TAPIJ

The Journal of the Association of Physicians of India
(Tamil Nadu State Chapter)

Vol. 9 Issue : 1 Jan - Apr 2017

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Association of Physicians of India

Tamil Nadu State Chapter

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Editor's Note

Dear colleagues,

Greetings of the season!

The objective of TAPIJ is to publish up-to-date, quality original research papers alongside relevant and insightful reviews. I am delighted to present first issue of TAPIJ of 2017, which has several informative articles, which covers various aspects of Medical sciences and unusual case reports.

This issue has two Original articles one on vascular dementia prevalence, causes and course and the second article on focused on Neurocysticercosis.

We have a good review article on the "Role of vitamin – D in Type 2 Diabetes Mellitus". This article emphasizes the importance of vitamin D in Diabetes particularly Type 2 Diabetes. Second review focused on the Antidiabetic agents with comorbid conditions.

This issue also includes, interesting case reports on Polycythemia vera – a rare presentation and a unique case of Pancreatic tuberculosis causing obstructive jaundice – a diagnostic dilemma was also discussed in detail.

Besides these, we have our usual articles on ECG, Dermatology and toxicology sections presents the valuable articles. This edition comes as a combination of various specialties to enlighten the readers and will add food for thought.

I am sure that this issue of TAPIJ with its articles on various aspects of medicine will explore both clinical and academic knowledge.

With warm regards,

Dr. Vijay Viswanathan

Contents

Original article

TAPI Journal Vol. 9, Issue 1, January – April 2017

Vascular Dementia Prevalence, Causes and Course

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Abstract:

Introduction: Cerebral small vessel disease is the most common cause for vascular dementia and characterized by the triad of leukoareosis, lacunar infarcts and microbleeds. In several ways the course is like degenerative dementia unlike the large artery disease. Its course can be partly arrested and prevented. Therefore it is important to know the factors which converts asymptomatic radiological feature in to clinical disease. *Patients and methods:* Patients with radiological evidence of small vessel disease were grouped in to those with and without dementia and submitted for detailed clinical, neuropsychological, biochemical and genetic factors which might play a role in vascular cognitive impairment. *Result:* Our study did not reveal any significant correlation with any parameter other than high blood pressure and non vegetarian diet. *Conclusion:* Hypertension control and adopting a vegetarian diet appears to be protective against development of vascular dementia in patients who have radiological evidence of cerebral small vessel disease.

Keywords: Small vessel disease, vascular cognitive impairment, RAAS system.

Key message: The single most important factor in preventing small vessel disease from progressing to vascular dementia is control of blood pressure and vegetarian diet.

Introduction:

Vascular dementia is the second most common dementia and unlike the degenerative dementias it is partly reversible and controllable. But mortality is high in view of co morbidities like heart disease. Small vessel disease is the most common cause for vascular cognitive decline (1). disease of deep penetrating vessels being end arteries will present with microbleeds, lacunar strokes and leukoareosis. Binswangers disease was first described in 1978 (2). German pathologist Otto Binswanger first published in a weekly in 1894 what he described as encephalitis subcorticalis pregressiva and later his student Alzheimer described pronounced atrophy of white matter and fatty degeneration of thin arterial and venous walls with narrowing of their lumen. Usually persons of both gender above 55 to 75 years are affected and may show symptoms referable to one lacune, progress fast, can have seizures, stepwise deterioration with periods of stability, pseudobulbar, pyramidal, extra pyramidal and gait changes with apathy, inertia, disinterest poor memory judgment altered affect and variable degree of involvement of language and visuospatial functions (3, 4). The common conditions associated are Hypertension, Amyloid angiopathy, CADASIL, Pseudoxanthoma elasticum, Antiphospholipid antibody syndrome, and to some extend with diabetes mellitus, polycythemia, syphilis, mucinous adenocarcinoma, thrombocytosis, hyperlipidemia and hyperglobulinemia (5, 6). Homocysteine is a sulphur containing amino acid derived as a intermediary product during metabolism of methionine becomes increased when vitamin B6, Folate, B12 which are required for its metabolism are deficient. This is also postulated to be increase the risk of small arterial strokes (7) as hypertension is the most important risk factor genes of Renin Angiotensin Aldosterone system (RAAS) are candidate genes in the pathogenesis of small vessel disease (8). Some authors reported that cognitive decline correlates with severity of periventricular white matter contributed to memory loss but not subcortical white matter (9, 10). As we have a ageing population and vascular

dementia might be preventable there is a need to identify the factors determining this condition.

Patients and methods:

Hundred and seven patients presenting at the Neurology OPD and Geriatric Clinic at NIMHANS are detected to have cerebral small vessel disease with cognitive impairment have been studied. A written informed consent was obtained from all participants. The following diagnostic criteria have been used for selection of patients

- Patients with cognitive impairment
- Neuro-imaging studies (cranial MRI) showing evidence suggestive of SVD

Exclusion criteria included sub cortical infarction >1.5 cm diameter, cortical infarction of any size, a potential source of cardiac source of embolism (Adams et al., 1993) and large vessel cerebrovascular disease, defined as carotid or vertebral artery stenosis >50%, mixed dementia and past history of CNS dysfunction.

Control group:

One hundred, age and gender-matched, subjects with SVD but without cognitive impairment have been studied. Informed consent was obtained for the study. After explaining details of the research to the participating subjects and obtaining a written informed consent, the following have been carried out. The participants were reviewed by one neurophysician and senior resident in neurology as per protocol.

i. Demographic data including details regarding the risk factors for stroke was recorded.
ii. After detailed clinical examination, the clinical data and blood pressure was recorded.
iii. HMSE, DSMIV for vascular cognitive decline and Hachinski Ischemic Scores were applied.
iv. 5 ml venous blood collected after an overnight fast from the median cubital vein for the genotyping and biochemical assay.

All patients underwent MRI, axial T2-weighted images were evaluated by Fazekas scale was used to score leukoaraiosis. Neuropsychological evaluation was done as per NIMHANS battery.

DNA Isolation: DNA was isolated from EDTA blood using phenol-chloroform-Isoamyalcohol protocol (Sambrook et.al. 2001).

Quantification of DNA: Quantification of DNA was done using Nanodrop ® 2000C (Thermo scientific, USA) according to manufacturer instruction.

Genotyping was done for Angiotensin-converting-enzyme (ACE) insertion/deletion polymorphism (ACE I/D *rs*.4646994, Aldosterone synthase (*CYP11B2* -344T/C) polymorphism (rs1799998): Aldosterone synthase (*CYP11B2* -344T/C) polymorphism (rs1799998): Angiotensin II receptor type I - *AT1R* 1166A/C gene polymorphism (rs5186): Endothelial nitric oxide gene 4b/4a variation (*eNOS* 4b/4a).

Serum angiotensin converting enzyme activity (ACE):

ACE activity in serum was measured spectrophotometrically using N-[3-(2-Furyl) acryloyl]- L -phenylalanyl-glycyl-glycine (FAPGG) as substrate according to Simonetta Ronca-Testoni method (Clin Chem 1986., 29/6, 1093-1096).

Plasma nitric oxide (NOx) level:

Plasma nitric oxide level was determined by measuring the stable metabolites, nitrite and nitrate by enzymatic reduction of nitrate to nitrite using nitrate reductase enzyme and combined detection with the acidic Griess reagent using the method of Verdon et al (1995).

Statistical analysis:

Statistical analysis was performed using SPSS 16.0 (IBM Corporation USA) and Graphpad prism v.5.0.1 (graph pad software USA). Differences between cognitive impaired and cognitively normal cases were assessed by chi square test for categorical variables and the t-test

for continuous parameters. The allele frequencies were compared between groups with the chi-square test. Univariate odds ratio (OR) and 95% confidence intervals (CI) were estimated. The combined effect was determined by the generation of a contingency table for logistic regression analysis, p value <0.05 was considered to be statistically significant.

Results:

Hundred and seven patients (67 males and 40 females) diagnosed with SVD and with cognitive impairment were recruited as cases after obtaining an informed consent. 100 subjects (68 males and 32 females) with normal cognitive function but with SVD were included as controls. The mean ages of patients and controls were 63.72±8.72 and 65.79±10.23 years, respectively. The demographic details of the study subjects are given in Table 1.

Table 1: Demographic features of the study participants

Features	Cases (n=107)	Controls (n=100)	P Value
Gender (male/female)	67/40	68/32	0.489
Mean age (years ± SD)	63.72±8.72	65.79±10.23	0.13
Obesity (%)	10.5	15.5	0.331
Smoking (%)	34.83	20.45	0.037*
Hypertension (%)	58.33	50	0.252
Diabetes mellitus (%)	44.21	48.8	0.524
Dyslipidemia (%)	21.17	22.7	0.805
Hyperhomocysteinemia (%)	31.7	25.53	0.664

*SD- standard deviation, *P value <0.05 considered as statistically significance*

Table 2 shows the clinical features of the study participants. Depression, behavioral problems, speech abnormalities, extrapyramidal features and gait abnormalities were more prevalent in cases. History of TIA and hemiparesis was more common in controls.

Table 2: Clinical features in the study group.

Features	Cases (n=107)	Controls (n=100)	*P Value*
Dementia(%)	100	0	
Depression (%)	7.14	0	0.0088*
Behavioral problems (%)	16.32	2.17	0.0009*
Speech abnormality (%)	6.12	3.26	0.35
Giddiness and vertigo (%)	4.08	15.2	0.008*
Cranial nerve palsy not due to 7th nerve (%)	1.02	2.17	0.52
Headache(%)	7.14	16.30	0.03*
Extrapyramidal symptoms (%)	2.04	1.08	0.6
Hemiplegia (%)	23.46	43.47	0.003*
Gait abnormality or due to hemiplegia (%)	3.06	0	0.05
Transient ischemic attack (%)	3.06	14.1	0.0058*
Others** (%)	3.06	5.43	0.41

***Others- neck pain, backache, incontinence: *P value <0.05 considered significant*

Table 3: MRI Fazekas scale v/s Cognitive function test

	Cognitive function test	Grade 01	Grade 02	Grade 03	Grade >3	p value
Cases	NNPB	53.5±9.46	61.17±17.60	58.05±19.53	56.72±15.3	0.745
(N=107)	HMSE	13±3.74	18±4.29	17.038±4.16	15.82±4.87	0.07
Control	NNPB	96.54±3.20	96.17±2.58	95.33±3.41	95.59±2.92	0.62
(N=100)	HMSE	29±1.60	28±1.5	28±2.08	27±1.8	0.03

NNPB-NIMHANS neuropsychological battery test, score of 100(<88- cognitively impaired); HMSE- Hindi mental state examination, score of 31 (<24- cognitively impaired); SD- standard deviation; P value <0.05 is considered statistically significant. All values are (Mean±SD)

Genotype frequencies of selected polymorphism and biochemical investigation results:

ACE I/D polymorphism and serum ACE activity:

Genotype distribution details of *ACE* I/D and serum Angiotensin converting enzyme (ACE) activity with respect to polymorphism are presented in table 5 and 6. Odds ratio at 95% CI was found to be 1.15(0.64-2.06) for II/DD genotype and 0.8434 (0.5-1.42) for II/ID genotype with no statistical significance. The mean serum ACE activity in cases and control was 24.14±14.52 and 27.14±14.52 respectively. With respect to Genotype, Serum ACE activity in cases and control was found to be 18.15±9.09, and 21.59±11.53U/L in II genotype individuals, 24.4±12.31 and 26.1±11.009U/L in ID genotype individuals, 30.5±14.74 and 37.29±18.1U/L in DD genotype individuals respectively. Even though significant difference in ACE activity was found within the genotypes, no significant difference was observed between cases and control ACE in relation to genotype.

Aldosterone synthase gene polymorphism (Cyp11b2 -344T/C) angiotensin type II receptor 1 (AT1R 1166 A/C) gene polymorphism:

Genotype distribution details of *CYP11B2* 344T/C and *AT1*R 1166A/C gene polymorphism are presented in table 9.Odds ratio at 95% CI was found to be 1.1023(0.66- 1.82) for TT/TC and 1.01(0.44 - 2.32) for TT/CC genotype in *CYP11B2* 344T/C polymorphism with no statistical significance. Similarly for *AT1*R 1166A/C polymorphism the odds ratio at 95% CI was 0.82(0.39 - 1.73) AA/AC genotype. As we did not find CC genotype in both cases and controls, Odds ratio for AA/CC genotype could not be calculated.

Observations:

The present study was taken to assess prevalence, risk factors and course of cognitive impairment in cerebral small vessel disease. Most of our patients with SVD among both cases and controls belonged to the 7th decade. Statistical significance was observed between cases and controls with respect to some clinical features like depression, gait abnormality and extrapyramidal

Table 04: Genotype frequency distribution of ACE I/D polymorphism

Genotype	Frequency		odds ratio at 95%CI	p Value
	Cases n=107 (%)	Controls n=100 (%)		
Wild (II)	38 (35.5)	33 (33.00)	1 (Ref)	
Hetero (ID)	37 (34.5)	41 (41.00)	0.8434 (0.5007 - 1.4206)	0.522
Mutant (DD)	32 (29.0)	26 (26.00)	1.1503 (0.6409 - 2.0645)	0.639

**P value <0.05 is considered as significant*

signs, but actual correlation could not be established due to limited samples number. Four patients passed away due to other system complications. Among the patients with cognitive dysfunction 74 patients were available for regular follow up and among them 50 patients had a stable course. It was also observed that, severity in Fazekas grading did not correlate with HMSE and Neuropsychological scores. Premorbid educational status did not alter the cognitive scores or HMSE scores and this indicates lack of association with cognitive reserve. Genotyping studies in *ACE I/D, CYP11B2 344T/C, AT1R 1166A/C* and *ENOS (4b/4a, 786T/C, and 894G/T)* did not find any difference in cases and controls as the frequency distribution of genotypes in both cases and controls did not significantly vary, except for the presence of TT genotype of e*NOS* 894 G/T polymorphism in cases only and none in controls. Hypertension appeared to be the single most important factor in cerebral small vessel disease.

Conclusion:

Hypertension and non vegetarian diet appears to be the single most common cause for cerebral small vessel disease and its complications. The severity of white matter scores as well as RAAS system associated gene polymorphisms do not seem to influence the course of white matter changes to dementia. Therefore regular blood pressure monitoring and co morbidity assessment is recommended in all vulnerable population.

Acknowledgement:

Ad–hoc project ICMR genetic determinants of cognitive impairment in cerebral small vessel disease IRIS-CELL NO 2011 -02620; file no 54/5/2011 -BMS

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Neurocysticercosis - An observational Study in a Tertiary Hospital

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Abstract:

Introduction: Neurocysticercosis (NCC), one of the major parasitic infections of the human central nervous system (CNS) is caused by the larval stage of the tapeworm *Taenia solium* andis very much under reported. Most common symptoms are seizures, raised intracranial pressure, blindness, encephalopathy and multifocal neurological deficits including dementia. Disease modifying treatment cannot be initiated in most patients as they have multiple lesions (MLNCC) and carry a very high risk of fatal encephalopathy once the organism dies. Therefore, only symptomatic treatment is given resulting in significant morbidity. So there is a need for prevention rather than treatment. ***Patients and methods:*** 60 patients were recruited for the study as per Del Brutto's criteria for definite or probable case of NCC. Details were collected from patients who were considered as probable NCC, regarding the demographic details like age, gender, socioeconomic status, symptoms, duration of illness, dietary habits and home. Patients were examined for muscle and ocular cysticercosis. Stool examination was not done in all patients. Radiological examination was done in all patients for location, number and stages of the lesions. CSF was analysed for cell count. The author also visited meat shops and slaughter houses. ***Results:*** Common presentation was seizures followed by headache, difficulty in vision and cognitive dysfunctions. Multiple NCC was observed in majority of patients in which vesicular stage cysts were common. The common cause for infection was low socioeconomic status, lack of proper sanitation and improper meat inspection. It was observed during our study that measly pork is not only sold in market but also considered a delicacy specially kept for children as it loses its elasticity and gets cooked easily. ***Conclusion:*** As against literature, our patients had multiple lesions of same age suggesting, probable infection from a single proglottid in a single exposure. It is likely that these are due to autoinfection and the patient is probably both the primary and intermediary host. Cognitive dysfunctions is seen in the active stage of the disease and correlated with alteration in cytokine levels and cholinesterase levels and number of lesions rather than site of the lesion.

Keywords: Neurocysticercosis, Prevention, Epilepsy, Encephalopathy, Treatment options

Key message: NCC is an eminently preventable but serious neurological disease with a wide spectrum of neurological manifestations carrying serious morbidity and mortality. Community based interventions with proper toileting facilities will prevent humans becoming the intermediary host by faeco-oral contamination. Shifting to vegetarian diet, cooking meat properly, banning measly pork by proper meat inspection will prevent primary infection and auto infection causing NCC.

Introduction:

Neurocysticercosis (NCC) is one of the major parasitic diseases of the central nervous system (CNS) in human beings, caused by the larval stage of the tapeworm, *Taenia solium*. Pigs are the intermediate host for the parasite and humans are the accidental hosts. NCC is the major cause of adult onset epilepsy in developing countries. It has been declared as "an important, neglected tropical disease" in 2010 by World Health Organization (WHO) as it ranks low in the government health sector policies (1). The disease is prevalent in regions where pigs roam freely,

people eat undercooked pig meat, open defecation is common, sanitary facilities are lacking and meat inspection is insufficient (2).

