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Letter
from the Editor’s Desk

“Breastfeeding is not only the cornerstone of a child’s healthy development; it is also the foundation of a country’s development.”

- Looking at this statement, it may seem a bit odd at the outset, to be linking a Nation’s development to a child’s nutrition mode but the thing is one needs to see the big picture and analyse the domino effects that result. Look at how far the ripples spread out from their point of origin and analyze what all is affected along its course. Breast feeding is a boon. Courtesy: God/Evolution. Whichever view you subscribe to, you would certainly agree it is a boon indeed. It ensures the offspring while in a vulnerable state is supplied all that is needed for it in the right proportions, in the right forms, in the right frequencies and hopefully with the right affection too. It ensures proper growth and development. Reduces morbidity and mortality and is extremely cost effective. Benefit extends not just to the offspring, but to the mother as well and it doesn’t end there. The better child, who can contribute more to the society, and the lesser cost of health care necessary for a hale and healthy child make not just the family better but the community too and by extension form a solid foundation on which the Nation can pitch for its development.

It is a small step, a Baby step if you will! But a necessary one. Ensure you do what you can to make sure it is a strong one!

Dr. P. Seenivasan,
Chief Editor SMJ,
HOD Dept of Community Medicine,
Govt. Stanley Medical College
The Objective is to find 5 Sets of 5 Interconnected words in this grid.

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<th>Klinefelter’s Syndrome</th>
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The Answer is on Page 134
LET’S NOT BEHEAD MEDICAL EDUCATION: A SINCERE MEDICAL TEACHER’S AGONY

Dr. V. Krishnan  
Department of Pharmacology  
Saveetha Medical College  
Chennai, India

INTRODUCTION:

From the time I joined my post graduation, what I have been observing from some colleagues of my specialty and other department is discouraging. This is common to comment students have changed. They are not listening class and merely seeks attendance. And, it is needless to hear the comment so from many of us is ‘we were learning each and every second from our professors lecture, these students are not passionate’. I want to question myself and those few medical teachers, how often we do sincere efforts in planning and delivering a lecture that will make a student to remember those points for considerable length of time. Is that all mistakes lay on students? What are all factors we should do from our side before commenting students? Let’s analyze one by one.

ARE YOU PASSIONATE TO TEACH?

When we look into each aspect of medical teaching, the most important is our attitude toward teaching. Are they listening our lecture? I was perplexed when I heard this for first time. I want to ask each and every one who says students are not passionate to learn, Are you passionate to teach? A editorial By Dr. Gitanjali about call for high standard in M.D Pharmacology exams spotlight one important point which is applicable here [1]. How many of us chosen our carrier with passion. Some of the candidates join the course just to add a master degree and some youngsters join the course with an option to settle down. This is bitter truth. Even if we have not taken this profession with passion, we must do justice at least for your portfolio if you do not want to do bit more in selfless way. How much ever we discuss nothing would change if attitude of the individual is not changed. We may not excel in our classroom in the initial stage but when you are way sincere and try by all the means to give good lecture, student will definitely respect you.

LET’S PLAN AND PREPARE DIFFERENT TOPICS

Common problem from our side is topic selection that is delivering the same topic over decades. Once the department staff members is settled, topics also decided for each faculty and sad part is hierarchy is followed in topic selection. We may argue ourselves when we teach our topics of interest we do it well, but real problem comes in when you deliver the same content. Most of time topic content is not altered in their visual material, be it a projector slides or PowerPoint presentation.. Possible solution for this may be topics must be rotated within faculty members. When we start preparing a new topic which may be unusual for us to teach we prepare it more consciously and refer
recent editions.

**LET’S COMMUNICATE EFFECTIVELY AND ENLIGHTENED THEM MORE**

Here comes the next important issue, topic preparation. Some of us spend little time for topic preparation. Thanks to the modern technology, no longer teacher depends on their memory, just be dependent on audiovisual aids. This is a very root cause for all the problems including making those few studious students disinterested. When our student feels nothing extra they would gain from our lecture it is not surprising they won’t anticipate your lecture. Here it’s worth to mention those ‘senior’ professors again for giving escaping reason for their under preparation, students should know basics first. There is no doubt students should know the basics well, but it is our duty to enlighten them what more they should know in that topic. One solution we could think of this problem is starts where postgraduate is getting trained.

**LET’S MAKE IT LIGHT & PRESENTABLE**

When we look upon Content presentation, with the help of projectors PowerPoint presentation is almost ubiquitous. Traditional black board method also can be utilised effectively[2]. I do not want to discuss superiority of one teaching aids over other but i want to emphasize teacher should dominate the content delivery rather depending on teaching aids. Proper use of PowerPoint presentation is must. The most disgusting point to discuss here is using of readymade available PowerPoint for classes. Topic may not cover what we highlights and that point might have been done for different target audience. Adequate time must be taken while preparing the slides. Teacher is not a reader most of the time a presenter merely reads each and every point. Adequate training must be given during post graduation time, most of the residents choose placement in medical colleges, but how many training we give usually for teaching? How many seminars or workshops are done for this? Medical education training is now mandatory for all medical teachers is a good move but i wish Medical council of India makes it compulsory during post graduation period.

**LET’S BE AUTHENTIC AND INFORMATIVE**

Taking class is an elegant act. Medical teaching is different from other teaching domain in its delivery. One must highlight the students how to read and what to read. When topic selection, presentation and preparation is done reluctantly class cannot be effective whoever handles it. Nobody is perfect when they start teaching but one must not fail to improvise every time. An efficient system to reduce this flaw is accepting student’s feedback. Three aspects must be covered in lecture; they are how far that topic should be prepared for university examination. Second how that particular topic carries clinical importance. Third, teacher must convey students competitive questions from the topic covered. Constructive feedback which is a component of micro teaching is neglected every time.

**LET’S STANDARDIZE OUR ASSESSMENT**

It is the most peril that is prevailing now; none of them want to assess students adequately on exam. Mode of exam is simplified; everybody is given pass irrespective of efforts taken by them. Most of the examiners never make an attempt to differentiate student efforts. How long we are going to do this? , Attitude towards exam must be changed, We need not add stress to our students but there are many definite ways to conduct exam so as to give eligibility to our students to go to next level.
THIS IS NOT A CRITICISM, SHARING OF A MEDICAL TEACHER’S AGONY

To conclude, I wanted to write this not to criticize but to analyse ourselves. It is not only one classroom, only your lecture. It decides medical standards indirectly. When we teach less, obviously we expect less. When you let your postgraduate to see this, he/she will do the same mostly till they teach. Each classroom; each lecture decides our standards worldwide. We must remember Classroom decides medical student professionalism and attitude and clinical decide their skills [3].

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Review Article
Why do we do basic research?
To learn about ourselves.

Research is to see what everybody else has seen, and to think what nobody else has thought.
INFORMATION:

Developmental variations of nerves, blood vessels, lymphatics, bones, joints, organs and almost all tissues in the body occur. Interesting variations and anomalies in the origin, site of origin, level of origin of both renal arteries and the length of renal arteries have long received the attention of the Anatomists and Surgeons. Kidneys are the paired organs with a paired arteries. A single renal artery is present in 70% of the individuals. The main renal artery vary in site of origin, level of origin of both renal arteries and in its length. The anatomical knowledge of variations may be important for the academic, surgical as well as radiological procedures and the present study is meant to high light the same.

