ALT level more than 60 IU/L, CSF pleocytosis with lymphocytic predominance and response to doxycycline strongly favour the diagnosis of scrub meningitis. Doxycycline is the drug of choice in scrub typhus but its penetration into brain or cerebrospinal fluid is only 15-30%. Rifampicin can be used for treatment of scrub meningitis which has a minimum inhibitory concentration of 0.0625–0.5 µg/mL.⁷

**References**

Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL)

Priyanka Vikas Kashyap¹, Sunil Jee Bhat², Sunil Bhatt³, Manira Dhasmana³

Abstract
Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) is one of the most common heritable cerebral arteriopathy. Responsible for stroke and dementia in young adults and can be diagnosed by skin biopsy. We report a case of a 42 year old man with recurrent transient ischemic attacks (TIA). A detailed neurologic examination revealed poor score in MMSE (20/30) defect mainly seen in recall, repetitions. Executive dysfunction, memory and language impairment were also found. Motor system examination revealed grade 3 power in right upper and lower limb with more severe weakness of distal muscles in form of grip weakness and slippage of chappals. Neuroimaging and genetic analysis for Notch-3 confirmed the diagnosis. Imaging studies suggested greater involvement in the temporal and frontal lobes along with deep areas of the brain.

Introduction
Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) is a hereditary early onset vascular disease causing recurrent ischemic subcortical infarcts featured by migraine with or without aura, cognitive impairment, psychiatric symptoms and progressively severe neurologic deficits.

The clinical manifestations include recurrent cerebral ischemic episodes, progressive cognitive deficit, and migraine mainly with aura, psychiatric symptoms and dementia.¹

Case Report
A 42-year-old, right-handed male presented with right sided hemiparesis and speech slurring. He had a similar episode 4 years back which recovered near-completely over a 10 month period. His wife noted that he had episodes of slurring of speech and sometimes transient weaknesses of right hand twice in the past 2 years. He also had sensitivity symptoms (paresthesia) and motor signs (faciobrachiocrural hemiparesis) to the left side two months prior to this stroke. The patient reported frequent episodes of migraine without any aura, frequency being more than four attacks per month. Clinical evolution progressed to cognitive impairment and worsening motor symptoms. Detailed physical and neurological examinations were done. The Mini-Mental State Examination (MMSE) revealed poor scores in recall, repetition, naming areas, total score being 20/30. However, an interview focusing on occupational aspects and activities of daily living (ADL), including the conducting and handling of personal finances, reported no significant functional problems, a finding corroborated by his wife. Electrocardiogram, laboratory investigations including glucose levels, lipid profile, and coagulation studies were normal. His serum vitamin B 12 was low (171pg/ml) and Homosysteine level was high (24.07umol/L). 2D echocardiography was normal.

The patient was submitted to MRI brain with MR angiography of neck vessels which revealed extensive areas of hypersignal in subcortical white matter, predominantly frontal, temporal and parietal, external and internal capsules, brain stem and presenting lacunar infarcts in the temporal and right parietal regions seen in T2 and FLAIR images (Figures 1, 2). Genetic analysis was carried out (DNA Laboratory INDIA located at Hyderabad) based on the direct DNA sequencing of exons 3 and 4 of the Notch 3 gene (chromosome 19), which revealed a heterozygous missense mutation c.397C > T (p.R 133C) at position 153 consistent with CADASIL diagnosis, confirming the etiology of the disease. We have called his siblings for clinico-radiological evaluation to look for any familial association.

Discussion

The term CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) refers to a hereditary systemic microangiopathy caused by mutations of the NOTCH3 gene located on chromosome 19.² It presents in young people with migraine attacks and recurrent ischemic strokes, leading to a progressive subcortical cognitive decline over several years.³

Though CADASIL is known for subcortical infarcts but intracortical involvement has been reported by Jouvent et al.⁴ Our patients presented with a clinical course and a radiological pattern similar to those described previously in the literature. The rarity of the case was the key factor to report it. There is delay in diagnosing because of low level of suspicion which is main cause for diagnostic errors. Multiple sclerosis was the most frequent misdiagnosis. Cognitive complaints in patients with advanced stages were common and the executive abilities were impaired in many cases as was in our case.

Several methods for diagnosing CADASIL have been proposed. The first Magnetic Resonance Imaging (MRI) characteristics of CADASIL were described in 1991.⁵ Notch 3 testing has been proposed as the primary
diagnostic approach, allowing the detection of 90% of affected individuals. Despite concerted research efforts, the mechanisms underlying cognitive dysfunction in CADASIL remain unclear. However, evidence suggests disruption of corticosubcortical or corticocortical connections and lacunar infarcts. Gain of function for the mutant Notch3 protein is likely mechanism for the CADASIL mutations and could be related to Notch3 activation.