Globally, 4 million people are infected with *T. solium* and for each tapeworm carrier about 10 people are infected with the cyst. Approximately, 50 million people are estimated to have cysticercosis across the world which may be an under reported value as there are no systematic population based studies till date (3).

NCC is usually associated to poverty and low socioeconomic conditions of a region. It is reported to be endemic in Latin American countries, sub Saharan Africa and many Asian countries including India. Due to immigration and travelling *T.solium* infections are reported in non-endemic regions like USA and European countries also. The disease is not reported much in Muslim dominated countries all over the world which might be due to the prohibition of pig meat consumption (4).

India being a diverse nation, each geographical region has different ethnicities, religious and cultural practices, food habits, hygienic conditions and sanitary facilities. These factors influence the prevalence of NCC also. The disease is reported mostly in the North Indian states like Uttar Pradesh, Punjab, and Bihar etc. which may be mainly due to the lack of sanitary facilities in these states (5). In our Institute we have observed most patients were from Dharmapuri in Tamil Nadu where sanitary facilities are not utilized properly. However, it is not reported from Kashmir which is a Muslim dominated state and Kerala where sanitary facilities are properly maintained.

Life cycle:

Human beings are the definitive hosts and pigs are intermediate hosts for the tapeworm. When humans consume undercooked pig muscle infected with the taeniid cysts, the scolex evaginates due to the action of gastric juices and gets attached to the intestinal wall with its suckers and hooks. Then, it gradually starts developing into an adult tapeworm with gravid proglottids at the distal end, the condition known as taeniasis. Each proglottid contains thousands of taeniid eggs which are shed to the environment each day through the faeces. The humans may become accidental intermediate hosts when these eggs re-enter humans due to autoinfection or through a carrier. Once these eggs reach the gastrointestinal tract of humans, they hatch and release the oncospheres. These microscopic oncospheres then penetrate the intestinal wall and enter the bloodstream to reach different muscles of the body (6). They may enter any of the organs of the human body and establish in the tissues to develop into a cyst; the condition known as cysticercosis. Neurocysticercosis (NCC), the most severe form of the disease is caused when the cyst happens to enter and establish in the CNS (7).

The larvae may enter and establish in brain parenchyma (parenchymal NCC), ventricular system, subarachnoid space or spinal cord (extraparenchymal NCC). The symptoms of the disease are pleomorphic and depend on the number, location, size and stage of the cysts and influenced by the immune response of the host also. Seizures are the most common clinical manifestations of NCC followed by raised intracranial pressure, headache, focal neurological deficits, cognitive decline and other psychiatric manifestations are observed. Diagnosis is according to the Del Brutto's criteria for NCC (8), (9). Antiparasitic drugs should be recommended only after complete evaluation of the patient as it is not recommended if the number of the lesions is more than 5 in CNS or if there is any cyst in ocular regions. This is because of the fact that after the administration of the antiparasitic drugs like Praziquantel or Albendazole, the cysts may start to degenerate and release antigens which may elicit immune response and in turn cause neurological morbidities (10).

Patients and Methods:

Sixty patients who visited the National Institute of Mental Health and Neurosciences, Bengaluru from April 2012- December 2016 were

recruited for the study as per Del Brutto's criteria for definite or probable case of NCC after obtaining ethical consent. Details were collected from patients who were considered as probable NCC, regarding the demographic details like age, gender and geographical location; data regarding the socioeconomic status like education, occupation, income and details of the symptoms, duration of illness, dietary habits, home sanitation including availability of toilets and sanitary conditions in their domicile. Patients were examined for presence of any muscular or skin nodules which may represent muscle cysticercosis. Ophthalmic examination was done to detect ocular cysticercosis. Stool examination was not done in all patients. Radiological examination was done in all patients either by CT or MRI for location, number and stages of the lesions. CSF was analysed for cell count, other chronic infections and cholinesterase levels. ACE levels were estimated and compared with control CSF of patients undergoing spinal anesthesia. The author also visited meat shops and slaughter houses.

Results:

Out of 60 NCC patients, 27 were females and 33 were males (Figure 1). Age ranged from 14- 62 years. Most of the patients were from semi-urban area and had primary education. Majority of them were either labourers or farmers with a low socioeconomic status. Among 60 patients, 42 were non vegetarians in which 38 had history of pig meat consumption also.

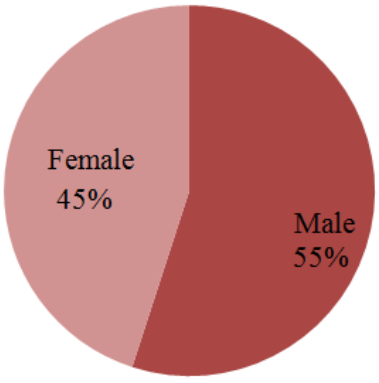


Figure 1. Percentage of Male and Female NCC patients.

Duration of illness ranged from 1 month to 2 years among the patients. 41 out of 60 patients had seizures as the most common and initial symptoms. This was followed by cognitive dysfunction in 15 and headache in 12 NCC patients. 6 patients had complaints of vision among which 2 had cysts in occipital lobe and 2 had lesions in ocular muscles (Figure 2). 4 patients did not have any toilet or sanitary facilities in their surroundings. Among those patients 2 belonged to Dharmapuri in Tamilnadu. One of the patients from that village had disseminated cysticercosis (Figure 3).

Figure 2.

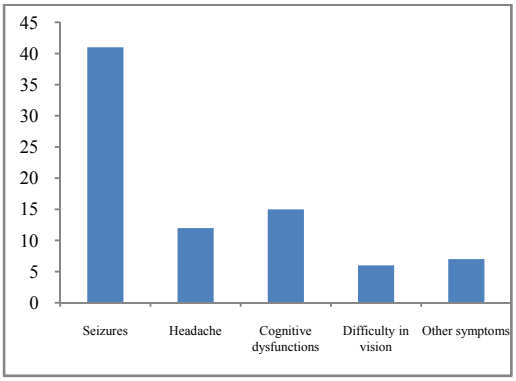
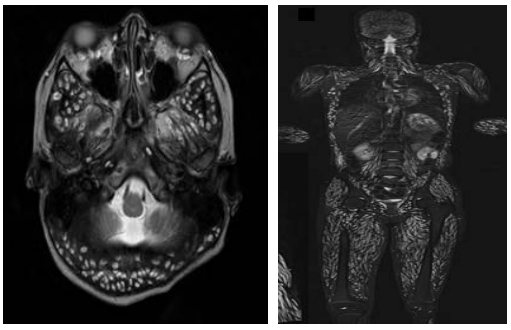


Figure 3.



Figuer 2 a) Symptoms in NCC patients,
2. b) Ocular NCC Figure 3. Disseminated cysticercosis

Muscle cysticercosis was observed in 8 patients during examination of skin and muscles for any nodules (Figure 4). Muscle biopsy of the patient with muscle cysticercosis (Figure 5) was done for the comparative proteomic analysis of *T. solium* cyst from human (Figure 6) and pig (Figure 7) muscle by Mass spectrometry (unpublished data).

Figure 4.

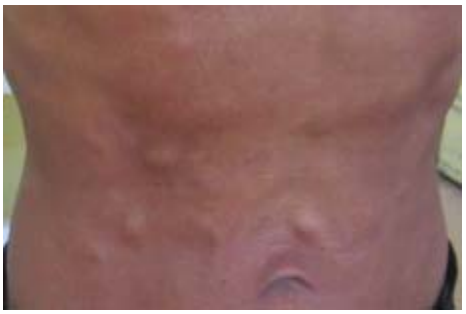


Figure 5.

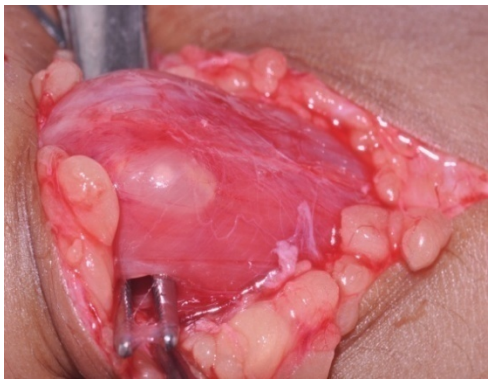


Fig 4.Nodular lesions of a patient with muscle cysticercosis; Fig 5. Muscle biopsy of a cysticercosis patient

Figure 6

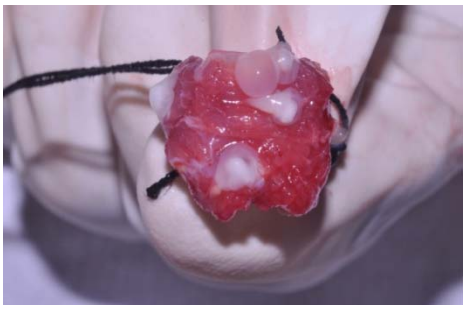


Figure 7

Figure 6. Cysts collected from a patient with muscle cysticercosis; Figure 7. Taenia solium cysts collected from infected pig meat

It was observed that most of the patients (27 out of 60) had multiple lesions (Figure 8) in which vesicular stage was the common stage of the cysts (Figure 9). 19 patients had solitary lesions (Figure 10). Parenchymal cysts were observed in all patients; frontal lobe having the most followed by parietal, temporal and occipital lobes (Figure 11), and 2 patients had intraventricular cysts (Figure 12) also.

Figure 8

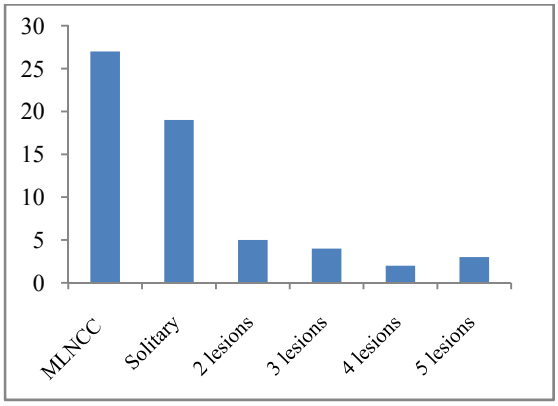


Figure 9

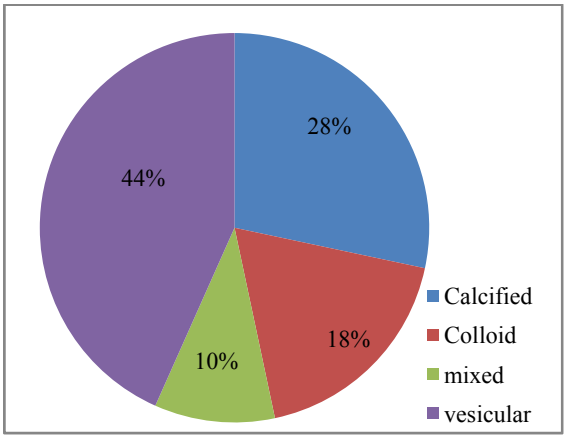


Figure 8. Distribution of No. of patients with no. of lesions in CNS; Figure 9. Stages of cysts in patients

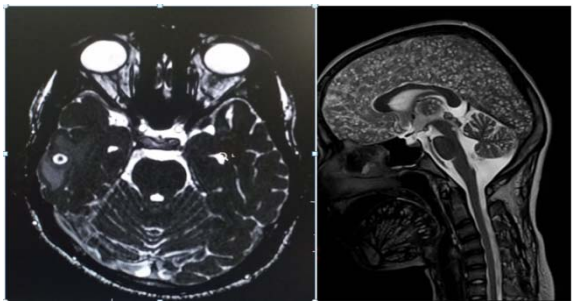


Figure 10. Single cyst and MLNCC

Figure 11

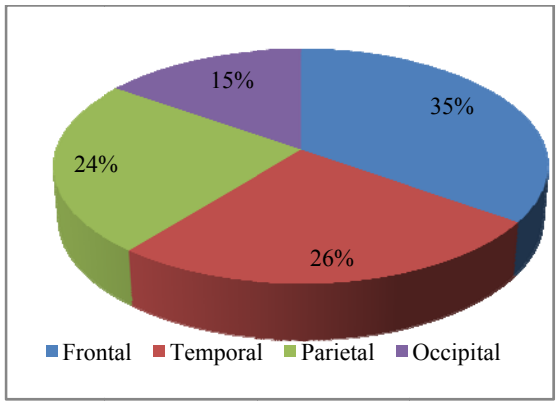
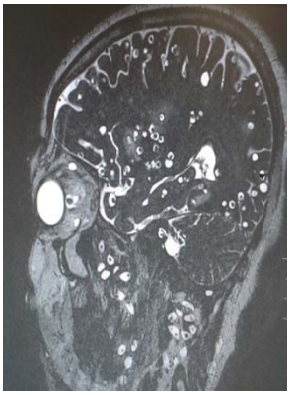


Figure 12 *Figure 13*



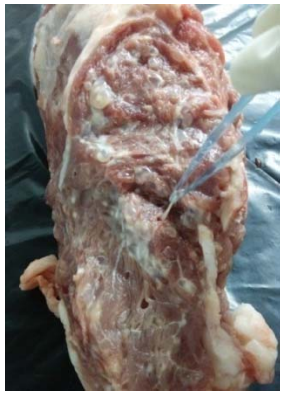


Figure 11. Percentage distribution of cysts in different lobes;

Figure 12. Intraventricular cyst;

Figure 13. Collection of Taenia solium cysts from infected pig muscle

CSF examination revealed cell count ranging from 0-36 cells/ mm^3. In our study, we have not done stool examination for every patient which might be a limitation. Because multiple lesions may be caused by autoinfection also if there is no proper hand hygiene.

During the study, we observed that infected pig meat is also sold in markets (Figure 13) and use of untreated sewage water being used for irrigation in many vegetable fields which is a potential source for spread of the disease.

Discussion:

NCC appears to be a common parasitic infection with serious neurological complications. As against information available in literature most of our patients had multiple lesions of the same age suggesting a possibility of autoinfection with a proglottids and thus same patient being both the primary and intermediate host. This is supported by a history of pig meat consumption in approximately 63% of the patients.

Vesicular stage was present in most of the patients and mainly located in frontal lobes which might be the cause for neurological morbidities. The cysts in occipital lobes and ocular muscles cause difficulty in vision in those patients. In those patients disease modifying treatment are not recommended as it may lead to blindness due to the release of cysticercal antigens and inflammatory response. It is the same in the case of patients with multiple cysts in any part of the CNS as it may elicit a strong immune response leading to neurological complications and associated morbidities. Apart from seizures and raised intracranial pressure, cognitive dysfunction is also seen which correlated with levels of interleukins as well ACE.

Conclusion:

NCC is a zoonotic disease which can be easily eradicated by taking few preventive steps. Important one is the use of proper sanitary facilities by constructing proper toilets in every house hold and making people aware about the need of hygienic surroundings. This will prevent humans becoming accidental intermediate host. Proper meat inspection should be there in slaughter houses and pig shops to check for infected meat which will prevent humans becoming definitive host. People should be aware of the importance of proper hand hygiene, washing vegetables well before use and importance of treatment for tapeworm carriers which can prevent spreading of the infection to other people. Diagnosis of the disease is still a major problem in developing nations like India where imaging techniques are not affordable or easily accessible in remote areas. Above all, the single definite remedy is observing vegetarianism which over a period of time will break the life cycle of the parasite and thus eradicate the disease. Vaccines are available for pigs but not for humans.

Acknowledgement

We would acknowledge The Director, NIMHANS for allowing us to conduct the study and University Grants Commission for supporting SRF by providing fellowship.

Conflict of Interest

No conflict of interest.

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Review Article

TAPI Journal Vol. 9, Issue 1, January – April 2017

Role of Vitamin D in T2DM – A Review

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Abstract:

Worldwide, the prevalence of Diabetes and Vitamin D deficiency is increasing. The current evidences suggested that correlation exist between the diagnosis of diabetes and low level of Vitamin D levels. Hypovitaminosis could be associated with the diabetes and insulin resistance which may explain the mechanisms involved in the pathogenesis of Diabetes.

Keywords: T2DM, Vitamin D, Hypovitaminosis.

Introduction:

Vitamin D deficiency and Diabetes Mellitus (DM) are two endemic disorders, showing high prevalence worldwide. It continues to be a public health problem in many countries despite the availability of cheap and effective means to prevent. An increased prevalence of Type 2 Diabetes Mellitus (T2DM) has been described in vitamin D-deficient subjects (1 - 3). The problem of Vitamin D Deficiency has been elevated due to the use of sunscreen, protective clothing and hats; increasing obesity, inappropriate ingestion of foods rich in vitamin D and ageing. The actions of vitamin D are not limited to skeletal health benefits and may extend to preservation of insulin secretion and insulin sensitivity. It is also associated with insulin resistance and to diabetes mellitus, thus affects the glucose homeostasis. Vitamin D inhibits the inflammatory responses caused by cytokines, diminishes stress in beta cells, which in turn avoids pancreatic cellular apoptosis. Along with these discoveries on a cellular level, there are possibilities that vitamin D could have a important role in the prevention of the beginning of insulin resistance.