MATERIALS AND METHODS:

25 unclaimed adult cadavers [male-13 and female-12] in the age group of 20 to 50 years have been used for a period of 3 years for the purpose of dissection of first year M.B.B.S., students in the Department of Anatomy, Madras Medical College, Chennai-3. After obtaining the cadavers, embalming was done. Cadavers were numbered and their gender and age were noted. Dissection was carried out as per Cunninghams manual to enter the posterior abdominal wall; the arterial supply to kidneys were explored along the length of abdominal aorta below the origin of superior mesentric artery.

RESULTS:

In the present study during routine dissection of 25 adult cadavers [13 male and 12 female] the following parameters were observed.
1. Origin
2. Site of origin
3. Level of origin of both main renal arteries
4. Length of both main renal arteries. From the point of origin to the point of branching was taken as length and measured.

1. Origin: Renal arteries on either side originated from abdominal aorta.
2. Site of origin: The renal artery was found to arise from the lateral surface of abdominal aorta in 24 adult
cadavers. In one cadaver left renal artery was found to arise from anterolateral surface of aorta where as in the same cadaver the right renal artery was from lateral surface [pic 1].

3. **Level of origin**: The right renal artery was found to arise at a higher level to left in 11 cadavers [44%] at a lower level to left in 13 cadavers [52%] and at the same level in 1 adult cadaver [4%]. [pic2], [pic3], [pic4].

4. **The mean length** of renal artery was 31.6 mm on the left and 41.6 mm on the right side.

**DISCUSSION:**

In this study of variations in main renal artery the following observations were made. Renal arteries are usually single, one renal artery supplying each kidney. In this study in 72% a single renal artery was found supplying the kidney which is concurrent with Dr. Henry Gray [1858].

1. Origin of renal artery is from abdominal aorta in all 25 cadavers which confirms the statement of Henry Gray [1858], J.C. Boileau Grant [1937], W. Henry HollinShead [1958].

2. Site of origin - In 49 specimens both right and left renal arteries arose from lateral surface of abdominal aorta except in 1 specimen on the left side it arose from anterolateral surface which is much lower than the result of Cicekciwasi A.E.et al [2005] and Salderriaga B; Pinto S.A and Ballesteros L.E [2008]. [chart1D].
3. Level of origin – Thomas Dwight [1907]6, J.D. Boyd et al [1956]7, Russel T. Woodburne [1957]8, Necdet Kocabiyik et al [2005]9 said that the right renal artery was at a lower level than the left. The right renal artery was observed to arise at a lower level than the left from abdominal aorta in 13 cadavers [52%]. John E. Skandalakis [2004]10 said that both renal arteries arise at the same level in 3 cases [10%]. Cicekcibasi A.E et al [2005]4 said that both renal arteries arise at the same level in 34.6%. In this study only one cadaver [4%] had both renal arteries arising at the same level from abdominal aorta which is much lesser than John E. Skandalakis [2004]10 and Cicekcibasi A.E et al [2005]4 (chart 2D).

4. Length of the renal artery – Jansheck et al [2004]11 reported greater length of right renal arteries [44 to 111mm]. Dhar P. Lal K [2005]12 said that the mean length of right and left renal was 31.05 +/- 12 mm and 25 +/- 9.5mm. Adam D. Tallenfeld [2007]13 said that the length of right and left renal artery is 48.7 +/- 16.2 and 38.5 +/- 12.6mm. In this study of 25 cadavers the mean length was 41.6mm on the right and 31.6mm on the left side which is less than Adam D. Tallenfeld 13 and Jansheck et al [2004]11 but more than Dhar P and Lal K [2005]12 (chart 4D).
CONCLUSION:

The comprehensive study of origin, site of origin, level of origin and length is to increase the awareness of the presence of such anatomical arrangements and allow a proper evaluation of the renal vascular anatomy. The knowledge of renal vascular anatomy and its variations are very much essential in case of renal transplantation, renal surgeries and radiologist performing various endourologic procedures and innumerable interventional techniques.

Financial support - nil
Conflict of interest - none.

REFERENCES:

ASSOCIATION OF APOLIPOPROTEIN B WITH CORONARY ARTERY DISEASE IN MEN

R. Mahalakshmi (1), R. Shanthi (2), M. Vijayalakshmi (3)

Abstract

Aim: To evaluate the association of non-conventional risk factors for atherosclerosis, serum ApoB levels in patients with and without CAD in comparison to conventional lipid parameters.

Methods: A case-control study on 100 subjects male subjects in the mean age of 51 yrs, with and without Coronary Artery Disease (CAD), confirmed by coronary angiogram was conducted and the levels of serum ApoB, Total cholesterol, serum triglycerides (TGL), serum Low density lipoprotein (LDL) and Serum High Density Lipoprotein (HDL) were estimated. Pearson’s correlation was done to find the association of ApoB and conventional lipid parameters with development of CAD.

Results: Patients with CAD had significantly high serum total cholesterol (193 ± 46), LDL-C (126 ± 43), HDL (36 ± 7) and Apo B (108 ± 24) levels compared to control subjects. However, serum TGL (155 ± 71) level did not show a significant difference between two groups. Pearson’s correlation coefficient shows that Apo B levels show moderate association with Total cholesterol & LDL levels in the CAD group. The data was recorded and analysed on SPSS system. The results of cases and controls were compared by student t-test. Apo B was correlated with lipid parameters by Pearson's correlation. A value of P<0.05 was considered significant.

Conclusion: Apo B is a better predictor of cardiovascular risk compared to conventional lipid profile.

Key Words: Apo B; LDL particle size; LDL; coronary artery disease

INTRODUCTION:

Cardiovascular Disease is a major cause of morbidity and mortality in developed as well as developing countries like India. Estimates from the Global Burden of Disease study shows that India is facing a huge burden of disease due to CAD. (1)

Many studies have proven the links between CAD and conventional lipid parameters like, Total Cholesterol, LDL cholesterol & HDL cholesterol. However, studies show that in patients with CAD, the levels of HDL & LDL cholesterol levels are within the traditionally acceptable range, thereby questioning the predictiveness of conventional lipid parameters. (6) This is probably due to the fact that the cholesterol content of these particles are variable. (2-5) Also the determination of the serum levels of lipoprotein were done solely on the basis of their cholesterol content.

After the recognition and characterization of the major lipoprotein classes, awareness of the apolipoproteins increased. Each LDL particle has one apolipoprotein-B 100 molecule. Measurement of apolipoprotein-B 100 gives an exact estimate of the LDL particle numbers. Because the cholesterol content of LDL is variable, LDL-cholesterol is not equivalent to the LDL particle. (7) Subsequently, as immunoassays for the measurements of apolipoproteins became available, evidence has accumulated that the assessment of apoproteins are a better measure for assessing the risk of Cardiovascular disease. Determination of fasting plasma Apo B, an indicator of LDL particles, provides additional information in assessing the risk of developing CHD. Several studies done in Western population link the risk of coronary atherosclerotic cardiovascular disease with plasma lipid, lipoprotein, and apolipoprotein concentrations, but the relationships between the apo B levels and coronary artery disease (CAD) have not been studied extensively in the South Indian population.

AIMS & OBJECTIVES:

1. To estimate serum total cholesterol, TGL, HDL, LDL & Apo B levels in angiographically determined CAD
patients with normal healthy volunteers.
2. To correlate Serum levels of Apo B with conventional lipid parameters in the study population.