Our patient had decreased MMSE score indicating cognitive impairment. Several large studies have investigated the profile of cognitive decline in CADASIL. In the present case, changes were evident in global performance (MMSE) and in language, memory, apraxia and executive function domains.

In the language domain, both naming ability and semantic verbal fluency (animal’s category) were compromised. Deficit in verbal fluency is frequently observed in CADASIL showed by Buffon et al. Memory in patients with CADASIL compromise in register/learning (immediate memory) and free recall and preserved recognition. Ideomotor apraxia has been reported in 15% of individuals with lesions confined to the thalamic or lenticular region. Periventricular deep white matter may play a crucial role in the development of apraxias, particularly ideomotor. Buffon et al suggested executive dysfunction in almost 90% of individuals fewer than 50 years of age and the mechanisms may be related progressive damage to white matter augmented ventricular volume.

Conclusion

This case exhibited a characteristic neuroimaging pattern, of the disease and was further confirmed by Notch-3 gene analysis, the signature of CADASIL. The rarity of the case and its association with apraxias made it the focus of interest. The disease is probably underdiagnosed and should be considered in young patients with recurrent small subcortical infarcts leading to dementia, but also in the patients with migraine especially with aura, transient ischemic attacks, and mood disturbances, where MRI reveals typical abnormalities in the subcortical white matter and basal ganglia. Our patient had low vitamin B12 levels, whether this attributed to cognitive impairment is still under consideration. Early imaging of siblings can clinch the familial occurrence and may benefit other members of the family by cognitive rehabilitation.

Acknowledgement

We would like to thank Prof. Elisabeth Tournier - Lasserve, Head of the service of the Laboratoire Génétique Moléculaire de l’Hôpital Lariboisière–Paris, for carrying out the genetic analysis.

References

Florey & Chain-Penicillin Isolation

Jayant Pai-Dhungat

Alexander Fleming published his landmark paper discussing antibacterial effect of Penicillium Notatum mould in 1928. However, Fleming was somehow unable to convince a true chemist to help him extract and stabilize precise antibacterial compound found in the mould broth filtrate. Had Fleming been able to do so, penicillin for medicinal use would possibly have developed a decade earlier. Domagk’s discovery of antibacterial activity of Prontosil (Sulpha) in 1939 raised the issue of chemotherapy with a new urgency. Isolation of new antibacterial stimulated matters further, when WW-II gave important military incentive to fight against infection.

Two people came forward to push Fleming’s work on penicillin further in 1940. Howard Walter Florey (1898-1968): an Australian-English pathologist and Ernst Boris Chain (1906-1979) a German-English biochemist at the Oxford University revisited Alexander Fleming’s neglected work on penicillin. Howard Florey obtained his medical degree in 1921 from University of Adelaide. He travelled to England as a Rhodes Scholar studying at Oxford and Cambridge and received a PhD. at Cambridge (1927). Ernst Chain was educated in Germany and received his degree in Chemistry and Physiology from Wilhelm University of Berlin (1930). He immigrated to England in 1933 due to Hitler’s anti Semitic policies. Chain was working under Sir Frederick Hopkins on phospholipids, when he was invited to Oxford to join Howard Florey (1935). Florey and Chain went on to isolate the actual anti-bacterial agent from the mould and obtained a yellow powder from mouldy broth that contained the agent, rather quickly in 1940. Chain was primarily responsible for working out the chemical process in isolating and concentrating the germ killing agent in penicillin. He theorized structure of penicillin, which was later confirmed by X-ray crystallography done by Dorothy Hodgkin. He also discovered enzyme penicillinase, which destroys penicillin. The duo showed that penicillin effectively cured bacterial infection in mice and a few human subjects having life threatening infective illnesses. These experiments proved that penicillin would work effectively in humans. Huge stumbling block was that it was enormously difficult to isolate enough penicillin to treat even one person.

Due to the pressures of WW-II in 1940, the Oxford team under Howard Florey as lab supervisor and Ernst Boris Chain as a biochemist discovered how to isolate the germ-killing agent penicillin. Florey devised a method of mass production of the drug; but the yield was low. Florey travelled to the US along with his team member Norman Heatley in order to interest pharmaceutical companies in producing the drug, and informed them about the process. Florey’s team succeeded in efficient extraction of penicillin and by 1945, Penicillin production became an industrial process for the Allies in WW-II. After the war, penicillin became an important medical work horse. Unlike other antibiotics discovered later, penicillin has remarkably low toxicity save for the anaphylactic shock.