Present review aimed to highlight the existing literature on vitamin D and Diabetes Mellitus, and its relationship. Taking in to consideration the major complications related with the clinical history of diabetes, in people with irregular life style, along with the low levels of vitamin D in these patients, thus the need of this hour is to study the role of vitamin D in Diabetes mellitus.

Overview of Vitamin D:

Vitamin D is naturally found as ergocalciferol (vitamin D2) in edible fungus, whereas colecalciferol (vitamin D3) is synthesized in the skin through sun light, and is available through fish oils extracted from cold and deep water fish such as tuna and salmon (4,5]. In the body approximately 80% - 90% of vitamin D are synthesised through skin, and the remaining through diet and supplements (6). Both ergocalciferol and the colecalciferol are biologically inactive and potentially equivalent, and they have the same ways of metabolization. In the presence of sunlight, UVB radiation (290 - 315 nm) was absorbed by 7-dehydrocholesterol in the plasmatic membrane of the epidermal keratinocytes and the dermal fibroblast. The energy is absorbed resulting in the reorganization of the double connections to form pre-vitamin D3. Once formed, vitamin D3 quickly suffers rearrangement of its double connections to form vitamin D3, which is thermodynamically more stable. Small intestine absorbs the vitamin D through dietary sources and supplements and makes its way to the blood stream, to be gathered with colecalciferol (vitamin D3) which comes from the epidermis (7). Adequate levels of vitamin D increase the absorption of calcium and phosphorus up to 30% - 40% and 80% respectively (8). An appropriate vitamin D

supplementation for general population is not available till date due to the factors such as different degrees of sunlight exposure, pigmentation in the skin and geographical location.

In general, vitamin D increases the innate immunity and also associated with the multifaceted requirement of acquired immunity (9). In a double blinded randomized clinical trial, 2000UI of colecalciferol was administed for 38 Type 1 Diabetes Mellitus (T1DM) patients for 18 months, showed a protective immunological effect, includes T regulators and decreased loss of beta cell function, however these findings are not enough to establish the association (10).

Vitamin D is a hormone, which is involved in integrity of the skeleton. Emerging studies have been focusing on the extra skeletal effects of vitamin D (11). Vitamin D deficiency showed a close relationship in the development of T2DM (12 -15). Further deficiency of Vitamin D also increases the risk of gestational diabetes (16,17). Evidence from the animal studies also highlighted that in vitamin D deficient animals, the synthesis of insulin and its secretion was impaired in beta cells. However glucose tolerance has been restored when vitamin D levels are reverted to the normal levels. For T2DM, vitamin D insufficiency (mild to moderate levels) has been considered as a risk factor. Among high risk patients, the development of T2DM has been lower in the patients with elevated levels plasma concentration of vitamin D (13). To maintain the optimal level of Vitamin D, two hours exposure of hands and face per week is sufficient. However food supplementation is necessary during pregnancy, lactation and also for newborns and young children's. Vitamin D can be obtained from dietary sources of vegetable (vitamin D2, ergocalciferol) or animal origin (vitamin D3, cholecalciferol).

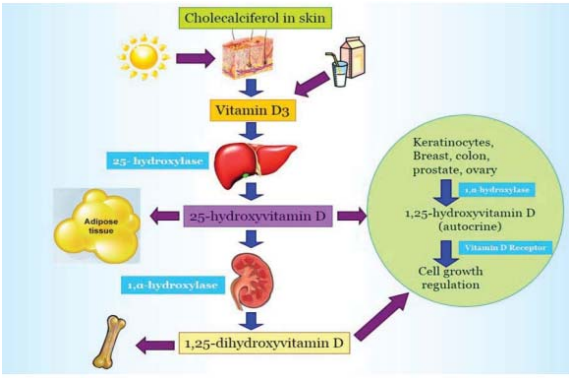

Figure 1. Synthesis of Vitamin D3 and the skeletal and extra skeletal effects of vitamin D (18).

Vitamin D3, as such is a biologically inert molecule which required two subsequent hydroxylation, one in liver (on C25) and another in kidney (on the α position of C1), to form an active metabolite 1, 25(OH)2D3 (Fig. 1). Both hydroxylation's (Liver, C25 and Kidney, α position of C1), belongs to cytochrome P450-dependent steroid hydroxylases (19). This metabolically active vitamin D and its analogues, plays a major role in pathogenesis of Type 1 DM. Beta cell function has been shown to be improved by 1,25(OH)2D3 in vitro and in vivo, and the avoidance of vitamin D deficiency is essential for normal beta cell function. The production of 1,25(OH)2D3 is regulated by several factors, particularly by levels of parathyroid hormone, although kidney 1α-hydroxylase is also subject to direct negative feedback inhibition by 1,25(OH)2D3.

The 1α-hydroxylation occurs in proximal convoluted tube, which eventually increases the 1α-hydroxylation mRNA, which is also presented in macrophages (20), dendritic cells (21) and keratinocytes. Thus, the extra renal production of 1,25(OH)2D3 has been regulated in many ways. For example, macrophage production is resistant to parathyroid hormone, perhaps it can be immune stimuli like IFN-γ and lipopolysaccharide (20). Whereas, 24-hydroxylase (hydroxylation enzyme), initiates the catabolic cascade of 25-hydroxyvitamin D3 and 1,25(OH)2D3 (22). Thus in circulating blood, all metabolites of vitamin D is

bound to a carrier protein known as vitamin D-binding protein (23).

Vitamin D and Type 2 Diabetes Mellitus:

In humans, vitamin D deficiency is linked with the IGT and T2DM (3, 24), and it has been confirmed in animal models (25, 26). The well known actions of vitamin D are, in bone metabolism, in kidneys and in parathyroid gland. Recently the anti-inflammatory and immunomodulatory effects have been raised in medical literature. Vitamin D Receptors (VDRs) in pancreatic β-cells play an major role in the progression of T2DM (27), which shows that the deficiency of vitamin D inhibits insulin secretion from pancreas (28), it is also related to insulin resistance and beta cell function in pancreas (3). Further, the active role of vitamin D in regulation of pancreas, particularly in beta cells has been described in earlier studies.

Effects of vitamin D and its metabolites on insulin synthesis and secretion:

In both animal model and humans, Vitamin D deficiency leads to impaired insulin secretion, and induces glucose tolerance, perhaps other hormones in islets were normal (29 - 31), whereas the replenishment of vitamin D rectifies the abnormalities (32 - 34). Vitamin D administration restores glucose stimulated insulin secretion and also indices, β-cell survival through modulating the effects of cytokines (35, 36). This might be due to the direct effect of vitamin D deficiency on beta cell, other effects such as impaired dietary requirement, hypocalcaemia, also play a major role. The use of 1,25(OH)2D3 for the prevention or cure of diabetes is limited by its hypercalcaemic and bone remodelling effects, as its protective effects are only observed in response to supra-physiological doses. It is likely that these analogues will find a use as beta cell- protective and -stimulating agents as adjuncts to the current treatment for T2DM.

Vitamin D plays a major role in regulation of plasma concentration of calcium through intestinal absorption and bone metabolism (37). Through beta cell, calcium flux and concentration, influences the secretion of insulin (38). Further vitamin D also regulates the function of calbindin, a systolic calcium-binding protein which is found in pancreatic β-cells. It also acts as a modulator of depolarizationstimulated insulin secretion through regulation of intracellular calcium (39) The concentration of parathyroid hormone was also regulated by vitamin D, which is associated with insulin synthesis and secretion in the pancreas (40).

Vitamin D insufficiency can be accessed through circulating 25-hydroxy vitamin D (25(OH)D), an suspected risk factor for T1DM(41, 42). Ecological based evidence suggested that increased rate of metabolic disorders such as diabetes and hypertension with increasing distance from equator (43, 44) highlighted the possible association of vitamin D deficiency with less sunlight. Recent studies showed that altered vitamin D and calcium homeostasis may play a major role in the development of T2DM (45 -47). A meta-analysis of eight observational studies highlighted that vitamin D intake or levels of vitamin D (as measured by blood 25(OH)D concentration) was associated with decreased risk of T2DM, whereas the pooled analysis of seven clinical trials of vitamin D supplementation did not show an effect on incident diabetes or measures of glycaemia(48.

To clarify the function of vitamin D on secretion of insulin and its action, certain mechanism has been extensively investigated. The association between vitamin D and DM is explained by the discovery of receptors of vitamin D (VDR) and 1α-hydroxylase enzyme inside beta cells; calcium -linking protein vitamin D-dependent (DBP) in the pancreatic tissue; and increase in the association between acquired and innate immunity (49).

The enzyme 1α-hydroxylase, present in beta cells, converts 25-hydroxy vitamin D in to 1,25(OH)2D, which intern connected to VDR, resulted in the formation of heterodimer VDR/RXR (retinoid x receptor). After the

translocation to the core of the cell, the complex is connected to Vitamin D's element of response (VERE) in the promoter of the insulin gene and activate the transcription of the insulin's gene, which promotes the cell's proliferation, differentiation and the immunomodulation (50,51). Recent evidences highlighted that the RVD gene polymorphism may confer genetic protection against T1DM and the polymorphism of the CYP27B1 gene has influence in the susceptibility for the T1DM (10, 52).

In T1DM, the process of chronic inflammatory process occurs due to infiltration of T (CD4+ and CD8+) cells, macrophages, B lymphocytes and NK cells in beta cells in pancreas. The macrophages and the dendritic cells secrete IL-12 which promotes the differentiation of the Th0 cells in Th1, stimulation those to secrete IFN-γ and IL-2 induces the migration of the T cytotoxic CD8+ cells, which are specifically against the auto antigens of the beta cells which in association with the class I molecules, cause the destruction of the beta cells through the mediated apoptosis by Fas and the release of perforin and granzyme. IL-1β, IFN-γ and TNF-α will stimulate this destruction of the cells. In vitamin D, the dendritic cells exposed to 1,25(OH)2D characterize by the reduced levels of the expression of the complex MHC Type II and co-stimulating molecules (CD40, CD80, CD86) which promotes a reduction of the presentation of antigens and a diminished secretion of IL-12, but an increase in production of IL-10, promoting, afterwards, the differentiation of lymphocytes Th2. The effects of 1,25(OH)2D on the acquired specific antigenic immunologic response, characterized preferably by the inhibition of the proliferation of lymphocytes T, especially the T cells helper 1 (Th1) (10).

Conclusion:

Although Vitamin D has been studied extensively based on the outcomes, literature showed that low plasma concentration of vitamin D might be linked with many disease conditions, thus it is difficult to draw a clear conclusion about the benefits. Upcoming evidences showed a major role of vitamin D in the pathogenesis of diabetes. Prospective studies highlighted the association between the different status of vitamin D and chronic disease such as diabetes and CKD. However, there are contradictory findings regarding whether restitution of normal vitamin D levels modifies the occurrence or clinical course of these diseases.

In conclusion, the possible benefits of vitamin D still remain unclear, existing literature shows that apart from preventing autoimmune diseases, vitamin D also helps in further treatment plan. The importance and benefits of vitamin D supplementation are still remains unclear for human health. Although there is a concern that vitamin D may be a surrogate marker for poor health status, further well-designed clinical trials are needed in this area. Although vitamin D is considered as a surrogate marker for poor health status, a well deigned prospective clinical study is required in this field. Diabetes and vitamin D insufficiency are frequent clinical condition worldwide, thus lots of efforts has been taken to implement the methods to monitor and develop effective therapies for their control.

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Anti-diabetic agent in Diabetes with Co-morbid condition

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Introduction:

Type 2 diabetes mellitus predisposes to multiple comorbidities as well as can newly be diagnosed in patient with coexisting morbidity eg, renal failure, liver disease, adding to the disease burden manifold. In either of the case, the choice of opting a noninsulin oral antidiabetic agent or continuing the previous oral antidiabetic agent is a challenge due to the problems of erratic glycemic control and potential toxicity of drugs. Even though insulin is the final frontier in type 2 DM with comorbidities, there is a burning need to explore the options of oral agents, due to the ever increasing armamentarium of oral antidiabetic drug families. There is still an unmet need of establishing guidelines for using OADs in single and overlapping comorbities like liver disease, renal failure, heart failure etc. The various OADs that can be used in T2DM patients with comorbidities and their effects are needed to be analysed.

Oral Anti-Diabetic Drugs (OADs) in T2DM with Liver disease:

The prevalence rate of diabetes in chronic liver disease is 12.3 - 57%[1]. The chronic liver disease and diabetes are similar type of long duration ailments observed in both developed and the developing countries. It is often suggested that both the conditions can be present simultaneously which can lead to long term complications[2]. In patients with chronic liver disease, management of diabetes mellitus can be challenging as most of the anti-diabetic agents are not indicated or its usage should be under strict guidance and regular follow-up[2]. A population based study (VERONA diabetes population) conducted by Trombetta and Spiazzi 2005, concluded that the mortality rate from cirrhosis in diabetic patients was higher than CV diseases[3]. In India it was observed that NASH was prevalent in about 6% of patients with chronic liver disease.

Spectrum of liver diseases in T2DM:

The broad spectrum of liver disease can be observed in in T2DM (Type 2 Diabetes Mellitus) patients. The conditions included in the spectrum are, deranged liver enzymes level, NAFLD (Non-Alcoholic Fatty Liver Disease), cirrhosis of liver, acute liver failure, hepatocellular carcinoma and idiopathic association of Hepatitis C with diabetes. The management of T2DM with hepatic insufficiency may be affected due to the general health condition of the patient. In most of the cases the management of T2DM in hepatic insufficiency is almost similar to cases without hepatic failure[4].

Metformin:

Metformin is a biguanide which evades metabolism in liver and is excreted by the renal system in an unchanged form[5]. The metformin as first line therapy is suggested in majority of the patients but not in cases with severe hepatic insufficiency as it may lead to lactic acidosis[4]. The incidence rate of lactic acidosis from the earlier studies has been reported to be in the range of (0.03–0.5) per 1000 patients. Metformin administration has been observed to be beneficial in patients suffering from NAFLD[6].

It is comparatively safe to use metformin in patients with a stable chronic liver disease but the molecule should be stopped in cases of progressive deterioration of liver and renal functions. At present, a dose of 1500 mg of metformin is recommended to be safe in hepatic disease[2]. In recent studies, it has been observed that metformin is beneficial in almost all the spectrum of liver disease and also has a potential

to protect against cancer and hepatocellular carcinoma[7]. The hypoglycemic episode with metformin is quite low as observed in several studies[8]. Further studies are required to evaluate maximum tolerated dose of metformin in liver disease.

Sulphonylureas:

Sulphonylureas are relatively safe in patients suffering from hepatic insufficiency, although they may not improve the insulin resistant conditions and insulin secretion which are observed in subjects with co-morbid conditions like alcoholic liver disease and pancreatic pathology[9]. Such patients may be beneficial with short acting glipizide and the patients suffering from hepatic encephalopathy, coagulopathy or ascites should be carefully followed up to counteract the hypoglycemic episodes. In the past, it was observed that jaundice and hepatitis has an association with the use of chlorpropamide[2].

The sulphonylureas are metabolised in the liver, thus in liver failure the major risk of sulfonylureas is hypoglycaemia. Moreover, the risk increases in associated conditions like under nourished liver disease with anorexia2,4.

In situation where metformin is contraindicated or not tolerated by the patients who has additional low body mass index, glucotoxicity and elevated glycated haemoglobin (HbA1c) level, Sulphonylureas may be the drug of choice.

The glyburide and glipizide undergoes first pass metabolism in the liver and the absorption of glipizide is affected by presence of food, whereas glyburide has no effect with meals. The recommended dose of glyburide and glipizide are 2.5 mg and 5 mg once daily respectively. Both the molecules should be started at low dose initially in cases of hepatic insufficiency[10].

Alpha Glucosidase Inhibitors (AGI):

The α-glucosidase inhibitors (AGI) have a significant role as a second line therapy in T2DM pts with liver disease. The mechanism of action of AGI is to inhibit the disaccharides to prevent glucose reabsorption from the gastro-intestinal tract. There are very limited studies conducted with such agents in diabetic patients with chronic liver disease. In a crossover placebo controlled study conducted by Gentle et al, in 2005, a significant improvement in postprandial blood sugar level was observed in patients treated with acarbose and suffering from hepatic encephalopathy[11]. Similarly, in a double blind RCT (Randomised Control Trial) with 100 patients suffering from compensated cirrhosis of liver, were on insulin and subsequently treated with acarbose. There was a greater control of both FBG and PPBG (Fasting and Post-prandial blood glucose) level with the use of acarbose[12]. Other molecules in the same class such as Miglitol are safe and not associated with liver toxicity. Similarly, Voglibose is also an effective therapy for NASH in a patient with poor lifestyle modifications. No dose adjustment is required in liver disease while using AGI for T2DM.

Thiazolidinediones (TZDs):

This group of drugs are peroxisome proliferator – activated receptor - γ agonists which enhance insulin sensitivity. There were several reports regarding adverse effects on liver and cardiovascular disease with Troglitazone (1997) and Rosiglitazone respectively. The pioglitazone is the only molecule remaining and in use presently for treatment modalities of NASH and NAFLD[13]. The FPG and the PPPG is lowered by pioglitazone along with the improvement in insulin sensitivity of muscle tissue and the liver[14]. Pioglitazone without dose modification can be safely given in patients with liver disease, except when transaminases are more than 3 times elevated, overt hepatic failure, edema, and heart failure and old age where risk of osteoporotic fracture is high periodic monitoring of transaminases 3 to 4 times a year is warranted[4].