MATERIALS AND METHODS:

This case control study was conducted in the Department of Biochemistry, Tertiary care teaching hospital in TamilNadu, India. The study protocol was approved by the Ethics committee of the hospital, and all subjects gave their informed consent before participation in the study.

The study was carried out on 100 male subjects involving 2 groups of individuals:
1. Coronary heart disease group
2. Control group

CORONARY HEART DISEASE GROUP:
It comprised of 50 male patients with an ECG documented episode of Myocardial infarction. All of them had 70% or more narrowing of atleast one of the major coronary arteries as shown by coronary angiography done at the Department of Cardiology, Stanley Medical College, Chennai. The mean age of the cases was 51.3 years.

CONTROL GROUP:
It consisted of 50 apparently healthy volunteers. All of them were free from symptoms and signs of CAD. The mean age of the control group was 51.8 yrs.

EXCLUSION CRITERIA:
Those individuals suffering from diabetes mellitus, impaired renal function, clinical features of familial hyperlipidemia were excluded from the study.

METHODOLOGY:
Under aseptic precautions 5 mL of fasting venous blood was drawn from all the participants. Samples were allowed to clot, then centrifuged for ten minutes and serum was separated. The serum sample was used for estimating following biochemical tests. The serum cholesterol was estimated by cholesterol oxidase and peroxidase method, serum triglycerides by glycerol phosphate oxidase and peroxidase method, serum HDL-C by direct immunoturbidimetry method, serum LDL-C calculated by Friedewald’s formula and serum VLDL-C is TG/5 in fully automated analyser (Beckman Coulter AU 480). ApolipoproteinB was determined in fresh serum by Immunoturbidimetry assay.

STATISTICAL ANALYSIS:
The statistical software SPSS was used for statistical analysis. Mean and standard deviation were estimated from the sample for each study group. The mean values were compared by Students’ independent t-test to calculate the p-value. Pearson’ co-efficient was estimated to assess the linear relationship among different variables within each study group. In the present study, p<0.05 was considered as the level of significance.

RESULTS:
The study group consisted of 100 male subjects with mean age of 51. The mean of age, BMI, waist circumference of the 100 subjects are listed in Tab-1. Mean BMI for cases with CHD (25.0+4.0) is significantly higher than the BMI for controls(23.1+2.6)(p=0.02). The Waist circumference was significantly higher in cases(89.3+3.6) than controls(87.7+2.9).

Tab-2 shows the age, Serum lipid levels, Apo B levels of CHD patients and controls respectively. Mean HDL for cases (36+7 mg/dL) is significantly lower than the mean HDL for controls(40+8 mg/dL ) (p=0.02). Mean LDL for
cases(126+43 mg/dL) is significantly higher than the mean LDL for controls(98+30 mg/dL)(p=0.001).

Mean ApoB level for cases (108+24 mg/dL) is significantly higher than the mean Apo B for controls(88+19  mg/dL) (p<0.0001). However, no other lipid parameters are significant among the cases and controls. Thus, increased Body mass index, decreased HDL, elevated Apo B are significant contributing factors to CHD(p<0.05).

Table 3 shows the Pearson’s correlation which was carried out to find the association of ApoB levels with other conventional lipid parameters. Apo B shows moderate degree of association with total cholesterol & LDL and a weak association with HDL.

**DISCUSSION:**

Coronary heart disease has been defined by WHO as a modern epidemic. It has been found that the risk profile is not uniform in all patient groups. Asian Indians settled in USA, Europe and Singapore have been found to have the highest incidence of CAD when compared to the local ethnic group.

LDL concentration is considered as an independent risk factor for the development of atherosclerosis and several practice guidelines recognize LDL-C as the primary target of therapy(8,9) .Despite the extensive data relating LDL-C to atherosclerosis, studies suggest that focusing only on LDL-C may not be an optimal strategy.(10) Possible explanation are

(1) evidence is increasing that triglyceride-rich lipoproteins, including very low-density lipoproteins (VLDL) and intermediate-density lipoproteins (IDL) are also atherogenic(11,12)

(2) Even in patients with normal LDL levels, a substantial percentage of them develop atherosclerotic vascular disease. (13) Furthermore, many patients who receive treatment and achieve recommended LDL-C goals even lower than 70 mg/dL still develop the complications of atherosclerotic vascular disease, which is referred to as residual risk.(14)

The possible explanation for this mismatch is that LDL particles are extremely heterogeneous with regard to the amount of cholesterol contained in the core of LDL particle (15) Patients with majority of cholesterol-depleted LDL particles (also called small dense LDL-C) may have a low serum concentration of LDL “cholesterol” but still have a large number of circulating atherogenic LDL particles(16). Patients with the same LDL-C concentration on a basic lipid profile might have markedly different number of LDL particles and different cardiovascular risk(17.) Hence it is difficult to extrapolate the number of atherogenic LDL particles from the serum LDL-C levels.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases(n=50) Mean+S.D</th>
<th>Controls(n=50) Mean+S.D</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>51.3 + 7.4</td>
<td>51.8 + 7.1</td>
<td>0.76 (NS)</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>155 + 71</td>
<td>144 + 57</td>
<td>0.48 (NS)</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dL)</td>
<td>193 + 46</td>
<td>167 + 32</td>
<td>0.005 (Sig)</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>36 + 7</td>
<td>40 + 8</td>
<td>0.02 (Sig)</td>
</tr>
<tr>
<td>VLDL (mg/dL)</td>
<td>31 + 14</td>
<td>29 + 11</td>
<td>0.63 (NS)</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>126 + 43</td>
<td>98 + 30</td>
<td>0.001 (Sig)</td>
</tr>
<tr>
<td>Apolipoprotein B (mg/dL)</td>
<td>108 + 24</td>
<td>88 + 19</td>
<td>&lt;0.0001 (Sig)</td>
</tr>
</tbody>
</table>

**TABLE II: COMPARISON OF CONVENTIONAL LIPID PARAMETERS & APO B LEVELS BETWEEN CASES AND CONTROLS**
Several studies propose measurement of apo B in conjunction with standard lipid testing to measure residual risk (18). Apo B is a major structural component of all the atherogenic lipoprotein particles, including LDL, VLDL, and IDL. Each of these lipoprotein particle carries only one apo B molecule; thus, the serum levels of apo B represents the total number of circulating atherogenic lipoprotein particles and provides a more precise evidence of a patient’s risk for cardiovascular events (19). Other potential advantages to the measurement of apo B includes that it does not require a fasting specimen, its low cost, and the World Health Organization–approved standard.

Though conventional risk factors have been found to be strongly associated with CAD, results of recent studies show that Apo B is a better marker of vascular disease. Since there is no data available on the plasma level of Apo B in native South Indian population, the present study investigates the relation of serum Apo B concentration in normal controls and compares it with that of established CAD patients in addition to conventional lipid parameters.

In this study, subjects were not stratified according to age since the difference in mean age of these groups was not statistically significant. The significant difference in BMI found in CAD patients is consistent with previous reports. This suggests that lifestyle modification in this ethnic group can reduce this independent risk factor for CAD in native population of South Indian Tamils.

In the present study, only an insignificant difference in triglyceride level was found in disease group when compared to normal subjects. This can be attributed to the fact that not all triglyceride rich lipoproteins are atherogenic and that VLDL and HDL are metabolically interrelated. Any effect on VLDL levels mediated via Apo B gene would directly affect HDL levels.

