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REVIEW ARTICLES

CASE REPORTS

EDITORIAL

OPJ - A LONG WAY TO GO

Manoj Kumar Mohapatra

It is gratifying to note that now OPJ is a journal with two issues in a year. It is possible with the help of editorial board, co-operation of authors, and support of Odisha State API. We have adopted a policy of publishing 2-4 original articles, 2-4 review articles, and 4-6 case reports in an issue.

The future of a journal depends on standard articles. Without it printing a journal is a mere wastage of stationery. Hence, our young physicians must take necessary steps to elevate the standard of the journal to a new peak by submitting standard articles.

Then the question arises regarding a standard article. Does it mean a new concept or a new idea? The answer is both yes and no. Yes, because any new idea or concept gives rise a good piece of scientific paper that requires publication. No, because repetition of an old idea can be turned to a standard publication provided the methodology, data analysis, and interpretation of data are scientific and robust.

It is a common perception among the authors is that their submitted article is of good standard and worthy of publication. They can't accept the rejection or delay in publication of their submitted article. Rejection is an opportunity for writing the article in a betterway. Therefore, work again and again on your paper to get the best and improve our OPJ. I hope it will soon be a journal with monthly and supplement issue.

Professor, Dept. of Medicine,
VSS Institute of Medical Science & Research, Burla

Citation - Mohapatra M K: OPJ- A Long Way to Go, Orissa Phys. J., 13 (2);2016:53

Chairman's Address-2016

MANAGEMENT OF HYPERTENSION – FROM GUIDELINES TO CLINICAL PRACTICE

Sisir Kumar Mahapatro

Hypertension poses a significant public health burden on cardiovascular health status and health care systems in India. Data from the Global Burden of Hypertension 2005 study, the GBD 2010 study and WHO 2011 NCD India specific data suggests an alarming rise in hypertension in Indian subcontinent.

The overall prevalence of hypertension in India has been estimated to be 29.8%. The rural and urban prevalence of hypertension are 27.6% and 33.8%, respectively. As can be seen in the graph on the slide, the prevalence of hypertension in urban India was almost similar across north, east, west and southern regions. However, the rural prevalence was highest among the Eastern parts of India.[1]

The trend analysis of the last 20 years suggest a convergence in hypertension prevalence in urban and rural populations. While the prevalence of hypertension in urban areas has stabilized at 28—33%, rural prevalence of hypertension has increased significantly from 10—12% at the turn of the century to 24– 27% currently.

Despite an increased prevalence of noncommunicable diseases in India, there is a wide gap between what is known and what is actually done for the prevention, detection and management of hypertension in India.1 Overall, about 33% urban and 25% rural Indians are hypertensive. Among these, only 42% urban Indians and 25% rural Indians are aware of their hypertensive status. Further, only 38% and 25% of urban and rural residents, respectively, are being treated for hypertension.

These data indicate that only about one-tenth of rural and one-fifth of urban Indian hypertensive population have their BP under control.[3] The slide shows the percentage of patients treated among those diagnosed with hypertension and percentage of population with BP under control.[4]

Human Essential HTN is a typical Example of complex, multifactorial and polygenic trait.There are several publications illustrating that a single gene mutation leads to the High BP. AME(Apparent Mineralocorticoid Excess Syndrome) AME is an autosomal recessive disorder causing hypertension and hypokalemia. AGT (Angiotensinogen Gene) The secretion of Angiotensinogen is generally determined.

Sympathetic Activation in Hypertension:

The SNS represents a major pathophysiological hallmark of both HTN & Renal failure and is an important target for the therapeutic intervention.

Cardiac Output: An increased CO results in increased blood pressure.

Chairman, API, Odisha State Branch

Citation - Mahapatro S K : Management of Hypertension – From Guidelines to Clinical Practice. Orissa Phys. J., 13 (2);2016: 54-59

The best understood endogenous & environmental determinants of BP include over activation of the SNS and RAAS & elevated intracellular Na+ & Ca++ levels. The exacerbating factors include obesity, sleep apnea, increased salt intake, excessive alcohol use, cigarette smoking, polycythemia, NSAID therapy and low K+ intake. The prevalence of HTN is seen in persons >65 & >55 yrs in men & women respectively.

Stress:

Proposed environmental factors include exposure to chronic stress. Several studies have suggested that chronic stress includes social conflict is associated with higher blood pressure.ABPM has shown that most people have their highest pressure during their working hours.

The most recent "ACD" guideline come from British Society of Hypertension and NICE. The chose 3 groups of agents.

A = ACEI /ARB ;C= CCB;D= Diuretics

The missing B is for β-Blocker which is downgraded. (Nevibolol may be an exception)

JNC 7 & JNC 8 recommends a Diuretic is the initial therapy.

ESC recommends whatever class seems appropriate for the patients, whereas WHO states any class may be used but a Diuretics is preferred.

IGH –III recommends ACEI/ARB/CCB/ Diuretics/Newer B-Blocker may be used for initial therapy

Guidelines for Selecting Drug Treatment for Hypertension

Sl No.	Class of Drug	Favored Indications	Possible Indications	Compelling Contraindications	Possible Contraindications
I	Diuretics(low dose thiazides)	Congestive heart failure Older adults with hypertension Systolic hypertension African origin subjects	Obesity	Gout	Pregnancy Dyslipidemia Metabolic syndrome Sexually active men
	Diuretics(loop)	Congestive heart failure Renal failure		Hypokalemia	
	Diuretics (antialdo)	Congestive heart failure Postinfarct Aldosteronism (First or Second Degree)	Refractory hypertension	Hyperkalemia Renal failure	Diabetic renal disease
II	CCBs	Angina, effort Older Adults Systolic hypertension	Peripheral vascular disease Diabetes African origin	Heart block Clinical heart failure (possible exception: amlodipine, but needs care)	Preexisting ankle edema
III	ACEI inhibitors	left ventricular dysfunction or failure Postinfarct Nephropathy, type1 diabetic or nondiabetic Proteinuria	CV protetion(BP already controlled) Type 2 nephropathy	Pregnancy Bilateral renal artery stenosis	Severe cough Severe aortic stenosis
IV	Angiotensin II Antagonists (ARBs)	ACE inhibitor cough Diabetes type 2 nephropathy including microalbuminuria LVH Heart failure	Postinfarct	Pregnancy Bilateral renal artery stenosis Hyperkalemia	Severe aortic stenosis
V	ß-Blockers	Angina Tachyarrhythmias Post-MI Heart failure(uptitrate)	Pregnancy Diabetes	Asthma, severe COPD Heart block	Obesity Metabolic syndrome Athletes and exercising patients Erectile dysfunction Peripheal vascular disease

Table - 2

Guideline Recommendations for initial Management of Hypertension

	Population	Goal BP	Initial drug options
NICE 2011[1]	General <80 years	<140/90 mmHg	<55 years: ACEI or ARB
	General >80 years	<150/90 mmHg	>55 years including black: CCB
ESH/ESC 2013[2]	General non-elderly	<140/90 mmHg	Diuretic, ß-blocker, CCB, ACEI, or ARB
	General elderly (60-79)years	<150/90mmHg (<140/90)*	
	General =80 years	<150/90 mmHg	
	Diabetes	<140/85 mmHg	ACEI or ARB
	CKD without proteinuria	<140/90 mmHg	ACEI or ARB
	CKD with proteinuria	<130/90 mmHg	
JNC 8 (2014)[3]	• General <60 years	<140/90 mmHg	Nonblack: thiazide-type diuretic, ACEI, ARB, or CCB
	• General = 60 years	<150/90 mmHg	Black: thiazide-type diuretic or CCB
	• CKD/diabetes	<140/90 mmHg	
ASH/ISH 2014[4]	General <60 years	<140/90 mmHg	Non-black: ACEI or ARB Black: CCB or thiazide/thiazide like diuretic
	General 60-79years	<140/90 mmHg	CCB or thiazide/thiazide like diuretic
	Elderly =80 years	<150/90 mmHg	
	Diabetes	<140/90 mmHg	ACEI or ARB
	CKD	<140/90 mmHg**	ACEI or ARB

*As per ESH/ESH, in fit elderly patients a target <140/90 mmHg can be tried. ** As commented by ASH/ISH, some experts still recommend <130/80 mm Hg

CHD: Coronary heart disease; CKD: Chronic kidney disease; CV: Cardiovascular; DBP: Diastolic blood pressure; SBP: Systolic blood pressure; TIA: Transient ischemic attack; CCB: Caldum channel blocker; ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blockers

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1. JNC 8 report 2014. 2. ESH/ESC Guidelines. 2013; 3. NICE Clinical Guidelines. 2011; 4. ASH/ISH Guidelines 2014.

Table 1 & 2 present the goal blood pressure and initial drug options as suggested by recent guideline recommendations for the management of hypertension from the 2011 National Institute of Clinical Excellence (NICE) guidelines, 2013 European Society of Hypertension (ESH)/ European Society of Cardiology (ESC), 2014 Joint National Committee (JNC), and 2014 American Society of Hypertension/ International Society of Hypertension guidelines.[4-7]

Compared to the previous 2007 hypertension guidelines, the 2013 Indian Guidelines on Hypertension (IGH-III) from the Association of Physicians of India (API) adopted a relatively less aggressive approach towards achieving the target BP.

There is a considerable variation in target BP goals between international and Indian guidelines. The current Indian guidelines recommends a target BP of:

1. Less than 140/90 mmHg in the young and middle aged
2. Less than 140/80 mmHg in patients with diabetes
3. Less than 130/85 mmHg in patients who survived a stroke

Less than 140-145/90mmHg in elderly patients[8].

The "Paradigm Shift" in the management of Hypertension should be based on assessment of global CV risk and not on baseline value of an individual risk factor or particular BP level.

Several clinical trials have shown that BP lowering reduces the risk of myocardial infarction by 20%-25%, risk of stroke by 35%-40% and risk of heart failure by 50%. Our medical fraternity cannot be proud of this reduction as a target of 65% risk reduction in hypertensive and 80% in general population is feasible.[9]

Furthermore, hypertension is associated with a constellation of CV risk factors such as the metabolic syndrome components, endothelial dysfunction, arterial stiffness and nephropathy that denotes its role in a multifactorial disease process.[1] Consequently, treatment of blood pressure alone is not sufficient for reducing cardiovascular risk.[10]

An optimal strategy would be to reduce CV risk which may include lifestyle modification, promoting adherence to therapy, early and aggressive target levels achievement and appropriate drug choice.[11]

In India, hypertension directly contributes to 57% of all stroke deaths and 24% of all CHD deaths.[1] Although heart attacks and strokes are leading causes of death and disability, they represent only the tip of the iceberg.[2] Despite these alarming findings, physicians in India concentrate only on blood pressure reduction *per se* and do not take other CV risk factors into consideration.

Given that hypertension is associated with a constellation of other risk factors, a multiple CVD risk factor approach is imperative to effectively control the CVD epidemic in the Indian subcontinent.[1,12] Using the global cardiovascular risk reduction is the gold standard in hypertension therapy.[12]

What should be our approach towards goals of lowering blood pressure? Should we "Go low" or say "No" to aggressive systolic BP goals.

This ongoing debate was addressed in the recent Systolic Blood Pressure Intervention Trial (SPRINT). The SPRINT evaluated the effects of intensive antihypertensive treatment with a systolic blood pressure (SBP) target of <120 mmHg compared to standard treatment with a SBP target of <140 mm Hg in 9361 hypertensive patients e"50 years of age with an average SBP of 130–180 mm Hg at high risk for cardiovascular (CV) events but without diabetes

The results of SPRINT trial are out and are as follows:

1. Reduction in primary composite outcome of myocardial infarction (MI) , non–MI acute coronary syndrome (ACS), stroke, acute decompensated heart failure, and cardiovascular death by 25% in the intensive therapy group compared to the standard therapy group
2. Reduction in all-cause mortality by 27% in the intensive therapy group
3. Rates of serious adverse events of hypotension, syncope, electrolyte abnormalities, and acute kidney injury or failure, but not of injurious falls, were higher in the intensive treatment group than in the standard-treatment group

The study result suggested that targeting a SBP of <120 mm Hg, in patients at high risk for CV events resulted in lower rates of fatal and nonfatal major CV events and death from any cause compared to SBP of <140 mmHg. The study was stopped early after a

median follow-up of 3.26 years due to a significantly lower rate of the primary composite outcome in the intensive treatment group.[13]

Telmisartan – relevant pharmacological characteristics with potential clinical implications

In the past 12 years, seven ARBs have been marketed. However, they differ in pharmacological profile and these differences might affect their efficacy. Telmisartan is highly lipophilic, far more than any other ARB; this should help in its ability to cross membranes and its biodistribution, hence its large volume of distribution.

Telmisartan's large volume of distribution means that there is both systemic and local AT_1 receptor blockade. Because the AT_1 receptor has pathological effects, including cell hypertrophy and fibrosis, the ability to block it at the tissue level may help to reduce target-organ damage.

The fast tmax of just 1 hour, insurmountable AT_1 receptor blockade and very long half-life of 24 hours ensure a rapid onset of action and a long duration of effect. These parameters could have clinical relevance because *in vivo* during AT_1 receptor blockade circulating levels of angiotensin II have been seen to rise, which could potentially compete for the AT_1 receptor and modulate blockade.

The low renal excretion makes it safe for use in patients with renal failure. Its high affinity and binding constant impart high potency and long-lasting effect. The ability of telmisartan to act as a partial antagonist of PPAR-gamma that is a major regulator of lipid and carbohydrate metabolism suggests that it is a possible mechanism by which telmisartan could improve glucose and lipid metabolism thereby improving total cardiovascular risk.[14]

Telmisartan is also a selective $PPAR_\gamma$ modulator: Effects on molecular, cellular and metabolic parameters *in vitro*

The metabolic syndrome is a common precursor of cardiovascular disease and type 2 diabetes. It is characterized by the clustering of insulin resistance, dyslipidaemia and increased blood pressure. Mutations in the peroxisome proliferator-activated receptor-gamma (PPAR-gamma) have been reported to cause the full-blown metabolic syndrome in humans.

Drugs that activate PPAR-gamma are effective agents for the prevention and treatment of insulin resistance and type 2 diabetes. Telmisartan is structurally unique among the other ARBs and it can function as a partial antagonist of PPARgamma.

This influences the expression of PPAR-gamma target genes involved in carbohydrate and lipid metabolism. In rats fed a high-fat, high-carbohydrate diet telmisartan can reduce glucose, insulin and triglyceride levels. None of the other commercially available ARBs appear to activate PPAR-gamma to the same extent as telmisartan.

The ability to block the AT_1-receptor and modulate PPAR-gamma confers potential benefits beyond blood pressure lowering, which include; increased insulin sensitivity, improved lipid profile, improved anti-inflammatory and anti-atherogenic risk profiles. These properties could provide superior clinical efficacy in hypertensive patients with insulin-resistant states such as metabolic syndrome and type 2 diabetes. Telmisartan might therefore have added benefits in treating cardiovascular patients with metabolic pathology and their associated end-organ micro- and macrovascular complications.[15,16]

Conclusion:

1. The lower is better in high CV risk patients.
2. If Hypertension is not controlled with a triple combination therapy (RAS + CCB + DIU) add Spironolactone.
3. Add Statin for CV Risk Reduction.
4. Sometimes with Devices.

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Original article

ORAL MAGNESIUM SUPPLEMENTATION IMPROVES NEPHROPATHY AMONG PATIENTS OF TYPE 2 DM WITH HYPOMAGNESAEMIA

Butungeshwar pradhan.[1]Sagnika Tripathy.[2] Tejeshwar Reddy.[3]

ABSTRACT

Background:

The relation between magnesium (Mg) deficiency and type 2 diabetes mellitus (type 2 DM) is well known. Low serum Mg levels have been related to the development of type 2 DM and metabolic syndrome. There is high prevalence of hypomagnesaemia in subjects with type 2 DM, especially in poorly controlled glycemic profile, with longer duration of disease and with its chronic complications. In type 2 DM nephropathy due to low Mg intake with insulin resistance and insulin deficiency, along with hyperglycemic osmotic diuresis increase urinary loss of Mg appears to be the most important mechanisms that may favor Mg depletion in both intracellular and extracellular level leading to early progression of chronic kidney disease (CKD) to end stage renal disease (ESRD).Benefits of oral Mg supplementation on metabolic profiles of diabetic subjects have been found in most ,but not in all clinical studies.

Objectives:

The present study was done to know,whether normalization of serum Mg levels in hypomagnesemic type 2 DM nephropathy by oral Mg supplementation, delay the early progression to ESRD.

Materials and Methods:

In consecutive seventy six cases of hypomagnsaemic diabetic nephropathy,alternatively in 39 patients magnesium oxide 400mg was given orally twice daily and 37 patients taken as control.Serum magnesium levels,24 hrs urinary total proteins and creatinine clearance study by CocroftGault formula was done at least 3 months interval in both groups three times during 24 months study period.All patients received standard treatment for confounding conditions i.e. glycemic control with diet, oral antidiabetics, insulins and control of blood pressure with ACEI/ARB as monotherapy or in combination with others.Data were collected and analyzed and p value was calculated by paired 't' test and p value <0.05 was considered statistically significant.

Results:

In this study of 76 cases of hypomagnesaemia diabetic nephropathy, in trial group (n=39) oral Mg supplementation decreased protienuria by 25.3% or

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315mg/dl from baseline and delay the early progression of creatinine clearance (GFR) of 6.5ml/min in comparison to control group (n=37) have further decrease in serum Mg levels and progression of proteinuria by 25.3% or 327mg/dl and there was faster deterioration of GFR to 10.4ml/min in the study period.

Conclusion:

Oral Mg supplementation corrects the Mg deficit in patients with type 2 DM hypomagnesaemic nephropathy, decrease proteinuria significantly and may delay the early progression to ESRD. Therefore, early screening for serum Mg deficiency and correction of deficit may delay the early progression of chronic renal disease to end stage renal disease. Further large prospective randomized, double-blind clinical studies are required to confirm its effects.

Keywords: Type 2 diabetes, microalbuminuria , proteinuria, nephropathy, hypomagnesaemia, oral Mg supplementation.

INTRODUCTION

Magnesium (Mg) is the fourth most abundant mineral present in the human body and the second intracellular cation in living cells after potassium. Most Mg in human body is intracellular (99%) and only 1% is in extracellular fluid. Preclinical hypomagnesaemia is considered with serum Mg level of d"0.75mmol/L or 1.8mg/dl and frank hypomagnesaemia with d" 0.61mmol/L or1.5mg/dl; indicative of a systemic Mg deficit. Depletion of intracellular and ionized Mg can be found in many subjects with total serum Mg still in the normal range due to lack of sensivity of total serum Mg measurement and ionized Mg measurement can help to identify low concentration of blood Mg.[1] The link between Mg deficiency and type 2 diabetes mellitus (DM) is well known. Type 2 DM is frequently associate with both intracellular and extracellular Mg depletion. There is high prevalence of hypomagnesaemia in subjects with type 2 DM, especially in poorly controlled glycemic profile, with longer duration of the disease and with presence of micro and macro vascular chronic complications.[2] The incidence of hypomagnesaemia in different studies ranges from 13.5% to 47.7% in type 2 DM.[3] At the cellular level, cytosolic free Mg levels are consistently reduced in subjects with type 2 DM, when compared to non-diabetics. An impairment of cellular Mg uptake mechanism and a decrease in cellular ATP level, may contribute at least in part , to explain the decreased in cellular Mg content observed in diabetic condition.t Mg deficit as a possible unifying mechanism of conditions associated to insulin resistance, including type 2 DM, metaboilicsyndrome, hypertension. The Mg deficiency could precede and cause post-receptorial resistance of insulin action and alter the glucose metabolism.[5]

Hypomagnesaemia has been related to elevated blood pressure,atherogenic dyslipidemia,impaired clotting,increase inflammatory burden (increased C-reactive proteins), oxidativestress, carotid wall thickness,endothelial dysfunction and coronary artery disease (CAD).[6]

Insulin enhances Mg reabsorption at the thick ascending limb (TAL) and distal convoluted tubules (DCT) of renal tubule.w The increased frequency of hypomagnesaemia in type 2 DM is presumably multifactorial. Insulin resistance or deficiency may exacerbate renal Mg wasting and hyperglycemia

induced glycosuria causes higher osmotic urinary excretion of Mg, recurrent metabolic acidosis with diabetic ketoacidosis (DKA) andhypoalbuminic state with decreased Mgbinding.[8,9,10] Hypomagnesaemia has been implicated in type 2 DM and its complications eg.Nephropathy, retinopathy, neuropathy etc. In a recent study it was found that type 2 DM with hypomagnesaemic nephropathy had 2.12 fold increased risk for ESRD in 23 months in comparison to hypomagnesaemic non-diabetic nephropathy in 44 months, indicating hypomagnesaemia is anovel predictor of ESRD in type 2 DM nephropathy.[11]. Lower Mg level associated with faster deterioration of renal function rate in type 2 DM.[3] In type 2 DM nephropathy with both microalbuminuria and overt proteinuria serum ionized Mg found to be decreased.[12] Clinical evidences of Mg supplementations on metabolic profiles of diabetic subjects are controversial,benefits having been found in many but not in all clinical studies.[13] Mg supplementation may improve glycemic concentrations in fasting and postprandial states and improves the insulin mediated glucose uptake and parallel increase in plasma and erythrocyte Mg concentrations and progressive increase in insulin sensivity.[14] Oral Mg supplementation also able to restore altered endothelial function in elderly diabetic subjects. Hence this study was done to know the effects of magnesium supplementation, whether it delay the progression of diabetic nephropathy in type 2 DM to ESRD.

MATERIALS AND METHODS:

This was a prospective single center, openlabel, comparative, study conducted between July 2013 to December 2015 at VIMSAR,Burla,Odisha, on type 2 DM patients with nephropathy attending to medical and nephrology OPD,define as proteinuria of ≥0.5gm/24 hrs and or serum creatinine ≥mg/dl and features of chronic kidney disease (CKD) on ultrasonography(USG) graded as stage I,II,III,It,tI, with serum Mg level <1.8mg/dl by enzymatic end point method,after exclusion of stage tI (ESRD),chronic diarrhea ,pancreatitis ,chronic alcoholism ,chronic diuretics use, Mg containing antacids,laxatives and other nephrotoxic drugs use and endocrine disorders. This study was approved by local ethical committee. Magnesium oxide 400mg twice daily was given to 39 hypomagnesaemia patients alternatively and 37 patients taken as control group. Serum magnesium levels, 24 hrs urinary total proteins and creatinine clearance study by CockcroftGault formula was done at least 3 months intervals in both group three times during study period. All patients received standard treatment for confounding conditions as needed i.e. glycemic control with diet, oralantidiabetic,insulins and control of blood pressure with ACEI/ARB asmonotherapy or in combination with others. Data were collected and analyzedand p value was calculated by paired ´t test and p value <0.05 was considered statistically significant.