Dipeptidyl peptidase-4 inhibitors:

The dipeptdyl peptidase -4 inhibitors are a new class of oral anti-diabetic agent is a glucose-

dependent insulinotropic polypeptide, which acts by prolonging the incretin peptides (GLP-1 and GIP). This leads to glucose-dependent secretion of insulin and prevents the secretion of glucagon. The DPP4 inhibitors are claimed to reduce the risk of hypoglycaemia and are supposed to be weight neutral15. The dosage of Sitagliptin need not be adjusted in mild to moderate hepatic insufficiency. The sitagliptin can be safely administered in diabetic patients with Childs Grade A or B hepatic insufficiency, whereas for Child Grade C the use of sitagliptin and vildagliptin is contraindicated or not recommended[16,17]. Both Linagliptin and Saxagliptin dose adjustment are not required in mild, moderate or even severe heaptic dysfunction[17].—Regarding Alogliptin no dose adjustment was required in mild to moderate hepatic impairment. On the whole DPP4 inhibitors are very good oral antidiabetic agents in mild to moderate hepatic dysfunction and to be used in caution in severe liver disease.

SGLT2 (Sodium glucose co-transporter type 2) Inhibitors

SGLT2 inhibitors act in an insulin-independent pathway through inhibition of glucose reuptake via SGLT2 co-transporter in renal tubules and causing glycosuria. Dapagliflozin 10mg/day, canagliflozin (100mg or 300mg/day) and empagliflozin (10 mg and 25mg/day) are the FDA approved SGLT2 inhibitors. The elimination of Dapagliflozin is primarily via glucuronidation to an inactive main metabolite in liver. In mild to moderate liver disease (Child pugh A,B) both dapagliflozin and canagliflozin need not be dose modified, whereas canagliflozin is not recommended in Child Pugh class C liver disease, dapagliflozin needs dose reduction to 5mg/day. On the other hand, there is no requirement of dose adjustment in case of empagliflozin with any grade of hepatic insufficiency18. As they are newer anti diabetic agents, further long term studies are needed regarding safety and effectiveness in liver disease.

OADs in T2DM with renal disease:

Metformin:

Metformin is absorbed in small intestine but this drug does not bind to plasma proteins and is excreted unchanged in urine, thus its use in CKD (Chronic Kidney Disease) is restricted. The United States Food and Drug Administration (FDA) label restricts the use of metformin up to Serum Creatinine(SCr) level of $\leq$1.5 mg/dl in men $\leq$1.4mg/dl in female[19]. It is reasonable to consider eGFR (estimated Glomerular Filtration Rate) cut off for metformin as the SCr value depends on weight, race, sex or age, thus only based on eGFR value KDIGO (Kidney Disease Improving Global Outcome) clinical guideline 2012 suggests to avoid use metformin below eGFR 30 ml/min/1.73 m^2, to review its' use between eGFR 30-45 ml/min/1.73 m^2, to use eGFR 45 ml/min/1.73 m^2 above[20].

Sulfonylureas:

The sulfonylurea is strongly protein bound, metabolized in liver and excreted in urine. Glimepiride, a third generation sulfonylurea, one of its' two metabolite has some pharmacologic activity. So, in case of reduced GFR patient; though glimepiride does not accumulate; the chance of hypoglycemia is there due to accumulation of active metabolite after reduced urinary excretion in those patient[21]. Thus KDIGO 2012 clinical guideline recommend to avoid, agents that are mainly excreted through renal route[20]. Glipizide, a short acting second generation sulfonylurea, metabolizes at liver and produce inactive metabolites, thus its half-life is unaffected by kidney function, so it is not necessary to reduce dose in CKD patient.[22]

After metabolism in liver, gliclazide, also a second generation sulfonylurea, produces almost eight metabolites and none of them has any recorded hypoglycemic activity and its' renal clearance is also low (0.5 ml/min) because of the high protein binding with <1% found in the urine, so, this can be used in CKD patients[23]. In case of glicazide, KDIGO 2012 clinical guideline suggests

to reduce dose if eGFR falls below 30 ml/min/1.73 m^2.[20]

Meglitinides:

Metiglinide or glinide binds with beta cell at islet of pancreas and stimulates insulin secretion, but their binding site is different from sulfonylurea. Compare to sulfonylurea, the duration of action of glinides is short around 3-4 hrs[19]. Repaglinide produces inactive metabolites and only 10% of primary drug is excreted by the kidneys in an unaltered form, so there the risk for hypoglycemia is less in CKD patients[24]. Still if eGFR <30 mL/min/1.73 m^2 it is recommended to start 0.5 mg with meal for repaglinide[19]. Nateglinide metabolizes in liver and produces some active metabolites of which some of them including 15 % of nateglinide together are being excreted through urine. So, in case of diminished renal function patient, the chances of accumulation of active metabolites of nateglinide is more, which increases the chances of hypoglycemia [24], so if the if eGFR <30 mL/min/1.73 m^2 it is recommended to start 60 mg with meal[19].

Dipeptidyl peptidase-4 inhibitors:

Now a days, using DPP-4 inhibitors has become preferred oral anti-diabetic agent in combination therapy in T2DM patients[25]. The excretion of sitagliptin, saxagliptin, alogliptin is predominantly through renal route[26, 27]. Thus, there is a need to reduce the dose for these DPP4 inhibitors in low eGFR patient. For linagliptin, 85% of this drug is being excreted through fecal route via the entero-hepatic system, whereas renal excretion accounts less than 5% , thus there is no need for dose adjustment in CKD patient according to eGFR level [24]. Newly launch teneligliptin of which only 34.4% drug is being excreted in unchanged form through urine and rest of the 65.6% drug is metabolized and excreted through renal and hepatic route but none of its' metabolites are active, thus there no dose adjustment is reqd[28].

SGLT2 inhibitors:

SGLT2 inhibitors; dapagliflozin, empagliflozin and canagliflozin, block the SGLT2 co-transporter selectively in proximal convoluted tubules, where 90% of glucose is reabsorbed[29, 30], thereby causing glycosuria and acting as an beta cell independent anti-hyperglycemic agent. In a study of empagliflozin (a SGLT2i) in patient with eGFR 45–60 ml/min/1.73 m^2, the HbA1c reduction of 0.3-0.4% were only observed but in eGFR < 45ml/min//1.73 m^2 the glycemic efficacy was not seen[20].

Dapagliflozin[31] is contraindicated and should be avoided in patients with eGFR less than <60 ml/min/1.73 m^2 although unpublished data claims that dapagliflozin can be prescribed with GFR less than 45 ml/min/1.73 m^2. In the case of canagliflozin, there is need to reduce dose to 100 mg/day between eGFR 45–60 ml/min/1.73 m^2, [32] and drugs advised to be stopped with further fall in eGFR. For empagliflozin to initiate with 10 mg/day and increase upto 25 mg/day and there is no dose reduction upto eGFR 45 ml/min and below that empagliflozin should be discontinued[33].

Alpha glucosidase inhibitors:

Acarbose and Miglitol accumulate in system if the eGFR decreases less than 30ml/min/1.73m^2. Although there is no dose reduction required in stage 3 kidney disease,

Class	Drug	eGFR 45-59	eGFR 30-44 ml/min	eGFR 29-15 ml/min	eGFR <15ml/min
DPP-4 inhibitors	Sitagliptin	No dose adjustment	50mg/day	25mg/day	25mg/day
	Vildagliptin		50mg/day	50mg/day	50mg/day
	Saxagliptin		2.5mg/day	2.5mg/day	2.5mg/day
	Alogliptin		12.5mg/day	6.25mg/day	6.25mg/day
	Linagliptin [5mg]	No dose adjustment	No dose adjustment	No dose adjustment	No dose adjustment
	Teneligliptin[28] [20mg/40 mg]	No dose adjustment	No dose adjustment	No dose adjustment	No dose adjustment

because of the risk of diarrhoea the alpha glucosidase inhibitors are not generally recommended as first line OADs.

Thiazolidinediones [TZDs]:

Pioglitazone can be used as second line therapy for glycemic control for patients on haemodialysis. [19] The most common concerns of pioglitazone are weight gain, fluid retention. Although no dose adjustment it required, pioglitazone is generally avoided in below eGFR 60 ml/min/1.73m^2 for possible worsening of fluid retention and fractures particularly with renal osteodystrophy[34].

Urogenital Infection:

Patients with T2DM patients are at the risk of developing genital infections and urinary tract infections (UTI) and there are several factors are responsible like as glucosuria, adherence of bacteria to the uroepithelium and immune dysfunction[35]. There are eight meta-analysis studies canagliflozin and dapagliflozin that compared the SGLT2 inhibitors with other anti-diabetes agents. For SGLT2i, both urinary tract infection and genital tract infection or genital mycotic infections are common[36]. Safety analysis based on 12 double blind placebo control trials of dapagliflozin shows urinary tract infection (UTI) and genital tract infections (GTI) or genital mycotic infection (GMI) both are common in patient on dapagliflozin compared to placebo. This result also similar in case of pooled analysis of canagliflozin and dapagliflozin too.

For across the studies of SGLT2i molecules, dapagliflozin, canagliflozin, and empagliflozin ; women are frequently infected with UTI or GTI/GMI compared to men in all treatment groups. Though there are chances of UTI or GTI/GMI in association with SGLT2i drug, still in most of the cases the incidence of infection is one and responds to standard anti-infective therapy and there is no history of recurrence[37].

In terms of renal safety is concern for type 2 diabetes patients, metformin are still preferred choice with little bit concern about eGFR level. In case of sulfonylurea and meglitinides group, short acting molecule like glipizide which is also having no active metabolite; can be used in CKD with T2 DM patients. For DPP4i, none of the molecule is causing harm towards renal tissue. The dose depends of routes of excretion, thus in some DPPP4i, there no dose adjustment is necessary.

OADs in T2DM with Heart disease:

Metformin:

The UKPDS clearly showed the benefits of metformin in reducing major adverse cardiac events and also no significant deleterious effects in heart failure. Meta-analyses have shown no significant increase in events of lactic acidosis in mild heart failure.[38, 39] So metformin can be safely used in T2DM even with mild heart failure and avoidance during events of tissue hypoxia like sepsis, renal failure, moderate to severe heart failure.

Sulfonylureas:

Sulfonylureas despite the theoretical risks of higher cardiovascular risk and increased mortality are the second most used oral antidiabetic agents in established coronary artery disease and heart failure in T2DM. In the ADVANCE trial, the intensive glucose control arm, achieved by highest optimum gliclazide doses showed neither a beneficial nor deleterious effect on major cardiovascular events or heart failure[40]. The possible increased cardiovascular risk of sulfonylureas, can be due to the ATP sensitive potassium channels – sulfonyl urea receptors (SUR2) in myocardium being inhibited, interfering with the mechanism of ischemic preconditioning in ischemic myocardium and therby interfering with recovery from compromised coronary circulation.[41] However glipizide, gliclazide and glimepride affinity to cardiac sulfonyl urea receptors is much less compared to older generation sulfonyl ureas, with glimepride having the highest, glipizide and gliclazide the least.[42]

Thiazolidinediones (TZDs):

Initially TZDs due to their unique mechanism of action via peroxisome proliferator –activated receptor agonism, were considered to have pleiotropic benefits in T2DM and cardiovascular disease. But fluid retention became a concern. The PROactive trial[43] showed a significant association between pioglitazone and heart failure hospitalisations. However this was not significantly associated with major adverse cardiac events. The other drug rosiglitazone, where meta-analyses showed a significant increase of cardiovascular death led to an alarm about the drug.[44] but the recently conducted trial RECORD (Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes) showed no difference in incidence of heart failure compared to placebo. This group of drug should be avoided in patients with heart failure and whether they can be used in T2DM with established cardiovascular disease patients at risk of heart failure is not yet clear.[45]

Dipeptidyl Peptidase-4 Inhibitors

DPP-4inhibitors prolong the availability of glucagon like peptide-1, and exerting antihyperglycemic effect via insulin dependent pathway. Animal models and human studies both have shown beneficial cardiovascular effects of DPP-4 inhibitors along with lack of hypoglycemia and weight neutrality makes the utility of these class of drugs in T2DM with heart disease a foreseen prospective.[46] In a short duration randomised trial of around 250 patients with vildagliptin, no change of worsening of heart failure was observed. [47] The SAVOR TIMI 53 (The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus) trial, showed that in comparison to placebo with saxagliptin there is no differences between the two groups regarding cardiovascular mortality, but there was a small but significant increase in hospitalisation for heart failure but no difference in translation of this effect into increased mortality. [48]

In case of Alogliptin, the EXAMINE (The Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care) trial, done in T2DM with patients with ACS (Acute Coronary Syndrome) history within 3 months, found no difference in cardiovascular mortality and death due to heart failure as in the SAVOR TIMI trial though a non-significant increase of hospitalization due to heart failure was there HR 1.193 (0.900 – 1.581).[49]

The TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin) trial showed that the increased heart failure occurrence was not a class effect of DPP-4 inhibitors. In this trail sitagliptin compared to placebo, showed non-inferiority in terms of cardiovascular mortality and no increased risk of heart failure[50]. A meta-analyses of about 70 studies on all DPP-4 inhibitors showed an odds ratio of 0.71[95% C.I 0.59-0.86] for CV events, implicating that they can be safely used in T2DM with no increased risk of CV events. [51]

Since the DPP-4 inhibitors are newer drugs further long term follow up studies are needed to establish their beneficial effects in cardiovascular disease in T2DM. The results of CAROLINA (Cardiovascular Outcome Study of Linagliptin versus Glimepiride in Patients with T2DM) study which compares linagliptin with glimepride in T2DM for outcomes in cardiovascular disease will be a good benchmark for DPP4 inhibitors as an efficacious antihyperglycemic agent in cardiovascular disease. [52]

SGLT2 inhibitors:

Dapagliflozin, canagliflozin and empagliflozin are the FDA approved SGLT2 inhibitor class of drugs. The cardiovascular safety and benefits of these drugs are awaited through studies like EMPA-REG Outcome, CANVAS, CREDENCE and DECLARE-TIMI 58. [43, 53] However the data available till now shows significant cardiovascular risk reduction by blood pressure lowering and weight loss. A meta-analysis

showed, systolic BP reduction and mild HbA1c lowering with no increase in major adverse cardiovascular events. [37]

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Case Report

TAPI Journal Vol. 9, Issue 1, January – April 2017

Polycythemia Vera –A Rare Presentation

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Abstract:

Polycythemia vera is a clonal disorder involving a multipotent hematopoietic progenitor cells. In the absence of physiological stimulus red cells, granulocytes and platelets accumulate. Polycythemia vera occurs in 2.5 per 100000 persons increasing with age. Women predominate in sporadic cases. It has been observed that only 1% of patients with Polycythemia vera, present with bleeding gums. Usually, they present with symptoms attributed to hyper-viscosity of blood. We present a case of polycythemia vera admitted with symptoms of gum bleeding which is an unusual presentation

Keywords: polycythemia vera, JAK 2 mutation, hyperviscosity, erythropoietin

Case study:

A 58 year old female had come with c/o generalized weakness, headache, dizziness, occasional bleeding of gums for more than 1 month. There was no history of blurring of vision, tinnitus, vomiting, and breathlessness.

On examination, patient was alert, oriented afebrile.

Vitals: BP – 170/100 mmHg – Rt. upper limb, 170/100 mmHg – Lt. upper limb

PR: 72/min, regular. All peripheral pulses felt equally.

No pallor, icterus, clubbing, cyanosis, lymphadenopathy, oedema.

CVS – S1S2+, RS – NVBS, Clear, abdomen – Soft, Non-tender, and No organomegaly.

CNS – No focal deficit.

Lab investigations revealed-Hb – 17.7 gm/dl,, RBC count – 7.31 millions/cu mm, Platelet count – 6.69 lakhs/cu mm, Total count – 18080 cells/cu mm, PCV – 63.7 %.

Red cell indices: MCV – 87.1 fl, MCH – 24.2 pg, MCHC – 27.8%, Total bilirubin 0.5 mg/dl, Direct bilirubin 0.1 mg/dl, Indirect bilirubin 0.4 mg/dl, SGOT – 31 IU/L,SGPT – 12 IU/L,ALP – 146 IU/L, Total protein – 7.4 gm/dl, Albumin – 4.2 gm/dl, GGT – 20 IU/L, Renal Function Test-Normal

Serum T3: 1.20 ng/ml (Ref. range: 0.8 – 2), Serum T4: 8.43 ug/dl (Ref. range: 5.1 – 14.1), Serum TSH: 3.610 uIU/ml. Serum Cancer Antigen 125: 12.2 U/mL (Ref. range: Less than 35)

RBC: Normocytic, Normochromic cells

WBC: Increased in number, neutrophils showing toxic changes, eosinophils increased in number.

Platelets: Increased in number. No hemoparasite seen.