Decreased HDL levels is a major risk factor for CAD. In this study also, mean HDL level of CAD group has been found to be significantly lower than that of control group.

The mean total cholesterol and LDL cholesterol levels of CAD group have been found to be significantly higher than those of the control group. This significant increase in LDL levels can be explained in view of the role of LDL cholesterol in pathophysiology of atherogenesis.

The level of serum Apo B obtained in apparently normal healthy control in the present study is lower than established normal range of 80-120 mg/dL. For control group with normal coronaries, more than 70% had a serum Apo B level of less than 100 mg/dL. These results are consistent with the level quoted in ethnic groups such as Chinese (20). Similar levels have also been reported in the study on North Indian population (21). However the results are not strictly comparable in the sense, our study is on male subjects only whereas the study on North Indians includes females and other confounding factors like smoking, hypertension and diabetes mellitus have not been excluded.

The present study demonstrates a higher level of Apolipoprotein B in coronary heart disease group (p<0.0001), when compared to normal group. Such an association also has been reported in studies on other ethnic groups viz Caucasians, Chinese and Koreans (22-25). Apo B has been proposed to be a better marker of CHD than conventional lipid parameters like total cholesterol, cholesterol subfractions and triglycerides.

**CONCLUSION:**

The current guidelines for the risk prediction in prevention of CAD emphasizes the use of LDL-C for risk assessment, but recent evidence suggests that apoB may be more strongly associated with CAD than LDL-C levels. This suggests that the measurement of apoB should be added to the routine lipid profile in order to assess the cardiovascular risk.

**REFERENCES:**

2. Achari V, Thakur AK. Association of major modifiable risk factors among patients with CAD - a retrospec-
**Assessment of Insulin resistance using Homeostatic Model for Assessment - Insulin Resistance (HOMA-IR) in Women of Reproductive Age with Polycystic Ovary Syndrome**

R. Shanthi (1), R. Mahalakshmi (2), M. Vijayalakshmi (3)

**Abstract**

**Introduction:** Polycystic ovary syndrome (PCOS) is the most frequent androgen disorder in women with a prevalence of 5% - 10%. Insulin resistance is the principle underlying disorder of PCOS.

**Objectives:** To evaluate insulin resistance in PCOS in reproductive age group by measuring fasting insulin, fasting plasma glucose, Glucose insulin Ratio and HOMA IR (Homeostatic Model Assessment- Insulin Resistance).

**Materials & methods:** This is an age matched comparative study. The study population included PCOS women and healthy females. Blood samples were analysed for fasting insulin, Plasma glucose and lipid profile. HOMA-IR and G/I ratio were calculated.

**Results:** Among the analysed parameters insulin, TGL and total cholesterol have increased from that of the level in controls to highly significant levels ($P = .003$ for insulin, $.001$ for TGL and TC), Among the calculated parameters HOMA-IR, VLDL c and LDL c are increased to highly significant levels ($p = .003$ for HOMA-IR, $.004$ for VLDL C and $.001$ for LDL c), while the G/I is not statistically significant.

**Conclusion:** HOMA-IR is increased to highly significant level in PCOS ($p .003$). Even though plasma glucose level does not show any significant elevation, insulin is increased to highly significant levels which increases the HOMA-IR. Hence it can be a better index for assessing Insulin Resistance.

**Key Words:** PCOS, HOMA-IR, Glucose/Insulin ratio, Insulin resistance

**INTRODUCTION:**

Polycystic ovary syndrome (PCOS) is the most frequent androgen disorder in women of reproductive age with a prevalence of 5% - 10%. The etiology and pathophysiology of PCOS remain unclear, and several risk factors such as genetics, environment, nutrition and lifestyle play a contributory role (1,2). It is characterized clinically by irregular or absent menstrual periods and hyperandrogenic manifestations, such as acne and hirsutism, with or without central obesity. Both hyperandrogenism and central obesity, aggravates insulin resistance, making them prone for Diabetes Mellitus. Currently, it is believed that insulin resistance and hyperinsulinemia cause characteristic clinical symptoms and hormonal abnormalities in polycystic ovary syndrome. It has been proved that hyperinsulinemia aggravated ovarian production of androgens (3,4).

Insulin resistance (IR) associated with hyperinsulinemia is found to affect approximately 50% of PCOS patients, both obese and slim (5). This results from the resistance of peripheral tissues to insulin and from decreased hepatic degradation. Resistance to insulin is most likely caused by tissue insulin receptor defects (6,7). Increased insulin concentrations cause hyperandrogenism. Insulin directly promotes ovarian steroidogenesis, and inhibits liver release of the sex hormone binding globulin (SHBG) and production of insulin-like growth factor binding protein 1 (IGFBP-1). Increased concentrations of IGF-1 additionally promote ovarian release of androgens (8).

The clinical diagnosis of IR is not so well established, and differentiating subjects with IR from those who are not is difficult because quantification of insulin sensitivity is
difficult.. However, IR is associated with an increased risk of type 2 diabetes, hypertension, dyslipidemia, obesity, hypercoagulability, endothelial dysfunction, and cardiovascular disease (CVD). Therefore, measurement of IR can be used as a screening tool.

Detection of glucose intolerance or IR in PCOS is achieved by many methods. The gold standard for assessing insulin sensitivity is by Hyperinsulinaemic euglycaemic clamp technique. However, this technique is very complex, cumbersome procedure and requires experienced personnel, making this technique unsuitable in clinical practice [8,9].

There are also many mathematical models to detect insulin resistance or insulin sensitivity in a clinical setting. This can help select the suitable candidates for insulin-sensitising drugs and for further planning of interventions. In the present study, the indices namely, fasting glucose: fasting insulin ratio (G/I) and homeostatic model assessment (HOMA), were calculated to assess insulin resistance in PCOS patients.

AIM & OBJECTIVES:

To evaluate insulin resistance in PCOS in reproductive age group by the determination of the levels of fasting plasma glucose and fasting plasma insulin, plasma glucose insulin ratio, lipid profile & calculation of homeostasis model assessment – IR from these values.

MATERIALS AND METHODS:

This case-control study was conducted in 58 PCOS women in the reproductive age group who consecutively attended the Endocrinology Unit of the Department of Obstetrics and Gynaecology, between May 2014 and January 2015. The diagnosis of PCOS was defined by the Revised Rotterdam Criteria 2003 [10]. The controls were 30 age-matched healthy females with regular cycles.

Exclusion criteria included the women who had previous surgery of one or both ovaries, used hormonal treatment, and took the medication for dyslipidemia within 3 months and/or received steroid within 6 months before participation in the study. The study protocol was approved by the Institutional Ethics Committee. Informed consent was obtained from all the study participants.

All the women with PCOS who participated in this study received a physical examination including measurement of vital signs and skin lesions, and anthropometric measurements. Age, body weight, height, waist circumference, blood pressure, and skin manifestations were recorded.

After overnight fasting for at least 12 hours, 5ml of venous blood samples was drawn under strict aseptic precautions. The sample was centrifuged, aliquoted for measurement of plasma glucose, lipid profile (Total cholesterol, Serum Triglycerides (TGL), HDL cholesterol), and plasma insulin. Glucose was estimated in plasma by GOD POD method.