RESULTS:

Fig.1.COMPARISON OF SERUM MG LEVEL ON FIRST VISIT & LAST VISIT (mg/dl)

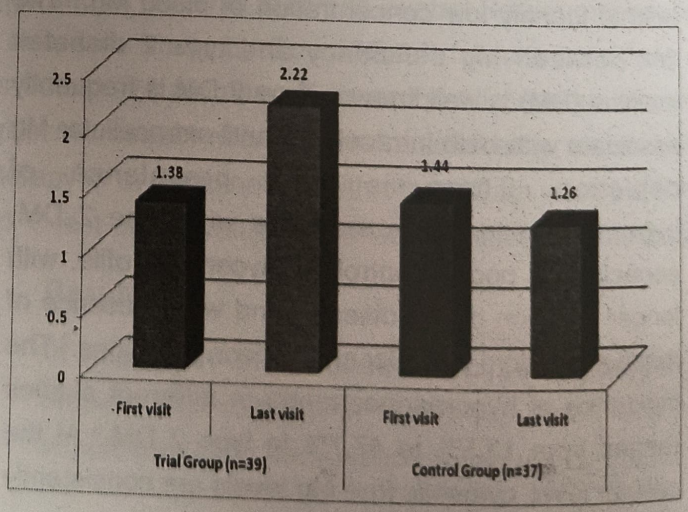

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Fig.1.COMPARISON OF SERUM MG LEVEL ON FIRST VISIT & LAST VISIT (mg/dl)

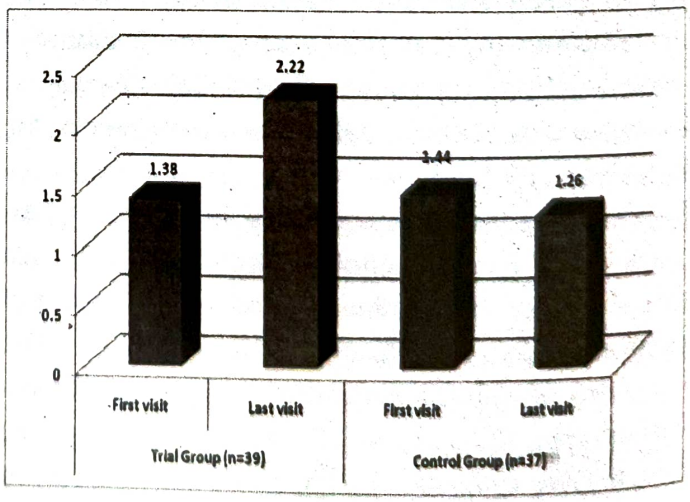
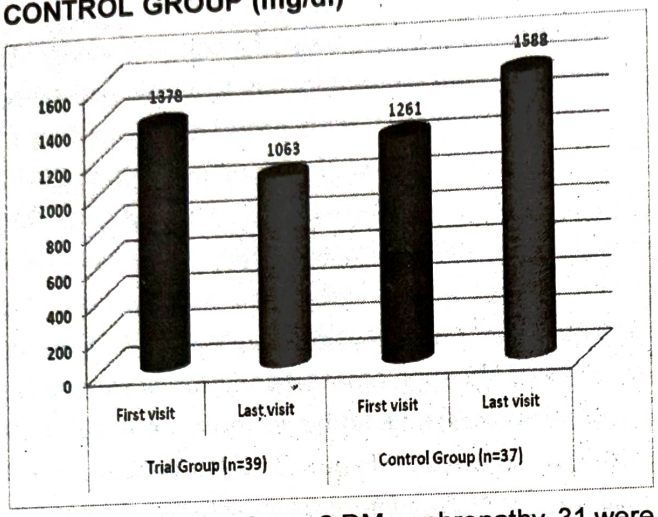


Fig.2.COMPARISON OF MEAN 24HRS PROTEINS LEVELS AT FIRST AND LAST VISIT IN TRIAL AND CONTROL GROUP (mg/dl)



Seventy-six cases of type 2 DM nephropathy, 31 were between age 41-50(40%) and 18(23.68%) were male and 13(17.1%) were female. About 36 were between 50-60 years (47.36%) and 19(42.36%) were male and 17(22.36%) were female. Nine (11.84%) were>60 years and 5male and 4 female. In total 42(55.26%) and 34(44.73%) were male and female respectively. Majority were between 40-60 years (88.15%).

Duration of diagnosis of diabetes was <5 years in 24(31.57%) of which 11(14.42%) were male and 13(17.1%) were female. Thirty-eight (50%) had history of diabetes 6-10 years and 22 (28.94%) were male and 16(21.05%) female. 14 (18.42%) had >10 years duration and 9(11.84%) male and 5 (6.575) female.

Comparison of serum Mg levels from baseline to last visit:

Average serum levels at baseline in trial group were 1.38mg/dl and at last visit it was 2.22mg/dl,there wasan increment of 0.84mg/dl. In control group baseline serum Mg level was 1.44mg/dl and at last visit it was 1.26mg/dl,there was decreased of 0.18mg/dl.(Fig.1).

Comparison of mean 24 hrs total proteinuria :

Baseline proteinuria in trial group was 1363mg/dl in male and 1413mg/dl in female, (total average baseline proteinuria 1378mg/day)and after last visit it was 1042mg/dl and 1063mg/dl in male and female respectively (total average1006mg/dl). There was significant decrease of in proteinuriaby 24% and 25% in male and female respectively or it was decreased on average by 315mg/dl in trial group. Baseline proteinuria in control group was 1346mg/dl and 1179mg/dl in male and female respectively (average1261mg/dl) and at last visit it was 1688mg/dl and 1474mg/dl respectively in male and female (average 1588mg/dl) suggesting progression of proteinuria by 25.4% and 25.02% in male and female respectively or increased by 327mg/dl on average in control group.(p <0.0018).(Fig.2).

Comparison of average creatinine clearance (GFR) :

In trial group baseline creatinine clearance was 45.3ml/min and 43.2ml/min in male and female respectively(average 44.7ml/min) and at last visit it was 39ml/min and 37.6ml/min in male and female respectively (average 38.2ml/min) and decrease of 14% and 13% in both male and female respectively or average 6.5ml/min decreased. In control group base line creatinine clearance was 49ml/min and 46ml/min in male and female respectively (average 47.9ml/min) and at last visit it was37.7ml/min and 37.3ml/min (total 37.5ml/min), creatinine clearance decreased by 23% and 19% in male and female respectively or total decrease of 10.4ml/min .

DISCUSSION: In this study Mg supplementation to type 2 DM nephropathy decreased proteinuria and slowed the progressive deterioration of GFR incomparison to controlled hypomagnesaemia

diabetic nephropathy patients with faster deterioration of GFR andprogression of proteinuria and further decreased concentration of serum Mg levels. There were no significant differences between sexes. In type 1 DM with albuminuria GFR decline about 1.2ml/min/ month without therapeutic intervention and in type 2 DM decline in GFR is more variable and may decline by 0.5ml/min/month and in some patients it may remain stable for long period.[1u] [1v] The clinical evidences of a clear effects of Mg supplementation on the metabolic profiles of diabetic subjects are controversial, as benefits found in many studies, but not in all clinical trials , may be due to the risk of many confounding factors has not been considered or may be related to small number of subjects and using different Mg doses and salts.[2] In a recent clinical randomized, double blind placebo controlled trial of oral Mg supplementation to prediabetics with frank hypomagnesaemia , decreased C-reactive proteins levels along with beneficial effects on fasting and postprandial glucose level and insulin sensivity.[17,18] Mg supplementation in diabetic patients with hypomagnesaemia corrects the deficit in intracellular free Mg levels, improves insulin sensivity and may protect against diabetic complications. The positive effects of a high intake of Mg on systemic inflammation and insulin resistance may help to explain at least some of its favorable effects.[2]

Insulin deficiency or resistance can affect the tubular absorption of Mg, leading to hypomagnesaemia in type 2 DM subjects.[19] Finally a vicious circle formed by mutual influence between insulin resistance and hypomagnesaemia results in aggravation of insulin resistance which can increase the risk of microalbuminemia.Proteinuria both as a consequence of glomerular damage and causes further damage since it can lead to inflammation and fibrosis in the renal tubules and loss of number of functional nephrons.[2p]

CONCLUSION:

A low Mg intake in the state of increased urinary Mg loss in diabetic nephropathy due to insulin resistance or insulin deficiency with proteinuria leading to hypomgnesaemia and faster progression to ESRD in type 2DM nephropathy. Benefits of Mg supplementation on diabetic nephropathy have been found in our study. There are no reports of Mg supplementation in diabetic nephropathy. However, benefits of Mg supplementation in metabolic profiles of diabetic subjects found in most , but not in all clinical studies.[2] Type 2 DM patients with microalbuminuria , intensive multifactorial treatment strategies targeting all known modifiable risk factors significantly reduces cardiovascular and microvascular complications and can exter' life expectancy by about 8 years in 21 years follow up.[21],Future larger ,prospective , randomized , double blind placebo controlled clinical studies are needed to support the potential role of Mg supplementation in diabetes mellitus and in its complications .[2]

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Original article

CLINICAL AND ETIOLOGICAL PROFILE OF ACUTE FEBRILE ILLNESS WITH THROMBOCYTOPENIA

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ABSTRACT

Background

Acute febrile illness (AFI) in tropical country like India is usually have an infectious etiology. They pose a therapeutic and diagnostic challenge as they lack organ specific signs and symptoms. When AFI is associated with thrombocytopenia they narrows down differential diagnosis and help to reach at specific diagnosis. Thrombocytopenia has an inverse relation to mortality and morbidity in various febrile illness.

Materials & Methods

This study was a prospective observational study conducted at VIMSAR, Burla from October, 2013 to October, 2015. We enrolled 113 patients of AFI with thrombocytopenia. All the patients were more than 14 year of age and having febrile illness of < 2 weeks duration along with thrombocytopenia were included in the study. Detailed history, physical examination, various biochemical and hematological examinations were done for the organ dysfunction and diagnosis of the patient.

Results

Out of 113 patients studied 67 (59.27%) were male and 46 (40.70%) female. Malaria 52 (46%) was the most common cause of AFI with thrombocytopenia, other etiologies identified were dengue fever 31 (27.43%), Viral fever 17 (15.04%), septicemia 7 (6.19%), Leptospirosis 4 (5.34%), Enteric fever 2 (1.76%). Very severe thrombocytopenia (Platelet count < 25,000/µl) observed in 8 (7.07%) cases. 35 cases showed complications related to thrombocytopenia, petechiae in 15 (42.85%) cases was most common. Mortality was seen in 11 (9.73%) cases. Malaria with 5 (45.45%) was leading cause. None had major life threatening bleeding manifestation.

Conclusion

Malaria is commonest cause of AFI with thrombocytopenia. Asymptomatic thrombocytopenia is present in maximum number of cases. Chances of bleeding manifestation increases with severity of thrombocytopenia.

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Key Words : Acute febrile illness, Thrombocytopenia

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INTRODUCTION :

Fever is the most ancient hall mark of disease. Fever is known as pyrexia from Greek "Pyretus" meaning fire. Febrile is from the latin word Febris, meaning fever[1]. Acute febrile illness is common cause of people seeking health care in India. Various tropical and subtropical infections present as acute febrile illness (AFI). They pose major diagnostic and therapeutic challenge to health care workers, particularly those working in limited resource setting.

Unlike the fever of unknown origin which enjoys the standard definition, acute febrile illness (AFI) or 'acute undifferentiated febrile illness' (AUFI), 'short febrile illness' lacks international consensus definition. Since FUO require duration of fever greater than three weeks, some authors define AFI as fever that resolves within three weeks[2]. More traditionally however AFI has been defined as fever of two weeks or shorter in duration and that lacks localized or organ specific clinical findings[3].

Fever by definition is an elevation of body temperature above the normal circadian range as a result of change in thermoregulatory centre located in the anterior hypothalamus. An AM temperature of > 37.2^{0}C (98.9^{0}F) or a P.M. temperature of > 37.7^0 C (99.9^0 F) would define fever[4].

The Normal blood platelet count is 150,000 – 450,000 / µl. Thrombocytopenia is defined as platelet count, less than 150,000/ µl[1]. This is due to decreased production, increased destruction (immunogenic and non-immunogenic), and increased sequestration in spleen. Infections being the commonest cause of thrombocytopenia[1]. Patients with an acute febrile illness in tropical countries like India usually have an infectious etiology and may have associated thrombocytopenia[1].

Commonly dengue, malaria, scrub typhus and other rickettsial infections, meningococci, leptospira and certain viral infections present as fever with thrombocytopenia[5]. Occasionally these patients can go on to develop a stormy course with multiorgan dysfunction requiring intensive care unit admission associated with high morbidity and mortality[6,7]. Thrombocytopenia in bacterial infections can occur as a part of sepsis with disseminated intravascular coagulation. Patients with sepsis may also develop hemophagocytic histiocytosis with phagocytosis of platelets and leucocytes in the bone marrow histiocytes. Both Gram-positive and Gram-negative bacterial infections can lead to sepsis.

Viruses (including Dengue) produce thrombocytopenia by various mechanisms like impaired platelet production as a result of direct viral invasion, toxic effect of viral proteins on thrombopoiesis, virus induced hemophagocytosis and increased platelet destruction caused by binding of virus induced autoantibodies or viral antigen antibody complexes[5].

Thrombocytopenia in malarial infection may appear even before fever, anemia and splenomegaly become manifest[8]. It can occur in both P. falciparum and P. vivax infection regardless the severity of infection. Immune mediated lysis, sequestration in the spleen and a dyspoietic process in marrow with diminished platelet production have all been postulated[8]. During early stages of malaria, platelet agglutination as a result of endothelial cell activation and release of activated von Willebrand factor occurs which may cause thrombocytopenia[9]. Occasionally platelets can be invaded by malaria parasite.

Thrombocytopenia in malaria is rarely severe and treatment is focused on eradication of malaria parasite.[10]

When AFI is associated with thrombocytopenia, it narrows down the differential diagnosis and help to reach at definite diagnosis.

Patients of AFI with thrombocytopenia many times do not have bleeding manifestations. Hence study of correlation between platelet counts and hemorrhagic manifestations will help us to know the correct time for infusion of platelets, thus avoiding unnecessary platelet transfusion.

Material and Methods :

This was a prospective mono-centric study undertaken at the department of General Medicine, VIMSAR, Burla in Sambalpur district of state of Odisha from October, 2013 to October, 2015. A total number of 113 patients of fever with thrombocytopenia admitted to medicine ward of VIMSAR were included in the study.

Inclusion Criteria : All fever patients of less than 2 weeks of duration with thrombocytopenia (< 150,000 / µl) admitted to medicine ward were included in the study.

Exclusion Criteria : Known cases of thrombocytopenia due to hematological disorders, malignancy, on chemotherapy, on immunosuppressants and other drug induced thrombocytopenia, idiopathic thrombocytopenia, patients having cardiac prosthetic valves, cirrhosis of liver, connective tissue disorders were excluded from the study.

Once the case was admitted with acute febrile illness (AFI) and thrombocytopenia, a careful history was recorded, general physical examination and detailed examination of various systems was done.

This was followed by routine investigations which included complete blood count, renal function test, liver function test,MP(QBC),MP(ICT),Elisa for Dengue, PT and INR, urine routine, ECG, USG, X-ray chest were done where ever indicated.

The platelet counting was done by 2 methods. Crude method : A film was made from EDTA blood and stained with romanswky stain. The count was considered adequate if there was 1 platelet found per 10 – 30 red cells. At 1000X magnification 7 – 20 platelet / oil immersion field. 3 part cell counter is an automated cell counter with features of counting RBC's, WBC's, platelets, blood indices and Hb concentration all together.

Platelet count was done on day 1, 3, 5 and then on discharge in patients with platelet count between 50,000/ µl – 150,000/ µl. In patients with platelet count less than 50,000 / µl – or having bleeding manifestation platelet count was repeated daily for at least 3 days or till rising trend of platelet was seen. Special investigations were done in order to achieve the diagnosis. Once the specific diagnosis was reached the patients were treated for it specifically and symptomatically. Platelet transfusion were considered in patients with platelet count of 10,000 / µl as absolute indication. Bleeding manifestation with any platelet count was another absolute indication for platelet transfusion.

RESULTS

The study of 113 patients of AFI with Thrombocytopenia, of which 67 (59.27%) male and 46 (40.70%) were female. There was 15 (13.27%), 31 (27.43%), 17(15.04%), 26 (23%), 13 (11.50%), 6 (5.30%), 5 (4.425) patients with age group of 14 - 19, 20 – 29, 30 – 39, 40 – 49, 50 – 59, 60 – 69, > 70

years respectively. Majority 31 (27.43%) cases were between 20 – 29 years of age.

The mean age (in years) for male (37.11+14.49) and for females (36.67+15.62).

Etiology is confirmed in 96 (84.,95%) cases out of 113, undiagnosed cases 17 (15.04%) were referred as viral fever.

Causes of AFI with thrombocytopenia

Malaria was most common cause with 52 (46%) cases, of which P.Falciparum comprise 35 cases, and P. Vivax 11 cases, mixed infection (PF + PV) comprise 6 cases. Second common cause was Dengue fever 31 (27.43%) cases, followed by viral fever 17 (15.04%), septicemia 7 (6.19%), leptospirosis 4 (5.35%), enteric fever least common cause with 2 (1.76%) cases. (Table1)

Table – 1 Etiology of AFI with thrombocytopenia

Diagnosis		No. of Cases	Percentage
Malaria	PF	35	46%
	PV	11	
	PF + PV	6	
Dengue fever		31	27.43%
Viral fever		17	15.04%
Septicemia		7	6.19%
Leptospirosis		4	5.35%
Enteric fever		2	1.76%
Grand Total :		113	100%

Thrombocytopenia and bleeding manifestations

There was increased trend of bleeding manifestations as the platelet count decreased. In the study 17 (15.04%) cases had count between 100,000 – 150,000 / µl, 57 (50.44%) cases between 50,000 – 100,000 / µl, 31 (27.43%) cases between, 25,000 – 50,000 / µl and 8 (7.07%) cases below 25,000 / µl platelet count. (Table 2 &4)

Table – 2 Severity of thrombocytopenia

Platelet count	No. of patients	Percentage
< 25,000 / µl	8	7.07%
25,000 - 50,000 / µl	31	27.43%
50,000 – 100,000 / µl	57	50.44%
100,000 – 150,000 / µl	17	15.04%
Total	113	100%

Bleeding manifestations were seen in total 35 cases out of which petechiae in 15 (42.85%) cases were most common, ecchymosis in 7 (20%) cases, subconjunctival bleeding 4 (11.452%), bleeding gums 3 (8.57%) cases & malena in 6 (17.14%) cases(Table3).

Table – 3 Bleeding Manifestations

Bleeding manifestations	Total No. of patients	Mean platelet count(/µl)
Petechiae	15	29733
Ecchymosis	7	38280
Subconjunctival bleeding	4	31000
Bleeding gums	3	28000
Malena	6	19000
Total	35	

Table – 4 : Severity of thrombocytopenia in cases :

Platelet Count	Malaria (n-52)	Dengue Fever (n-31)	Viral fever (n-17)	Leptospirosis (n-4)	Septicemia (n-7)	Enteric fever (n-2)	Total (n-113)
< 25,000 / µl (n-8)	2	4	0	2	0	0	8 (7.07%)
25,000 - 50,000 / µl (n-31)	12	15	2	1	1	0	31 (27.43%)
50,000 – 100,000 / µl 9N-57)	30	10	10	1	4	2	57 (50.44%)
100,000 – 150,000 / µl (n-17)	8	2	5	0	2	0	17 (15.04%)

Outcome of patients

Of the total 113 cases studied, mortality was seen in 11 (9.73%) cases, maximum mortality was seen in malaria with 5 cases followed by 3 cases of septicemia, 2 cases of leptospirosis, and 1 case of dengue fever. Death were due to multiorgan failure in all the cases(Table5)

Table – 5 Outcome of patients :

Diagnosis	Good outcome	Mortality	Total
Malaria	47	5	52
Dengue fever	30	1	31
Viral fever	17	0	17
Septicemia	4	3	7
Leptospirosis	2	2	4
Enteric fever	2	0	2

Discussion :

Comparision of cause of thrombocytopenia

In our study the etiology of AFI with thrombocytopenia was malaria (46%), dengue fever (27.43%), viral fever (15.04%), septicemia 6.19%), leptospirosis (5.35%), enteric fever (1.76%) cases. Comparing these results with other studies conducted by others, in which malaria is most common cause of febrile thrombocytopenia, while in another study septicemia is most common cause.

Table – 6 Etiology of AFI with thrombocytopenia in different studies:

Diagnosis	Patil P et al	Lohitashwa SB et al	Nair et al	Present study
Malaria	54%	41%	9.2%	46%
Dengue fever	15%	14%	13.8%	27.4%
Septicemia	4%	19%	26.6%	6.1%
Enteric fever	6%	24%	14.7%	1.76%
Others	21%	2%	18.8%	21%

Comparison of the bleeding manifestations :

In our study bleeding manifestations are seen in 35 (30.97%) cases, as compared to 23% case in other studies[1,11,12]. Purpura (15 cases) is most common form of bleeding manifestation in our study. Similar results were observed in prithwiraj[1] study, in which 17 (73.9%) cases developed petechiae as most common form of bleeding manifestation. In our study ecchymosis observed in (7) cases, gum bleeding (3) cases, subconjunctival bleed (4) and malena (6) cases. Prithwiraj et al[1] observed epistaxis in (1) cases, Hematuria (3) cases and PR bleed in (2) cases.

Comparing outcome of cases :

In our study out of 113 cases studied, mortality observed in 11 (9.37%). Good outcome seen in 90.63%) cases. Malaria is most common cause of mortality with 5 (45.45%) of total deaths. Followed by septicemia 3 (27.27%), leptospirosis 2 (18.18%), dengue fever 1 (9.09%) cases. In Prithwiraj et al[1] study septicemia is most common cause of mortality, contributing 60% of total deaths. In Srinivas et al[11] study septicemia account for 78% and dengue fever in 22% of mortality cases.

Table – 7 : Outcome of patients

Disease	Patil P et al %	Lohitashwa SB et al %	Present Study %
Malaria	20	—	45.45
Septicemia	60	78	27.27
Dengue fever	—	22	9.09
Other	20	—	18.18

Conclusion :

Malaria was commonest cause of AFI with thrombocytopenia. Asymptomatic thrombocytopenia is present in maximum number of cases. Chances of bleeding manifestation increases with severity of thrombocytopenia. Petechiae was the most common form of bleeding manifestation observed,apart from gum bleeding, ecchymosis, malena and subconjunctival hemorrhage.

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Original article

EPIDEMIOLOGY OF SEVERE SEPSIS & SEPTIC SHOCK IN ODISHA

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ABSTRACT

Aim: To determine the Epidemiology of Severe Sepsis and Septic Shock and their trends in mortality in adult patients admitted to ICU in BHUBANESWAR.

Material & Methods: All consecutive adult (>18 years) ICU patients with Severe Sepsis and Septic Shock from September 2003 to December 2010 were prospectively analysed till discharge or death in ICU in a medical-surgical mixed ICU in a tertiary care hospital in Bhubaneswar.

Results: 806 cases were studied over a period of 7 years & 4 months. Severe sepsis was present in 35.4% of cases and septic shock in 64.6% of cases. The most common source of Sepsis was lungs (25%). Gram negative bacteria was the predominant type of infection (66.76%). The average APACHE II score was 18.62±6.4 and the average SOFA score was 8.22±3.83. The overall mortality was 53.47%. The mortality remained the same over 7 years of the study.

Conclusion: The mortality of Sepsis in India is till high. There has been no decrease in mortality of Sepsis over the 7 years of the study. Future studies need to be done to find out the causes for high mortality of Sepsis in India.

INTRODUCTION:

Sepsis is one of the leading causes of inhospital mortality and morbidity among medical and surgical patients. Severe sepsis accounts for one in five admissions to intensive care units (ICUs) and is the leading cause of death in the noncoronary ICU.[1] Most of the epidemiological data regarding the incidence and mortality of sepsis have emerged from western countries. Data from India show 28.3% of ICU cases had Severe Sepsis or Septic Shock with mortality of 34.0%.[2] Over the last 20 years, multiple randomized controlled trials (RCTs) have attempted to identify new treatments to improve the survival of these patients. It is unknown whether progress has been made in India in decreasing their mortality rate. Therefore we intended to do a prospective observational study to know the epidemiology of Severe Sepsis and Septic Shock and also look at the trends in mortality over a period of seven years of all consecutive cases of severe sepsis and septic shock.