Impression: Neutrophilic leucocytosis with eosinophilia and reactive thrombocytosis

PT INR: 1.33 (Normal: 0.9 – 1.1), Ferritin: 12.5 ng/ml (Ref. range: Male: 30 – 400; Female: 13 – 150)

Bone marrow aspiration revealed a dry tap.

Erythropoietin (EPO): 1.93 mIU/mL (Ref. range: 3.7 – 31.5 mIU/mL)

JAK2 (Janus kinase-2 gene) mutation: V617F mutation in exon 14 of JAK2 gene was detected in the leukocytes

Based on the above findings and investigations which revealed a marked increase in hemoglobin, PCV and hematocrit, a baseline diagnosis of polycythemia was made. Further evaluation revealed evidence of primary polycythemia which was eventually confirmed by JAK2 exon 14 mutation assay. Hence, the patient was diagnosed as a case of Polycythemia vera.

In this case, JAK2 Exon 14 mutation Assay – was detected. JAK2 V617F mutation and

erythropoietin (Epo) level are key in the diagnosis of erythrocytosis. If the JAK2V617F mutation is positive and Epo level is low, then it confirms the diagnosis of PV (JAK2 V617F mutation is positive in 97% of PV patients). Patient was treated with venesection after which patients symptoms recovered well.

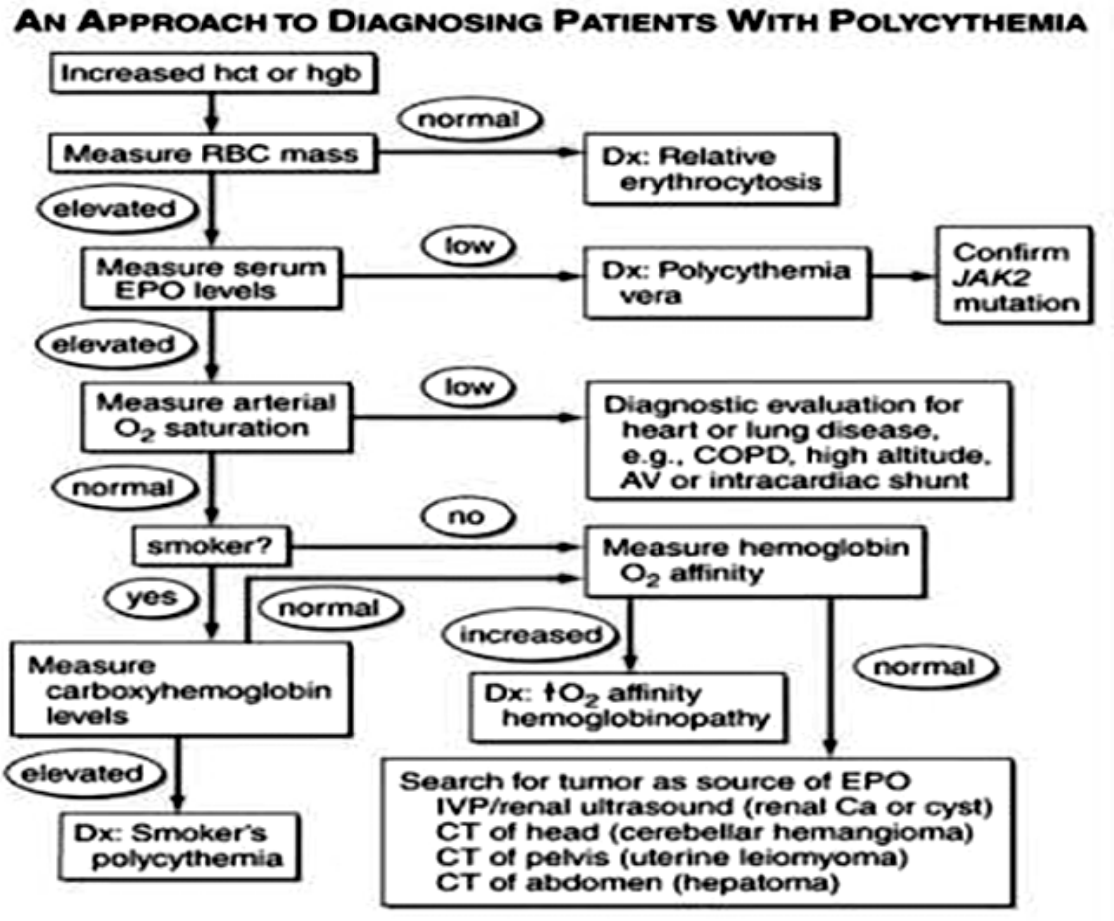
Discussion:

Polycythemia vera is a clonal disorder involving a multipotent hematopoietic progenitor cells. In the absence of physiological stimulus red cells, granulocytes and platelets accumulate. Polycythemia vera occurs in 2.5 per 100000 persons increasing with age. Women predominate in sporadic cases. The etiology is unknown. No consistent cytogenetic abnormality has been associated with polycythemia vera.JAK2 mutation plays a central role in pathogenesis of polycythemia vera. If the JAK2V617F mutation is positive and Epo level is low, then it confirms the diagnosis of PV (JAK2 V617F mutation is positive in 97% of PV patients). JAK2 is an essential kinase in the erythropoitin (EPO) receptor signal transduction pathway. Constitutive JAK2 kinase activity results in EPO-independent proliferation of the erythrocyte precursors.

JAK2[1] is also involved in the JAK2-STAT5 pathways of the thrombopoietin receptor (MPL) and the Granulocyte Colony-Stimulating factor Receptor (GCSF-R). A V617F mutation can thus lead to proliferation of multiple cell lines, therefore patients with PV often have elevated platelets and leukocyte as well. JAK2[2] is directly involved in the intracellular signaling following exposure to cytokines to which polycythemia vera progenitor cells display hypersensitivity.

Etiology:

Primary polcythemia: Polycythemia rubra vera;



Decrease in EPO

Secondary polycythemia: Caused by physiologically appropriate increase in erythropoitein

Inappropriate increase in erythropoietin

Appropriate EPO increase: High altitudes, Pulmonary disease and alveolar hypoventilation

Congenital cardiovascular diseases, Familial congenital Polycythemia, Heavy cigarette smoking

Inappropriate EPO increase:

- Renal carcinoma
- Uterine tumors, HCC

Diagnostic criteria of PV:

Major WHO criteria:

- Hemoglobin > 18.5 g/dL in men and > 16.5 g/dL in women, or other evidence of increased red blood cell volume
- Presence of JAK2 V617F or other functionally similar mutation, such as JAK2 exon 14 mutation
- Elevated RBC mass > 25% above mean normal predicted value
- Hb or Hct > 99th percentile of method-specific reference range for age, sex

Minor criteria:

- Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) and prominent erythroid, granulocytic, and megakaryocytic proliferation
- Serum erythropoietin level below the reference range for normal
- Endogenous erythroid colony formation in vitro
- The only history positive for this patient was presence of bleeding gums and headache. Patient was also a newly diagnosed hypertensive.
- Investigations showed elevated Hb, PCV, RBC and platelets
- Decreased EPO, and JAK2 mutation was detected.
- Arterial oxygen saturation – Normal
- After ruling out all the secondary causes of polycythemia, a most appropriate diagnosis of primary polycythemia was made.
- Patient was treated by doing phlebotomy, ~400 – 500ml per week.
- After subsequent episodes of phlebotomy, she became symptomatically better. Currently the patient is in regular follow up.

The word polycythemia indicates increase in RBCs, WBCs and platelets. Mostly it indicates an increase in pure RBCs alone or erythrocythemia which is a more specific term. Relative polycythemia can also result from decreased plasma volume. True polycythemia is due to an increase in the RBC mass. It is included in a group of diseases which are known as myeloproliferative disorders (MPD). Polycythemia is a Chronic myeloproliferative disorder (CMPD) which is characterized by proliferation of one or more myeloid cell lineages. It can also be called as panmyelosis as it involves increased production of all 3 cell lines, most common of the myeloproliferative disorders. Incidence is more common in men. According to the WHO Classification of Hematopoietic and Lymphoid Neoplasms [3] 2008 myeloproliferative neoplasms are divided into categories by diagnostic characteristics Chronic myelogenous leukemia (CML); Essential thrombocythemia (ET); Polycythemia vera (PV) and Primary myelofibrosis (PMF).

Symptoms:

Usually insidious in onset with symptoms of headache, dizziness, vertigo, tinnitus, visual disturbances, angina pectoris, intermittent claudication.

Signs:

Splenomegaly, hepatomegaly, plethora or ruddy complexion, pruritus, erythromelalgia-palms & feet may become red, warm tender and hypertension.

Complications:

Bleeding complications such as epistaxis, gum bleeding, ecchymoses, and gastrointestinal (GI) bleeding. Thrombotic complications like venous thrombosis or thromboembolism, increased prevalence of stroke, other arterial thromboses. Budd-chiari syndrome

Over time, polycythemia vera may convert to myelofibrosis or to CML. In approximately 5% of cases, PV progresses to AML, which is usually refractory to therapy.

Management[4]

- Aspirin
- Phlebotomy
- Myelosuppressive therapy:
- Hydroxyurea: acts to decrease all three blood lines. Long term use can lead to leukemogenesis (~15 years). May cause nausea, vomiting, constipation, and diarrhoea are very common with doses >60mg/kg
- Interferon-alpha: decreases both the red cell number and the frequency of thrombo-haemorrhagic events. It affects the stem cell compartment, and reversal of JAK2 mutational status can be seen. It must be administered subcutaneously and can cause fever, arthralgias, myalgias, alopecia, anorexia, peripheral neuropathies, and depression. ACE inhibitors should be avoided with interferon-alpha, as this may lead to granulocytopenia and thrombocytopenia.

Recent advances:

- JAK2 Inhibitors - Ruxolitinib (Jakafi)
- Anagrelide – primarily effects platelet production and is more commonly used in PV for thrombocytosis. S/e include palpitations, tachycardia, nausea, diarrhoea and fluid retention.
- Prognosis:
- Patients with polycythemia vera who are treated, have a mortality rate similar to age-matched controls.
- Death is secondary to thrombosis in 30-40% patients.
- Myelofibrosis is the cause of death in ~5% of patients, and haemorrhage is the cause in 2-10% of patients.

Conclusion:

Polycythemia vera is a clonal disorder involving a multipotent hematopoietic [5] progenitor cells. In the absence of physiological stimulus red cells, granulocytes and platelets accumulate. Polycythemia vera occurs in 2.5 per 100000 persons increasing with age. Women predominate in sporadic cases. It has been observed that only 1% of patients with polycythemia vera, present with bleeding gums. Usually, they present with symptoms attributed to hyper-viscosity of blood. We present a case of polycythemia vera admitted with symptoms of gum bleeding which is an unusual presentation

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Pancreatic Tuberculosis Causing Obstructive Jaundice - A Diagnostic Dilemma

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Abstract:

We report here a middle age gentleman who had pancreatic tuberculosis and tuberculous biliary stricture whose clinical and radiological presentation mimic malignancy creating a diagnostic dilemma. However the outcome after anti- tuberculosis therapy was excellent.

Introduction

Abdominal tuberculosis is common in developing countries next to pulmonary tuberculosis yet isolated pancreatic tuberculosis is unusual and obstructive jaundice secondary to pancreatic obiliary tuberculosis is extremely is rare[1]. Pancreatic tuberculosis can have various clinical presentations such as acute pancreatitis, portal vein thrombosis and obstructive jaundice with pancreatic mass mimicking malignancy [2].

Case Report

A 62 year old male presented to medical emergency room with c/o yellowish discoloration of skin and eyes of one day duration (Figure 1). The patient stated that he had dull, intermittent mid epigastric pain for past one week. He admitted having nausea, generalized itching and passing high colored urine. He also admitted having unintentional weight loss around 8 kilograms in 6 months. He denied use of any medications, illicit drugs, alcohol, tobacco and previous blood transfusions and had never participated in any sexual activity nor travelled abroad. He had history of cutaneous tuberculosis (scrofuloderma) in his adolescence (Figure 2). His family history was non contributory.

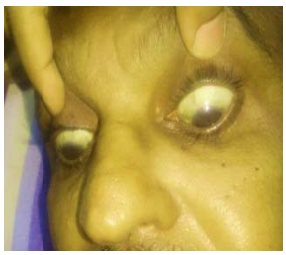

Figure 1

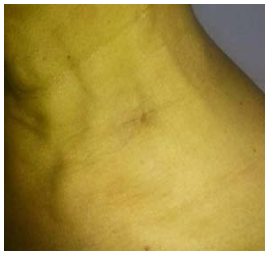

Figure 2

On physical examination his eyes were icteric and there was mild epigastric tenderness. Total bilirubin was 2.7mg/dl with direct bilirubin 1.5mg/dl. Liver transaminases were elevated and ALP (Alkaline Phosphatase) was noted to be 725IU/L. Viral markers were negative. His urine was positive for urobilinogen and bilirubin. His chest radiograph was normal with clear lung fields. His acute phase reactants ESR (50mm/hr) and CRP (C - reactive protein) were raised and Mantoux testing for tuberculosis yielded an induration of 30mm and was strongly positive. AnIGRA (Interferon Gamma Release Assay) for tuberculosis was performed and turned out to be positive (182.60IU/L), whereas tumour markers CA-19.9 (Carbohydrate Antigen 19.9) and AFP (Alfa Feto Protein) were negative. Sonography of abdomen showed a huge distended gallbladder. CT (computed tomography) of abdomen revealed central IHBR dilatation along with dilated CHD and proximal CBD (Common Bile duct) and shows tapering just above the head of pancreas - suggestive of Mid CBD stricture (Figure 3&4).

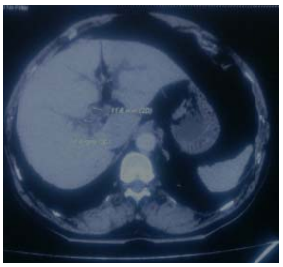

Figure 3

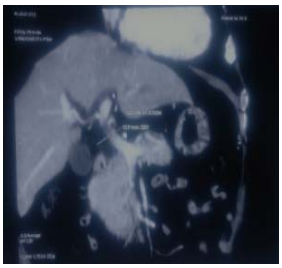

Figure 4

MRCP (Magnetic Resonance Cholangio Pancreatography) showed ill defined T1 hypointense lesion in posterosuperior aspect of proximal body of pancreas showing restricted diffusion with few enlarged peripancreatic and left para aortic lypmhnodes showing restricted diffusion (Figure 5&6).

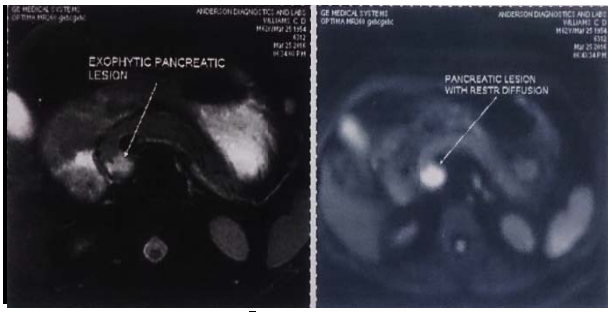

Figure 5

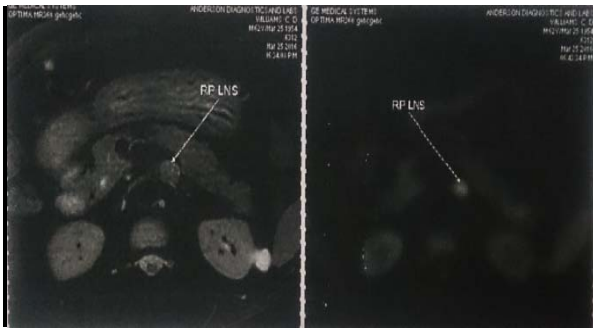

Figure 6

64 slice FDG PET CT Abdomen scan showed metabolically active ill defined lesion – 22*17mm in relation to intrapancreatic CBD along the postersuperior aspect of proximal body of pancreas (Figure 7). Few metabolically active enlarged peripancreatic and aortocaval lymph nodes – 16*14mm around the celiac axis- highly suggestive of primary pancreatic tumour/ mid common bileduct tumour with upper retroperitoneal lymphnodal spread (Figure 8&9).