<p>| TABLE 1: COMPARISON OF THE MEAN LEVELS OF BLOOD PARAMETERS IN PCOS FEMALES WITH CONTROL |
|----------------------------------------|---------------------------------|------------------|-----------------|----------------|-----------------|-----------------|-----------------|---------------|---------------|</p>
<table>
<thead>
<tr>
<th>BLOOD PARAMETERS</th>
<th>Plasma Glucose mg/dl</th>
<th>Insulin Micro μu/ml</th>
<th>G/I</th>
<th>HOMA IR</th>
<th>T G L mg/dl</th>
<th>TC mg/dl</th>
<th>H D L c mg/dl</th>
<th>VLDL c mg/dl</th>
<th>L D L c mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Mean 82.37</td>
<td>24.87</td>
<td>6.13</td>
<td>5.09</td>
<td>103.70</td>
<td>164.27</td>
<td>46.71</td>
<td>23.11</td>
<td>93.02</td>
<td></td>
</tr>
<tr>
<td>SD 7.09</td>
<td>16.38</td>
<td>5.96</td>
<td>3.43</td>
<td>29.31</td>
<td>26.99</td>
<td>9.44</td>
<td>14.34</td>
<td>26.43</td>
<td></td>
</tr>
<tr>
<td>PCOS Mean 85.74</td>
<td>38.45</td>
<td>3.83</td>
<td>8.22</td>
<td>159.74</td>
<td>195.95</td>
<td>41.95</td>
<td>30.82</td>
<td>117.83</td>
<td></td>
</tr>
<tr>
<td>SD 9.89</td>
<td>21.72</td>
<td>4.10</td>
<td>5.07</td>
<td>51.40</td>
<td>37.06</td>
<td>8.57</td>
<td>10.19</td>
<td>35.91</td>
<td></td>
</tr>
<tr>
<td>p value 0.10</td>
<td>0.003</td>
<td>0.04</td>
<td>0.003</td>
<td>0.001</td>
<td>0.001</td>
<td>0.02</td>
<td>0.004</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>NS</td>
<td>HS</td>
<td>S</td>
<td>HS</td>
<td>HS</td>
<td>S</td>
<td>HS</td>
<td>HS</td>
<td></td>
</tr>
</tbody>
</table>

NS-Not significant, S-Significant, HS-Highly significant.
TGL estimated by GPO-PAP Method, total Cholesterol by CHOD-PAP method, HDL by phosphotungstic acid method, LDL-Cholesterol, VLDL Cholesterol calculated by Friedwald’s Formula. Serum Insulin was estimated by ELISA. Glucose Insulin ratio calculated from the values obtained.

The homeostatic model assessment value for insulin resistance (HOMA IR) is calculated as follows:

\[ \text{HOMA - IR} = \left( \frac{\text{Glucose in mg/dl} \times 0.05551 \times \text{Insulin in } \mu\text{u/ml}}{22.5} \right) \]

### RESULTS:

The mean and standard deviation of biochemical parameters namely fasting plasma glucose, fasting insulin, serum triglycerides, total cholesterol, high density lipoprotein cholesterol and the calculated parameters, very low density lipoprotein cholesterol of all the subjects selected for study, along with the calculated Glucose Insulin ratio and Homeostasis model assessment insulin resistance (HOMA - IR) were analysed.

To determine how far the levels of blood parameters varied in the 2 groups, the mean levels in cases were compared with that of controls in Table 1. The statistical significance for the variation in the levels of the blood parameters between the 2 groups is determined from the p value which is arrived at using the student’s ‘t’ test. On scrutinising Table I, it is found that among the analysed parameters insulin, TGL and total cholesterol have increased from that of the level in controls to highly significant levels (P = .003 for insulin, .001 for TGL and TC). On the other hand HDL c is found to be significantly lowered (p = .02). Among the calculated parameters HOMA - IR, VLDL c and LDL c are increased to highly significant levels (p = .003 for HOMA - IR, .004 for VLDL C and .001 for LDL c), while the G/I is not statistically significant.

Table II shows the correlation of plasma insulin to fasting plasma glucose (FPG) and the lipid parameters by using Karl Pearson’s correlation coefficient.

<table>
<thead>
<tr>
<th>FI</th>
<th>r Value</th>
<th>Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>PL glucose</td>
<td>0.12</td>
<td>Poor</td>
</tr>
<tr>
<td>TGL</td>
<td>0.097</td>
<td>Poor</td>
</tr>
<tr>
<td>TC</td>
<td>0.038</td>
<td>Poor</td>
</tr>
<tr>
<td>HDLc</td>
<td>0.082</td>
<td>Poor</td>
</tr>
<tr>
<td>PL glucose</td>
<td>0.17</td>
<td>Poor</td>
</tr>
<tr>
<td>TGL</td>
<td>0.267</td>
<td>Fair +ve</td>
</tr>
<tr>
<td>TC</td>
<td>0.238</td>
<td>Fair +ve</td>
</tr>
<tr>
<td>HDLc</td>
<td>-0.286</td>
<td>Fair -ve</td>
</tr>
</tbody>
</table>

0.0 - 0.2 Poor Correlation 0.4 - 0.6 Moderate Correlation 0.6 - 0.8 Substantial Correlation 0.8 - 1.0 Very Good Correlation
**DISCUSSION:**

Polycystic ovary syndrome is a common condition characterised by menstrual abnormalities and clinical or biochemical features of hyperandrogenism. PCOS is now recognised to be a metabolic syndrome and its effects are found to manifest at all ages. The metabolic alterations in PCOS can be attributed to insulin resistance and the consequent development of hyperinsulinemia. Insulin resistance is due to alterations in β-cell function and found to play a major role in impairment of glucose tolerance and the development of frank diabetes in women with PCOS.

The prevalence of insulin resistance in women with PCOS can be assessed by Fasting Plasma Glucose (FBG), although a normal FBG does not necessarily rule out glucose intolerance. There are several other methods to assess sensitivity to insulin. The gold standard for assessment of insulin sensitivity is the hyperinsulinemic-euglycemic clamp technique. However this technique is laborious, cumbersome and expensive and is not suitable for routine clinical use. Other methods, such as measurement of serum fasting insulin levels, HOMA, G/I ratio, are easier to perform and cost effective and have been shown to correlate well with clamp techniques. Based on these, this study was conducted to evaluate insulin sensitivity by using the above discussed methods.

The mean value of fasting insulin (24.87 ± 16.38 µu/ml) in controls is found to be at the higher end of 2 - 25 µu/ml as quoted by Carl. A Burits, which could probably be attributed to the fact that obese individuals have not been excluded in the control group; it is a well known fact that obesity is associated with insulin resistance which can lead to hyperinsulinemia (11). Moreover it can also be due to the different race of the subjects analysed in this study compared to Carl. A Burits who arrived at from western population.

Fasting plasma insulin which shows a highly significant elevation in PCOS from the control level is attributed to the insulin resistance as it has been well established that there is a strong association between PCOS and insulin resistance which will lead to impaired glucose tolerance and compensatory hyperinsulinemia which is the most significant metabolic abnormality in PCOS.

Careful scrutiny of the levels of insulin in the 58 PCOS subjects revealed that 42 of them have mild to moderate elevation as per the criteria of C. Ronal Kaln et al., the remaining 16 had levels within reference range. This coincides with the finding of Catherin Marin Deugarte et al., who have stated that though insulin resistance is a common abnormality in PCOS it is not an universal feature (11).