MATERIAL AND METHODS:

We conducted a prospective observational cohort study in a tertiary care medical surgical mixed ICU in eastern India. We followed 828 adult patients with a diagnosis of Severe Sepsis or Septic Shock consecutively from September 2003 to December

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2010, until their discharge or death from ICU. Twenty-two patients were excluded for incomplete data. Tropical infections like malaria were excluded in the study. For all patients we collected the following data at ICU admission: age, gender, hospital and ICU admission diagnosis, APACHE II score, and associated underlying diseases. During the following days, we looked for severe sepsis and septic shock criteria, as well as recorded the sequential organ failure assessment (SOFA) score. Nosocomial infection was diagnosed according to CDC criteria for nosocomial infection.[3] Community-acquired infection was diagnosed by clinical, radiological and microbiological parameters. Severe sepsis was defined as evidence of infection and at least one organ dysfunction (cardiovascular, respiratory, renal, haematological, hepatic or metabolic). Septic shock was defined as severe sepsis and vasoactive drug requirement as per ACCP/SCCM definition.[4]

Blood, sputum/tracheal secretion, urine, cerebrospinal fluid and wound/skin secretion samples were obtained for culture as directed by the attending physician.

Data were analyzed by SPSS version 20.

RESULTS:

For the whole cohort there were 69.4% males 30.6% females with mean age of 52.91 (±16.6) years, mean length of ICU stay was 7.33±7.86 days, and the overall mortality rate of 53.47%. Severe sepsis constituted 35.4% of cases and septic shock 64.6% of cases. The patient characteristics are presented in Table 1. The primary site of infection was lungs (25%), followed by urine (13%), Abdominopelvic (12%), skin and soft tissue (8%), and primary bacteraemia (6%). In 34% of cases the source of infection could not be ascertained (Table 2). Most of the admissions (86.1%) were due to medical causes and only 13.8% were after surgery. Mechanical ventilation was needed in 68% of cases and renal replacement was done in 21.33% of cases.

Community acquired infections constituted (80.4%) and 19.6% of the infections were nosocomial. Four patients were admitted with community acquired infection but developed nosocomial infection during hospital stay.

Major Microorganisms:

Predominately gram-negative organisms (66.76%) were grown (table 3). E.coli(21.66%) was the most predominate followed by Pseudomonas(15.88%), Klebsiella(12.99%), Acinetobacter(9.74%) and Enterobacter(6.49%). Gram-positive organisms included Staphylococcus (19.85%), Enterococcus (7.22%) and Others(6.13%) (Table 3, Fig 1).

Antibiotics:

Major antibiotics used empirically as first choice were Piperacillin tazobactum (50%), Meropenem (21%), Imipenem (13%), Teicoplanin (20%), Cefoperazone-sulbactam (7.5%), Ofloxacin (2%) (Table 4).

Mortality

Overall mortality was 53.47%. The mortality in Severe Sepsis cases was 20% whereas in Septic Shock it was 80%. As per Apache II prediction our mortality was higher (table 5). From 2004 to 2010 the overall mortality varied from 48% 62% without significant decrease over the years (table 6). There were 22 LAMAs (Left Against Medical Advice).

DISCUSSION:

Median age in our study was 52.91(±16.6) years. In the INDICAPS study[5] representing 124 ICUs from all over India the median age was similar

(53.8±17.7years) whereas it was higher (58.17 and 59.2 years) in the studies by Todi et al.[11] and Bhattacharya et al.[6] respectively. In the Mosaics study[7] representing Asia- Pacific region including India the median age was higher (59.2 years). In a meta-analysis of 36 multi-centric severe sepsis studies throughout the world (none from India) with 14,418 patients the average age was 61 years.[8] Finally a study from New York, USA had a median age of 69 years.[9] Therefore majority of Sepsis patients in Indian ICUs are in the 5th-6th decade. Our patients were little younger.

Our study had 69.4% males 30.6% females. The INDICAPS study[5] had 63.4% males, Bhattacharya et al.[6] had 62% males, Mosaics study[5] 61.7%, Stevenson et al.[8] meta-analysis had 60% males, and the Novosad et al.[9] study had 52% males. There seems to be preferential allocation of health resources to males in resource limited areas.

Co-morbidities were present in 53.1% of cases. Most patients (97%) had at least one comorbidity in the study from New York[9] whereas 35% of patients had co-morbidities in the study by Kaukonen et al.[10] Diabetes was the most common co-morbidity in our study (31.7%). It was similar in other studies (Bhattacharya et al 33.7% and Novosad et al 35%).[6,9]

The median length of ICU stay in survivors in our study was 8.05(±7.25) days. Average ICU stay of survivors was 11 days in the study by Todi et al[11] and Bhattacharya et al.[6] The median length of hospital stay was 9 days in the study by Novosad et al.[9]

The primary site of infection was lungs (25%), followed by urine (13%), Abdominopelvic (12%), skin and soft tissue (8%), and primary bacteraemia (6%). In 37% of cases the source of infection could not be ascertained. Respiratory tract infection was the major source of sepsis in ICU (53.7%), followed by the urinary tract, primary blood stream infections and gastrointestinal tract as per Bhattacharya et al.[6] Todi et al. also found lungs as the most common source of infection(57.45%).[11] In the study by Novosad et al. the most common illnesses leading to sepsis was pneumonia (35%), urinary tract infections (25%), gastrointestinal infections (11%), and skin/soft tissue infections (11%). The source of infection seems to be similar throughout India and the world. In the study by Novosad et al. pathogens were isolated from blood cultures of 30% patients and from urine cultures of 28%. In 31% of patients with sepsis, no pathogen was identified in any culture or nonculture based tests.[9]

In our study predominately gram-negative organisms (66.76%) were grown. E.coli(21.66%) was the most predominate followed by Pseudomonas(15.88%), Klebsiella(12.99%), Acinetobacter(9.74%) and Enterobacter(6.49%). Gram-positive organisms included Staphylococcus(19.85%), Enterococcus (7.22%) and Others(6.13%). In the INDICAPS study 69.4% isolates were Gram-negative, 17% gram positive and 7.6% were fungi. Pseudomonas(19.3%), Acinetobacter(16.4%) and Klebsiella Pneumoniae(15.5%) and E.coli(14%) were the organisms isolated.[5] Gram negative organisms (72.45%) were predominant in the study by Todi et al.[11]The most common organisms isolated by Bhattacharya et al. was Pseudomonas(32.7%), Klebsiella(22%), Staphylococcus(18.1%), E.coli(14.5%).[6]

Gram negative organisms are the most predominant in Indian ICUs but the microbiological pattern varies in different ICUs. Every ICU should be aware about

its local flora and use appropriate antibiotics to improve outcomes of Sepsis patients.

Piperacillin tazobactum was the most common antibiotic used empirically in our study followed by carbapenems, teicoplanin and cephalosporins from of 2003 to 2010.

In the INDICAPS study (2010-2011) the most common antibiotics used were carbapenems followed by cephalosporins, piperacillin tazobactum, teicoplanin, fluconazole and fluroquinolones.[5]

In the Bhattacharya et al. study in 2012-13 the most common antibiotic used was carbapenems followed by linezolid, fluoroquinolones, cephalosporins and piperracillin tazobactum.[6]

The pattern of antibiotic use in different ICUs in India is different. It reflects the different local flora and changes of resistance pattern over the years. The empiric antibiotic of first choice has changed to carbapenems indicating increasing resistance to earlier antibiotics over the years.

The mortality in our study was 53.47%. The first published Indian data had a ICU mortality for severe sepsis of 59.26%.[11] Subsequently Indian data from the Mosaics study had a mortality of 38.2%[5] and the Indicaps study had a mortality of 40.5% in the subgroup without tropical infections.[6] The mortality in the Bhattacharya et al study[6] was 48.4% and that by Mohan et al. was 53%.[12] In a meta-analysis of 32 severe sepsis trials the ICU mortality in Severe Sepsis over the last 2 decades was 33.2%.[8] In the Australian and New Zealand study the mortality of severe sepsis declined from 35% in 2000 to 18.4% in 2012.[10]

Compared to the mortality throughout the world our mortality is high and comparable to the mortality of other Indian ICUs. It has not changed over the 7 years of the study. Stevenson proposes that the declining mortality throughout the world may be due to improved processes of care. Potentially effective improvements include earlier antibiotic administration, increased early fluid resuscitation, improvements in mechanical ventilation strategies, or increased intensivist staffing. Stevenson concludes that the mechanism for the mortality decline in severe sepsis is unclear and warrants further study.[8] Kaukonen concludes that the overall changes in ICU practice rather than the management of sepsis explain most of there findings why Sepsis mortality has decreased in Australia & New Zealand.[10] We need to improve the standard of care in our ICUs in India and do further studies to identify the causes of high mortality in Sepsis in India.

Our study includes 22 cases of LAMA. LAMA is a reality in Indian ICUs due to the unresolved legal status of withholding and withdrawal of support at the end of life. Most of them are due to financial reasons.

CONCLUSION:

Sepsis causes high mortality (53.47%) in our ICU. Lung is the most common source of Sepsis in our ICU. Gram negative organisms are the predominant isolates in Sepsis. The mortality has not decreased over 7 years. Further studies need to be done to identify causes of high mortality in Indian ICUs.

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Table 1. PATIENT CHARACTERISTIC: ALL PATIENTS DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

	ALL (n=806)	NON SURVIVORS (n=431)	SURVIVORS (n=353)	LAMA (n=22)	P value	Odds Ratio (95%CI)
Septic Shock	521 (64.6%)	345 (80%)	158 (44.8%)	16 (77.7%)	0.000	4.64 (3.34 - 6.34)
Severe Sepsis	285 (35.4%)	86 (20%)	195 (55.2%)	6 (22.3%)	0.273	0.216 (0.16 – 0.3)
Age (mean±SD)	52.91±16.6	53.03±17	52.22±16.13	61.9±13.66	0.029	
Sex						
Male	559 (69.4%)	306 (71%)	240 (68%)	13 (59.1%)		1.18 (0.86 – 1.59)
Female	247 (30.6%)	125 (29%)	113 (32%)	9 (40.9%)		0.85 (0.63 – 1.14)
ICU Stay (mean±SD)	7.33±7.86	6.69±8.28	8.05±7.25	8.45±7.82	0.042	
Hospital Stay (mean±SD)	15.02±16.32	10.78±14.29	20.23±17.31	14.4±13.41	0.000	
Etiology						
Medical	694 (86.1%)	378 (87.7%)	299 (84.7%)	16 (72.7%)		
Surgical	111 (13.8%)	51 (11.8%)	54 (15.3%)	6 (27.3%)		
Medical+Surgical	1 (0.1%)	1 (0.2)	Nil	0 (Nil)		
Co-morbidities						
DM	256 (31.7%)	129 (29.9%)	117 (33.1%)	10 (45.5%)	0.123	0.834
CCF	35 (4.3%)	21 (4.9%)	12 (3.4%)	2 (9.1%)	0.698	1.321
COPD	44 (5.4%)	30 (6.9%)	14 (4%)	Nil	0.031	
CRF	59 (7.3%)	36 (8.4%)	22 (6.2%)	1 (4.5%)	0.215	1.395
CLD	26 (3.2%)	24 (5.6%)	2 (0.6%)	Nil	0.000	10.998
CANCER	13 (1.6%)	9 (2.1%)	4 (1.1%)	Nil	0.224	1.978
STEROID	47 (5.8%)	35 (8.1%)	11 (3.1%)	1 (4.5%)	0.006	
CHRONIC DISEASE	66 (8.2%)	38 (8.8%)	27 (7.6%)	1 (4.5%)	0.415	1.198
IMMUNOSUPPRESSED	29 (3.6%)	20 (4.6%)	9 (2.5%)	1 (4.5%)	0.075	
TRAUMA	27 (3.3%)	17 (3.9%)	9 (2.5%)	1 (4.5%)	0.415	1.499
Total Co morbidities						
0	378 (46.9%)	186 (43.2%)	184 (52.1%)	8 (36.4%)		
1	291 (36.1%)	159 (36.9%)	121 (34.3%)	11 (50%)		
2	109 (13.5%)	69 (16%)	39 (11%)	1 (4.5%)		
3	26 (3.2%)	16 (3.7%)	8 (2.3%)	2 (9.1%)		
>4	2 (0.2%)	1 (0.2%)	1 (0.3%)	Nil		
Community Acquired	548(80.4%)					
Nosocomial	158(19.6%)					
Clinical Features						
Fever	403 (50%)	184 (42.7%)	208 (58.9%)	11 (50%)	0.000	
Tachycardia	746 (92.6%)	394 (91.4%)	331 (93.8%)	21 (95.5%)	0.212	
Tachypnea	786 (97.5%)	421 (97.7%)	345 (97.7%)	20 (90.9%)	0.379	
Leukocytosis	571 (70.8%)	311 (72.2%)	242 (68.6%)	18 (81.8%)	0.634	

Organ Dysfunction	ALL (n=806)	NON SURVIVORS (n=431)	SURVIVORS (n=353)	LAMA (n=22)		
CVS	521 (64.6%)	345 (80%)	158 (44.8%)	16 (77.7%)	0.000	
Respiratory	637 (79%)	369 (85.6%)	251 (71.1%)	17 (77.3%)	0.000	
Renal	465 (57.7%)	292 (67.7%)	161 (45.6%)	12 (54.5%)	0.000	
Hepatic	170 (21.1%)	113 (26.2)	52 (14.7%)	5 (22.7%)	0.001	
Hematological	122 (15.1%)	86 (20%)	36 (10.2%)	Nil	0.000	
Metabolic	99 (12.3%)	72 (16.7%)	25 (7.1%)	2 (9.1%)	0.000	
CNS	155 (19.2%)	93 (21.6%)	61 (17.3%)	1 (4.5%)	0.032	
No. of organ dysfunction						
0	8 (0.6%)	5 (1.2%)	Nil	Nil		
1	98 (12.2%)	79 (18.3%)	19 (5.4%)	Nil		
2	286 (35.5%)	150 (34.8%)	130 (36.8%)	6 (27.3%)		
3	250 (31%)	109 (25.3%)	131 (37.1%)	10 (45.5%)		
4	107 (13.3%)	57 (13.2%)	48 (13.6 %)	2 (9.1%)		
>5	60 (7.4%)	31 (7.2%)	25 (7.1%)	4 (18.2%)		
Severity of Illness						
SOFA (mean±SD)	8.22 ± 3.83	9.65 ± 3.78	6.5 ± 3.14	7.54 ± 3.58	0.000	
APACHE II (mean±SD)	18.62 ± 6.4	20.34 ± 6.37	16.46 ± 5.78	19.5 ± 6.34	0.000	
INTERVENTIONS						
Mechanical Ventilation	548(68%)	357(65%)	175(32%)	16(3%)	0.000	
Renal Replacement Therapy	172(21.33%)	120(69.76%)	46(26.74%)	6(3.5%)	0.000	

Table 2: Primary Site of Infection

Primary Site of Infection	Total
Lungs	201(25%)
Urine	108(13%)
Abdpelvic	96(12%)
Skin	67(8%)
Bacteraemia	45(6%)
CNS	12(1%)
CVS	2
Joint	1
Sinocranial	1
Unknown	73(34%)
Total	806 (100%)

Table 3: Organisms

Organisms	number	%
E.coli	60	21.66
Pseudomonas	44	15.88
Klebsiella	36	12.99
Acinetobacter	27	9.74
Enterobacter	18	6.49
Gram -ve		66.76
Staph	55	19.85
Enterococcus	20	7.22
Gram +ve		27.07
Others	17	6.17
Total	277	100.00

Fig 1.Organisms

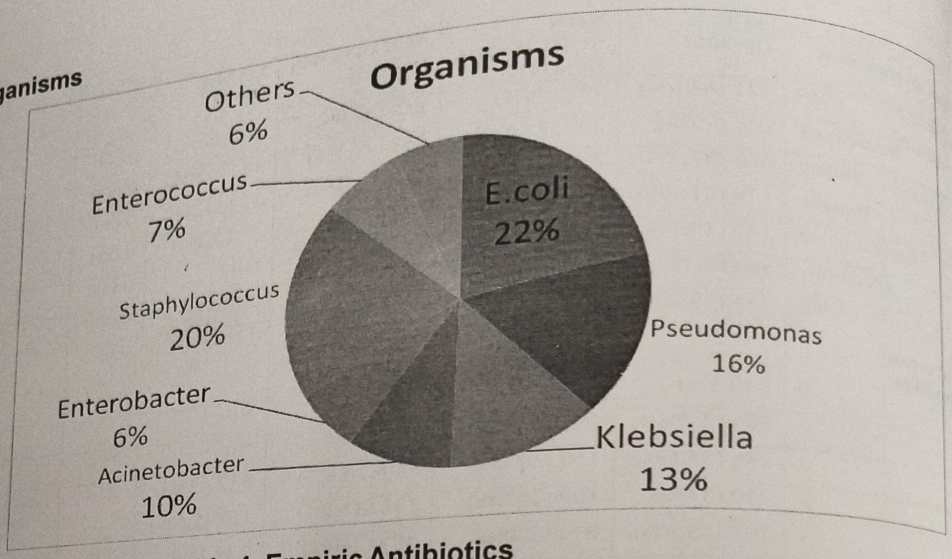
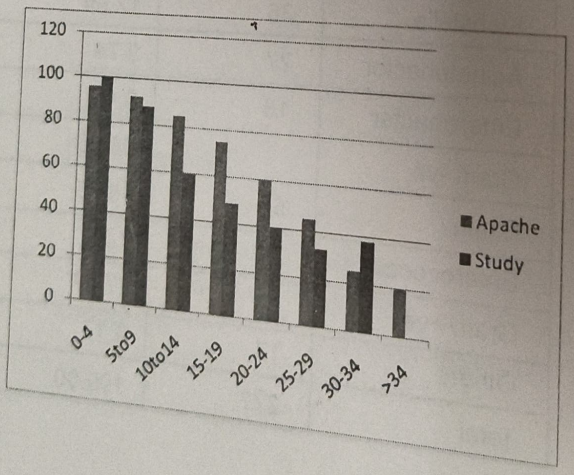


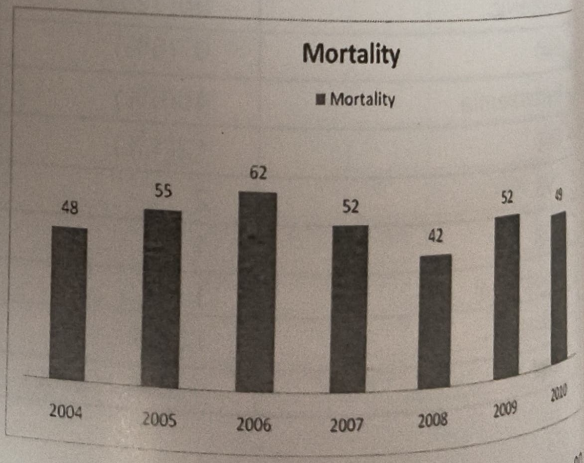
Table 4: Empiric Antibiotics

Antibiotic	%
Piperacillin-tazobactum	49.6
Meropenem	21.25
Imipenem	12.99
Cefoperazone-sulbactum	7.48
Ofloxacin	2.36
Others	
Teicoplanin	20.66

Survival According to Apache II



Year wise Mortality 2004-2010



Review article

FUNCTIONAL DYSPEPSIA – PATHOPHYSIOLOGY, CLINICAL FEATURES, CURRENT APPROACH & MANAGEMENT

Karun Mahesh Koolagere Puttaswamy,* Malati Murmu,** Ayaskanta Kar,*** Ashok Kumar Behera***

ABSTRACT

Functional dyspepsia is a very common gastrointestinal disorder observed in the general population, in general outpatient clinic and clinical specialty. It is associated with several treatments, hospitalization, prescription and use of several drugs. Moreover, it is related to self medication, absenteeism and also loss of productivity.The aetiology of Functional Dyspepsia is unknown but various pathophysiological mechanisms may account for them. Impaired meal induced relaxation of the proximal stomach, visceral hypersensitivity to distension,gastric motor abnormalities, as well as disturbed central nervous function, have all been implicated as important pathophysiological mechanisms causing dyspeptic symptoms, but overlap is frequent. The objective of this review is to summarize the pathophysiological mechanisms, clinical features, approach & management of functional dyspepsia.

Keywords: Functional dyspepsia, epigastric pain, early satiation, postprandial fullness, epigastric burning, *Helicobacter pylori.*

Introduction

Dyspepsia is derived from the Greek words 'dys-' and 'pepse-' which means "difficult digestion".In current medical terminology, dyspepsia refers to a heterogeneous group of symptoms located in the upper abdomen[1].Functional dyspepsia is an exclusion diagnosis and it is classified as a chronic abdominal pain-related functional disorder, characterized by the presence of persistent or recurrent pain or discomfort centered in the upper abdomen, neither relief by defecation, nor association with the onset of a change in stool frequency or form. Dyspepsia is one of the most common gastrointestinal disorders to be faced in clinical practice, with prevalence up to 40% in population-based study so that the economic impact is very high. When dyspepsia is not a manifestation of an organic pathology such as gastroesophageal reflux disease (GERD) or peptic ulcer disease (PUD), then it is classified as functional dyspepsia (FD). FD markedly reduces patients' quality of life, similarly to mild heart failure and menopause. Pathophysiology of FD is not completely understood yet and several pathophysiological mechanisms have been proposed to underlie symptoms. Central processing of visceral stimuli, low-grade inflammation in the duodenum, genetic factors,psychosocial factors and Helicobacter pylori infectionare the main emerging hypothesis[2] investigated.Many treatments have been proposed (diet, eradication of H. pylori and drugs such as

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prokinetic agents or proton pump inhibitors) but no one was satisfactory[3], now light is thrown on developing newer drugs with the understanding of pathophysiology.

Definition

The overlap between symptoms of gastric origin and symptoms of presumed esophageal origin (especially GERD) has remained an area of controversy. However, with time, definitions of dyspepsia have evolved to become more restrictive and more focused on symptoms thought to arise from the gastroduodenal region, not the esophagus. Earlier definitions considered dyspepsia to comprise all upper abdominal and retrosternal sensations—in effect, all symptoms considered to be referable to the proximal alimentary tract[4]

(a) DYSPEPSIA as defined by ROME III consensus committee. Presence of symptoms considered by the physician to originate from the gastroduodenal region[5].

Atleast 3 months, with onset at least 6 months previously, of one or more of the following four cardinal symptoms:1. Bothersome postprandial fullness, 2. Early satiation, 3. Epigastric pain, 4. Epigastric burning

(b) FUNCTIONAL DYSPEPSIA: In patients with dyspepsia, additional clinical investigations may identify underlying organic diseases that is likely to cause the symptoms. In these persons, symptoms are due to an organic cause of dyspepsia.But in the majority of persons with dyspeptic symptoms, no organic abnormality is identified by routine clinical evaluation including endoscopy, and these patients are considered to haveFunctional dyspepsia.

Pathophysiology

The pathophysiology of functional dyspepsia is unclear. Research has focused upon the following factors:

A) Gastric motor function, B) Impaired Gastric accommodation to a meal, C) Hypersensitivity to gastric distension D) Visceral sensitivity& E) Altered Duodenal sensitivity to Lipids or Acid

A) Gastric motor function

Normal gastrointestinal motor function is a complex series of events that requires coordination of the sympathetic and parasympathetic nervous systems, neurons within the stomach and intestine, and the smooth muscle cells of the gut. Abnormalities in this process can lead to a delay in gastric emptying (gastroparesis), a disorder that is characterized by complaints of nausea, vomiting, early or easy satiety, bloating, and weight loss[6].