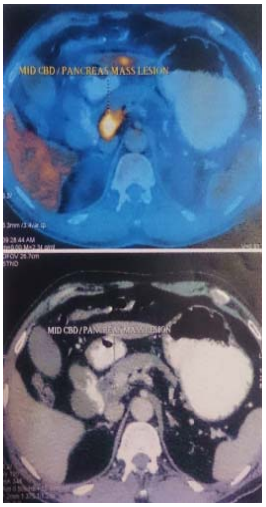

Figure 7

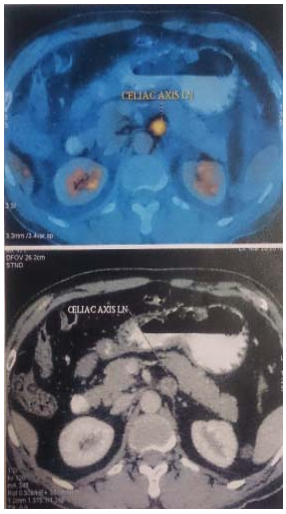

Figure 8

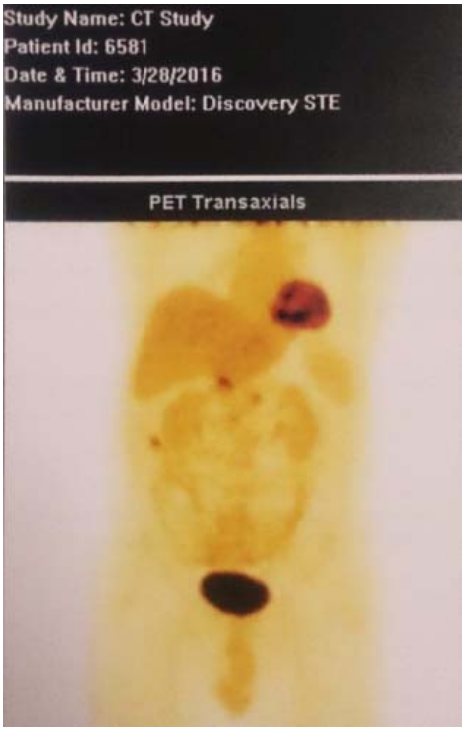

Figure 9

A provisional diagnosis of Obstructive Jaundice secondary to biliary stricture, ? Pancreatic tuberculosis was made and patient was posted for Explorative laparotomy. Intraoperative findings included multiple matted lymphnodes with abscess in retroduodenal, pericholedochal and

aortocaval region. Examination of frozen sections of nodal biopsy showed granulomas with giant cells and no evidence of malignancy. Cholecystectomy with choledochoduodenostomy was done along with excision of multiple nodes for HPE examination. Although special stain for AFB and fungus were negative histopathological examination revealed lymphnode tissue with epithelioid granuloma and Langhan's type giant cells. Necrosis is minimal however nodal stromal fibrosis is evident (Figure 10).

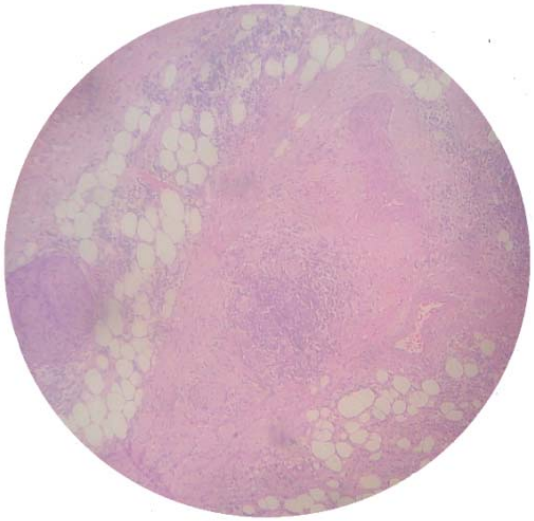

Figure 10.

Patient was started on antituberculous therapy with Isoniazid, Rifampin, Pyrazinamide and Ethambutol. Patient reported improvement of symptoms one week after ATT and was advised regular follow up.

Discussion:

Pathogenesis:

Possible mechanism of invasion of pancreas:

- Hematogenous spread
- Direct spread from contiguous lymph nodes
- Dormant bacilli in old tuberculosis lesion can reactivate in immuno-suppressed state[3-4]

Pancreatic tuberculosis presents with vague symptoms like epigastric pain, fever, anorexia, weight loss, jaundice and pancreatic mass. However isolated pancreatic tuberculosis can present as obstructive jaundice by following mechanism:

- Pancreatic tuberculosis causing pseudoneoplastic obstructive jaundice[5]
- Secondary to tuberculous lymphadenitis causing compression[6]
- Biliary stricture secondary to biliary tuberculosis mimicking cholangiocarcinoma, as in our case[7]
- Retroperitoneal mass causing true biliary obstruction[8]

Diagnosis:

Pancreatic tuberculosis closely mimics pancreatic carcinoma both in clinical presentation and radiological appearance. Non-invasive imaging studies such as ultrasonography, CT and MRI scan can localize a mass lesion in the pancreas but are unable to rule out malignancy or help establish a precise diagnosis. Even the use of fluorodeoxyglucose-positron emission tomography (FDG-PET) CT scan is non-specific for distinguishing between malignancy and tuberculosis, with both lesions exhibiting high uptake of FDG[9]. Routine investigations are usually non-specific.

In contrast to non-invasive techniques, invasive diagnostic techniques are more reliable and definitive. These invasive techniques include CT/US-guided percutaneous biopsy, EUS (Endoscopic Ultrasound)-guided FNAC (Fine Needle Aspiration Cytology) or surgical biopsy that can be either laparoscopic or open[10]. However our patient presented with mid CBD stricture, and was in need of a diversion procedure hence posted for Exploratory laparotomy. Bile duct strictures, independent of etiology, can cause significant morbidity from recurrent obstructive

jaundice, right upper quadrant abdominal pain, biliary stones, and recurrent episodes of ascending cholangitis[11].

Treatment:

Although diagnosis of pancreatic tuberculosis is difficult, majority of patients with pancreatic tuberculosis respond favorably to anti-tubercular treatment. This comprises multi-drug anti-tuberculous chemotherapy for six months as recommended by the World Health Organization (WHO) guidelines[12].FDG-PET/CT may provide an important noninvasive means of evaluating therapeutic response in patients with peripancreatic TB with a decrease in metabolism of the tuberculous lesions after successful anti-tubercular treatment (ATT)[13].

Conclusion:

Interestingly, in addition to pancreatic tuberculosis, this case was also complicated by mid CBD stricture, difficult for a preoperative diagnosis. With the advent of PET CT, it is important for the physicians to be aware of the artifacts and pitfalls related to interpretation of these modalities, to correlate clinically and optimize patient care. False positive FDG PET results for pancreatic cancer and can also occur in active pancreatitis; pancreatic tuberculosis and autoimmune pancreatitis [14]. However the early stage of pancreatic cancer can be falsely negative [15].

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Ibutilide for Pharmacological Cardioversion of Atrial Flutter/ Fibrillation

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Case 1:

A 31year old female, a known case of rheumatic mitral stenosis came with complaints of palpitations and dyspnoea since 24 hours. The patient's heart rate was varying between 100-120 bpm. Her blood pressure was 100/60 mmHg, with serum levels of K^+ =3.5 mEq/L, and Mg^+= 2.3 mg/dl. ECG (Figure 1) revealed '*Atypical atrial flutter with variable atrio-ventricular conduction*'. After ruling out pregnancy and clots in the atria, she was administered 1mg intravenous Ibutilide over 10 minutes. She reverted to sinus rhythm in 3 minutes of completion of infusion. However, a minute before she transiently had developed prolonged QT interval, ventricular bigeminy and a short self-terminating episode of torsades de pointes (TdP) (Figure 2). She was given 1G intravenous magnesium. Her QTc interval normalized by 10th minute and she remained in stable sinus rhythm at discharge after overnight observation. She was prescribed oral amiodarone to maintain sinus rhythm.

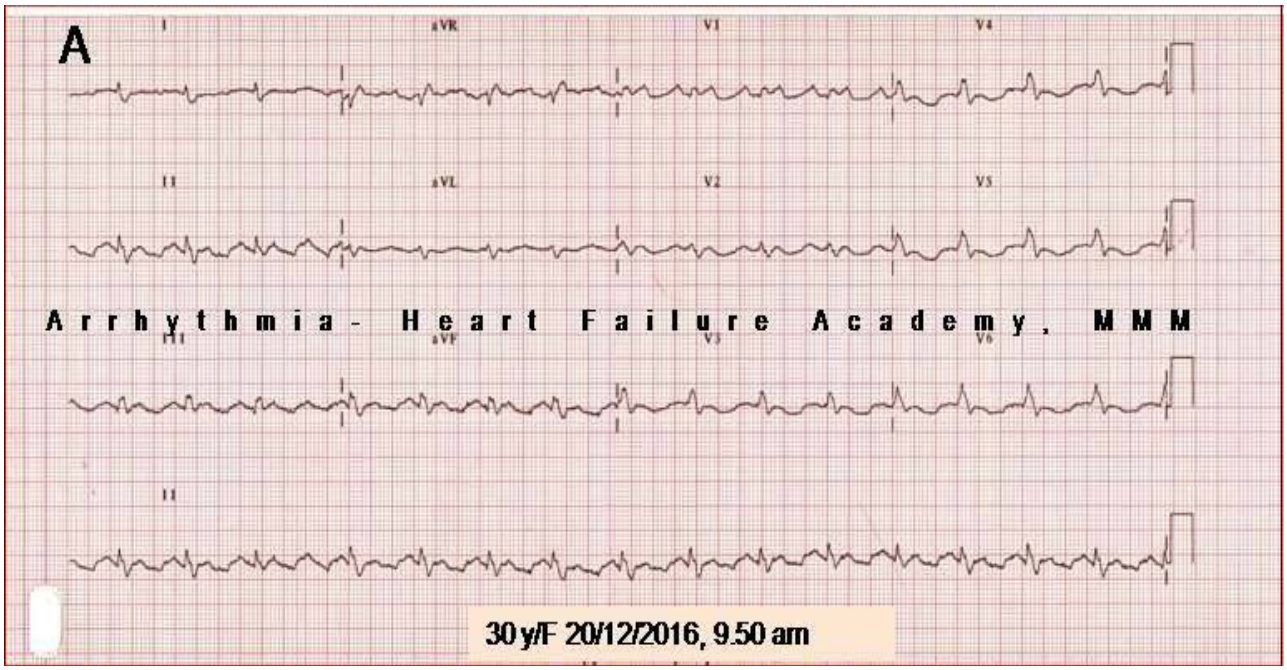
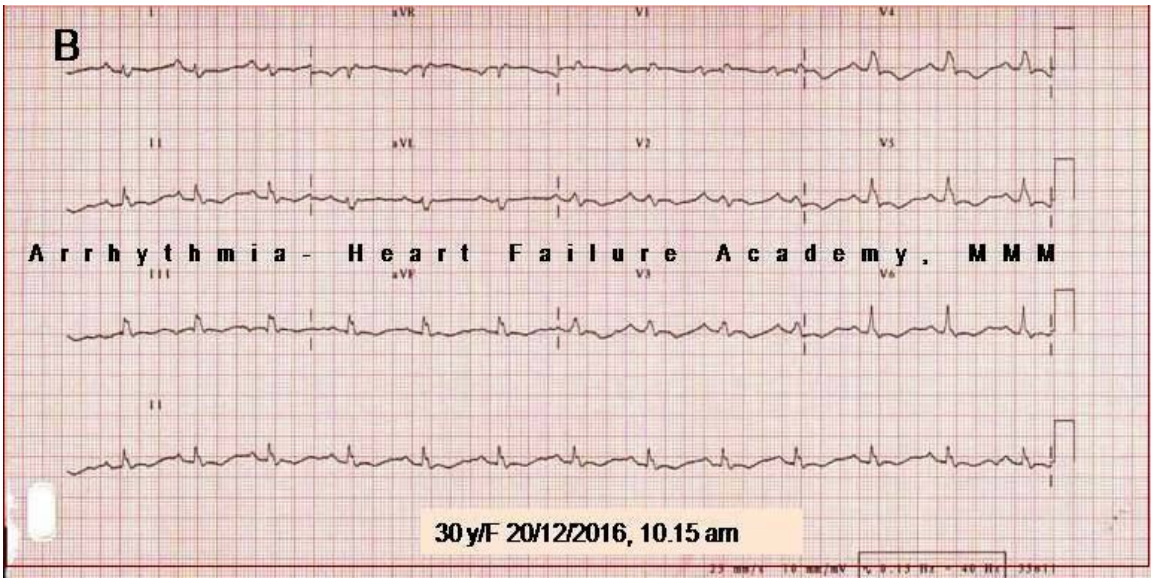


Figure 1: ECG of Case 1, showing atypical atrial flutter (A) and pharmacological cardioversion to sinus rhythm



(B) after intravenous Ibutilide administration

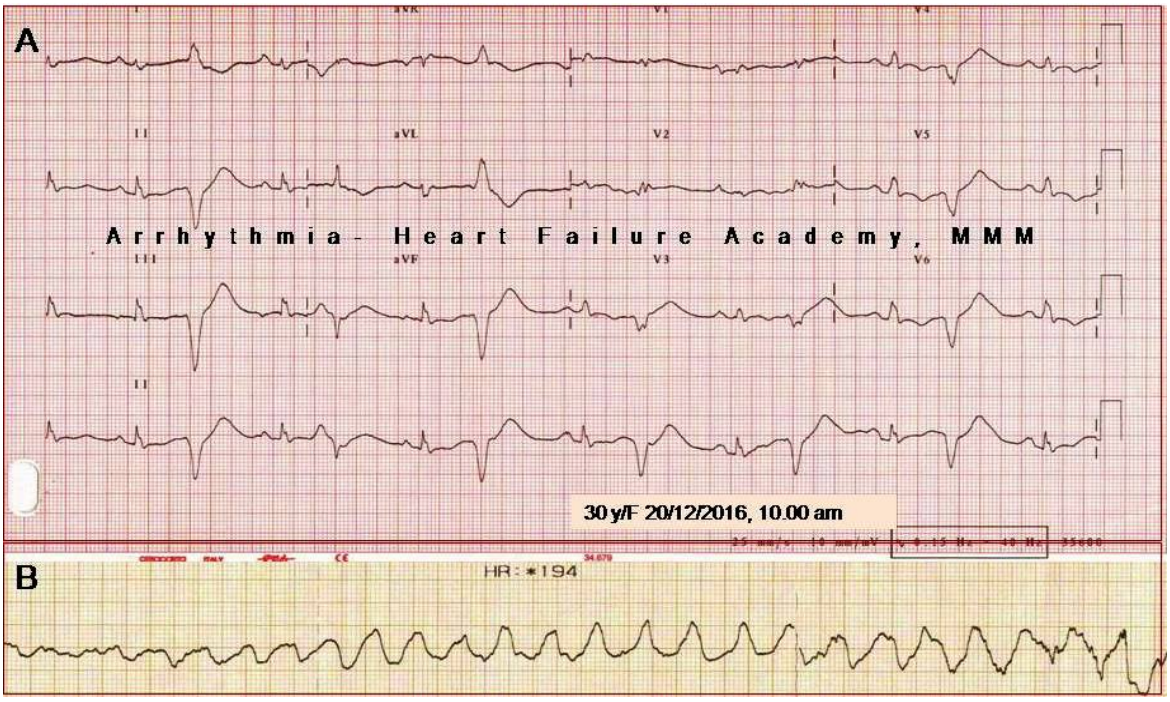


Figure 2: ECG of Case 1, showing prolongation of QT interval with ventricular bigeminy (A) and a transient episode of polymorphic ventricular tachycardia (TdP) (B)

Case 2:

A 69 year old female, a known case of chronic kidney disease and hypertension with left ventricular hypertrophy and severe left ventricular dysfunction in echocardiography, had been extubated just 2 days prior after recovering from sepsis due to severe lower respiratory tract infection. During recovery, she developed gradually worsening breathlessness. The ECG showed '*Atrial fibrillation and fast ventricular rate*' (Figure 3A). She was hemodynamically stable and hence a decision to attempt pharmacological cardioversion was taken considering the high risks

of reintubation involved due to sedation required for DC cardioversion. AF persisted even after 1mg of intravenous Ibutilide. Hence a second bolus of 1mg was given which resulted in successful cardioversion to sinus rhythm. The QTc interval measured 480ms (Figure 3B). She was started on oral amiodarone to maintain sinus rhythm.