The absence of any significance for glucose in PCOS inspite of insulin resistance is attributed to the prevention of plasma glucose elevation by the compensatory hyperinsulinemia which is a consequence of insulin resistance. This fact has been also emphasised by Serdar E. Bulun et al., who have stated that in PCOS subjects with insulin resistance normal glucose level is maintained at the expense of increased circulating insulin to overcome the underlying defect (12).

The Glucose-Insulin ratio derived from the above plasma glucose and insulin is not statistically significant in PCOS (p = .04), because the numerator glucose level has not changed statistically while the denominator insulin level has increased to highly significant levels in PCOS.

HOMA - IR is increased to highly significant level in PCOS (p = .003) because it is arrived at using the formula. Even though plasma glucose level does not show any significant elevation, insulin is increased to highly significant levels which increases the HOMA - IR to a highly significant levels in PCOS.

. Using the criteria of Marilyn R. Richard (13), G/I ratio of more than 4.5 excludes insulin resistance. It is observed that 46 PCOS out of 58 subjects in this study have values less than 4.5. Hence 79.3% of PCOS subjects have insulin resistance in this study which is higher to the percentage arrived by Carmina E et al., which is 65.4(14). This difference in insulin resistance in PCOS can be attributed to the racial difference of the subjects analysed in this study from that of the former study by Carmina E et al., as genetic predisposition has also been identified as one of the etiological causes for the syndrome (15). Moreover even in controls group where the mean is 6.13, 15 out of 30 subjects have G/I ratio less than 4.5 indicating that 50% of the controls selected have insulin resistance which has led to hyperinsulinemia in these subjects. The lower glucose insulin ratio in some control subjects can be attributed to the obesity of these individuals who have been selected in the control group as it has been reviewed that insulin resistance is associated with obesity (16-18).

Assessment of insulin resistance using HOMA - IR levels, based on Elizabeth G., Nabel, had found that HOMA - IR more than 3.8 indicates insulin resistance. It is observed that 46 PCOS out of 58 subjects have HOMA - IR levels more than 3.8 assuring that 79.3% of subjects with PCOS have insulin resistance which is similar finding to that.
obtained from G/I ratio.

Among the lipid parameters, TGL, TC, VLDLc and LDLc show a highly significant elevation from the level in controls, while HDLc shows a significant decrease. It is well documented fact that insulin resistance in PCOS can cause alteration in lipid metabolism (19, 20). Hence the elevation of lipid parameters can be the result of dyslipidemia which in one of the complication in PCOS. The significant decrease in HDL-c in PCOS can be attributed to the increased rate of HDL degradation which can exceed the rate of its synthesis.

CONCLUSION:

HOMA-IR is an easily obtainable, safe, low cost, and less invasive test than performing OGTT for assessing IR. HOMA-IR can used as a screening test for glucose intolerance in PCOS women

REFERENCES:


InTr Oduc TIOn: Infertility has emerged as a significant psychosocial problem today with approximately 15% of married couples being infertile [1]. Tubal pathology is responsible for 30-40% of cases of infertility. Hysterosalphingography by using non-ionic contrast (10 ml) is the most commonly utilized technique for evaluation of fallopian tubes.

Major technological advances in diagnostic ultrasound have led to improved image quality with respect to vaginal probes. The presence of periovarian fluid indicates the patency of tubes in sonosalphingography.

The present study undertaken in Barnard Institute of Radiology gives our experience in sonosalphingography in 35 cases of infertility over a period of one year, in evaluating sonosalphingogram as a minimally invasive technique in assessment of tubal patency with hysterosalphingogram as gold standard.

mATerIALS And meThOdS: Our study included 35 patients who presented with infertility in the gynaecology department of our hospital.

Abstract

Aim: The objective of present study is to evaluate the efficacy of sonosalphingogram in evaluating patent tubes in infertility patients with hysterosalphingogram as gold standard. Materials and methods: Sonosalphingogram was compared with hysterosalphingogram for assessment of tubal patency. A total of 35 patients with a history of one year of infertility were included. Each woman underwent sonosalphingogram on 8th and hysterosalphingogram on 10th post-menstrual day. For sonosalphingogram, normal saline (10-20 ml) was used for evaluation of tubal patency.

Results: The concordance between sonosalphingogram and hysterosalphingogram was 93%. The sensitivity and specificity was 90% and 94% respectively. The positive predictive value was 96% and negative predictive value was 82%.

Conclusions: It is possible that for all infertility patients sonosalphingogram can be applied as a screening test. In patients with negative and suspicious findings in sonosalphingogram, hysterosalphingogram can be done.

Key-words: Hysterosalphingogram, Infertility, Sonohysterogram, Sonosalphingogram, Tubal patency, Key Messages: Sonosalphingogram is ideal as a first line investigation in infertile female patients.

INTRODUCTION:

Infertility has emerged as a significant psychosocial problem today with approximately 15% of married couples being infertile [1]. Tubal pathology is responsible for 30-40% of cases of infertility. Hysterosalphingography by using non-ionic contrast (10 ml) is the most commonly utilized technique for evaluation of fallopian tubes. [2] Major technological advances in diagnostic ultrasound have led to improved image quality with respect to vaginal probes. The presence of periovarian fluid indicates the patency of tubes in sonosalphingography.

The present study undertaken in Barnard Institute of Radiology gives our experience in sonosalphingography in 35 cases of infertility over a period of one year, in evaluating sonosalphingogram as a minimally invasive technique in assessment of tubal patency with hysterosalphingogram as gold standard.

MATERIALS AND METHODS:

Inclusion criteria: Age 18-40 years Normal results of semen analysis of the partner Unprotected intercourse for more than one year Exclusion criteria: Less than a year of unprotected intercourse Medical or hormonal dysfunction Azoospermia Active PID

Detailed history is taken regarding type and duration of infertility, menstrual cycle, contraceptive use, tuberculosis, endometriosis, tubal surgery and uterine intervention. Following this, cases were assessed clinically. Consent was obtained from each patient for undergoing the studies. After a brief clinical evaluation, every patient underwent transbdominal sonogram for evaluation of the pelvis, following which a transvaginal and saline infusion sonography were performed. Transvaginal trasducer of 7.5 MHz frequency Aloka make was used. Catheter which has a
balloon tip preventing backflow of fluid, thus causing good uterine distension and better endometrial visualization is used like 8 Fr Foley's catheter and Cooks balloon hysterosalpingography catheter.

**SONOSALPHINGOGRAPHY:**

The procedure was done during the midfollicular phase on the 8th day. A preliminary transvaginal sonogram is done to determine the type and the degree of the uterine version. With the patient in lithotomy position, a speculum is introduced into the vagina and cervix is cleaned with antiseptic solution. Sterile saline is infused through the catheter to remove the air which can cause echogenic artifacts. The anterior lip of cervix is held with valsellum. The catheter is inserted into the uterine cavity. Once the catheter is in place, the balloon is inflated; the speculum is carefully removed. The vaginal probe is then re-inserted. The position of the catheter is then re-assessed. The catheter is pulled back gently to the level of internal os under real time ultrasound monitoring. Sterile saline (about 5 to 8 ml) is infused through the catheter. The endometrial cavity is assessed for polyps, fibroid and adhesions. (Fig 1B). After studying the endometrial cavity, the probe is angulated in such a way that uterine cornua and that side ovary is noted in a single plane. 10 ml of saline is infused again. The presence of periovarian fluid is noted which infers tubal patency. (Fig 1C,D) The same procedure is repeated for other side tube. In case of bilateral tubal block, instillation of saline results in uterine
distension and pain. If there is already small amount of fluid before saline instillation, there will be increase in fluid if the tubes are patent. In case of prolapsed ovaries into the pouch of Douglas, it would not be possible to identify whether both the tubes are patent, as fluid from one side would also surround the other ovary.