The frequency of delayed gastric emptying ranges from 20-50 percent of patients complaining of dyspepsia [5]. However, there is generally a poor correlation between these entities.Antral hypomotility has been found in a similar proportion of patients, but its relationship to symptoms is also uncertain. Up to 10 percent of patients have fast gastric emptying, which may also be associated with dyspepsia.

B) Impaired Gastric accommodation to a meal

Gastric compliance is lower in patients with functional dyspepsia than in healthy controls. The motor functions of the proximal and distal stomach differ remarkably. Whereas the distal stomach regulates gastric emptying of solids by grinding and sieving the content until the particles are small enough to pass through the pylorus, the proximal

stomach serves mainly as a reservoir during and after ingestion of a meal.Accomodation of the stomach to a meal results from vagally mediated reflex relaxation of the proximal stomach, thereby enabling the stomach to handle large intragastric volumes without a rise in intragastric pressure[7].

Studies using Drink test, Intragastric manometry and SPECT(single photon emission computed tomography) scanning have shown that ingestion of a meal is associated with a drop in intragastric pressure followed by gradual recovery of the pressure during continued ingestion of nutrients.Studies have identified impaired gastric accommodation in roughly 40 percent of patients with functional dyspepsia, although a number ofstudies have found an association between impaired accommodation and early satiation or weight loss[6], others have failed to find such an association.

C) Visceral hypersensitivity

Visceral hypersensitivity defined as abnormally enhanced perception of visceral stimuli, i.e., lowered threshold for induction of pain by gastric distension in the presence of normal gastric compliance. Visceral hypersensitivity has been consistently demonstrated in patients with functional dyspepsia.However, isobaric gastric distention elicited more upper abdominal discomfort in the patients with dyspepsiaThe level at which visceral hypersensitivity is generated is unclear, and there is evidence for involvement of tension-sensitive mechanoreceptors as well as alterations at the level of visceral afferent nerves and the central nervous system[8].

D) Altered Duodenal sensitivity to Lipids or Acid

Patients with functional dyspepsia are also more sensitive to acid infusion into the duodenal bulb (which produced nausea and fewer duodenal pressure waves) compared to controls.Patients with functional dyspepsia, duodenal perfusion of nutrient lipids, but not glucose enhances the perception of gastric distension through a mechanism that requires lipid digestion and the subsequent release of cholecystokinin[9].

Pathogenic factors

The cause of symptoms in patients with functional dyspepsia has not been established, but evidence exists for i. Genetic susceptibility, ii. Infectious factors &iii. Psychological factors

i. Genetic susceptibility

Population studies have suggested that genetic factors contribute to functional dyspepsia. The frequency of dyspepsia in first degree relatives of affected patients is increased compared to their spouses.Polymorphism of the G-protein beta polypeptide 3 (GNB3) gene have been associated with the risk of functional dyspepsia; the specific polymorphism and an association with dyspepsia subgroups have been inconsistent in studies from different parts of the world[10].

ii. Infectious factors

1.Helicobacter pylori infection:

Although a possible role for H. pylori infection in functional dyspepsia is suggested by several potential pathogenic mechanisms, a clear association among these factors, H. pylori, and functional dyspepsia has not been established.H. pylori is a well known cause of chronic active gastritis. However, gastritis is probably not the cause of symptoms in most patients with functional dyspepsia. A consistent link between findings on endoscopy and dyspepsia has not been found.H. pylori may cause altered

smooth muscle dysfunction due to the induction of an inflammatory response or by the initiation of an antibody response. However, most studies have not found an association between H. pylori and abnormal gastric motor function in patients with functional dyspepsia. In one report, for example, the gastric function of 27 patients with functional dyspepsia and H. pylori infection was compared to that of 38 uninfected patients with functional dyspepsia . The gastric emptying time was similar in both groups.The inflammatory response induced by H. pylori may lower the discomfort threshold to gastric distension by causing alterations in the enteric or central nervous system . However, visceral hypersensitivity did not appear to be important in at least one study which found that H. pylori positive and negative patients with functional dyspepsia had no difference in the perception of mechanically-induced gastric distension[3].

2.Post infection Functional dyspepsia:

Compared with patients who had functional dyspepsia of unspecified onset, patients with a history suggestive of postinfection functional dyspepsia were more likely to report symptoms of early satiation, weight loss, nausea and vomiting and had a higher frequency of impaired accommodation of the proximal stomach. In a prospective cohort study, functional dyspepsia was increased 5-fold in patients 1 year after after acute *salmonella* gastroenteritis, compared with subjects who had not had gastroenteritis[11].

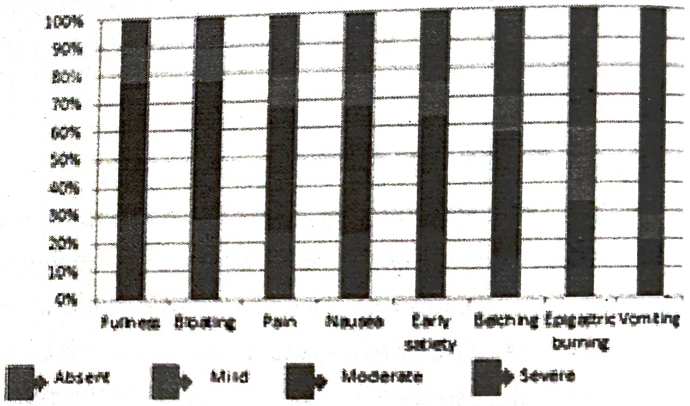
iii. Psychosocial factors

The most common psychiatric comorbidities in patients with functional dypepsia areAnxiety, Depressive or somatoform disorders &Recent or remote history of physical or sexual abuse. Symptom severity in patients with functional dyspepsia seen at tertiary care center is more strongly related to psychosocial factors than to abnormalities of gastric sensorimotor function[12].

Clinical features & diagnostic criteria

Symptoms

Dyspepsia symptom complex is broader than the 4 cardinal symptoms that constitute the ROME III definition and includes multiple symptoms such as [13]bloating, postprandial fullness, epigastric pain,early satiation, belching&nausea and vomiting.However there is considerable heterogeneity by the number of symptoms patients report depicted by the graph below which considers the frequency of symptoms in patients with FD.



Frequency of symptoms (percent of patients) and their severity in 874 patients with functional dyspepsia in tertiary referral centers. (Unpublished, University of Gastroenterology, Leuven, Belgium)

Classification of functional dyspepsia

ROME III criteria divide functional dyspepsia into two types:1. Epigastric Pain Syndrome (Epigastric pain / Epigastric burning) and 2. Post- prandial Distress Syndrome (Bothersome postprandial fullness /Early satiation)

Diagnostic criteria (according to ROME III Consensus Committee)

Epigastric pain syndrome

Definitive criteriamust include all i.e., 1. Pain or burning which is localised to the epigastrium of at least moderate severity, at least once per week, 2. Pain is intermittent, 3. Not generalised or localised to other abdominal or chest regions, 4. Not relieved by defecation or passage of flatus& 5. Not fulfilling criteria for gallbladder or sphincter of Oddi disorders

Supportive criteriaincludes 1. Pain may be of a burning quality but without a retrosternal component, 2. Pain is commonly induced or relieved by ingestion of a meal but may occur while fasting, 3. Postprandial distress syndrome may coexist

Postprandial distress syndrome

Definitive criteriamust include 1 or both of the following i.e., 1. Bothersome postprandial fullness, occuring after ordinary sized meals, at least several times per week, 2. Early satiation that prevents finishing a regular meal, at least several times per week

Supportive criteriaincludes 1. Upper abdominal bloating or postprandial nausea or excessive belching can be present, 2. Epigastric pain syndrome may coexist

Approach

Like other diseases it includes history and physical examination,laboratory testing, additional investigations, initial management(prompt upper GI endoscopy and directed treatment, test and treat for Helicobacter pylori infection, empirical antisecretory drug therapy), treatment of functional dyspepsia

History& Examination

Dyspeptic symptoms (postprandial fullness, epigastric pain,early satiation, epigastric burning,abdominal pain, nausea, bloating after meals),pain and nausea on waking in the morning is characteristic, history of stress factors such as worries, concern about employment and family affairs.Examination reveals inappropriate abdominal tenderness.All the organic causes of dyspepsia like drug intake, pregnancy,alcohol abuse etc to be excluded.Along with age >55 years, suspect gastric malignancy[7] if there is unintended weight loss, Persistent vomiting, Progressive dysphagia, Odynophagia, anemia, hematemesis, palpable abdominal mass or lymphadenopathy, unexplained iron deficiency anemia, persistent vomiting, family history of upper gastrointestinal cancer, previous gastric surgery& jaundice.

Laboratory testing

Complete Blood Count, serum electrolytes, liver function tests, thyroid function tests, serum amylase& lipase, stool testing for ova and parasites, upper GI endoscopy& test for HP infection

Initial management:

In most cases, the patient's history and physical examination will allow dyspepsia to be distinguished from symptoms suggestive of esophageal, pancreatic, or biliary disease. But we should be aware of the fact that patient's history and physical findings, and even the presence of alarm symptoms, are unreliable in distinguishing functional from organic cause of dyspepsia. Therefore, most guidelines and recommendations advocate prompt endoscopy when risk factors for an organic cause of dyspepsia are present. The optimal management strategy for the majority of patients who do not have a risk factor for an organic cause of dyspepsia remains a matter of debate & controversy; several

approaches have been proposed. Available options include

1. Prompt endoscopy and directed treatment

Diagnostic upper GI endoscopy allows direct detection of organic causes such as peptic ulcer, malignancy. Endoscopy before any therapy has been initiated is still the gold standard for diagnosing upper GI disorders[15]

Advantages includesdetection of H.pylori infection by mucosal biopsy & it is claimed to detect gastric cancer at an early curable stage

Disadvantages are expensive, invasive and it may not have a major impact on treatment, patients found to have peptic ulcer or erosive esophagitis will receive antisecretory drug therapy & those with negative result, functional dyspepsia and non-erosive GERD are likely diagnoses, both of which can be treated empirically with antisecretory drug therapy

2. Test and treat for H.pylori infection

H.pylori is causally associated with the majority of peptic ulcers and is the most important risk factor for gastric cancer. Because of the involvement of H.pylori in peptic ulcer disease several consensus advocates noninvasive testing for H.pylori in young patients(<45 to 55 years) with uncomplicated dyspepsia. Patients with positive test result should receive eradication therapy, whereas patients with negative test result should be treated empirically, usually with PPI[2].

Advantages include cure of peptic ulcer disease, prevention of future peptic ulcers, eradication of H.pylori eliminates chronic gastritis and in theory may contribute to a reduction in the risk of HP-associated gastric cancer.

Tests for detection of H.pylori infection Urea breath test (carbon isotope urea breath test or UBT)95% sensitive & specific, serological tests for H.pylori antibodies 92% sensitive & specific, stool antigen test for H.pylori antigen 80% sensitive & specific and endoscopy guided biopsy for Leifson staining and culture purposes

1. Initiation of empirical therapy

Initial empirical antisecretory drug therapy is widely used in primary care for patients with uninvestigated dyspepsia. This approach is attractive because it controls symptoms and heals lesions in most patients with underlying GERD or PUD and may be beneficial in up to one third of patients with functional dyspepsia.PPI provide superior symptom relief compared with H2RAs, and the response usually occurs within 2 weeks of therapy[4].

Disadvantages include rapid symptomatic relapse after cessation of therapy and the potential for rebound gastric hypersecretion, so many patients require long term PPI therapy

Additional investigations may be pursued in patients with progressive or refractory symptoms that do not react to initial management.Testing for celiac disease & Giardia infection, abdominal USG or CT and gastric emptying test using scintigraphy or a breath test

Treatment of Functional dyspepsia :

General measures&Pharmacologic treatment (Acid suppressive drugs, eradication of HP infection, prokinetic drugs, antidepressants, new drug development and psychological therapies)

General measures:

Reassurance and education are of primary importance in patients with functional dyspepsia.

Inspite of normal findings at endoscopy, the patient should be given a confident and positive diagnosis. Lifestyle and dietary are usually prescribed to patients with functional dyspepsia, but the impact of dietary interventions has not been studied systematically. Cessation of smoking and consumption of alcohol are thought to be helpful. Avoidance of aspirin & other NSAIDs is commonly recommended and seems sensible.

Diet: Having patients eat smaller, more frequent meals seems logical, because the presence of lipids in the duodenum enhances gastric sensitivity, avoiding meals with a high fat content may be advisable. Similarly consumption of spicy foods containing capsaican and other irritants is often discouraged. Coffee may aggravate symptoms in some cases and if implicated should be avoided.The foods that caused the highest aggravation of symptoms were sausage and bolognas, pickles vinegar, soft drinks, grain, tea, salt, pizza, watermelon, red pepper, and macaroni. However, the most frequent foods that led to the alleviation of symptoms were apples, rice, rock candy, bread, caraway seed, dates, honey, yogurt, quince, and walnut[16].

Pharmacologic treatment

A. Acid suppressive drugs

Histamine2 receptor blockers&proton pump inhibitors(PPI)

FD patients with some degree of heartburn have been more likely to respond to PPI treatment. This suggests that, mechanistically, some of the modest beneficial effect of PPI treatment in FD patients may be through the treatment of coexisting reflux symptoms. Alternatively, improving acid-induced injury or acid-induced hypersensitivity to gastric or duodenal mucosa may also contribute to symptom resolution. Overall, the effectiveness of PPI treatment in FD appears modest with a therapeutic gain of approximately 7–10%. Although some patients who carry the diagnosis of FD will respond favourably to PPI treatment, these agents should not be continued in those who do not respond after a reasonable treatment period of 4–8 weeks.A comparison of PPI therapy to H_2RA therapy in a study of 588 participants with nonulcer dyspepsia showed a trend towards a better outcome based on global dyspepsia cure with a PPI, although the difference was not statistically significant[17].

In general PPI therapy to be most effective in the group with overlapping reflux, less effective in the group with epigastric pain.

B. Eradication of H.pylori infection

Although management of dyspepsia or H. pylori eradication differs, eradication of H. pylori should be considered for á good clinical outcome in patients with FD in countries with high H. pylori prevalence. No difference for symptom relief exists between sequential and triple therapy in patients with FD[6]

Standard triple therapy: Omeprazole 20 mg BD, Amoxicillin trihydrate 1000 mg BD and clarithromycin 500 mg BD for 14 daysorSequential therapy:First 7 days: Omeprazole 20 mg BD plus amoxicilline 1000 mg BD and subsequent 7 days of Omeprazole 20 mg BD, Metronidazole 500 mg BD and Clarithromycin 500 mg BD

C. Prokinetic agents (D_2 receptor antagonist , 5 HT_4 agonist and 5 HT_3 antagonist)

Gastric prokinetic agents are a heterogeneous class of compounds that act through different types of receptors. The efficacy of available prokinetic agents in patients with functional dyspepsia has been controversial.Domperidone and cisapride are superior to placebo with a relative risk reduction of 33%.Metoclopramide and domperidone are dopamine receptor antagonists with a stimulatory effect on upper GI motility. Unlike metoclopramide, which may cause serious neurologic adverse effects, domperidone does not cross the blood brain barrier.Cisapride facilitates acetylcholine release in the myenteric plexus via 5-hydroxytryptamine 4 (5-HT_4) receptor agonism and accelerates gastric emptying.

a)Metoclopramide(D_2 antagonism and 5-HT_4agonism10 mg TDS oral or i.m)& b) Domperidone(D_2 antagonism)do not cross BBB, main action on CTZ (10-40 mg TDS)

In summary, although prokinetic agents are conceptually appealing given their potential to improve gastric emptying, and are commonly used throughout the world, the results in FD patients are underwhelming[17].

D. Antidepressants

Antidepressants are commonly used to treat functional GI disorders that do not initially respond to conventional approaches

a) Tricyclic antidepressants: (Amitriptyline, at 10 mg each day with slow escalation to 50 or 75 mg/day; &Desipramine at 10–50 mg q day)[17] MoA:Antidepressants have been thought to decrease visceral sensitivity and b) Selective Serotonin Reuptake Inhibitors (Trazadone) &Selective Serotonine and Norepinephrine Reuptake Inhibitors (Duloxetine, Venlafaxine) MoA: increased gastric accommodation in healthy subjects

In summary, although TCAs appear to make theoretical sense for the treatment of FD, the exceedingly small amount of data that are available makes it difficult to determine whether TCAs are effective in FD[17].

E. Recent recommendations in treatment

To enhance gastric accommodation a. 5-HT_{1A} receptor agonist (Buspirone, Tandospirone)[18], b. 5-HT_3 receptor antagonist (Ondensetron)[19] and c. 5-HT_4 receptor agonist (Prucalopride, Velusetrag/ATI-7505) [20] 2. To enhance release of acetylcholine by Cholineesterase inhibitor [Acotiamide (Z-338, YM443)] 100 mg three times a day[213]. Complementary and alternative medications[(21)] includesherbal preparation (containing extracts of Bitter candy tuft, Matricaria flower, licorice root and lemon balm)

F. Psychological therapies

Behavioral therapy& hypnotherapy

Conclusion

Research over the past decade has provided significant advances in the understanding of the pathophysiology in functional dyspepsia. However, the precise mechanisms underlying symptom generation in functional dyspepsia remain incompletely understood. There is an emerging consensus that the various clinical manifestations (including nongastrointestinal comorbid symptoms) of chronic abdominal pain can best be viewed as a dysregulation in the complex interplay between events occurring in the gut lumen (including enteric microbiota), the gut mucosa, the enteric nervous

system (ENS), and the central nervous system (CNS), leading to alterations in sensation, motility, mood and affect.

The treatment of FD remains unsatisfactory for many patients. Dietary advice is routinely provided although there are few data available to support clinicians' recommendations. Eradication of H. pylori improves dyspeptic symptoms in only 7% of patients treated, while H2RAs are somewhat better. Prokinetic agents are theoretically appealing for FD patients with delayed gastric emptying. Promotility agents (e.g. domperidone) are available& are commonly used by patients for a number of reasons. STW-5 has demonstrated benefit in patients with FD, although the mechanism of action is unknown. Hypnotherapy is likely to improve global symptoms in FD patients.

In areas with H. pylori prevalence >10% patients with a normal endoscopy (without gastric biopsies having been performed) should be tested for H. pylori using either a breath test or stool antigen test, and if positive, treated. Empiric treatment for H. pylori based only on symptoms is not recommended. After H. pyloritreatment, the majority of FD patients will have persistent symptoms, and empiric therapy for 6–8 weeks with a once-daily PPI is reasonable. If symptoms persist then a low-dose TCA may be initiated (e.g. amitriptyline at 10 mg each day with slow escalation to 50 or 75 mg/day; alternatively desipramine at 10–50 mg q day). If symptoms persist, then a trial of a prokinetic agent is reasonable, especially if the patient has concomitant symptoms of nausea and/or postprandial fullness. Alternatively, other anti-nociceptive agents can be used, recognising the lack of evidence from prospective trials to guide clinical care. Finally, if the patient wishes to pursue alternative therapies, a referral to a hypnotherapist may be offered.

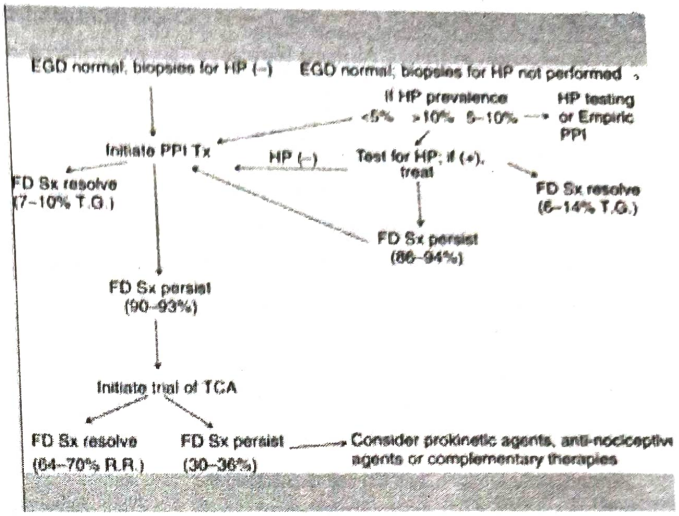


Figure :Proposed treatment algorithm for FD. In this algorithm the patient with dyspepsia undergoes an upper endoscopy which, by definition, has to be grossly normal.

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Review article

PATHOPHYSIOLOGY AND MANAGEMENT STRATEGIES OF POSTPRANDIAL HYPERGLYCEMIA

Butungeshwar Pradhan.[1] Sagnika Tripathy.[2]

ABSTRACT

Background: Postprandial hyperglycemia (PPHG) is the highest concentration of plasma glucose over any time of a day, usually found postprandially or after 2-hour postglucosechallenge.Development of PPHG coincide with an impairement or absence of the first-phase insulin response, a decrease in insulin sensitivity in the peripheral tissues and decreased suppression of hepatic glucose output (HGO) after meal. Considerable data have accumulated indicating that elevated PPHG levels, even in the absence of fasting hyperglycemia, increases the risk of cardiovascular diseases(CVD) with increase in morbidity and mortality. There is high prevalence of elevated PPHG in patients with type 2 diabetes mellitus(type 2 DM), who are seemingly well controlled with diet,exercise and medical therapy even with normal fasting plasma glucose(FPG) and HbA1c value <7% as recommended byADA.There is intrrelationship between FPG and PPHG i.e. the higher the FPG ,the higher the PPHG and vice versa. Understanding the pathophysiology of PPHG and FPG in different clinical states of type 2 DM is important . A triad model of diabetes management strategies in which all the three parameters i.e.HbA1c,PPHG,FPG leveis are considered and anti-hyperglycemic agents that preferentially target PPHG along with FPG and HbA1c are strongly suggested and rational use of current treatment strategies to optimize diabetes control indivdually can reduce complications.

Keywords: Type 2 diabetes,postprandialhyperglycemia,pathophysiology, treatment.

INTRODUCTION:

Postprandial hyperglycemia (PPHG) is the highest concentrations of blood glucose over any time of a day, usually found postprandially or after 2hrs post glucose challenge. In people with normal glucose tolerance plasma glucose generally rise no higher than 7.8mmol/L(140mg/dl) in response to meals and typically returns to premeal levels within two to three hours and in 75gms of OGTT 2 hour PPG is <140mg/dl. Excessive postprandial hyperglycemia may act in a vicious circle with harmful effects on both the β-cells and insulin sensitive tissue. There occurs progressive deterioration of diabetes in terms of impaired insulin secretion and insulin action due to glucotoxicity [1] and lipotoxicity. Excessive PPHG excursion initiate a cascade of proatherogenic events, activation of low grade inflammation and blood coagulation as well as oxidative stress, endothelial dysfunction.[2] . It is an independent risk factor for cardiovascular disease(CVD).[3,4]

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During progression of impaired glucose tolerance (IGT) to type 2 DM, when the PPHG reached about 140mg/dl , the β-cells can no longer increase insulin secretion and insulin concentrations decreased. At this stage hepatic glucose output (HGO) begins to increase as insufficient insulin unable to suppress HGO and fasting plasma glucose(FPG) increased.