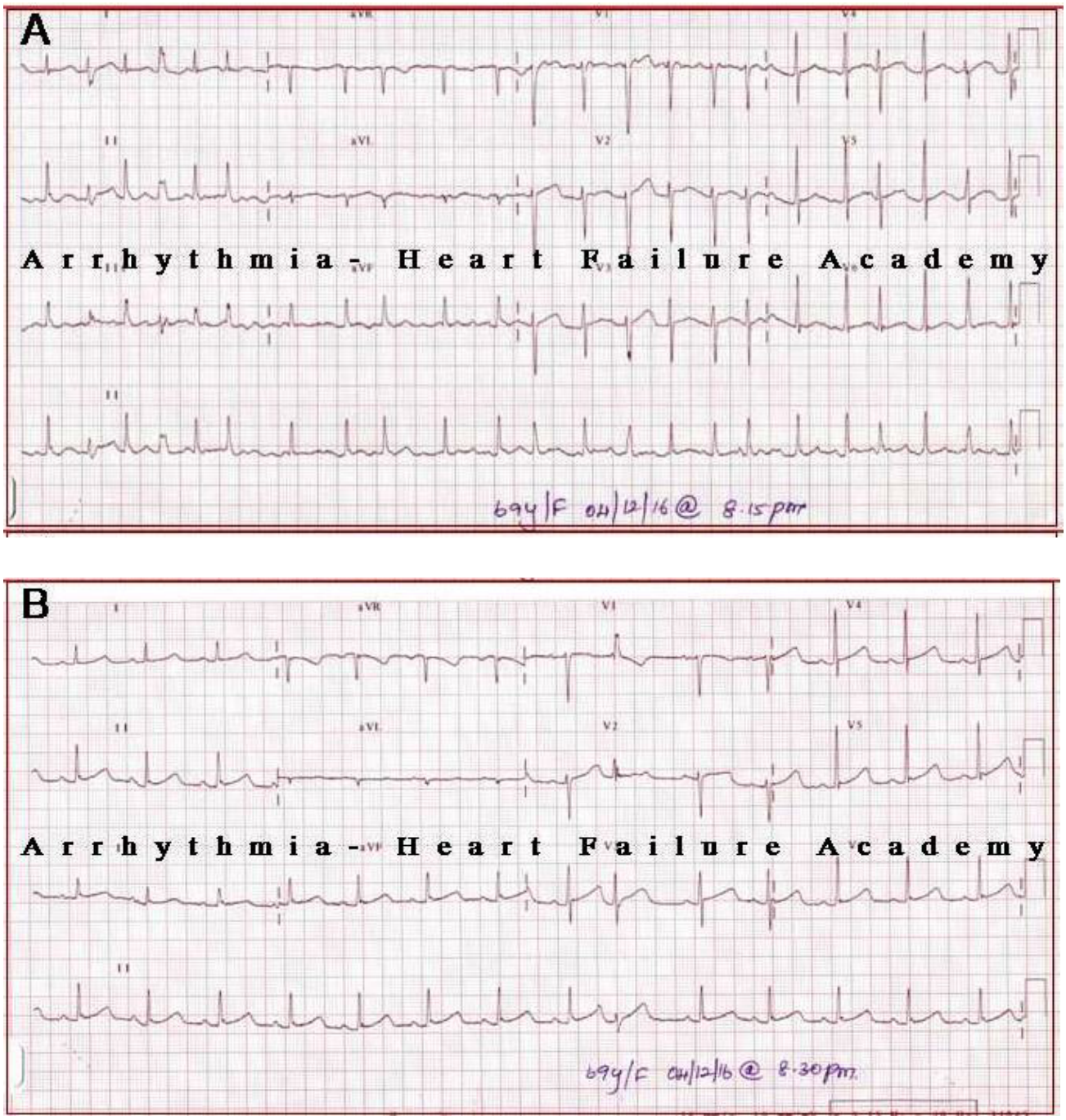


Figure 3: ECG of Case 2 showing Atrial fibrillation (A), cardioversion to sinus rhythm (B) after Ibutilide administration

Discussion:

The risk of respiratory depression and need for intubation due to the sedation/anesthesia given for elective DC cardioversion is high in the elderly and in patients with multiple comorbidities. Pharmacological cardioversion is an effective alternative in such circumstances. Among the

intravenous agents used for pharmacological cardioversion for atrial arrythmias, Ibutilide has high cardioversion rates for atrial flutter (76%) and atrial fibrillation (51%) compared to Procainamide (20% for atrial flutter), Sotalol (18% for atrial flutter/fibrillation) and Amiodarone (29% for atrial flutter, 67% for atrial fibrillation). Ibutilide converts AF within few minutes of infusion, quickest among the available agents.[1,2,3] Ibutilide is a class III antiarrythmic agent that prolongs action potential duration by blocking the delayed rectifier potassium current (Ikr channels) of the myocardium. Ibutilide is indicated for the rapid conversion of atrial fibrillation (AF) or flutter with no structural heart disease. The drug is uncommonly used, especially in India despite its efficacy, possibly because of non-availability and costs.

Ibutilide has been studied even in structural heart diseases, [2] however it needs to be used cautiously as the chances of QT prolongation and development of polymorphic ventricular tachycardia (4-8%) are higher. Before drug administration, patients should be screened carefully to exclude high-risk individuals, such as those with a QTc interval exceeding 440 ms or bradycardia. Serum potassium and magnesium levels should be measured, and replacement therapy should be given to correct any deficits. Continuous cardiac monitoring for at least 4 hours after administration, proper resuscitation kit including a defibrillator and temporary pacing to treat sustained ventricular tachycardia such as torsade de pointes and bradycardia should be available. Adequate information about the indications, dosing, pharmacokinetics and precautions is necessary to consider this potent antiarrythmic agent in the treatment for atrial arrythmias.[4]

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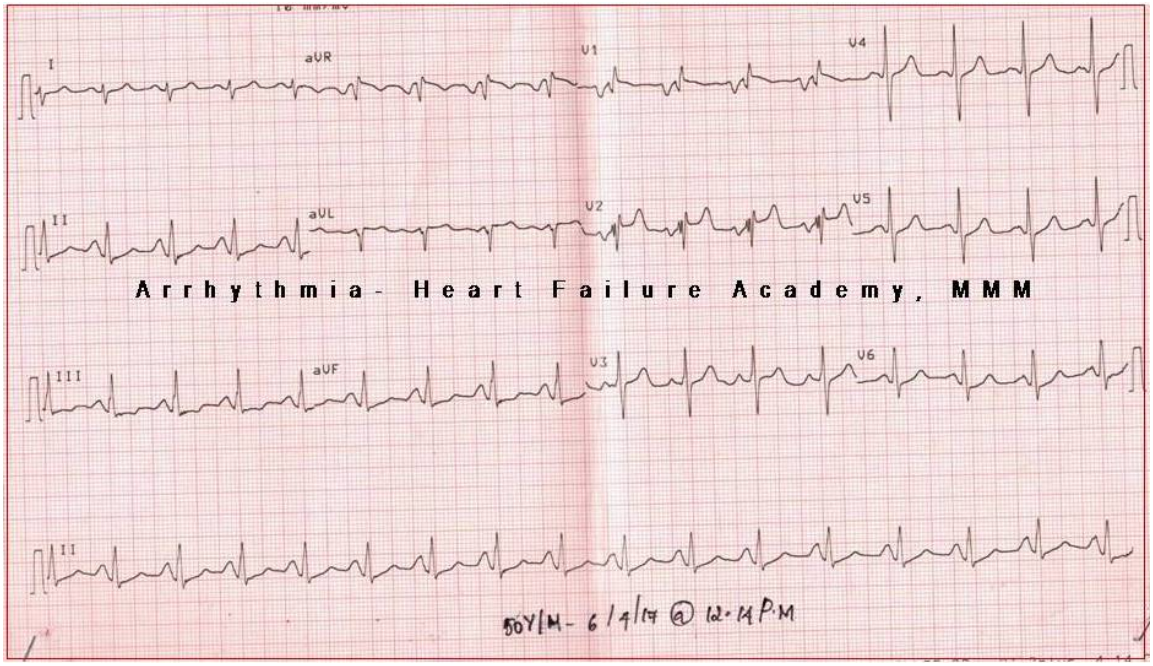
TAPI Journal Vol. 9, Issue 1, January – April 2017

ECG QUIZ

Deep Chandh Raja, Ulhas M. Pandurangi

Dept of Cardiac Electrophysiology & Pacing, Arrhythmia-Heart Failure Academy. The Madras Medical Mission



Question: A case of Rheumatic heart disease, what could be the significant valvular lesion?

Answer: Mitral Stenosis

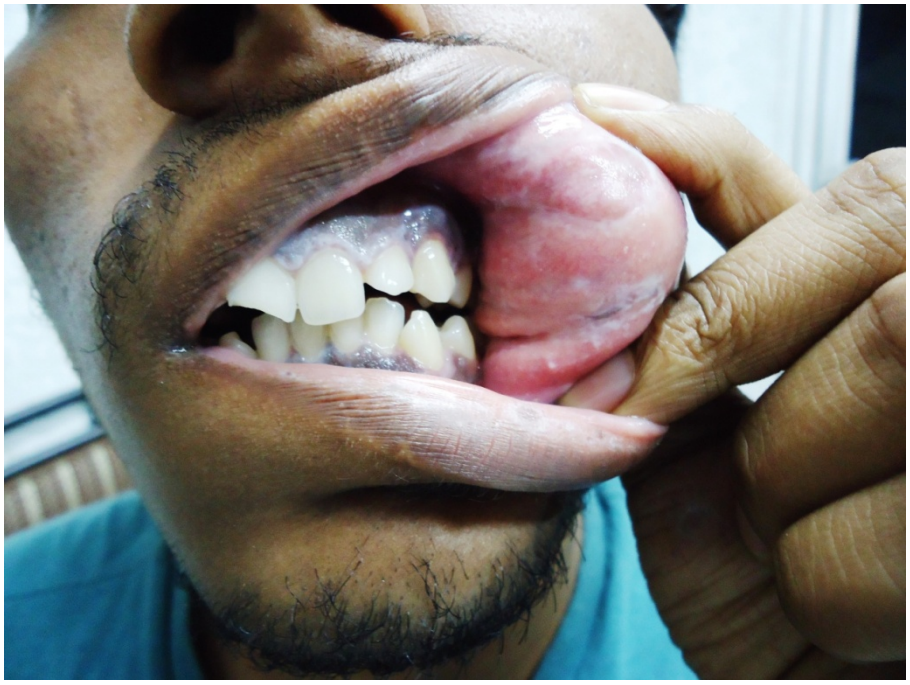
On the basis of the ECG, the significant lesion most likely is 'Mitral Stenosis', which eventually was confirmed by 2D echocardiography. In this ECG, left atrial enlargement is seen by the increased negative terminal forces in lead V1 (Morris index=0.08 mm.sec, normal ≤0.03 mm.sec). Right atrial enlargement is also evident in the form of increased amplitude of P wave (0.3mv, Normal ≤0.25mv) in lead II and P wave axis of +90°. Right ventricular hypertrophy is also evident by a rightward mean frontal QRS axis (+90°), S1S2S3 pattern in the limb leads and qR pattern in V1. The left ventricular under filling can be deduced by decreasing QRS amplitude in leads V5 and V6 as compared to lead V4 and also by the rightward QRS axis. The combination of left atrial enlargement, right ventricular hypertrophy and right atrial enlargement is a characteristic ECG triad of severe mitral stenosis.

TAPI Journal Vol. 9, Issue 1, January – April 2017

Dermatology Photo Feature

Prof. Jayakar Thomas & Dr. Deepthi Ravi

Senior Resident, Department of Skin & STD, Sree Balaji Medical College & Hospital, Chennai



A 25- year- old male presented with a three-month history of mouth pain, sensitivity to hot foods, and general oral discomfort. He mentioned that his mouth sometimes bleeds after he brushes his teeth. On examination, white lace-like striations of the buccal and gingival mucosae were seen. Systemic examination was normal.

DIAGNOSIS

Oral lichen planus (OLP)

PATHOGENESIS

OLP is a T-cell mediated autoimmune disease in which the auto-cytotoxic CD8+ T cells trigger apoptosis of the basal cells of the oral epithelium. An early event in the disease mechanism involves keratinocyte antigen expression or unmasking of an antigen that may be a self-peptide or a heat shock protein. Following this, T cells (mostly CD8+, and some CD4+ cells) migrate into the epithelium either due to random encounter of antigen during routine surveillance or a chemokine-mediated migration toward basal keratinocytes. These migrated CD8+ cells are activated directly by antigen binding to major histocompatibility complex (MHC)-1 on keratinocyte or through activated CD4+ lymphocytes. In addition, the number of Langerhans cells in OLP lesions is increased along with up regulation of MHC-II expression; subsequent antigen presentation to CD4+ cells and Interleukin (IL)-12 activates CD4 + T helper cells which activate CD8+ T cells through receptor interaction, interferon γ (INF – γ) and IL-2. The activated CD8+ T cells in turn kill the basal keratinocytes.

Description/Clinical Picture

Lichen planus is a chronic inflammatory disease that affects the skin and the mucus membrane. Oral lichen planus (OLP), the mucosal counterpart of cutaneous lichen planus, presents frequently in the fourth decade of life and affects women more than men. The disease affects 1–2% of the population. It is seen clinically as reticular, papular, plaque-like, erosive, atrophic or bullous

types. Intraorally, the buccal mucosa, tongue and the gingiva are commonly involved although other sites may be rarely affected. Oral mucosal lesions present alone or with concomitant skin lesions. The skin lesions present as violaceous flat-topped papules in ankles, wrist, and genitalia, but characteristically the facial skin is mostly spared.

Management

Corticosteroids are the most commonly used group of drugs for the treatment of OLP. The rationale behind their usage is their ability to modulate inflammation and immune response. They act by reducing the lymphocytic exudate and stabilizing the lysosomal membrane. Topical midpotency corticosteroids such as triamcinolone acetonide, high-potent fluorinated corticosteroids such as fluocinonide acetonide, disodium betamethasone phosphate, and more recently, superpotent halogenated corticosteroids such as clobetasol are used based on the severity of the lesion. The greatest disadvantage in using topical corticosteroids is their lack of adherence to the mucosa for a sufficient length of time. Although trials were done using topical steroids along with adhesive base, no study shows their superiority when compared to steroids without the base (carboxymethyl cellulose). However, the studies also recommend the usage of adhesive paste used for dentures, which contains only inactive ingredients as a vehicle to carry the topical application. This has shown excellent bioadhesive properties, due to its high molecular weight (above 100,000) and the flexibility of the polymeric chain. Small and accessible erosive lesions located on the gingiva and palate can be treated by the use of an adherent paste in a made-to-measure tray (custom tray), which allows for accurate control over the contact time and ensures that the entire lesional surface is exposed to the drugs. Patients with widespread forms of OLP are prescribed high-potent and superpotent corticosteroids mouthwashes and intralesional injections. Long-term use of topical steroid can lead to the development of secondary candidiasis which necessitates antifungal therapy. The potential tachyphylaxis and adrenal insufficiency is high when using superpotent steroids like clobetasol l, especially when used for a longer period of time. Systemic corticosteroids are reserved for recalcitrant erosive or erythematous LP where topical approaches have failed. Systemic prednisolone is the drug of choice, but should be used at the lowest possible dosage for the shortest duration (40–80 mg for 5–7 days).

Topical tacrolimus and pimecrolimus can also be used.

Oral Cyclosporine is useful, but the side effect profile warrants great caution.

Oral Dapsone, 100 mg daily is a safe and economical alternative after checking hemoglobin levels.

Contributed by:
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TAPI Journal Vol. 9, Issue 1, January – April 2017

Toxicology Clinics-Bench to Bed Side
Seafood Toxicity - Something Fishy- I

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Introduction:

Seafood poisoning, occurs as a result of human consumption of food harvested from the sea. Patients seeking treatment for seafood-borne illnesses may present a diagnostic challenge to the care provider as they may have variable presentations of signs and symptoms, different degrees of severity, as well as unclear timelines in relation to ingestion. The scope of seafood-borne illness is vast and with increased travel and expanding seafood trade, the likelihood of a care provider seeing a seafood-borne illness is increasing.

1. What is the most common fish poisoning?

   Ciguatera is considered to be the most common food-borne disease related to the consumption of finfish worldwide.

2. What is the cause for ciguatera poisoning?

   It is due to ingestion of large predatory reef fish from the tropics. It does not occur in cold water fish.

3. How does fish get infected?

   The toxin is synthesized by specific bacteria after phagocytosis by the benthic dinoflagellate *Gambierdiscus toxicus*, which adheres to dead coral surfaces and bottom-associated algae. The toxin is then concentrated in the food web as the dinoflagellates are eaten by herbivorous fish species that graze on algae and detritus. These fish are in turn eaten by the larger marine carnivores, which may then be eaten by human.

4. How do the infected fish look like?

   Ciguatera infected fish look, smell, and taste normal. At time it can taste 'peppery'.

5. What is Ciguatoxin?

   Ciguatoxin is a lipid-soluble polyether compound and synthesized by specific bacteria after phagocytosis by the benthic dinoflagellate *Gambierdiscus toxicus*, which adheres to dead coral surfaces and bottom-associated algae.

6. Does the toxin get neutralized by cooking?

   No, the toxin is not affected by heat or freezing. Thus may affect humans even if fish are properly cooked.

7. Where does toxin get accumulates in fish?

   The toxin get concentrates more in fish organs than muscle.

8. How does toxin acts in human?

   Ciguatoxins acts by increasing the nerve membrane excitability through their action on voltage-gated sodium channels.

9. What are the clinical features of ciguatera poisoning?

   A bizarre poisoning syndrome but usually includes gastrointestinal, neurologic, and/or cardiovascular symptoms. The symptoms usually start 1–6 hours after the ingestion of fish containing the toxins. The re-exposure to the toxin often leads to worse symptoms.

10. What are the clinical courses of ciguatera poisoning?

    The gastro intestinal symptom initially starts as diarrhea, nausea, and vomiting. These symptoms typically last just a few

days and followed by weakness and fatigue, with occasional hypotension or bradycardia. The features of peripheral neuropathy including dysesthesia, dental pain, and paradoxical disturbance of thermal sensation, are the hallmarks and may last up to 6 months or longer. Ataxia and seizures have also been described.

11. Is ciguatoxins secreted in the breast milk?

    Yes, ciguatera toxin is secreted in breast milk and freely crosses the placenta.

12. Can ciguatera be a sexually transmitted disease?

    Yes, ciguatera toxin is capable of producing symptomatology in both males and females following sexual intercourse as it are present in the semen of men affected.

13. What is meant by Hot-cold reversal in ciguatera poisoning?

    It is better termed as cold allodynia. It is considered as almost pathognomonic of ciguatera poisoning. This phenomenon is probably not a true reversal of temperature sensation; rather pain sensation is altered such that cold is experienced as a burning pain.