Florey was knighted in 1944 & Chain in 1969. The 1945, Nobel Prize in Physiology or Medicine was shared amongst bacteriologist Alexander Fleming, pathologist Howard Florey and biochemist Ernst Chain.

Professor of Medicine (Retd.), TN Medical College, Hon. Physician, Bhatia Hospital, Mumbai, Maharashtra
Complementary mechanisms of Oxyphenbutazone and Metformin to address multiple facets in T2DM

Reduced hyperglycemia
Surrogate Tobacco Advertising during Durga Puja in Kolkata

Rudrajit Paul

1Associate Professor, Department of Medicine, Midnapore Medical College, Midnapore, West Bengal

Sir,

The Durga Puja is a famous Hindu religious festival in Kolkata. Idols of the Hindu goddess Durga are worshipped in makeshift temples called “pandal” which are surrounded by art installations, colourful lights and music. This is celebrated every year, over 5—6 days, all over the city. Huge number of people, roughly estimated at 15-25 million, visit the city during this festival from all over Eastern India. A large number of these visitors are children and adolescents. Naturally, all the major consumer product companies have their ads and displays placed prominently at strategic locations all over the city to attract potential customers. This correspondence is about surrogate advertising techniques used by tobacco companies during this festival. Tobacco is responsible for many of the diseases with which patients come to the internist.

During the current (2018) Durga Puja in Kolkata, large temporary billboards displaying ads for “pan masala” could be seen all over the city near the puja pandals. Multiple brands were present and separate displays were made in all the major languages, i.e. English, Bengali and Hindi. The billboards were placed at prominent places, near bus stops, at entrance of pandals or at street crossings. One brand also used innovative techniques like 3D cut-outs and artistic installations. The billboards featured the name of the product prominently with eye-catching cut-outs and artistic installations. The advertisement and Regulation of Trade and Commerce, Production, Supply and Distribution) Act (2003). However, like the alcohol industry, the tobacco industry is also adept at surrogate advertising. Surrogate advertising is a technique of duplicating the brand image of one product in a different product, when the original product is banned from being advertised in the mass media. This is also known as brand extension and is a devious way of bypassing the law.

In India, advertisement of tobacco products in any form is completely prohibited. This is according to the Tobacco Products (Prohibition of Advertisement and Regulation of Trade and Commerce, Production, Supply and Distribution) Act (2003). However, like the alcohol industry, the tobacco industry is also adept at surrogate advertising. Surrogate advertising is a technique of duplicating the brand image of one product in a different product, when the original product is banned from being advertised in the mass media. This is also known as brand extension and is a devious way of bypassing the law.

In India, tobacco is popular in both smoking and smokeless forms. The smokeless forms are more popular. The GATS 2015-16 report for India showed that currently almost 30% of adult men and 13% of adult women in India use smokeless tobacco (SLT). Thus, SLT is a multi-billion dollar industry in India and its advertisement campaigns are equally aggressive.

A study from Bangalore, India assessed the effect of surrogate advertising on consumers. Gutkha and other SLT products are often promoted under the surrogate of pan masala. It was seen that potential consumers were well aware of the actual product and such surrogate advertising actually increased the consumption of the tobacco product. Thus, such prominent advertising of tobacco surrogate brands during a festival will likely result in an increase in consumption, especially among the adolescents.

Even if such advertisements are taken at their face value, that is, as ads for pan masala, still their displayed products are not harmless. Pan masala contains areca nut. In recent scientific studies, areca nut (supari) has been shown to have various adverse effects on different systems and moreover, it is also a carcinogen. Thus, advertisement of even these products in a festival frequented by adolescents is not advisable.

This issue is highlighted because the Indian government is trying to curb the menace of tobacco in various ways. Recently a famous Hollywood actor was severely criticized for endorsing a “mouth-freshener” pan masala brand. Physicians are, and should be, at the forefront of tobacco control and elimination programs. Physicians are often summoned by the media and/or administrative officials as experts. Thus, physicians should be aware of such advertising techniques and their effect on different sections of the society. This will help in better health education to patients.