INCIDENCE OF PPHG AND CONTRIBUTIONS OF FPG AND PPHG TO HbA1C:

Incidence of PPHG of >8.89mmol/L (160mg/dl) was present at least once in a week in a study of large number of patients with type 2 DM without insulin therapy in 84% and 81% of them have at least one deltaglucose (the difference between the pre and postprandial glucose) was e"2.22mmol/L(40mg/dl). Among patients with good metabolic control, 38% had >40% of PPHG value of >8.89mmol/L(160mg/dl) and 36% had >40% deltaglucose e"2.22mmol/L(40mg/dl) ,indicating PPHG is very frequent phenomenon in type 2 DM patients on active treatment and can occurs even when metabolic control is apparently good.t In type 2 DM as HbA1c increases from <5% to e"7% , FPG increase to approximately 40%, where as PPHG values increase to 80%. By the time diabetes is diagnosed , 50% reduction of β-cell functions found.u

Increase PPHG often preceds FPG changes in the natural history of type 2DM. About 10% of type 2 DM patients with 2hrs PPHG>200mg/dl on OGTT have FPG <126mg/dl and 39% of cases have HbA1c <7%. An unifying concept is at ~ 6.5% of HbA1c when FPG is close to normal, PPHG contributes 70% and FPG to30% of HbA1c and at HbA1c of e" 8% FPG contributes 70% and PPHG 30% of HbA1c.v

SIGNIFICANCE OF POSTPRANDIAL HYPERGLYCEMIA :-

Derived from clinical observations and animal experimentsand in women with pregnancy, monitoring of FPG do not provide adequate indications of maternal control and risk of macrosomia.w There is a linear relationship between risk of cardiovascular disease (CVD) deaths and 2hrs oral glucose tolerance test (OGTT) and increased mortality evident at PPHG of approximately 90mg/dl which is well bellow the current definition of type 2DMx IGT subjects have 3-fold increased risk for corotid stenosis than normal glucose tolerance(NGT) and have 2 fold increase in relative risk of deaths from CVD.. Acute hyperglycemias havedelecterious effects on arterial wall due to oxidative stress, endothelial dysfunction and postprandial lipemia.y All component of glucose triad FPG,HbA1C and PPHG should be considered in the management of type2DM.[1]p .[11]

PPHG GOAL:

Various international bodies have proposed different optimal goal for PPHG. While IDF 2011 advocated a level of less than 9.0mmol/L(160mg/dl).American college of endocrinology conference recommended 2-hour postprandial plasma glucose levels of <140mg/dl and ADA suggest more relaxed target of <180mg/dl.The EASD/IDF-Europe advocated postprandial target of <7.5mmol/L(135mg/dl)[12]'y .In a consensus statement on clinical practice in India recommended target for PPHG control individualized between 140-180mg/dl based on each patient's clinical status .[13]

PATHOPHYSIOLOGY OF POSTPRANDIAL HYPERGLYCEMIA.

Before discussion on pathogenesis of type 2DM ,first must start with a review of mechanisms involved in the maintainance of normal glucose homeostasis in the basal or postabsorptive state and following ingestion of typical mixed meals.

NORMAL SUBJECTS IN FASTING STATE (POST ABSORPTIVE STATE):

There is basal level of insulin secretion and a slight increase in the basal glucagon secretion,which increase HGO to require basal glucose requirement of body and normally HGO is 150-250mg/min .Insulin dependent peripheral glucose utilization is almost nil and glucose utilization by liver and adipose tissues is minimal .Non- insulin dependent glucose utilization by brain,blood cells and renal medulla goes on ,which is almost 200mg/min and in brain saturated at 40mg/dl of serum glucose. Thus,HGO is equal to whole body glucose disposal at any time .[1]t Normally liver store glucose as glycogen of 70gms at a given time and in fasting state about 75% of HGO comes from glycogenolysis and 25% from gluconeogenesis, which constitute the normal fasting blood glucose levels maintain between 65—110mg/dl and.there is narrow variability in glucose excursions.

AFTER CARBOHYDRATE INGESTION (POSTPRANDIAL STATE).

After food ingestion the liver is no longer the main source of glucose and 75% of glucose derived form ingested food goes to muscles and 4-5% to the adipose tissue. Rest 25% taken up by the splanchinic tissue mainly liver. The increase in blood glucose level immediately after meal trggers insulin secretion by the β-cells of pancrease and causes fall in glucagon secretion and reduction of HGO of about 50% that of fasting rate and glucose uptake in the extra hepatic insulin sensitive tissues are stimulated ,while lipolysis is inhibited in non-diabetic subjects .

In type 2 DM there is failure to suppress glucagon or even paradoxically increase glucagon secretion due to defective insulin secretion and insulin resistance. [1]u

NORMAL GLUCOSE TOLERANCE TEST (NGT).

Pathophysiology of oral glucose tolerance is better corelated with pathophysiology of development of PPHG and type 2 DM. In normal subjects glucose stimulate insulin release with a rapid fast phase lasting 5-10 minutes follwed by a prolonged second phase with episodic increase in amplitudes every 2-3 hours,which persists for the entire duration of the high glucose stimulous ie.5.5—17mmol/L(99-306mg/dl) with half maximal stimulation at 8mmol/L(144mg/dl) and there is no insulin release at<5mmol/L (90mg/dl) of glucose.

After intake of glucose, hepatic retension is about 55%,went for glycogen synthesis,Triglyceride formation and glycolysis. Non-insulindependent peripheral glucose uptake is about 25% and insulin dependent peripheral glucose uptake is 15% and unmetabolized rest glucose goes to plasma glucose space of about 5%.The first phage insulin secretion control the peripheral glucose levels between the 30-60 minutes of glucose ingestion.

IMPAIRED GLUCOSE TOLERANCE TEST(IGT):

In IGT the first phage insulin secretion is defective due to β-cell dysfunction and insulin resistance gives rise to highest peripheral glucose levels of e"140mg/dl between the 30-60 minutes . Hepatic glucose retension is only 25% and about 75% of oral glucose or meal derived glucose escape the liver into peripheral glucose space, since the second phage of insulin release is adequate,the peripheral tissue glucose uptake is increased and the second hour plasma glucose levels are e" 140—<200mg/dl . The first phage insulin secretion is better correlated to the first hour of OGTT and normaly< 140mg/dl. As FPG increases the fasting insulin concentration increases propertionately. However, when FPG rise

to e" 150mg/dl the insulin secretion falls and HGO increased from FPG of e" 140 mg/dl.

THE 2 HOURS POSTPRANDIAL HYPERGLYCEMIA:

It is related to severe loss of first phage insulin secretion and delayed or loss of second phase insulin secretions. The hepatic glucose uptake after 100 gms of glucose is < 25% and about >75% of meal derived glucose spill over to peripheral glucose space and HGO is uninhibited. As there is marked peripheral insulin resistanc, plasma glucose levels exceed e" 200mg/dl at 2hrs. However,the FPG may be within normal levels in about 10% of patients . In classic OGTT curve this stage gives rise to blood glucose levels of e" 200mg/dl between 90-120 minutes. In type 2DM haveboth fasting hyperglycemia and high postprandial hyperglycemia, exacerbated by high carbohydrate diets.

MECHANISMS OF ELEVATED PPHG IN IN TYPE 2 DM:

Normally glucose enters the circulation from two main sources , after meals ingestion, the true postprandial blood glucose and endogenous glucose production from liver and kidney by glycogenolysis (75%) and by gluconeogenesis (25%).

The elevated PPHG in people with type 2 DM could be due to following causes:

1. Defect in 1st phase insulin secretion of β-cells.
2. Excessive appearance of meals derived glucose into the circulation, the true PPHG due to high glycemic index diet.
3. Excessive endogenous hepatic glucose output.
4. Reduced utilization of glucose in peripheral insulin sensitive tissues.
5. Lack of postprandial suppression of glucagon secretion by uninhibited α-cells of pancreas.
6. Defective incretin responses.
7. Amylin deficiency.
8. Low hypothalamic dopamine level and excessive sympathetic tone within the central nervous system.

(1).DEFECT IN 1ST PHASE INSULIN SECRETION.

In people with IGT and type 2DM with postprandial hyperglycemia, less reduction in glucagon secretion, resulting in inappropriate glucose production in the liver and inefficient glucose uptake in peripheral tisues, consequently increased PPHG level[1]v and the capacity to secrete additional amount of insulin to compensate for insulin resistance is reduced.[1]w [1]x Loss of second phase insulin secretion is roughly 25% (IGT) to 50% in type 2 DM and the first phase insulin secretion is completely lost in type 2DM.In type 2 DM with mild increase in FPG (140mg/dl) plasma insulin level during an OGTT or mixed meal is usually elevated in absolute term. However, relative to the severity of insulin resistance and prevailing hyperglycemia even the elevated insulin is deficient indicating β-cell malfunction.[1]u

(2). EXCESSIVE APPEARANCE OF MEAL DERIVED GLUCOSE INTO THE CIRCULATION, (TRUE PPHG).

An excessive appearance of glucose from meals is not the primary cause of increased PPHG in type 2 DM and play much smaller role in determining the mean day-long plasma glucose concentrations (mean blood glucose) than does the elevated fasting plasma glucose. After each main meal i.e., breakfast, lunch and dinner increase in plasma glucose is about 35-

40mg/dl ,but returns to the baseline value by the 4-6 hrs of food ingestion and their contribution to the day-long hyperglycemia is only about 22mg%.[1]y For example, in a patient with FPG of 190mg/dl(10.5mmol/L) indicates an increase in basal glucose level of 100mg/dl(5.6mmol/L) above baseline FPG of 90mg/dl(5mmol/L) of non-diabetic control, persist for 24hrs and after each three main meals the increase in plasma glucose is by about 35-40mg/dl, but returns to baseline by 4-6hrs (average 5hrs) and the hyperglycemic index accounted by the excursion of increase in plasma glucose due to meals will be 525mg/dl .Thus ,the contribution of PPHG to day long hyperglycemia is only about 22mg/dl. [2]p

Intestinal glucose entry is a function of dietary compositions and glycemic index (GI) of foods and the complex digestive process as well as intestinal motility and also related to incretin response. Alphaglucosidase inhibitors slow the digestion of complex carbohydrates at the brush border of intestine and shift the site of absorption of glucose to lower intestine, thus decreases the PPHG.

(3). EXCESSIVE POSTPRANDIAL ENDOGENOUS HEPATIC GLUCOSE PRODUCTION.

Endogenous glucose production by the liver and kidney is higher in people with type 2DM in fasting state and after meal ingestion, due to insulin deficiency, insulin resistance and increased circulating glucagon. In diabetics endogenous glucose production takes about 5-6hrs after a meal in comparison to non-diabetics in negligible time. The contribution of liver on glucose homeostasis depends on the following factors:

i. Insulin sensitivity of the hepatocytes.

ii. Ratio of insulin to glucagon.(ratio of β-cells to α-cells of pancreas).

iii. Responsiveness of glycogenolysis and neoglucogenesis to hormone modulation.

A small increment in basal insulin level even to < twice the basal state decrease HGO by 80% and there is no rise of glucagon level , inhibit glycogenolysis which is very insulin sensitive but larger insulin doses are required to suppress both glycogenolysis, neoglucogenesis and HGO .

In type 2DM due to insulin deficiency and insulin resistance of hepatocytes, glycogen depletion take place early but gluconeogenesis persists unabated and contribute to increased HGO of 150-250mg/min. In this stage though the HGO is in normal limit ,it is relatively high in the background of peripheral hyperglycemia .[21] Thus the liver is the primary site of metabolic defect in type 2DM.

(4).REDUCED UTILIZATION OF GLUCOSE IN THE PERIPHERAL INSULIN SENSITIVE TISSUES.

In type 2 DM, glucose utilization in the fasting state is not insulin mediated and glucose utilization increase with each meal ingestion in both diabetics and non-diabetics,but the rates of glucose utilization in diabetics is not appropriate for the prevailing hyperglycemia in comparison to non-diabetics. The major metabolic consequence of insulin resistance is overproduction of glucose by the liver and kidneys. Fasting insulin levels may be normal or increased relative to normoglycemic individual but are clearly inappropriate for the degree of hyperglycemia.

(5).LACK OF POSTPRANDIAL SUPPRESSION OF GLUCAGON SECRETION OF PANCREATIC α-CELLS.

When insulin secretion is impaired ,there occurs lack of suppression of glucagon secretion and there is increased hepatic glucose production. Thus inhibitor of glucagon secretion or action are likely to be useful in treatment of postprandial hyperglycemia .

(6).DEFECTIVE POSTPRANDIAL INCRETIN RESPONSE.

Orally administered glucose lead to greater insulin response than intravenous glucose is called incretineffect.Theincretins are secreted by the gastrointestinal tract in respons to food ingestion immediately within 5-10 minutes by the neuroendocrine cells from upper small intestine K-cells secretes gastric inhibitory peptide or glucose dependent insulinotropic peptide (GIP), and from lower small intestine and upper colon's L-cells secretes Glucagon like peptide -1(GLP-1).Incretin effect is responsible for approximately 30-60% of the postprandial C-peptide response depending on the amount of cabohydrates and fat riched diets consumed. In type 2 DM incretin effect is markedly reduced or absent and exogenous administration of GLP-1 restore the defect. GIP account for approximately 60% of the total incretin effects.[2223] GLP-1 enhance glucose induced insulin secretion and contribute to the incretin effect. Plasma concentration of GLP-1 increases after a meal ingestion to 3— 8 folds.GLP-1 decrease PPHG by its endocrine effect on pancreatic 1st phase insulin secretion but also decrease gastric emptying and both GLP-1 and GIP maintain normoglycemia after meal ingestion and GLP-1 is essential for control of fasting glucose .

GLP-1 receptor is expressed in the pancreatic α-cells and β-ceils. Activation of GLP-1 and GIP receptors leads to increase insulin secretion in glucose dependent manner, directly stimulated by substrates.Thus, presence of some β-cell is necessary for increase insulin secretion in type 2DM subjects . The GLP-1 and GIP are responsible for 50-70% of postprandial insulin release. In addition GLP-1 suppress glucagon secretion and delays gastric emptying by inhibiting gastroduodenalmotility.The delay in gastric emptying caused by GLP-1 is associated with an increase in satiety and reduce food intake.[23] Both GLP-1 and GIP are rapidly broken down by Dipeptidyl dipeptidase-4 enzyme (DPP-4) after secretion within 2 minutes,[2]t and endogenous GLP-1 is impractical as a therapeutic agent.However ,several synthetic DPP-4 resistant GLP-1 analogues have been developed [23] called incretinmimetics as they have same action as endogenous GLP-1.

The 2012 ADA/ESAD position statement for management of hyperglycemia in patients with type 2 DM indicate at multiple point throughout treatment and indicated that GLP-1 agonists may be considered as add on therapy for patients who fail initial treatment or can be considered as initial monotherapy when other antidiabeticscan not be used or as part of several three or four drug combination excluding DPP-4 inhibitors(DPP-4i) .[2]u There are currently three GLP-1 analogues approved for clinical use, ie. Exenatide, Exenatide LAR and Liraglutide.Albuglutide and dulaglutideare other GLP-1 analogue with prolong half-life. Exenatidereduces PPHG by decreasing HGO[2]v .It is given 5µg twice daily by s.c. injection morning and evening before meal, decreases HbA1c by 1.74%. Exenatide LAR 2mg is given once weekly achieved better HbA1C control but lesser PPHG lowering than exenatide twice daily. Liraglutide is a long acting incretinmimetic given 0.6—1.8mg/day as monotherapy and in add-on therapy reduces both FPG and PPHG given once daily.

DPP-4 INHIBITORS:(DPP-4i OR GLIPTINS).

The DPP-4i decrease the breakdown of GLP-1 and GIP through inhibition of the DPP-4 enzymes and prolong the action of GLP-1 and GIP improve both α-cell and β-cell responsiveness to glucose. [2]w

Inhibition of DPP-4 increases prandial insulin secretion and suppresses glucagon secretion, thereby decreasing HGO and improving peripheral glucose uptake decrease PPHG. [2x] For DPP-4i to effective, some residual insulin secreting β-cells must remain. All DPP-4 inhibitors are given orally daily and ADA/EASD 2012 position statement recommend include DPP-4i as an option for add-on therapy in patients who fail to reach their glycemic targets.[2u] The DPP-4i sitagliptin, saxagliptin, linagliptin are approved in US . Other available are vildagliptin, alogliptin, teneligliptin, dutogliptin etc. Dose adjustment is require in CKD for all DPP-4i, except linagliptin.

(7). AMYLIN DEFICIENCY.

Amylin is a β-cells hormone co-located and co-secreted with insulin in response to nutrient intake in molar ratio of approximately 1:100 in healthy subjects. In fasting state there is low basal concentration that rapidly increase following meal intake .It exerts its effect as a neuroendocrine hormone activating specific amylin receptors in the brain (area postrema) and also have paracrine effect on α-cells.In brain via binding to its receptors stimulate three key action that together help control rate of glucose appearance into the circulation during postprandial period by (i) Suppression of glucagon secretion acting on α-cells.(ii) Modulates feeding behavior, decrease food intake and (iii) satiogeniceffect.Thus, amylin is considered to be a complementary hormone to insulin as both contributing to the maintainance of normal postprandial glucose concentration,(Insulin promote increase glucose dissappearance in postprandial period ,where as amylin decrease glucose appearance in the postprandial periods.) In type 1 DM there is absolute deficiency of both insulin and amylin ,but in type 2 DM ther is progressive decline of both insulin and amylin and indivdual with insulin resistance also have amylin resistance.[2y] Pramlintide acetate is a synthetic analogue of amylin soluble and non-aggregating with similar mode of action of amylin, indicated as an adjunct to meal time insulin in type 1 and type 2DM who fail to achieve desired glucose control despite optimal insulin therapy with or without concurrent sulfonylureas and or metformin. Pramlintidesuppress postprandial glucagon secretion as with insulin also slow gastric emptying in presence of hyperglycemia but not in presence of hypoglycemia, preserves the couter regulatory hormones in presence of hypoglycemia unlike insulin. Pramlintide 120μg s.c.beforefood decrease calorie intake by approximately 30% , independent of nausea.[3p]

(8).LOW HYPOTHALAMIC DOPAMINE LEVELS AND EXCESSIVE SYMPATHETIC TONE IN CENTRAL NERVOUS SYSTEM .

Bromocriptine 0.8mg orally adminstered within 2 hours of awakening is believed to augment low hypothalamic dopamine levels and inhibit excessive sympathetic tone within the central nervous system resulting in reduction of lipolysis, gluconeogenesis and improve in insulinsensitivity in obese type 2 DM patients resulting reduction of HGO ,gluconeogenesis,lowering of free fatty acids and triglyceride and decreases FPG ,PPHG and HbA1c by 0.5-0.7%. [31] The dose can be increase weekly till 1.6 to 4.8mg/day for maximal effect.

MANAGEMENT STRATEGIES OF POSTPRANDIAL HYPERGLYCEMIA .

Dietary counseling,regular physical exercise and wieght loss have been recommended for all diabetics. The total amount and nature of the carbohydrates consumed are important and low carbohydrate/low glycemic index diets can reduce PPHG .

FPG and PPHG are interrelated, thus when increased FPG is associated with high PPHG treatment strategies should targeted to control FPG first with use of insulins or sulfonylurea to correct insulin deficit and metformin,thiazolindiones(TZDs) to address insulin resistance can correct FPG as well as PPHG . The insulin secretagogue sulfonylureas (SUs) and insulin sensitizers metformine and TZDs primary affect FPG.To the extent that FPG are reduced,so are PPHG .The SUs primarily improve late insulin release and metformine primarily act by decreasing HGO in fasting state which is not the major factor involved in PPHG.[1]x Thus,combinations of agents that correct insulin deficit by insulins or increasing insulin secretions by SUs and increasing insulin sensitivity bymetformine and TZDs and decreasing HGO can control FPG and PPHG.However, the increment in PPHG levels are largely unaffected.

Considering the pathophysiologic defects of isolated postprandial hyperglycemia in type 2 DM therapeutic modalities are directed against them to restore or mimic the normal physiologic insulin profile by use of secretaguesmeglitinidesi.e.repaglinide,andnataglinide which increase early insulin release given orally prior to meals , or α-glucosidase inhibitors i.e.acarbose ,meglitol and voglibose which delay cabohydrate digestion by selectively inhibiting glucosidase enzymes in the brush border of the small intestine given with each main meals. They slow digestion and absorption of carbohydrates and reduces postprandial rise in plasma glucose also increases the secretion of GLP-1 . As early insulin release is main defect in PPHG,rapid-acting insulins analogues specifically targeting PPHG are Insulin Lispro and Aspart given prior to meals to mimic early insulin release are rapidly absorbed after injection with faster onset of action, and shorter duration of action, with less chance of hypoglycemia unlike human regular insulin,providing peak plasma levels for 40-50 minutes with duration of action of 2-4 hours(vs 4-6 hours of regular insulin).The GLP-1 analogues or incretinmimetics or DPP-4i can be considered as alternatives. An excellent indicatin for these agents is when metformine,SU,or pioglitazone is contraindicated or not tolerated or when avoidance of hypoglycemia and wieght gain is a prioriy.A GLP-1 agonist may be recommended over DPP-4i when weight loss is priority or when greater reduction of HbA1c is desired.A general approach that may work well is to include a DPP-4i or GLP-1agonist as part of the regimen on the basis of patient specific factors.In older and CKD patients a DPP-4i may be a good choice ,either alone or in combination with other agents.A DPP-4i or GLP-1 agonist may also be used effectively in cojunction with TZDs,SUs, and sodium glucose cotransporter-2 inhibitors. In addition DPP-4i or GLP-1 agonist may be considered as an adjunct with basal insulin regimens in leiu of other more complicated regimens .

Additional treament may be required for those who are not control with conventional treatment are sympatholytic bromocrtptine in obese type 2 DM and newer amylin analogue pramlintide acetate in insulin resistance cases as adjunct to insulin.

CONCLUSION:

There is high prevalence of PPHG and may be elevated in patients who are seemingly well controlled with ADA recommeded HbA1c level of <7% and FPG <126mg/dl. The link between PPHG and CVD risk is well known. There is interrelationship between FPG and PPHG. The pathophysiology of PPHG is being well known .Defect in early insulin release is main cause along with insulin resistance leading to

high HGO is main contributing factor. Current treatment guidelines for type 2 DM emphasize the importance of controlling PPHG along with FPG and HbA1c levels to optimize glycemic control which may result in a lower risk of cardiovascular morbidity and mortality.

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ZIKA VIRUS

Review article

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INTRODUCTION:

ZIKA virus, a mosquito borne flavivirus is gaining more global attention recently posing a pandemic spread. It's named after the ZIKA forest of UGANDA where it was first isolated from a rhesus macaque[1]. It remains as a silent pathogen in many; not expressing its virulence, and if at all, only in an innocent way masquerading other viral illnesses raising a difficult challenge of early diagnosis. The deficiency of proper screening methods, and specific treatment or preventive vaccines makes the confinement of the viral transmission a serious challenge. An unprecedented outbreak due to this mosquito borne virus accelerating neurological complications is currently circulating in an autochthonous way in Latin America and Caribbean. Still, half way across the world, Indian subcontinent, nurturing the favourable milieu for this virus is under a serious threat for a possible outbreak in near future. Recent evidences of neurological disorders, including microcephaly and GBS,being linked to Zika virus remains circumstantial, but the new clinical and epidemiological data points towards a causal role of the virus.

HISTORY:

The virus was isolated from a rhesus macaque monkey in April 1947 in zika forest of Uganda by the scientists of Yellow Fever Institute. It was first isolated from mosquito A. africanus from the same place in 1948[1]. Since then many outbreaks and epidemics have been reported worldwide. The further history of outbreaks and spread of virus has been shown in Fig 1.