The normal findings include uniform distension of the cavity, homogenous single layer thickness of endometrium, periovarian fluid and fluid in cul-de-sac.

The abnormal finding included periovarian fluid, ovarian cysts (Fig 2A), thickened endometrium (focal or diffuse), atrophic endometrium, polyps, myomas (Fig 3) and uterine synechiae.

The transducer and the catheter are removed. The patient is put under observation for one hour. Mild spotting and pain are common. These patients are put on analgesics.

**HYSTEROSAPHINGOGRAM:**

The procedure was done on tenth day of menstrual cycle. Informed consent is obtained from the patient. After the patient has emptied her bladder, pelvic examination is done. The patient is brought to the end of the table. The local area is cleansed with povidone. Then the speculum is inserted. The cervix is visualized and cleansed with povidone. Valsellum is applied at 12'0 clock position.

![Fig 2C: No periovarian fluid suggestive of tubal block](image)

![Fig 3: Subserosal fibroid](image)

![Fig 4: Free spill of contrast with dispersion in the peritoneal cavity](image)

Leech- Wilkinson canula is inserted after pushing air out with contrast. Under fluoroscopic guidance, about 10 ml of contrast pushed. Contour of the uterine cavity and spill from both ends of the fallopian tubes are noted. Spot films are taken: one to visualize the spill and the other at 1 minute to note for free dispersion of the contrast in the peritoneal cavity. The site of block if present is noted.
Results

<table>
<thead>
<tr>
<th></th>
<th>Number of tubes</th>
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</tr>
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<tr>
<td></td>
<td>Right</td>
<td>Left</td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>Periovarian fluid</td>
<td>26</td>
<td>27</td>
<td>Peritoneal spill</td>
<td>25</td>
</tr>
<tr>
<td>No periovarian fluid</td>
<td>8</td>
<td>7</td>
<td>No Peritoneal spill</td>
<td>8</td>
</tr>
</tbody>
</table>

Tubal patency – Diagnosis by sonosalpingogram

Procedure Patent Blocked

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<tr>
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<tr>
<td>SSG</td>
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<td>16</td>
</tr>
<tr>
<td>HSG</td>
<td>54</td>
<td>14</td>
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</table>

Comparison of HSG and SSG

Patent tubes Blocked tubes Total

<table>
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<tr>
<th>SSG</th>
<th>HSG</th>
<th>Patent tubes</th>
<th>Blocked tubes</th>
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</thead>
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<td>3</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 FN</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50</td>
<td>18</td>
<td>68</td>
</tr>
</tbody>
</table>

Statistical table

TP- true positive, FP- false positive, TN- true positive, FN- false negative

Sensitivity of patent tubes by sonosalpingogram is found to be 98.1% while specificity is 83.3%

Accuracy is 94.1% while positive predictive value is 94.2% and negative predictive value is 93.7%

Pathology

<table>
<thead>
<tr>
<th></th>
<th>SSG</th>
<th>HSG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrosalphinx</td>
<td>nil</td>
<td>3</td>
</tr>
<tr>
<td>Ovarian cyst</td>
<td>3</td>
<td>Nil</td>
</tr>
<tr>
<td>Uterine fibroid</td>
<td>2</td>
<td>Nil</td>
</tr>
<tr>
<td>Submucosal polyp</td>
<td>2</td>
<td>Nil</td>
</tr>
</tbody>
</table>

Associated pathology

The associated pathology was more easily demonstrable with SSG according to my study.
RESULTS:

30 cases of primary infertility and 5 cases of secondary infertility were studied. The mean age of primary infertility cases was 25.5 years and the mean age for secondary infertility cases was 28 years. The mean duration of infertility was 4.4 yrs in primary cases and 3.6 yrs in secondary cases. One case of primary infertility had undergone myomectomy for cervical fibroid. In secondary infertility, one had undergone puerperal sterilization and another one had right partial salpingectomy.

In one case, both the ovaries were prolapsed into the pouch of Douglas. Hence it was difficult to ascertain the sides which were patent. Subsequently both the tubes were shown to be patent in hysterosalphingogram. Hence this case was not taken into consideration. In 54 tubes, peritoneal spill suggestive of tubal patency was seen. In 14 tubes, there was no spill suggestive of blocked tubes. 4 patients had unilateral block and 5 patients had bilateral block. Of those unilaterally blocked tubes, 3 were in right side and 1 was in left side. The advantage of hysterosalphingogram is identifying site and side of block.

DISCUSSION:

On analysis, 30/35 cases were found to be primary infertility and 5/35 were of secondary infertility. Mean age of primary and secondary infertility was 25.5 and 28 years respectively. The mean duration of infertility was 4.4 and 3.6 years in primary and secondary infertility respectively.

By hysterosalphingography, peritoneal spill was seen in 56 tubes which are suggestive of patency. In 14 tubes, no peritoneal spill was seen which is suggestive of tubal block. Of these, 4 patients had unilateral block and 5 has bilateral block. Of the patients with unilateral block, 3 showed block in right tube and 1 in left tube. The advantage of hysterosalphingogram is identifying site and side of block.
contrast material if vascular intravasation occurs. In general, however, lymphatic or vascular intravasation is clinically insignificant and not dangerous.[6]

**CONCLUSION:**

Sonosalpingogram is an easy outpatient procedure, cost-effective procedure. It is free from radiation hazard and allergic reactions. The diagnostic accuracy is almost equal to that of hysteroscopy and laparoscopy[7]. It is a better screening procedure in infertility work-up. Sonosalpingography can be done as a patency test in initial work-up of infertile patients. In patients with negative or suspicious findings radiographic salphingography can be done. A simplified approach will lead to significant reduction in both time and cost of investigating an infertile couple.

**REFERENCES:**

2. Fallopian tubal patency assessed by ultrasound following fluid injection. TS Richman et al, Radiology 1984; 152;507
EVALUATION OF CT GUIDED NEUROLYSIS IN THE MANAGEMENT OF PAIN IN INFILTRATIVE PELVIC MALIGNANCIES

D. Ramesh (1), K. P. Kasivisalakshi (2), S. Kalpana (3)

INTRODUCTION:

Infiltrative cancer pain still eludes the medical community for a definitive treatment. CT guided neurolytic procedures have been used in a variety of locations and for pain of varied etiologies [1]. The sympathetic chain from the stellate ganglion, celiac plexus, lumbar ganglia, hypogastric plexus, and presacral ganglia have all been selectively destroyed to derive pain relief [2]. This study was undertaken to evaluate the effectiveness of CT guided neurolytic procedures in the palliative management of pain due to infiltrative pelvic malignancies.

MATERIALS AND METHODS:

The study was done in our institute for a period of one year. The patients were referred from the Department of Radiotherapy and from pain clinic. Twenty two patients in the age group of 30-50 years underwent CT guided neurolytic procedures in the following distribution, Lumbar Sympathectomy – 12 and Presacral & Precoccygeal Sympathectomy – 10.