14. Is there any mortality reported?

    Till now no fatalities have been documented.

15. What are the investigations to confirm the ciguatera poisoning?

    Ciguatera is diagnosed clinically. Currently, no available biomarkers accurately confirm exposure in humans. Both an ELISA and HPLC test are available to confirm the presence of ciguatoxin in fish flesh but are not used in acute treatment.

16. What is the treatment for the ciguatera poisoning?

    It is totally symptomatic, intravenous fluids for hypovolaemia, benzodiazepines for seizures, Mannitol (0.5-1g/kg IV, ideally within 72 hours of symptom onset) and chronic neuropsychiatric symptoms may respond to fluoxetine, and neuropathic pain may respond to amitriptyline and/or gabapentin.

17. What is Scombroid fish poisoning?

    Scombroid poisoning occurs after the ingestion of fish with high histamine levels due to improper processing or storage. It is one of the most common causes of morbidity associated with fish intake.

18. **How the toxin that causes scombroid produced?**

    Scombrotoxin consists of histamine (and probably other biogenic amines) produced by the breakdown of histidine in the muscles of poorly refrigerated fish. The conversion of fish muscle histidine to histamine is enzymatically catalysed by histidine decarboxylase produced by the gram-negative bacterium *Morganella morganii*. This occurs at temperatures above 16C. Histamine is heat-stable and remains present after cooking, freezing, canning or smoking, so scombroid poisoning can occur even when poorly refrigerated fish has been properly cooked. Hence the symptoms can mimic an allergic reaction.

19. What are the clinical features of Scombroid fish poisoning?

    Symptoms begin within 10 to 90 minutes after ingestion. Gastrointestinal symptoms can include abdominal cramps, nausea, vomiting and diarrhea. Flushing, rash, urticaria(generally widespread erythema, usually lacking wheals), palpitations, headache, dizziness, sweating, and burning of the mouth and throat. Severe complications rarely occur like bronchospasm, respiratory distress and vasodilatory shock. The rashes last 2–

5 hours and other symptoms usually disappear within 3–36 hours.

20. What are the investigations to confirm the Scombroid fish poisoning?

    The diagnosis is generally by clinical judgment. However, it can be confirmed by measurement of histamine in spoiled fish or by measuring plasma histamine level or histamine metabolites (e.g., n-methylhistamine) in patient's urine.

21. What is the differential diagnosis of Scombroid fish poisoning?

    Scombroid poisoning is frequently misdiagnosed

22. What is the management of scombroid poisoning?

    Most instances of scombroid poisoning are self-limited. Rapid-acting antihistamines (usually H1-receptor antagonists) often used. Adrenaline and corticosteroids are generally not indicated.

Further reading:

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Acknowledgments:

We thank Prof. P. Thirumalaikolandusubramanian, M.D for the critical review.

T A P I J

The Journal of the Association of Physicians of India (Tamil Nadu State Chapter)

Honorary Editor:

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3. With each diskette, a printout of manuscript must be sent in the event of CD damage/virus.

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Discussion: This should emphasize the new and important aspects of the study and conclusions that follow from them. Do not repeat in detail data given in the results section. Include in the discussion the implications of the findings and their limitations and relate briefly the observations to relevant studies.

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Photographs should be of good quality and on glossy paper. Illustrations and graphs should be drawn on thick white paper with India ink. They should not be pasted on papers. The numbers should be marked at the back in pencil and the top should be marked by arrow. Legends should be typed on a separate sheet. Each should be brief but sufficiently descriptive to be complete by itself.

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The pattern of References should be as follows.

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Subject to the approval of the Governing Body in an ordinary or a special meeting, I agree to become a member and if admitted, to abide by the Rules and Regulations of the Association.

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Xerox copies of registration with Medical Council and Postgraduation Certificate by a recognised university should accompany the application form

N.B. Kindly read carefully the rules and regulations printed overleaf before filling this form.

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LIFE MEMBERS : Life Members are required to posses a post-graduate degree such as MD/DNB, DM, or equivalent in internal medicine from any institution or university recognised by the Medical Council of India and/or approved by the Governing Body of the Association. MD General Medicine / Internal medicine includes specialities such as Cardiology, Gastroenterology, Diabetology, Nephrology, Neurology, Clinical Haematology, Chest & Tuberculosis, Endocrinology, Gerontology, Infectious Diseases, Allergy, Immunology, Rheumatology, Medical Oncology and others approved by the Governing Body notified by the General Body. Life membership shall be open to citizens of India only.

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5.2.1.2 Continuous membership of the Association of Physicians of India for not less than 7 yrs.

5.2.1.3 Should have made a significant contribution to research / teaching / development in the field of medicine.

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	Address Residence		Address Office	
4.	Tel.:	Fax : Mobile	E-mail:	
5.	Postgraduate degree in Medicine	Year of passing	Institute	University
	Other Professional Qualifications	Year	Speciality / Subjects	University / Institute
a.				
b.				
c.				
d.				
	Certificates Attached			
6.	Experience in Medical Profession after Postgraduation in Medicine			

Name of Hospital / Clinic / Organisation & Location	Number of Beds (if applicable)	Period Served year wise (From-To)

7.	Publications: List below. (If number of publications in Journals exceeds 8, publications which can qualify as research papers may be listed under Research section 9.)	
a) Number of Publications in Indexed National / International Journals.		Attach title page / Abstract as Appendix
b) Number of Chapter in Books / monograms		
c) Editorship of National level or State level: Book /Monogram/Update Series		
8.	Honours And Awards (list below with photocopy of proof)	
(a) Oration in National / State Association Meeting		

Title of Oration	Organisation	Year

8 (b) Award National / International / or State level		
Title of Award	Organisation	Year

9.	Research work (list below)	
(a) Research sanctioned & funded by Research Agency		Attach Letter of sanction.
(b) Departmental Research. (To qualify, the findings should be published in National/International Journal) Do not include papers already listed under Publications		Attach title page / Abstract

10.	Contribution to API (list below and attach proof)		
Post held in Organisation / Meeting	Name of Organisation / Meeting / CME	National / Zonal / Under API/ICP	Year

11.	Participation in CME or Scientific Sessions of API or ICP as Faculty		
Speaker / Chairperson / Other	Title of Talk / Session	Name of Meeting	Year

12.	Social welfare / Community service. (Include under the headings given below, with documentary evidence) (a) Emergency services during National calamities (Quakes/ Floods/Cyclones, etc) (b) Public education Programme (Radio), TV talk/ writing in news papers . (c) Service in Rural Areas	
Service		Evidence

N.B : No handwritten application will be accepted. * To be typed on separate page
*One original and seven Xerox copies of sets to be submitted
Last date for receiving the application form is 31st May 2011.
Address : Turf Estate, No. 006 & 007, Dr. E. Moses Road, Opp. Shakti Mill Compound, Mahalaxmi (West), Mumbai – 400 011.

Indian College of Physicians

Citation

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

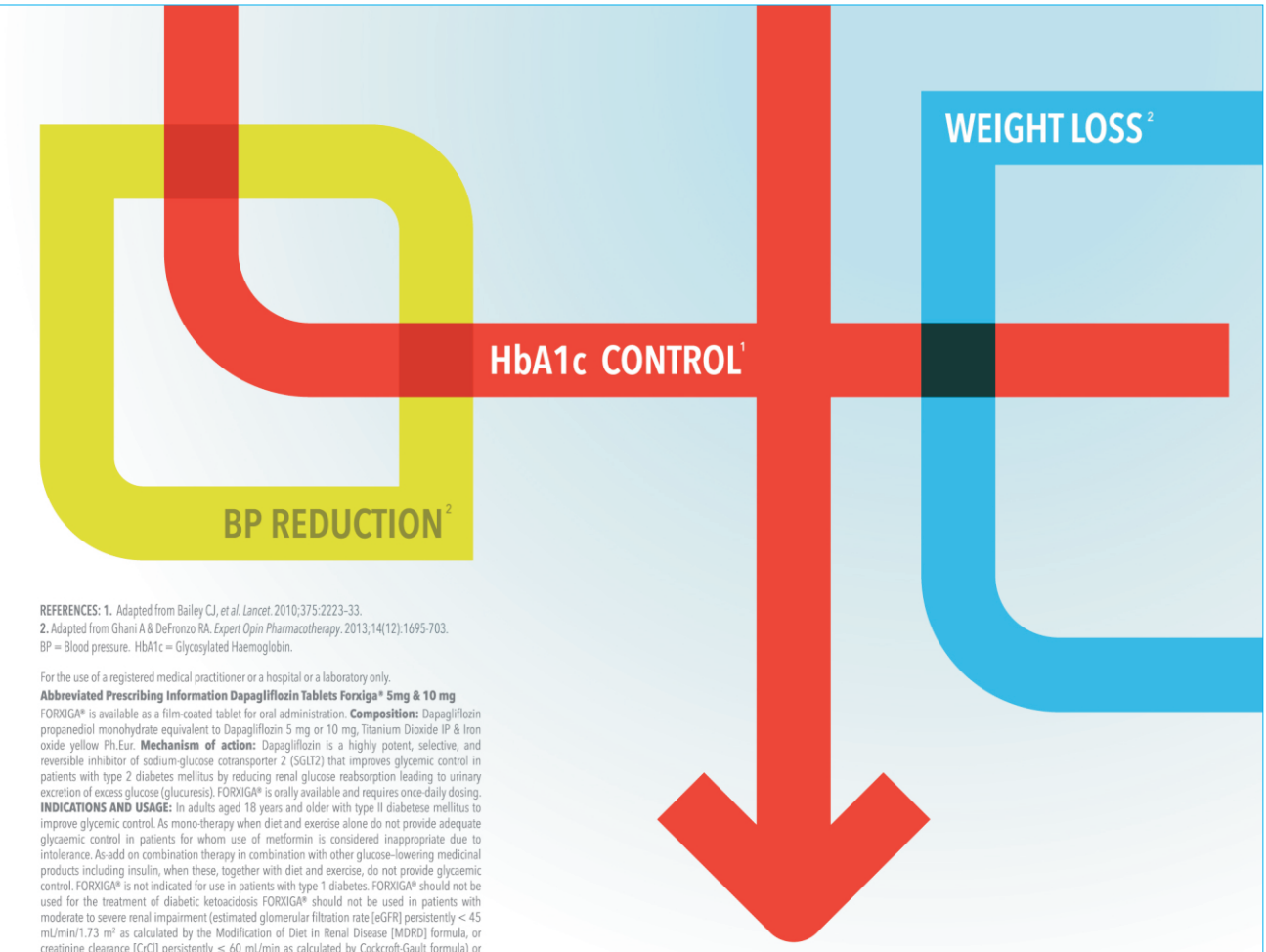
Name _____ Name _____

Membership No._____ Membership No. _____

Signature Proposer _____ Signature Seconder _____

Note:- The Fellowship form should be proposed and seconded by Founder Fellow / Fellow of ICP only. In case there are more than 3 nominations by any proposer/seconder, the first three nominations in order of receipt in API Office and complete in all respects will be considered for award of Fellowship of ICP and the others rejected for consideration.

Available on API and JAPI websites: www. apiindia.org & www.japi.org



REFERENCES: 1. Adapted from Bailey CJ, *et al. Lancet.* 2010;375:2223–33.
2. Adapted from Ghani A & DeFronzo RA. *Expert Opin Pharmacotherapy.* 2013;14(12):1695-703.
BP = Blood pressure. HbA1c = Glycosylated Haemoglobin.

For the use of a registered medical practitioner or a hospital or a laboratory only.

Abbreviated Prescribing Information Dapagliflozin Tablets Forxiga® 5mg & 10 mg

FORXIGA® is available as a film-coated tablet for oral administration. **Composition:** Dapagliflozin propanediol monohydrate equivalent to Dapagliflozin 5 mg or 10 mg, Titanium Dioxide IP & Iron oxide yellow Ph.Eur. **Mechanism of action:** Dapagliflozin is a highly potent, selective, and reversible inhibitor of sodium-glucose cotransporter 2 (SGLT2) that improves glycemic control in patients with type 2 diabetes mellitus by reducing renal glucose reabsorption leading to urinary excretion of excess glucose (glucuresis). FORXIGA® is orally available and requires once-daily dosing. **INDICATIONS AND USAGE:** In adults aged 18 years and older with type II diabetese mellitus to improve glycemic control. As mono-therapy when diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance. As-add on combination therapy in combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide glycaemic control. FORXIGA® is not indicated for use in patients with type 1 diabetes. FORXIGA® should not be used for the treatment of diabetic ketoacidosis FORXIGA® should not be used in patients with moderate to severe renal impairment (estimated glomerular filtration rate [eGFR] persistently < 45 mL/min/1.73 m^2 as calculated by the Modification of Diet in Renal Disease [MDRD] formula, or creatinine clearance [CrCl] persistently ≤ 60 mL/min as calculated by Cockcroft-Gault formula) or end-stage renal disease (ESRD). **DOSAGE AND ADMINISTRATION:** The recommended dose of FORXIGA® is 10 mg taken once daily at anytime of the day regardless of meals. **Monotherapy and Add-On Combination Therapy** he recommended dose of FORXIGA® is 10 mg once daily as monotherapy or as add-on to combination therapy with metformin (with or without SU), a thiazolidinedione, a sulfonylurea, a DPP4-inhibitor (with or without metformin), or insulin (with or without oral antidiabetic therapy, either metformin plus insulin dual therapy or metformin plus sulfonylurea plus insulin triple therapy). **Renal Impairment *Patients with Mild Renal Impairment (eGFR ≥60 to <90 mL/min/1.73 m^2)*** he pool of 21 double-blind, active- and placebo-controlled, clinical safety and efficacy studies included 53% (4906/9339) of patients with mild renal impairment. The mean change from baseline in hemoglobin A1c (HbA1c) and the placebo-corrected mean HbA1c change at 24 weeks was −1.03% and −0.54%, respectively, for FORXIGA® 10 mg (n=562). The safety profile in patients with mild renal impairment is similar to that in the overall population. ***Patients with Moderate Renal Impairment (eGFR ≥30 to <60 mL/min/1.73 m^2)*** The pool of 21 active- and placebo-controlled clinical studies included 11% (1055/9339) of patients with moderate renal impairment. The mean change from baseline in HbA1c and the placebo-corrected mean HbA1c change at 24 weeks was −0.87% and 0.39%, respectively, for FORXIGA® 10 mg (n=85). Safety in patients with moderate renal impairment was assessed in a pooled analysis of 12 clinical studies (384 patients, 88% with eGFR ≥45 to <60 mL/min/1.73 m^2. In the short-term plus long-term safety pool up to 102 weeks, the safety profile remained similar. ***Patients with Severe Renal Impairment (eGFR <30 mL/min/1.73 m^2)*** Patients with Severe Renal Impairment (eGFR <30 mL/min/1.73 m^2) or ESRD, were not included in clinical studies. Based on its mechanism of action, FORXIGA® was not anticipated to be effective in these populations. **Use in Patients at Risk for Volume Depletion** The diuretic effect of FORXIGA® decreases intravascular volume. For patients at risk for volume depletion or dehydration due to co-existing conditions (such as patients with extremely poor glycaemic control, elderly patients and those on concomitant diuretics), a 5-mg starting dose of FORXIGA® may be appropriate. These patients should also be instructed to take water appropriately and carefully monitored. When symptoms of volume depletion arise, appropriate measures including fluid replacement or temporary interruption of FORXIGA® should be considered. **Ketoacidosis** Patients treated with FORXIGA® who present with signs and symptoms consistent with ketoacidosis, including nausea, vomiting, abdominal pain, malaise and shortness of breath, should be assessed for ketoacidosis, even if blood glucose levels are below 14 mmol/L (250 mg/dL). If ketoacidosis is suspected, discontinuation or temporary interruption of FORXIGA should be considered and the patient should be promptly evaluated. **CONTRAINDICATIONS:** FORXIGA® is contraindicated in patients with a history of any serious hypersensitivity reaction to the active substance or to any of the excipients. **ADVERSE REACTIONS:** The overall incidence of adverse events for the 13-study, short-term, placebo-controlled pool (short-term treatment) in patients treated with FORXIGA® 10 mg was 60.0% compared to 55.7% for the placebo group. Discontinuation of therapy due to adverse events in patients who received FORXIGA® 10 mg was 4.3% compared to 3.6% for the placebo group. The most commonly reported events leading to discontinuation and reported in at least 3 FORXIGA® 10 mg-treated patients were renal impairment (0.8%), decrease in creatinine clearance (0.6%), increased blood creatinine (0.3%), urinary tract infections (0.2%), and vulvovaginal mycotic infection (0.1%). **Incompatibilities: Not applicable.** Shelf life: refer **outer pack.** Storage: **Do not store above 30°C.** Pack size: **refer to outer carton FORXIGA® is a Registered Trademark of the AstraZeneca group of companies.**

For Further Information Contact: AstraZeneca Pharma India Limited, Block N1, 12th Floor, Manyata Embassy Business Park, Outer Ring Road, Rachenahalli, Bangalore- 560045.

For more information refer full prescribing information

API V3: Dec 2015 based on the package insert Version 5, dated 09th Dec 2015.

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