EPIDEMIOLOGY:

Since 2007, Zika virus transmission has been documented in 46 countries and territories with 34 countries among those exhibiting autochthonous transmission, or locally acquired infection, 6 countries with evidences of virus in circulation, 5 countries where viral outbreak has already ceased and 1 country with a locally acquired case but without vector borne transmission[2]. Travel warnings are issued by the governments or health agencies of UK, Ireland, New Zealand, Canada, and European Union. A total of 52 cases of travel associated Zika viral infection had been reported from USA[3]. In the epidemiologic year of 2015 the incidence of zika has been increasing at an alarming rate with the number of new countries or territories introduced to this infection stretch to more than double. The prevalence and incidence of zika fever with its endemic zones worldwide is shown in Fig 2. In the last 2 years there has been an alarming increase in the incidence of infection, mainly in Latin America and Caribbean showing autochthonous transmission. The prevalence of the disease in Brazil itself is estimated to be 1.5 million making it the most affected followed by Colombia with around 25000 reported and 1331

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confirmed cases. Cape Verde has reported more than 7000 suspected cases[4].

VIROLOGY:

Family: Flaviviridae

Genus: Flavivirus (related to the dengue, yellow fever, Japanese encephalitis, and West Nile virus)

Structure:

Is similar to other flavivirus. It is an enveloped virus with icosahedral symmetry. It has a nonsegmented, single stranded, positive- sense RNA genome. It is related to the Spondweni virus, responsible for Spondweni fever (characterised by fever, chills, nausea, headache, malaise, and nose bleeds) and is one of the two viruses in the Spondweni virus clade[5].

The RNA genome genes encode three structural proteins which encapsulate the virus and seven non-structural proteins. The replicated RNA strand is held within a nucleocapsid formed from 12kDa protein blocks; the capsid is contained within a host derived membrane modified with two viral glycoproteins. Replication of the viral genome would first require creation of an anti-sense nucleotide strand. Sequence and structural comparisons of the zika virus(ZIKV) envelope(E) protein with other flaviviruses show that parts of the E protein closely resemble the neurovirulent West Nile and Japanese encephalitis viruses, while others similar to DENV(dengue virus).the virus particle was observed tonbe structurally stable even when incubated at 40°C, in contrast to the less thermally stable DENV. This is also reflected in the infectivity of ZIKV compared to DENV serotypes 2 and 4 at different temperatures. The cryo- electron microscopy structure shows a virus with a more compact surface. The structural stability of the virus may help it to survive in the harsh conditions of semen, saliva and urine.[6]

There are two lineages for Zika virus[5]

ASIAN ← LINEAGES → AFRICAN

a) Asian strain: the strain seen in French Polynesia (the first outbreak outside Asia and Africa) in 2013. Phylogenetic studies reveal that the virus spreading in Americas is most closely related to this strain.

b) African strain: Western hemisphere Zika virus is found to be 89% related to African genotype.

LIFE CYCLE:

It is primarily an enzootic cycle, mosquito-monkey- mosquito, with man as incidental host. The primary vertebrate host is monkey. (Fig 3).

TRANSMISSION:

1)Vector borne:

It is primarily transmitted by the female *Aedes aegypti* mosquito, during its blood meal, in order to lay eggs. It is usually a daytime active mosquito. Zika virus has also been isolated from a number of arboreal mosquito species in the *Aedes* genus like *A. Albopictus, A. Africanus, A. Apicoargenteus, A. Furcifer, A. Hensilli, A.luteocephalus,* and *A. Vittatus.* The extrinsic incubation period in mosquitoes is about 10 days. It has also been detected in other mosquitoes like *Anopheles coustani, Mansonia uniformis,* and *Culex perfuscus* although this alone does not incriminate them as a vector[7]. The societal risk of Zika virus can be controlled by limiting the distribution of the mosquito species that transmit it. The global distribution of the primary vector, *Aedes aegypti* is expanding due to global trade and travel. Recent studies conclude that these mosquitoes which

are common in tropical climate are adapting for persistence in northern climate in a challenging pace.

2) Sexual transmission[8]:

Till now, there are 3 reported cases indicating the possibility of sexual transmission of Zika virus. 14 additional cases of possible sexual transmission are under investigation. It can be spread by a man to his sex partners. It's unknown if women can transmit it to their sexual partners. In known cases of likely sexual transmission, the men had symptoms. But the virus can be spread before, during and after men have symptoms. The virus can be present in semen longer than in blood.

CDC (Centers for Disease Control and Prevention) recommendations[9]

a) Men who reside in or have travelled to an area of active Zika virus transmission who have a pregnant partner should abstain from sexual activity or consistently and correctly use condoms during sex for the duration of pregnancy.

b) Men who reside in or have travelled to an area of active Zika virus transmission and their non- pregnant sex partners "might consider" abstinence or condom use.

The CDC did not specify how long these practices should be followed with non- pregnant partners as the "incidence and duration of shedding in the male genitourinary tract is limited to one case report and that "testing of men for the purpose of assessing risk for sexual transmission is not recommended"

3) During pregnancy:

The viral RNA has been isolated from the amniotic fluid and chorionic villi of human placenta in women whose foetuses had microcephaly. Vertical transmission of ZIKV from an infected mother to the developing fetus in utero reflects tropism for placental cells. In particular, ZIKV antigen was detected in placental macrophages and histiocytes in the intervillous space. Several studies have confirmed Hofbauer cells are targets of viral infection in vivo and in vitro. In contrast, syncitiotrophoblasts have been shown to be resistant to infection by phylogenetically related, historic ZIKV strains at early times following infection[10]. The chance for mother to child infection causing microcephaly is strongly suspected but not yet scientifically proven. Zika virus has been isolated from the breast milk of infected mothers during their infective periods. But the breast feeding practices are to be entertained since the benefits clearly outnumber the risks[11].

4) Blood transfusion:

There has not been any confirmed blood transfusion transmission cases reported so far. The cases of blood transfusion transmission cases reported in Brazil are currently being investigated. Evidences during the previous outbreaks points to the possibility of transmission via blood. During the French Polynesian outbreak, 2.8% of blood donors tested positive for Zika and in other previous outbreaks, the virus has been found in blood donors.The possibility of blood borne infection can't be ruled out as 80% of people infected with the Zika virus don't show any symptoms; they may not know they have been infected[12].

ZIKA FEVER:

Symptoms:

About 1 in 5 people infected with Zika virus shows symptoms. The most common symptoms of Zika are fever, maculopapular rash, joint pain, muscle

pain, headache, and conjunctivitis. The symptoms are similar to other arboviral infections like dengue. The rash starts fading in two days and the fever subsides within three days with only the rash remaining. The incubation period is not known, but is likely to be a few days to a few weeks. The illness is usually mild, lasting for around 2- 7 days[13]. People usually don't get sick enough to go to hospitals, and the mortality due to Zika is very rare, many people might not realise they have been infected.

Diagnosis:

Zika virus usually remains in the blood of an infected person for about a week but it may remain longer in some. Infection can be suspected based on symptoms and recent history (residence or travel to an area where Zika virus is found to be present). The diagnosis can only be confirmed by isolation of virus from the blood or testing for the presence of RNA through PCR from blood or other body fluids, such as urine or saliva. False positive results can occur as the virus can cross react with other flaviviruses such as Dengue, West Nile and yellow fever[13].

Differential diagnosis:

It mimics other flavivirus infection making it difficult to diagnosis and showing false positive laboratory results. The various aspects of other flaviviral infections is compared with zika fever.

ZIKA	DENGUE	CHIKUNGUNYA
Slight fever	High fever	Sudden fever
Headache	Intense headache	Headache
Conjunctivitis	Retro- orbital pain	
Joint pain, myalgia	Myalgia, joint pain	Strong joint pain, myalgia
Heat rash	Heat rash	Heat rash
Microcephaly in newborns		
Guillain Barre syndrome	Swelling of lymphatic glands	
	Haemorrhages which can be fatal	
		Joint pains can last for years

Treatment:

Once infected, the person is likely to be protected from future infections. No vaccine or remedial drugs are available so far. Only symptomatic management is necessary with rest, plenty of fluids and paracetamol (acetaminophen) to relieve fever and pain[14]. Aspirin and NSAIDS should be used only when dengue has been ruled out to reduce the risk of bleeding. Adequate protective measures has to be taken to prevent the infected persons from further mosquito exposure during the first few days of illness to prevent other mosquitoes from becoming infected and reduce the risk of local transmission.The works for the development of an effective vaccine is in an uphill process. An Indian company, Bharat Biotech International is working on the vaccine development and the animal trials of the inactivated version commences on late February[15].

Prevention and Control:

Mosquitoes and their breeding sites pose a significant risk factor for Zika virus infection. Prevention and control relies on reducing mosquitoes through source reduction (removal and modification of breeding sites) and reducing contact between mosquitoes and people. People infected with any flaviviral infection should be prevented from exposure to mosquitoes for the first few days so as to reduce the incidence of newly infected mosquitoes, controlling the local transmission.

Prevention can be achieved by using insect repellents regularly; wearing clothes(preferably light colored) that cover as much of the body as possible; using physical barriers such as window screens, closed doors and windows; and if needed additional personal protection, such as sleeping under mosquito nets during the day. It is of prime importance to empty, clean or cover containers regularly that can store water, such as buckets, drums, pots etc. Other mosquito breeding sites should be cleaned and removed including flower pots, used tyres and roof gutters.

Greenlid, a Canadian company has come up with a biodegradable compost bin coated with a layer of insecticide which can be used instead of flower pots and buckets, setting a lethal trap in the common breeding grounds of the mosquito.

Repellent should contain DEET(N, N- diethyl-3 – methylbenzamide), IR3535(3-[N-acetyl-N-butyl]-aminopropionic acid ethyl ester) or icaridin (1-piperidinecarboxylic acid, 2-(2-hydroxyethyl)-1-methylpropylester). Product label instructions should be strictly followed[16].

During outbreaks, health authorities may advise that spraying of the insecticides be carried out. Travellers should take the basic precautions to protect them from mosquito bites.

Complications:

During the outbreaks in French Polynesia and Brazil, regional authorities reported potential neurological and auto immune complications of Zika virus disease[17]. An increase in the incidence of Guillain-Barre Syndrome which coincided with the Zika virus infections in general public and increase in babies born with microcephaly in Brazil are being investigated. Researches on such cases reveal an increasing body of evidence on the link between Zika virus and microcephaly. Other potential causes are also being investigated.

Incidence of Microcephaly:

Microcephaly is a condition where the baby has a head that is smaller when compared with other babies of same sex and age (Fig 4). A head circumference cut off <2 SD or <3rd percentile is more sensitive for identifying neonates with possible microcephaly, while <3SD is more specific indicating severe microcephaly. Babies born with microcephaly are at increased risk of developmental delay and intellectual disability with higher chances for convulsions, and physical impairments affecting hearing and vision.

Precise timing of proliferation/ self-renewal of neural progenitor cells(NPCs) and of their differentiation, neuronal migration and maturation are essential for normal mammalian brain development. Disturbances of these processes leads to developmental brain disorders including microcephaly.ZIKV strain MR766 has been shown to be capable of infecting NPCs derived from human

induced pluripotent stem cells (hiPSCs). Zika virus infection induces apoptotic cell death and deregulation of cell cycle progression of hiPSCs, reducing their viability and growth as neurospheres and brain organoids[18].

Ministry of Brazil has reported 4783 cases of microcephaly and / or CNS malformation, with 404 confirmed cases. Of the confirmed cases 387 compatible with a congenital infection and remaining 17 had confirmation of Zika virus infection. Out of the 76 death due to congenital malformations, since january 2015, zika virus was identified in foetal tissue in 5 cases. In French Polynesia, since 2013, the incidence of child birth with congenital malformations is showing an above average number[19,20].

Incidence of Guillain Barre Syndrome(GBS):

It is a disorder in an autoimmune disorder that affects the peripheral motor nerves with occassional involvement of sensory nerves as well. Countries in Latin America show an increase in the incidence of GBS in the context of Zika virus outbreak. In Brazil, a state of Bahia reported about 42 cases of GBS with 26 of them confirmed of Zika virus infection in a single month of July 2015. There are many other contemporary reports from Latin America showing higher incidence of GBS. In French Polynesia, all 42 cases identified during the outbreak were tested positive for Zika and Dengue infection. Investigations to determine the cause of infection are ongoing in countries with increased incidence of GBS[21].

Zika in India:

India falls in the most dangerous zone for Zika virus infection. All the favourable conditions suitable for the viral spread is prevelant in India. The primary vector *Aedes aegypti* is present in India spreading other Flavivirus like Dengue virus. Indian subcontinent, nurturing the favourable milieu for this virus is under a serious threat for a possible outbreak in near future. India plans to step up Zika virus watch as WHO warns of explosive spread.

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Fig 1: History of ZIKA

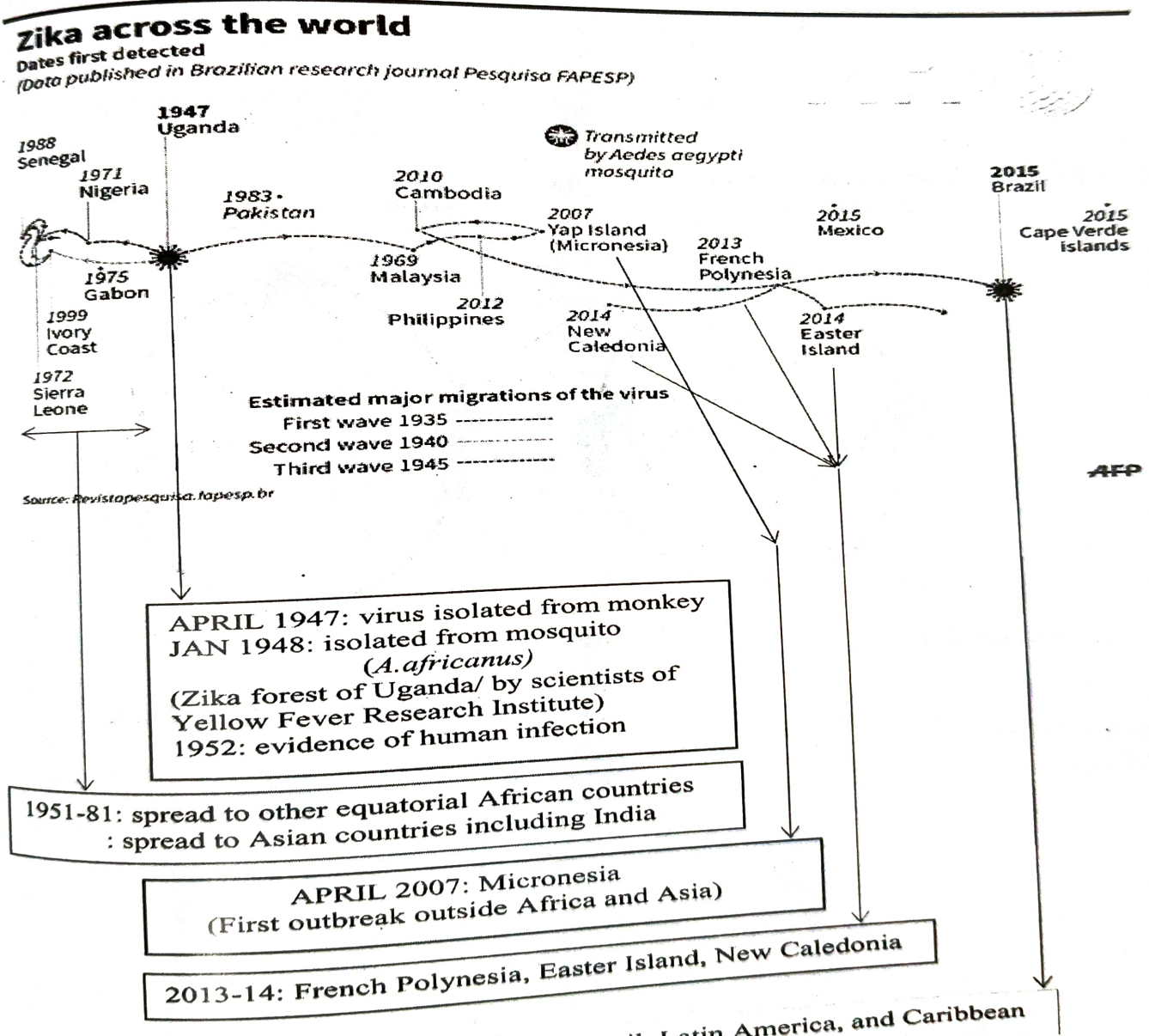


Fig 2: Zika infection: past and present[4].

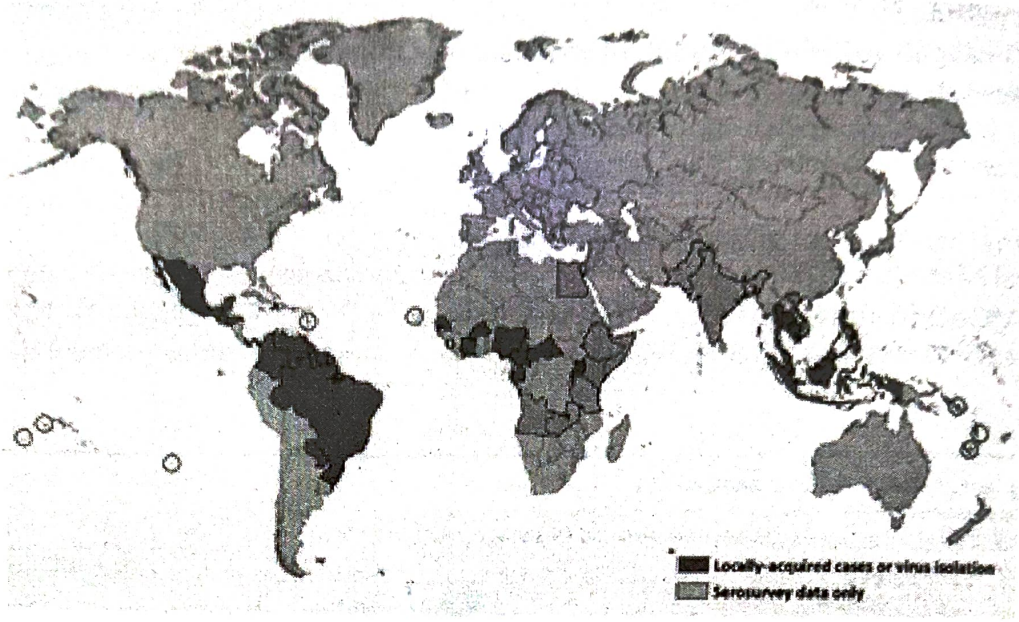


Fig 3: life cycle and spread of the virus

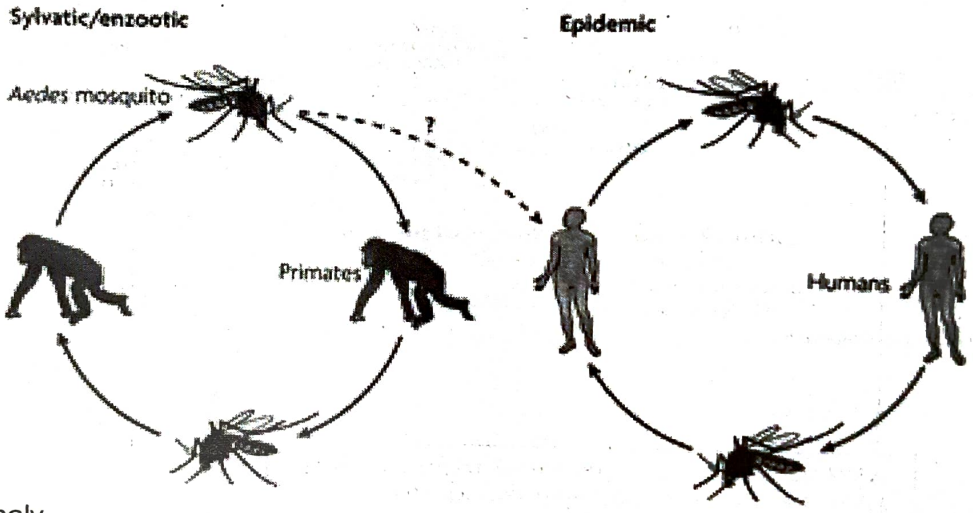
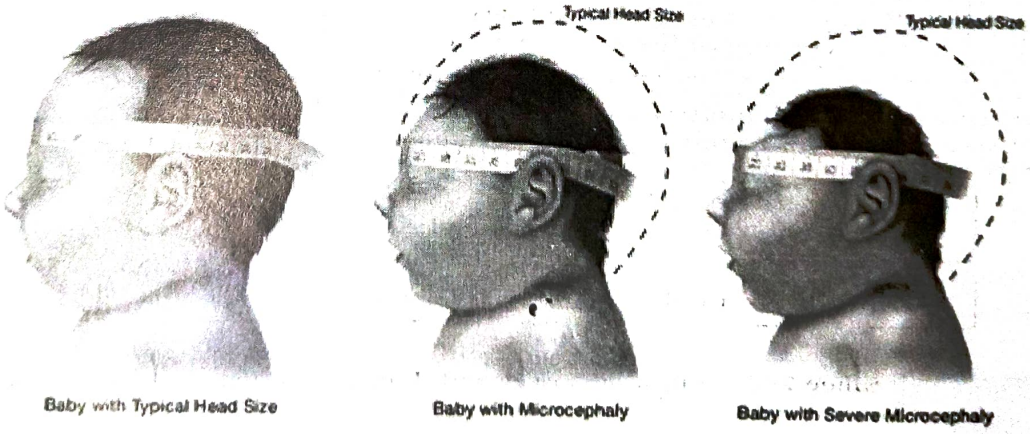


Fig 4: microcephaly



Review article

SGLT2 INHIBITORS AND DIABETES MELLITUS-CURRENT IMPLICATIONS AND FUTURE DIRECTION

Deepak Kumar Dash*, Subash Ranjan Behera*, Arun Kumar Choudhury**, Binoy Kumar Mohanty***, Anoj Kumar Baliarsinha****

INTRODUCTION

Diabetes mellitus is a chronic metabolic disease that lowers life expectancy by up to 15 years, increases cardiac risk by two to four-fold, and leads to various micro and macro vascular complications[1]. Pharmacologic therapy and therapeutic lifestyle changes can effectively manage diabetes mellitus and prevent or delay the progression of diabetic complications. Sodium-glucose co-transporter-2 (SGLT2) inhibitors are a newly developed class of oral anti-diabetic drugs (OADs) with a unique mechanism of action that have demonstrated modest weight loss and low risk of hypoglycemia when given as monotherapy. This mini review describes the pharmacology, pharmacokinetics, various pleiotropic effects of SGLT2 inhibitors and current place in therapy for management of diabetes mellitus.

History

The history of SGLT2i dates back to 1835 when the first SGLTi *phlorizin* was discovered, which was derived from apple tree bark. Because of its non-selective nature, it caused severe gastrointestinal symptoms. Due to this and to its poor oral bioavailability, work on its development could not continue [2].However with discovery and approval of new SGLT2i molecules, this class of drugs has come to lime light and are billed as the next big thing in antidiabetic drug basket..

Mechanism of action

SGLT2 inhibitors work by inhibiting SGLT2 in the PCT, to prevent reabsorption of glucose and facilitate its excretion in urine. As glucose is excreted, its plasma levels fall leading to an improvement in all glycemic parameters [3]. This mechanism of action is dependent on blood glucose levels and is independent of the actions of insulin. Thus, there is minimal potential for hypoglycemia, and no risk of overstimulation or fatigue of the beta cells [4]. An additional advantage of SGLT2 inhibitors is that these agents are effective at all stages of type 2 diabetes mellitus [3].However as SGLT2 is also expressed in pancreatic α-cells, SGLT2i cause a robust increase in plasma glucagon in T2DM patients [5].