References


Coinfections in Tropical Fevers: An Emerging Phenomenon

Sujeet Raina

Assistant Professor, Dr. Rajendra Prasad Govt. Medical College, Kangra, Himachal Pradesh

Sir,

I read the update article “Tropical coinfections: clinical implications” by Yeolekar ME with great interest. I congratulate the author for the nicely written update and the journal for timely publishing the article. In tropical countries like India, acute undifferentiated fevers particularly in monsoons and post monsoon period pose a serious challenge in terms of morbidity, mortality and economic
Serological and clinical evidence of areas with high endemicity for diseases often. They should be more common in tropical countries. The coinfections cover both the diseases. Coinfections is rational to treat with drugs which without molecular diagnostic tests. It dual positivity can't be ruled out cases. 10 patient among ten IgM ELISA positive chain reaction (PCR) based molecular these infections is limited. Polymerase of various serological tests among time serological tests used for the reactivity while reporting coinfections? these single point serology based tests clinical features and IgM ELISA. Are coinfection diagnosis are based on of scrub typhus and leptospirosis (ELISA), which use cutoffs derived enzyme linked immunosorbant assay (ELISA), use which cutoffs derived from low endemicity areas. Majority of scrub typhus and leptospirosis coinfection diagnosis are based on clinical features and IgM ELISA. Are these single point serology based tests for leptospirosis and scrub typhus giving fallacious results due to cross reactivity while reporting coinfections? Is it the limitation of single point of time serological tests used for the diagnosis? Data on cross reactivity of various serological tests among these infections is limited. Polymerase chain reaction (PCR) based molecular assays confirmed scrub typhus and leptospirosis dual infection in only one patient among ten IgM ELISA positive cases.10 An important question arises now? In daily clinical practice the possibility of cross reactivity and genuine serological dual positivity can't be ruled out without molecular diagnostic tests. It is rational to treat with drugs which cover both the diseases. Coinfections can be a serious public health issue in tropical countries. The coinfections scenarios need to be reported more often. They should be more common in areas with high endemicity for diseases causing acute undifferentiated febrile illness. Studies should be designed for molecular confirmation and ruling out cross reactivity. It is also necessary to develop a robust local population based seroprevalence data based on the serological tests.

References

Uttar Pradesh Association of Physicians of India Position Statement: Betel Quid (Paan) and Diabetes
Shridhar Dwivedi1, Nisha2
1Senior Consultant Cardiologist, National Heart Institute, New Delhi, “PhD Research Scholar (Clinical Research),” Delhi Pharmacetical Sciences and Research University, New Delhi
Sir,
We have read above Position Statement on Betel Quid and Diabetes with great interest as it is of pan Indian relevance and has global impact too.1 Betel quid is chewed by many people not only in Uttar Pradesh but also in Madhya Pradesh, Bihar, Jharkhand, Chhattisgarh, Gujarat, and by migrants from these states to other parts of India like National Capital Region.2 We also know that diabetes has become an epidemic like disease in urban and rural part of entire India. Betel quid contains betel leaf (Piper betel), areca nut (Areca catechu), slaked lime (Ca(OH)2), tobacco (Nicotiana tabacum) and katha (Acacia catechu) some of which mainly betel nut and tobacco are highly addictive, and have diabetogenic activity besides adverse cardiovascular effects and oncogenic potential.3 Another aspect of betel quid saga is its adverse health effect on the betel quid sellers due to continuous exposure to betel quid containing resins extract of Acacia catechu, baked shell lime, betel nut and tobacco. This leads to a condition called as ‘Betel Quid Seller Syndrome’ characterized by central obesity, diabetes, insulin resistance and/or ischemic heart disease.4 This syndrome is due to prolonged hours of sitting, absorption of nicotine and arecoline through damaged finger and palm epithelium in betel quid sellers. It is therefore important that we should strongly emphasize upon betel quid sellers to think of alternative occupation in view of the known hazard of developing diabetes, premature coronary artery disease (CAD) or oral cancer because of their prolonged contact with areca nut, nicotine and other toxic ingredients present in betel quid. In fact, one of our young betel quid seller who had central obesity and prediabetes switched over to the hardware shop fearing possibility of future diabetes. His father and two other elder siblings who are in the same trade have already full blown diabetes, hypertension and CAD.
The recommendations made in the above Position Statement hold true not only for entire India but in other South Asian Countries and countries which have sizable migrant Indians because of their proclivity to betel quid chewing habits.

References
3. Dwivedi S, Agarwal A, Dev M. All in the name of flavor, fragrance and freshness: Commonly used smokeless tobacco preparations in and around a tertiary hospital in India. Indian Journal of Medical Research 2012; 83:841.
3 LAWS OF MOTION

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<table>
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<tr>
<th>CHROMIUM PICOLINATE (250 mcg)</th>
<th>ZINC (15 mg)</th>
<th>SELENIUM (100 mcg)</th>
<th>LYCOPENE (5 mg)</th>
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<tr>
<td>VIT B2 (100 mcg)</td>
<td>VIT B6 (3 mg)</td>
<td>VIT B12 (25 mg)</td>
<td>POLY C &amp; A (0.5 mg)</td>
</tr>
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