Pharmacokinetics

The oral bioavailability of the SGLT2i range from 60-78% and achieves maximum concentration 1-2 hours after administration. The elimination half-life ranges from 10.2-13.1 hours and have a once-daily dosing. Drug metabolism is primarily through glucuronidation by the liver and excretion of the drug is mainly by means of the urinary and fecal route. Since the SGLT2 inhibitors reduce the reabsorption

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of glucose in the kidney and reduce filtration rates, patients with renal impairment will require additional monitoring and/or dose adjustment.

Dosage

The three SGLT2i currently approved by FDA are Canagliflozin (2013), Dapagliflozin (2014) and Empagliflozin (2014).The dosage schedule have been summarized in Table1

Benefits additional to glycemic control

Weight Loss

SGLT-2 inhibitors cause a reduction in body weight, ranging from about 1 to 5 kg [6]. A greater fall is seen in patients with long-standing diabetes and in those with a higher baseline weight. Glucosuria, produced by SGLT2 inhibitors, causes caloric loss and a decrease in body weight. Approximately two-thirds of the weight loss is fat, with subcutaneous and mesenteric fat loss contributing equally to the reduction in total body fat [7].Volume depletion due to natriuresis/dieresis may contribute to weight loss. Concomitant use of SGLT2i can attenuate or neutralize weight gain due to insulin, if given in combination with insulin [6].

BP Reduction

SGLT-2 inhibitors cause a decrease in systolic/diastolic blood pressure (4–5/1–2 mmHg) which is not dose dependent [8]. Natriuretic effect combined with the more long-term reduction in body weight, contributes, in part, to decreases in blood pressure. Blood pressure reduction is not accompanied by an increase in heart rate and is independent of background antihypertensive therapy suggesting that SGLT2 inhibition might reduce sympathetic tone.

Lipid profile

SGLT2 inhibitors cause a small increase in plasma LDL and HDL cholesterol and a decrease in plasma triglycerides [9]; LDL/HDL cholesterol ratio remains unchanged. The mechanism by which SGLT2 inhibitors cause these changes in lipid profile remains unknown. Weight loss can explain, in part, the decrease in triglycerides and increase in HDL cholesterol.

Uric Acid

SGLT2 inhibitors promote uric acid excretion and reduce the plasma uric acid concentration by 0.7% mg/dl. The reduction in plasma uric acid concentration may play a role for reduction of blood pressure and vascular damage in long term. This may contribute to the slowing of diabetic nephropathy observed in the EMPA-REG OUTCOME study [10].

Reduction in CV mortality

The recently published EMPA-REG OUTCOME study (Empagliflozin Cardiovascular

Outcome Event Trial in Type 2 Diabetes Mellitus Patients) demonstrated that in T2DM patients with high CVD risk Empagliflozin reduced the primary major adverse cardiac event end point (CV death, nonfatal myocardial infarction and nonfatal stroke) by 14%. This beneficial effect was driven by a 38% reduction in CV mortality with no significant decrease in nonfatal myocardial infarction or stroke. Hemodynamic effects, specifically reduced blood pressure and decreased extracellular volume, are responsible for the reduction in CV mortality and heart failure hospitalization[10].Evaluation of CV safety for Canagliflozin in CANVAS(CANagliflozin cardioVascular Assessment Study) and Dapagliflozin

in DECLARE trial (Dapagliflozin Effect on Cardiovascular Events) are pending.

Beneficial effect on heart

SGLT2 inhibitors shift whole-body metabolism from glucose to fat oxidation [11]. Two and four weeks of treatment with dapagliflozin caused a 14% increase in fat oxidation and 20% reduction in glucose oxidation.. Because the amount of oxygen required to generate the same amount of ATP is greater with fat compared with glucose, the shift from glucose to fat oxidation would increase myocardial oxygen demand. Conversion of acetyl CoA, the end product of FA oxidation, to ketones, is favored by the SGLT2 inhibitor–induced stimulation of glucagon secretion [11]. The rise in plasma ketone concentration is small (0.3–0.6 meq/L). The heart avidly extracts and consumes ketone bodies and ketone body oxidation may improve cardiac muscle efficiency [12].

Adverse event profile

Uro-genital tract infections are the most frequently noticed adverse events in subjects on SGLT2i [13], especially in women and in uncircumcised men. Common infections include vulvitis, vulvo-vaginitis in women and balanitis, balanoposthitis in men. Genital infections are thought to be caused by an increased glucose load in the urinary tract, which encourages fungal growth. The incidence of urinary tract infections does not increase with SGLT2i therapy.

Volume depletion and orthostatic hypotension can occur due to osmotic diuresis associated with SGLT2i use. In randomized-controlled trials, however, the incidence of these adverse events has been minimal (3%) [14]. The extra diuresis experienced per day is 350- 450 ml (one extra void per day) and does not cause nocturia. The diuresis seen with SGLT2i may result in slight transient increase in serum creatinine and blood urea, with a corresponding fall in glomerular filtration rate (GFR).

Risk of hypoglycemia is minimal with SGLT2i, as they have a non-insulin-based mechanism of action. However, hypoglycemia may occur when these molecules are used in combination with other anti-diabetic drugs, including metformin.

SGLT2 inhibitors use leads to a *slight reduction in bone formation* and a rise in bone resorption markers, although there are no major changes on bone mineral density. A 102-week study with Dapagliflozin did not identify any changes in markers of bone turnover as compared to placebo when added to metformin [15].Recently published secondary outcome in CANVAS trial showed fracture risk was increased with Canagliflozin treatment, who were older, with a prior history/risk of cardiovascular disease, and with lower baseline eGFR and higher baseline diuretic use. The increase in fractures may be mediated by falls; however, the cause of increased fracture risk with Canagliflozin is unknown [16].

Bladder cancer has been reported in patients treated with SGLT2i in clinical trials [17], but there is insufficient data to determine if these cases were related to the effects of SGLT2 medications.

Emerging New Concern: Case reports of *ketoacidosis(euglycemic)* have been identified in post-marketing surveillance, and the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) have found in their review of these cases that the incidence of ketoacidosis to be infrequent[18]. If ketoacidosis is suspected or if patient is at risk for ketoacidosis, the SGLT2 agent should be discontinued immediately. Caution should be exerted while prescribing SGLT2i

to Type1 DM as an off label agent because most such cases of DKA have been reported in them.

Place in current management protocol

The safety and efficacy of SGLT2 inhibitors have not yet been established in the pediatric (<18 years of age) or type 1 diabetes population. The American Diabetes Association (ADA) guidelines recommend SGLT2 inhibitors as second line therapy after metformin if HbA1c target is not achieved. SGLT2 inhibitors as monotherapy or in combination with another anti-diabetic treatment such as metformin or sulfonylurea have demonstrated efficacy in glycemic control with HgA1c reduction of 0.5-1.0 %.

Future Direction

New SGLT2 inhibitors, such as ipragliflozin, tofogliflozin and luseogliflozin are in the pipeline and may offer additional options to help achieve therapeutic goals [19, 20].

Summary

SGLT2 inhibitors are a new class of medications that have expanded the treatment options for T2DM. This class of medications offers adjunctive glycemic control and has favorable drug characteristics including once-daily frequency, oral route of administration and low risk of hypoglycemia. The additional effects of weight loss, blood pressure reduction and improved lipid parameters (especially HDL) makes them an attractive drug option for diabetes mellitus.

SGLT2i	Excretion	Dosing	Dose Adjustment	HbA1C Reduction
Canagliflozin	Feces-41.5% Urine-33%	100mg PO daily;may increase to 300mg PO daily	eGFR45-60ml/ min/1.73m2- max 100mg/ day ,eGFR<45ml/min/ 1.73m2-avoid use	100mg:0.77% 300mg:1.03%
Dapagliflozin	Feces-21% Urine-75%	5mg PO daily; may increase to 10mg PO daily	eGFR<60ml/min/ 1.73m2-Avoid use	5mg:0.8% 10mg:0.9%
Empagliflozin	Feces-41.2% Urine-54.4%	10mg PO daily; may increase to 25mg PO daily	eGFR<45ml/ min/1.73m2- Avoid use	10mg:0.7% 25mg:0.8%

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Case Report

ACUTE PULMONARY EMBOLISM IN PROTEIN S DEFICIENCY: 2 RARE CASE REPORTSOF YOUNG MALE PRESENTING WITH BREATHLESSNESS

Asit Behera*, Mamata Singh**, Tanmay Das***, Maya Gantayet****

ABSTRACT

We describe 2 case reports of young active otherwise healthy male , presenting with dry irritating cough and shortness of breath of short duration .A persistent tachycardia, tachypnoea, negative Troponin T, test , with dilated right atrium (RA), right ventricle (RV) and elevated pulmonary artery (PA) pressure on echocardiography made us suspect pulmonary artery embolism .Computed tomography pulmonary angiography (CTPA) done urgently confirmed diagnosis of pulmonary artery thrombosis . Prompt treatment with antifibrinolytic and anticoagulant relieved them from symptoms and saved them from a mortal condition.Later on Protein S deficiency was established.

Keywords: *young male, shortness of breath, pulmonary embolism, protein S deficiency*

INTRODUCTION

Pulmonary Embolism (PE) is a frequent cause of death in India and worldwide.[1] Its varied symptoms and signs of presentation makes it difficult to diagnose. It is mostly diagnosed in autopsy or tertiary care hospital.[1] An autopsy study on 1000 medical patients done at a tertiary centerrevealed PE was present in 15.9% of the cases and also reported that 79.8% were below the age of 50 years.[2] People with hereditary Protein S deficiency have 2 to 11 fold increased risk for developing deep vein thrombosis (DVT) or PE.[3] Protein S is a vitamin – K dependent anticoagulant, acts as cofactor for protein C coagulation pathway. Around 1-5% of cases of protein S deficiency are associated venous thrombosis, < 0.5% with arterial thrombosis.[4]Protein S deficiency is now known to be related to genetic defect.

Case 1

A 38-year-old young, active male presented with complaints of persistent irritating dry cough for 4 days and one episode of hemoptysis. He had no fever, chest pain or recent trauma. He was non-smoker,non-diabetic, normotensive. He did not have any family history of Pulmonary Tuberculosis. In his family his elder brother had coronary heart disease and undergone Percutaneous transluminal coronary angioplasty (PTCA)

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On arrival to the emergency department he had a blood pressure (BP) of 110/78 mmHg , heart rate (HR) of 130 per minute and respiratory rate (RR) of 30 breath per minute and oxygen saturation (SpO_2)of 92% in room air.

Laboratory findings complete blood count, coagulation profile,Liver function test, Electrolytes ,urea , creatinine, blood glucose, lipid profile , normal electrolytes were within normal limit. Chest X ray was normal. Troponin T was negative

Initial electrocardiogram (ECG) showed sinus tachycardia at a rate of 130 per minute . His arterial blood gas had PH - 7.5, PCO_2- 24mmHg and PO_2- 102mmHg with 3 litres of oxygen in high flow mask. Patient remained to be symptomatic with persistent tachycardia and tachypnoea.Two dimensional echocardiogram (2D ECHO) revealed no regional wall motion abnormality, good left ventricle (LV) function , mild diastolic dysfunction, dilated RA, RV, Mild pulmonary arterial hypertension (PAH), tricuspid regurgitation (TR) gradient 39mmHg, possibility of PE was thought. D Dimer was positive. Computed tomography pulmonary angiography (CTPA)done suggestive of thrombosis in right and left pulmonary artery(figure 1)with patchy pulmonary infarcts. Venous Doppler of lower limb showed focal thrombosis in left popliteal vein.

He was thrombolysed with alteplase10mg bolus followed by 90mg over 2hrsfollowed by unfractionated heparin infusion for 2 days and low molecular weight heparin (LMWH) enoxaparin 60mg subcutaneously twice daily for 3 dxays. APTT was maintained between 60- 90 sec, he was started on oral anticoagulant with strict monitoring of international normalized ratio (INR). There was improvement in his oxygen saturation and heart rate during and after thrombolysis. His repeat angiography showed partial resolution of thrombus.(figure 2).2D ECHO was normal. Further investigation showed Antithrombin III -102 %,homocysteine -6.53µmol/l , antinuclear antibody –ve, Protein C -132% but his Protein S level was low of 26%.(N= 77- 143%). He was discharged on day five with oral anticoagulant. He was followed up in outpatient department after 15days with PT INR report. He was asymptomatic with HR of 60/sec and RR-20/mins.

Case 2

A 29 year old active male presented with shortness of breath and palpitation for 3 days. No personal history of diabetes mellitus, hypertension or coronary artery disease. He had no fever, cough, hemoptysis or any recent trauma. No history to suggest cardiovascular risk factor.

Physical examination revealed a well-developed and well-nourished man with BP of 90/60 mmHg, HR - 120/min, RR -18/min and SpO_2- 97% in room air. Routine investigation: Hb-16.3gm%, TLC-11,300/cu.mm with (P -70%, L-28%), .PT/INR-1.3, sodium-136meq/litre , potassium - 4.4meq/litre, liver function and renal function test normal. Chest X ray normal. Troponin T was negative. ECG showed sinus tachycardia and ECHO showed dilated RA, RV and moderate TR with severe PAH (75mmHg).Contrast enhanced computed tomography (CECT) thorax showed thrombus in main pulmonary artery(MPA), hepatic vein and inferior vena cava (IVC) extending up to renal vein. (Figure.3), (Figure.4)USG abdomen and pelvis showed thrombus in hepatic veins, IVC extending up to right renal vein. Venous Doppler of lower limb was normal.

He was thrombolysed with Tenectiplase 40mg over 2 minutes followed by unfractionated heparin

for 48hrs then with LMWH enoxaparin 60mg subcutaneously twice daily for 5 days. INR was maintained between 2 to 3.Warfarin was started on day 2.Repeat CECT thorax was done on day 3 showed small thrombus in MPA.(figure 5). ECHO screening revealed decrease in PA pressure (37mmHg). Further investigation showed Antithrombin III -98 %, homocysteine – 9.24µmol/l , antinuclear antibody –ve, Protein C -98%, but he had Protein S deficiency with value of 30%.(N= 77-143%). Patient became stable was discharged on day 5. Followed up in OPD and was asymptomatic.

Discussion

The gold standard for pulmonary embolism diagnosis is Computed tomography pulmonary artery (CTPA), however it is only available in tertiary care center hence it is often diagnosed late. [5] We suggest to do 2D ECHO which is readily available and it is a surrogate maker of pulmonary embolism in the form of dilated RA and RV and raised TR gradient. Once pulmonary embolism is suspected CTPA and thrombophilia screening can be done to confirm the diagnosis and its predisposing factor.

Literature searching for pulmonary embolism in young active person has resulted in causes like medical or surgical conditions, calf pain secondary to DVT, OCP intake, high altitude exposures, Paget-Schroetter syndrome (effort thrombosis)and thrombophillia(Protein C and S deficiency)[1],[2],[6],[7]. Thrombophillia is associated with Venous thromboembolism which comprises of pulmonary embolism and deep vein thrombosis, however thrombophillia per se is not usually associated with pulmonary embolism.It is rare that in our 2 cases they had thrombophillia but without any precipitating factor to cause PE.

Conclusion

All embolisms are of acute onset and can be fatal. Now a days incidence of thromboembolism are on rise and may present in unrelated cases as reported in literature. Earlier this was reported more often in western countries. But the peculiarity in our case is that both the cases are young active male with no prior predisposing factor who later on found to have thrombophillia , leading to thrombo-embolism. Any young person with unexplained tachycardia and tachypnoea should be evaluated intensively, at least with 2D ECHO to rule out pulmonary embolism .Thrombophillia work up should be done in every patient of venous thromboembolism as Protein C and S deficiency are not so rare a disease in our clinical practice

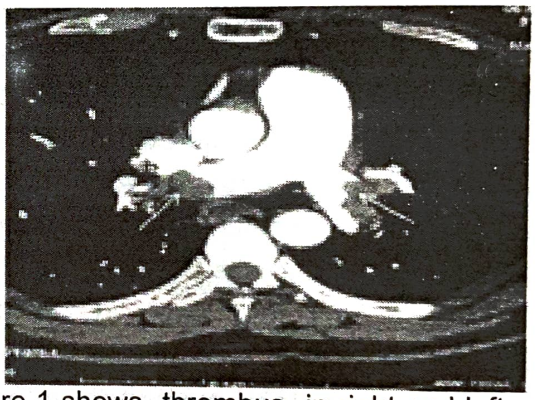

Figure 1 shows thrombus in right and left pulmonary infarct (white arrow)

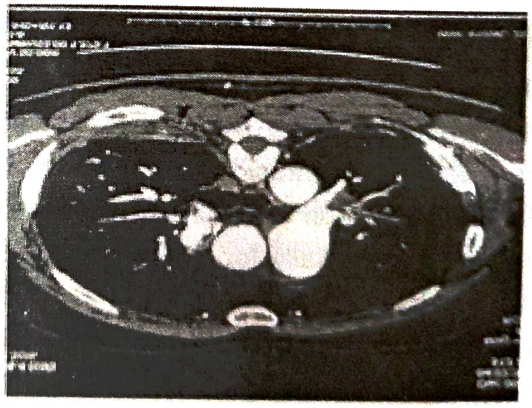

Figure 2 shows resolution in thrombus (white arrow)

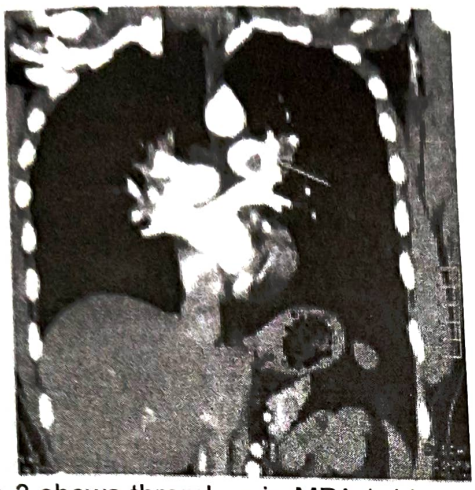

Figure 3 shows thrombus in MPA (white arrow)

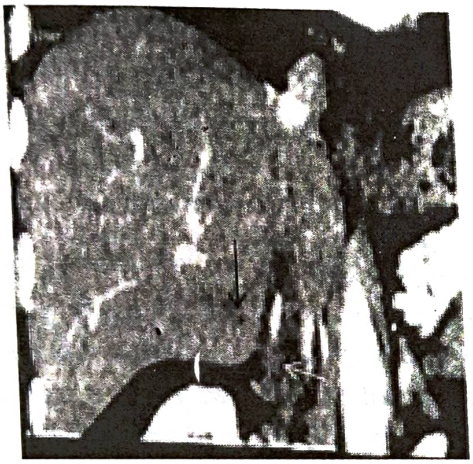

Figure 4 shows thrombus in IVC (white arrow) and hepatic vein (black arrow)

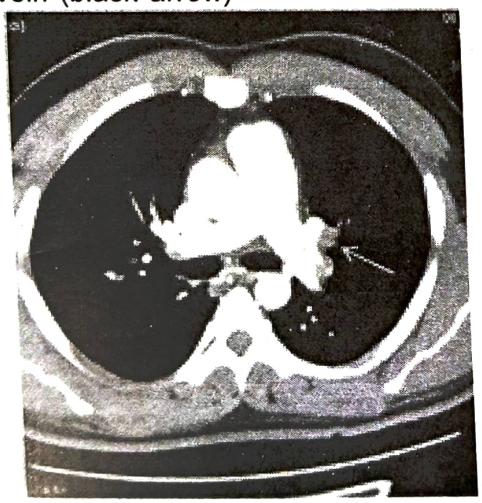

Figure 5 shows organised thrombus in MPA (white arrow)

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Case Report

PHENYTOIN INDUCED PURPLE GLOVE SYNDROME – A RARE CASE REPORT

Shankar Ramchandani*, Laxmikanta Dash**, Pradeep Kumar Mohanty***,
Lagendra Kumar Singh****, Ashok Kumar Behera****

ABSTRACT

Intravenous phenytoin may give rise to purple glove syndrome a rare complication with serious consequences including gangrene. Exact mechanism is unknown, but three stages of PGS identified i.e.,stage of appearance, Stage of progression, stage of resolution. During stage of progression, PGS can be identified as either mild or severe. Mild case may heal spontaneously when appropriate measures are taken such as elevation of effected limb, application of gentle heat and measures to prevent secondary injuries. Severe case may require fasciotomy or amputation.

INTRODUCTION

Purple glove syndrome (PGS) is a delayed soft tissue injury of the hand and forearm following intravenous administration of phenytoin characterised by pain, discoloration and oedema which is frequently seen[1]. Treatment is supportive and most cases resolves within days to weeks and in few cases if it is neglected results in the gangrene formation and requires amputation.

CASE REPORT

A hypertensive male of 64years came to the department of internal medicine, VIMSAR Burla with deep purple discoloration of skin over left wrist and gangrene of digits after 36 hours of phenytoin infusion on left dorsal vein in a peripheral hospital following two episodes of generalised tonic clonic seizure[(2)]. The patient was diagnosed 10 years back as a case of neurocysticercosis in VIMSAR, Burla and was on oral phenytoin which the patient discontinued for seven days and developed withdrawal seizure. Three hours after infusion of phenytoin at peripheral facility the patient developed serious pain around injection site after regaining of consciousness. Six hours later he developed multiple petechiae on left hand and digits of left hand. Black discoloration of skin over digits of left hand developed 18 hours later and the case was referred to VIMSAR, Burla[(3)].

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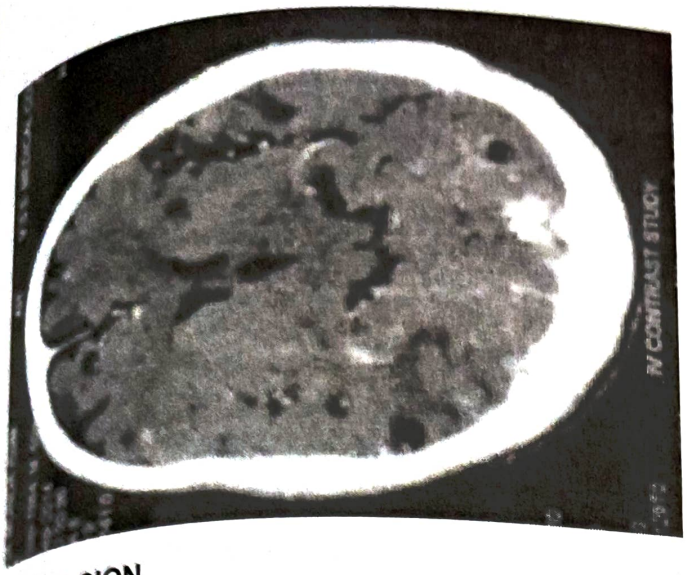

DISCUSSION

Purple glove syndrome (PGS) usually occurs after administration of phenytoin through small dorsal hand veins. In stage of appearance, a pale blue or dark purple discoloration appears around IV site 2-12 hours after the administration of IV phenytoin. In mild cases where there is no extravasation, only pale blue discoloration area with slightly raised border may occur without induration. The discoloration without induration differentiate it from common IV infiltration. Further, PGS spreads to forearm and hand during 1st 24 hours which is unlike IV infiltration. In stage of progression (the next 12-16 hours) presents with oedema and discoloration which continues to spread around pads of fingers, hand and forearm. The degree of discoloration, oedema and tissue damage may be dose related. Typically, in mild cases arterial blood flow is present, skin turns reddish purple, capillary refill is brisk and arm feels warm. This is usually a partial thickness injury. In severe cases arterial circulation may be occluded resulting dusky red coloration of skin without capillary refill and cold extremities leading to full thickness soft tissue injuries. The extensive deep reddish purple discoloration that evenly covers a large area is likely to blister. Smaller deep purple or blackened purple discoloration may be only areas that will blister, but those areas that appear almost blackened may eventually feel hard and insensitive like an eschar, PGS is exquisitely painful in all stages[1]. Finally the stage of healing occurs by receeding of discoloration from outer edges towards the original site of injury. Mild edema resolves with simple elevation of limb. Severe oedema may progress rapidly to occlude radial and ulnar artery, necessitating emergency surgical intervention such as fasciotomy. The patient was at risk of developing PGS because he is elderly, has a history of hypertension and unable to indicate pain at the site and time of injection due to postictal confusion. This could have been prevented if timely management in the form of limb elevation, gentle heat application, removal of IV line and blood pressure measurement of effected limb and fasciotomy[5]. The type, amount and method of administration of flush solution may be factors contributing to PGS. The preferred solution is normal saline packaged in an IV bag and delivered through piggy-backed IV line. In the absence of these the phenytoin can be simply added to required amount of normal saline and infused at a rate not more than 50mg/min[6].

CONCLUSION

PGS is preventable if diagnosed early and treated early. It can be minimised by substituting IV phenytoin by fosphenytoin and many new anticonvulsants.

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Case Report

MATERNALLY-INHERITED DIABETES WITH DEAFNESS – A RARE FORM OF DIABETES

Binoy Kumar Mohanty***, Arun Kumar Choudhury**, Subash Ranjan Behera*, Swayam Sidha Mangaraj*, Debarchan Jena*, Pratap Kumar Mishra*, Deepak Kumar Dash*, Anoj Kumar Baliarsinha****

INTRODUCTION:

Maternally-inherited diabetes with deafness (MIDD) is a rare form of monogenic diabetes that results, in most cases, from an A-to-G transition at position 3243 of mitochondrial DNA (m.3243A>G) in the mitochondrial-encoded tRNA leucine (UUA/G) gene. As the name suggests, this condition is characterized by maternally-inherited diabetes and bilateral sensorineural hearing impairment. A characteristic of mitochondrial cytopathies is the progressive multi systemic involvement with the development of more symptoms during the course of the disease. We report here the case of a patient with MIDD who presented with severe hyperglycemia.

CASE REPORT:

A 28 year old male presented for evaluation of severe hyperglycemia.. He was diagnosed with DM one year back with initial blood glucose of >350 mg/dl with osmotic symptoms. He was on OAD for last one year with poor glycemic control. Due to this poor glycemic control the patient attended the Endocrinology OPD and was admitted for detailed evaluation. The patient's height and weight were 146 cm and 35 kg, respectively, with a body mass index of 16.19 kg/m^2. The patient's mother aged 60years has never been diagnosed with diabetes or hearing impairment. On examination he was found to have short stature, microcephaly and evidence of bilateral ear SNHL (mild to mod) (Figure 1). There was no evidence of myopathy or cardiomyopathy. Ophthalmological evaluation revealed presence of peri papillary pigmentary changes without feature of diabetic retinopathy. The possibility of MIDD was considered Based on the findings of diabetes mellitus, sensori-neural hearing impairment, microcephaly, short stature and maculopathy with pigmentary changes, the patient was suspected to have MIDD. Glucose tolerance test was performed in his mother, father and two sisters, with normal glucose tolerance levels in all except one daughter. Audiometric test reveals abnormal hearing pattern (SNHL) in his mother and one of his sister. One of his sisters was found to have mild SNHL & IGT. Routine biochemical tests showed renal function test, liver function test and electrolytes. Urinary albumin excretion and eGFR (107.66 ml/min/m^2) were normal. Ophthalmological examination revealed ocular fundus without diabetic retinopathy and with pigmented retinopathy. The patient was started on premix insulin therapy and was discharged after achieving euglycemia after one week. Genetic analysis for mitochondrial mutation study could not be done due to non availability of the test at our centre.

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Department of Endocrinology, S.C.B. M.C., Cuttack

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DISCUSSION

Maternally inherited diabetes and deafness (MIDD) is a rare form of diabetes that results, in most cases, from an A-to-G transition at position 3243 of mitochondrial DNA (m.3243A>G) in the mitochondrial-encoded tRNA leucine (UUA/G) gene. Besides this point mutation, there are other less frequent variants also associated with MIDD (1).MIDD is characterized, as the name suggests, by maternally-inherited diabetes and bilateral neurosensory hearing impairment. Although the age of diabetes onset is variable, many patients are young. The mean age at diagnosis of diabetes is 38.8 ± 9.6 years, ranging from 12 to 67 years, and that the presentation is either type 1or type 2 diabetes(2). In type 2-like phenotype the patients can initially be treated with diet or sulphonylurea, but they may develop insulin dependency (3, 4). Impairment of insulin secretory capacity was demonstrated in individuals carrying the m.3243A>G mutation, possibly the primary defect contributing to the development of *diabetes mellitus* (5). Possibly, the early primary defect in individuals carrying the m.3243A>G mutation is the impairment of insulin secretory capacity due to the progressive reduction in oxidative phosphorylation involving the glucose-sensing mechanism of beta-cells (5). The preferential replication of mtDNA molecules carrying the 3243 mutation over wild-type molecules may also be involved in the progressive loss of insulin secretion (3). A characteristic of mitochondrial cytopathies is the progressive multisystemic involvement, with the development of more symptoms during the course of the disease. Besides diabetes mellitus and deafness, the main features of MIDD, other organs may be involved. Metabolically active organs, such as muscle, retina, myocardium, cochlea, kidney, and brain are frequently affected. Myopathy is manifested as painful muscle weakness affecting the lower limbs. Muscular disorders were observed in 43% of MIDD patients (2). Macular retinal dystrophy is the most common ophthalmic abnormality, observed in 86% of patients with MIDD (6). This condition includes pigmented lesions in the retina, and atrophy of the choroid or retinal epithelium, a "salt and pepper" pigmentary retinopathy, generally without consequences on visual acuity (1). Patients with MIDD also have considerable risk for cardiac disorders. Left ventricular hypertrophy, Wolff-Parkinson-White syndrome and other cardiac conduction abnormalities, as well as heart failure have been reported in these patients (1, 7). In addition to diabetes, short stature is the most common endocrine manifestation of MIDD, and a deficiency in the release of growth hormone has been reported (9).CoenzymeQ10 (CoQ10) plays a central role in the mitochondrial respiratory chain. It acts as an electron carrier, supporting adenosine triphosphate (ATP) synthesis in the inner mitochondrial membrane. In addition, CoQ10 has also antioxidant and membrane-stabilizing properties (8). Previous reports showed beneficial effects of CoQ10 on some neuromuscular symptoms, prevention of progressive insulin secretory defect, exercise intolerance, hearing loss, myocardial dysfunction, and intestinal pseudo-obstruction in MIDD patients (10). The m.3243 A>G mutation causes an alteration of the tertiary structure of the tRNA Leu leading to abnormal dimerization of the molecule. Defects in mitochondrial protein synthesis & respiratory activity, increased oxidative stress, impaired calcium homeostasis, reduced mitochondrial membrane potential, and increased apoptosis were observed in patients carrying the m.3243A>G mutation .

CONCLUSION:

Early diagnosis of MIDD is essential from therapeutic point of view. Such patients require insulin therapy early in their disease course. Important co-morbidities include hearing loss, myopathy, arrhythmia and cardiomyopathy & neurological disorder. These could be life threatening in some cases if not recognized and treated early. A strong clinical suspicion is required to identify such cases from commonly occurring T2 DM because of important therapeutic consideration.

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Case Report

TUBERCULOUS MENINGITIS WITH CERVICAL SPINAL TUBERCULOSIS PRESENTING AS QUADRIPARAESIS – A RARE PRESENTATION

Nishant Debta, D Ramchandran*, Subash Behera**, Sarita Behera***, Sarat Ch Singh***, S K Tripathy*****

ABSTRACT

Most of the information about spinal cord and nerve root involvement in tuberculous meningitis is available in the form of isolated case reports or case series. The disease commonly affects the thoracolumbar spine presenting clinically as paraplegia or paraparaesis. Involvment of the cervical spine is a rare occurrence, comprising of 2-3% of all the cases of TB spine and incidence being 0.03% of all the cases .Due to relative rarity of the involvement of cervical spine in tuberculosis, we report this unusual presentation of TB meningitis presenting with quadriparaesis and cervical spine involvement.

Keywords : Cervical spine , Quadriparaesis, Tuberculous meningitis

INTRODUCTION

Central nervous system involvement, one of the most devastating clinical manifestations of tuberculosis is noted in 5 to 10% of extrapulmonary tuberculosis cases, and accounts for approximately 1% of all tuberculosis cases.[1,6] Tuberculous meningitis complicates about 1 in 300 of every untreated cases of tuberculosis globally.[1] Tuberculous meningitis affects the spinal cord and nerve roots. The spinal column is involved in less than 1% of all cases of tuberculosis.[1,7] Spinal involvement manifests in several forms, like tuberculous radiculomyelitis, spinal tuberculoma, myelitis, syringomyelia, tuberculous spinal arachnoiditis, vertebral tuberculosis and very rarely spinal tuberculous abscess.[1,3] Spinal TB is a very dangerous type of skeletal TB as it can be associated with neurologic deficit due to compression of adjacent neural structures and significant spinal deformity.[1,7] The disease commonly affects the thoracolumbar spine and infection of the cervical spine is a rare occurrence.[3]

Tuberculosis of the cervical spine(Pott's disease) is uncommon, incidence being 0.03% of all the cases and comprising of 2-3% of all the cases of TB spine and has the propensity of causing instability and neurological deficits.[3,4] The most common site involved is the vertebral body. Neural arch, transverse process or spinous process is seen to be involved in 10 % of patients.[3]

CASE REPORT

A 16 year-old male was admitted with history of intermittent fever for past 3 months and history of headache, vomiting, irritablity associated with cough with scanty expectoration not associated with hemoptysis. The patient noticed weakness and numbness of all four limbs for the past 1 month. There was no history of trauma in head or neck region, no

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convulsions, altered sensorium . There was no history of past tuberculosis. No family history of tuberculosis could be traced.

On examination, the weight was 40 kg. The patient was conscious and febrile. Pallor was present. Pulse rate was 108 per minute, blood pressure 104/70 mm of Hg. There was no significant lymphadenopathy. Cardio-vascular, respiratory and abdomen examination were normal.

Neurological system examination revealed left lateral rectus palsy(Figure 1) , power in bilateral upper and lower limbs grade 3/5. There was presence of exaggerated deep tendon reflexes bilaterally with presence of ankle and knee clonus and absence of abdominal reflex. Plantar reflex was bilateral extensor. There was diminished sensations upto C4 level. Neck rigidity was present , kernig's sign and brudzinski's sign were positive.

Investigations revealed haemoglobin- 7.8gm/dl, total leucocyte count 8200/mm^3 with neutrophils 62 % and lymphocytes 34 %. ESR – 80 mm/1st hour. Total platelet count -1.8lakh/mm^3.Liver and renal functions tests were within normal limits. Viral markers were negative.

Chest X ray and ultrasound abdomen pelvis were normal. X ray cervical spine did not reveal any abnormality. Opthalmoscopy revealed no papilloedema. As there was delay from patient 's side to do MRI scan , a guarded lumbar puncture was done.

CSF study revealed – total cell count – 450 cells/iL with lymphocytes – 80% , polymorphs – 20%. Sugar – 28 mg/dL , Protein – 220 mg/dL and ADA – 38. The CSF microscopy, culture and sensitivity were negative and no acid-fast bacilli were isolated from the CSF.

MRI Cervical spine showed C1 to C7 variable cord compression by paraspinal granulomatous contents/abscess and associated C3 , C4 chronic discitis and variable enhancement of vertebral bodies – all features suggestive of Cervical Spinal Tuberculosis with sequale. Patient was started on Cat I DOTS regimen and steroids.

DISCUSSION

We present here a case of tubercular meningitis with the rare association of tubercular cervical myelopathy. The patient had presented with fever, headache, vomiting , irritability and found to have left lateral rectus palsy along with positive kernig's and brudzinsky sign . Hence, a provisional diagnosis of tubercular meningitis was made and the quadriparaesis of 1 month duration needed further evaluation. After initial investigation tubercular meningitis was confirmed and patient was put on anti tubercular drugs(ATT). After few days , MRI of cervical spine was done and found to have tubercular cervical spine , while patient was already on anti tubercular drugs. Hence ATT was continued and neurosurgical consultation was done for possible decompressive surgery.

Spinal tuberculosis consists of Pott's spine and Pott's paraplegia, non-osseous spinal tuberculoma and spinal meningitis .[1,7] A spinal form of tuberculous meningitis may result from rupture of Rich's focus into the spinal arachnoid space rather than the basal meninges which presents with progressive spinal cord compression [4] The incidence of paraparesis in patients with Pott's spine varies from 27% to 47% and quadriparaesis is rare presentation.[1] Tuberculosis of the cervical spine (Pott's disease) is uncommon, incidence being 0.03% of all the cases and comprising of 2-3% of all the cases of TB spine. Involvement of lower cervical spine is a rarity

especially below the level of C4 [3,5] . Formation of a cold abscess around the vertebral lesion is another characteristic feature of spinal tuberculosis, the incidence lowest being in the cervical region.[5,7] In adult cervical tuberculosis, disease is more localized and produces less pus. Males are affected more often than females in most series, and the disease generally affects young persons.[1,2]

Cord compression is more common in adults. The propensity of cervical lesions to cause neurologic deficit may explained by the fact that the spinal canal in this region is small relative to the diameter of the cervical cord. [4,5] The mechanism of neurologic symptoms in cervical spine TB include local inflammatory response, tuberculous vasculitis and ischemia, subluxation of the vertebrae, abscess on the spinal cord or nerve root and impingement of the discs.[3] .Spinal cord compression in Pott's spine is mainly caused by pressure from a paraspinal abscess. The level of spinal cord involvement determines the extent of neurological manifestations.[1] In cervical spinal tuberculosis, patients manifest with symptoms of cord or root compression. The earliest signs are pain, weakness, and numbness of the upper and lower extremities, eventually progressing to quadreplegia.[3] In the cervical region, the pus accumulates behind prevertebral fascia to form a retropharyngeal abscess which can produce considerable pressure effects such as dysphagia, respiratory distress, or hoarseness of voice.[4,6]. The atlanto-axial region may also be involved in less than 1% of cases presenting as torticollis.[1] MRI is the most sensitive tool in evaluating abnormalities in spinal tuberculosis, especially gadolinium-enhanced T1-weighted image because it provides better bone enhancement and extent of compression of neural structures by the adjacent bone and soft tissues. [3,5]

The patients of spinal tuberculosis can be treated non-surgically with antitubercular drugs, steroids and immobilization. Decompression of the spinal cord is performed in those cases who don't show progressive recovery after a fair trial of conservative treatment or in those in whom neurological complication develops during conservative treatment.[1,4,7]

CONCLUSION

Tuberculosis of the cervical spine (Pott's disease) is uncommon and rare presentation in tuberculous meningitis . The single most important determinant of outcome, for both survival and sequelae, is the stage of tuberculous meningitis at which treatment has been started. Hence a high degree of clinical suspicion is required as the prognosis is improved by early diagnosis and rapid intervention.

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LEGENDS:

Figure 1 – Left Lateral Rectus palsy

Figure- 2 Coronal and Axial Section of MRI Spine showing C1 to C7 variable cord compression by paraspinal granulomatous contents, , myelomalacia and edema from C3 to C7 and discitis

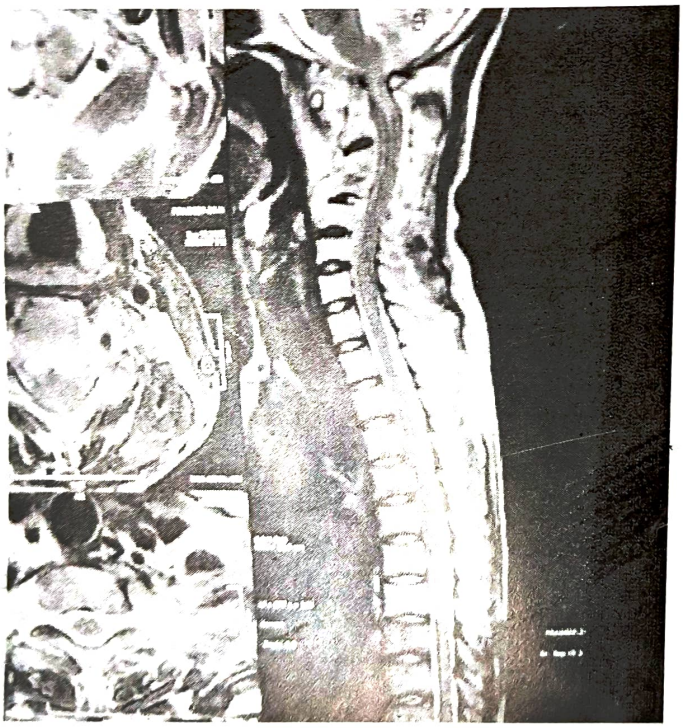
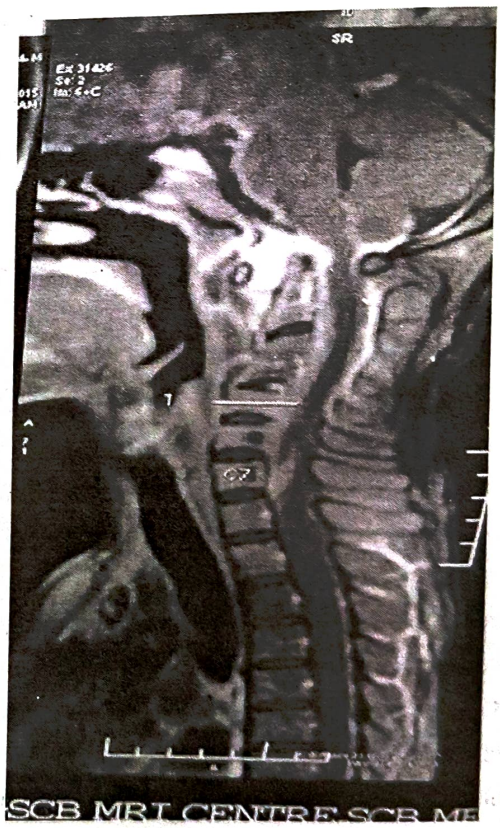


Figure 3 - Sagittal section of MRI Spine showing marrow edema from C3 to C7 an discitis and variable enhancement of vertebral bodies.



INSTRUCTIONS TO AUTHORS

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Preparation of Manuscripts:

Manuscripts must be prepared in accordance with "Uniform requirements for Manuscripts submitted to Biomedical Journals" developed by the International Committee of Medical Journal Editors (October 2008). However, the requirements for OPJ are as follows.

Types of Manuscripts for OPJ.

1. Chairman's address: From this year it has been decided that OPJ will publish the address of Chairman of API, Odisha chapter as such. OPJ also welcomes Ex-Chairman's address for publication.

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These include randomized controlled trials, intervention studies, studies of screening and diagnostic test, outcome studies, cost effectiveness analyses, case-control series, and surveys with high response rate. The text of original articles amounting to up to 3000 words (excluding Abstract, references and Tables) should be divided into sections with the headings Abstract, Key-words, Introduction, Material and Methods, Results, Discussion, References, Tables and Figure legends.

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Statistics: Whenever possible quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Authors should report losses to observation (such as, dropouts from a clinical trial). When data are summarized in the Results section, specify the statistical methods used to analyze them. Avoid non-technical uses of technical terms in statistics, such as 'random' (which implies a randomizing device), 'normal', 'significant', 'correlations', and 'sample'. Define statistical terms, abbreviations, and most symbols. Specify the computer software used. Use upper italics (P= 0.048). For all P values include the exact value (If unable to produce the exact value mention < or > than 0.05 or 0.001). Mean differences in continuous variables, proportions in categorical variables and relative risks including odds ratios and hazard ratios should be accompanied by their confidence intervals.

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When data are summarized in the Results section, give numeric results not only as derivatives (for example, percentages) but also as the absolute numbers from which the derivatives were calculated, and specify the statistical

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It is expected that these articles would be written by individuals who have done substantial work on the subject or are considered experts in the field.

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New, interesting and rare cases can be reported. They should be unique, describing a great diagnostic or therapeutic challenge and providing a learning point for the readers. Cases with clinical significance or implications will be given priority. These communications could be of up to 1000 words (excluding Abstract and references) and should have the following headings: Abstract (unstructured), Key-words, Introduction, Case report, Discussion, Reference, Tables and Legends in that order.

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These should be short and decisive observations. They should preferably be related to articles previously published in the Journal or views expressed in the journal. Preliminary observations that need a later paper for validation can be given as letter to the Editor. The letter could have up to 500 words and 3 references. It could be generally authored by not more than four authors.

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Editorial, Guest Editorial, Pictorial CME, Documentation, Commentary and Opinion are solicited by the editorial board.

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Use the style of the examples below, which are based on the formats used by the NLM *in Index Medicus*. The titles of journals *should be abbreviated* according to the style used in Index Medicus. Use complete name of the journal for non-indexed journals. Avoid using abstracts as references. Information from manuscripts submitted but

not accepted should be cited in the text as "unpublished observations" with written permission from the source. Avoid citing a "personal communication" unless it provides essential information not available from a public source, in which case the name of the person and date of communication should be cited in parentheses in the text.

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Example (From above): Mohapatra MK, Acharya S, Ranjit M. TLR-2 I/D polymorphism protects from multiple complications in falcipaum malaria. The journal of Infectious diseases, Photon. 2013;112:215-221.

The details of writing the citation in the references are given below.

1.Articles in Journals:

Example: 1. Mohapatra MK, Das SP. The Malaria Severity Score: a method for severity assessment and risk prediction of hospital mortality for falciparum malaria in adults. *J Asso Phys Ind* 2009;57:119-25.

When there are more than 4 authors et al should be written after mentioning the name of 4th. author. The name of the journal should be written in italics and in short form without a stop in between.

2. *Reference from a book.* While referring a text book the details of the book has to be mentioned along with the article.

Example-1: Mohapatra MK. Current status of drug resistance malaria in India. *Med Update* Ed. Agarwal AK 2009; Part-I: 9-25.

Example-2: Jameson JL, Kopp P. Principles of Human Genetics, In Harrison's Principle of Internal Medicine, McGraw Hill, 17th edn., Eds, Fauci AS, Braunwald E, Kasper DL, Hauser SL, et al. 2008; Vol-1:385-406.

3.Electronic Sources as reference

Journal article on the Internet:

Patel DK, Mohapatra MK, Thomas AG, Patel S, Purohit P. Procalcitonin as a biomarker of bacterial infection in sickle cell vaso-occlusive crisis. *Mediterr J Hematol Infect Dis.* 2014, 6: e2014018, DPI:10.4084/MJHID.2014.018. http://www.mjhid.org/article/view/12525.

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- Tables should be self-explanatory and should not duplicate textual material.
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Title : Ectopic Cushing's Syndrome due to Thymic Carcinoid- A Case Report

Authors: Dr. Pratap Kumar Mishra, Dr.Debarchan Jena, Dr. Swayamsidha Mangaraj, Dr.Ritesh Kumar Agrawala, Dr.Arun Kumar Choudhury, Dr.Binoy Kumar Mohanty, Dr.Anoj Kumar Baliarsinha