The study was conducted after obtaining proper informed consent from the patient. As this was a prospective controlled study, ethical committee approval from Institutional Ethics Committee, Madras Medical College, was obtained.

Inclusion criteria
Pain due to infiltrative pelvic malignancy

Exclusion criteria
Pelvic pain due to other causes and treatable malignancies.

The patients with bleeding diathesis, local infection, gross & topical deformities, hypersensitivity to local anaesthetics were excluded from the study.

CT GUIDED CHEMICAL LUMBAR SYMPATECTOMY:

Under strict aseptic precautions the procedure is performed. Intravenous radiographic contrast is injected and axial scans are taken at the levels of L2 and L3 vertebrae. The ureters are visualized and the best access route is determined.
selected, taking into account degenerative osteophytic changes. Patient is placed in prone position. A determination of the puncture point, the puncture angle and the distance to the skin is made. After local anaesthesia of the skin at puncture site, a 22 G fine Chiba needle is advanced through the psoas muscle in paravertebral location in to the ganglion or its immediate vicinity.

Check scans are taken and the accurate positioning of the needle is achieved. (Fig 1) Local anaesthesia is injected to demonstrate the effect on the sympathetic tone. By injection of contrast medium, the anticipated distribution of alcohol in the region of the sympathetic trunk can be checked (Fig 2). For neurolysis of the sympathetic trunk only 3ml of absolute alcohol is injected. (Fig3)

Surface temperature over lower limb was taken before and after the procedure. The intensity of pain was assessed by the visual analogue scale and Graceley’s verbal descriptor scale before the procedure. After the procedure the patients were assessed for pain immediately, then at 24 hours, 7 days, 1 month and 2 months.

CT GUIDED NEUROLYSIS OF THE PRESACRAL AND PRECOCCYGEAL SYMPATHETIC TRUNK:

Under aseptic precaution and patient in left lateral position, after infiltrating the skin with 2% lignocaine, a fine 22G Chiba needle is inserted and advanced under CT guidance, so that it passes just under the greater sciatic notch to lie in the presacral region. (Fig 4)

After the needle tip is accurately positioned dilute contrast medium is injected to assess the potential space. (Fig 5)

Then 5 ml of absolute alcohol is injected. (Fig 6)

Pain was assessed before the procedure. The methods used were the visual analogue scale and Graceley’s verbal descriptor scale. After the procedure patients were assessed for pain immediately, then at 24 hours, 7 days, 1 month and 2 months.

OBSERVATION AND RESULTS:

After the procedure all the patients were closely monitored for the immediate and long term effects with regard to:

- Duration and quality of pain relief.
- Signs of sympathetic blockade.
- Possible side effects and complications.
- Dosage of analgesic at 1 month.
CHEMICAL LUMBAR SYMPATHECTOMY:

The age of the patient varied from 34 to 50 years with a mean age of 41.8 years. The pre procedure pain score varied from 5 to 10 with an average score 7.4. 10 out of 12 patient ie. 83% had greater than 50% of pain relief immediately after the procedure. At 24 hours also, 83% had greater than 50% relief as immediately after procedure. At 7 days, 10 patients reported more than 50% relief and one patient had full recurrence of pain and another one patient still below than 50% of relief. At one month still only one patient had full recurrence of pain and 9 patients had more than 50% relief. At 2 months one patient had died, 7 patients had more than 50% pain relief.(table 1)

TEMPERATURE CHANGE

The pre procedure temperature in patients of Lumbar neurolysis ranged from 35.4C to 36.6C with a mean temperature of 35.92C. The post procedure temperature ranged from 36.9C to 38C with a mean temperature of 37.83C. The difference in pre procedure temperature was found to be statistically significant. The rise in temperature varied from 0.9C to 2.5C. Eleven patients (92%) had a rise in temperature of greater than 1C. Only one patient had less than 1C temperature rise.

COMPLICATIONS

In one patient bloody tap was noted and in another patient hypotension noted in the lumbar neurolysis group. No other complication noted during follow-up.

ANALGESIC REQUIREMENT

When the requirement of analgesic drugs at 1 month was compared, with pre procedure requirements, one patient does not at all required drug, 8 patients needed only less than 50% of original dose. 2 patients still needed 50% of original dose. Only one patient who had full recurrence of pain, the required analgesic dose actually increased.
PRESACRAL AND PREOCYGEAL NEUROLYSIS:

The age of the patients varied from 30 to 46 years with an average age of 38.2 years. The pre procedure pain score varied from 5 to 10 with an average score of 77/10. 8 out of 10 patients had greater than 50% pain relief immediately after the procedure. At 24 hours post procedure all the patients had more than 50% pain relief. At 7 days 8 patients reported more than 50% relief, 2 patients reported less than 50% relief. At 1 month, one patient had full recurrence of pain, only 5 patients still had more than 50% relief. By 2 months one patient had died. Only 4 patients still had more than 50% pain relief. (Table 2)

ANALGESIC REQUIREMENT

There was a significant reduction in requirement of analgesic drugs. When the requirement of analgesic drugs at 1 month was compared, with pre procedure requirements, 5 patients needed only 25% of original dose. 4 patients still needed 50% of original dose. Only one patient who had full recurrence of pain, the required analgesic dose actually increased.

DISCUSSION:

The cancer pain is often debilitating and reduces the quality of remaining life. [3] The accuracy of CT guided sympatholysis is unparalleled [4]. Pain could be assessed by its sensory intensity, visual analog. Both intensity and relief are assessed and categorized by Graceley’s scale and visual analog scale. [5] Surface temperature could be assessed by thermography. The magnitude of the temperature increase after sympathetic blockade depends on baseline values. [6]

Greater increase are noted in patients with lower pre-block

<table>
<thead>
<tr>
<th>Pain Relief</th>
<th>No. of patients (Total 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Immediate</td>
</tr>
<tr>
<td>Nil</td>
<td>-</td>
</tr>
<tr>
<td>&lt; 50%</td>
<td>2</td>
</tr>
<tr>
<td>&gt;50%</td>
<td>10</td>
</tr>
</tbody>
</table>

TABLE:1 Pain relief in patients(CHEMICAL LUMBAR SYMPATHECTOMY)

<table>
<thead>
<tr>
<th>Pain Relief</th>
<th>No. of patients (Total 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Immediate</td>
</tr>
<tr>
<td>Nil</td>
<td>-</td>
</tr>
<tr>
<td>&lt; 50%</td>
<td>2</td>
</tr>
<tr>
<td>&gt;50%</td>
<td>8</td>
</tr>
</tbody>
</table>

TABLE:2 Pain relief in patients(PRESACRAL AND PREOCYGEAL NEUROLYSIS)
temperatures. The lower extremity temperature is best assessed in anterior thigh, medial aspect of thigh and dorsum of foot and great toe. Both affected and unaffected site to be monitored.

The efficacy of sympathetic block could be assessed by skin plethysmography, ice- response and cold pressor tests. Both types of neurolysis by either means significantly reduced pain but then, the effectiveness was dependent upon the consistency of the vertebra, the status of adjacent soft tissues where the ganglia rests.

Local anesthetic used during the procedure helps in confirming sympathetically mediated leg pain syndrome as a diagnostic sympathetic block. As a therapeutic intervention, it prevents alcohol induced irritant pain during neurolysis. Nearly 40% patients had good pain relief at 2 months in our study and the rest had relief at 2 months.

Except for blood tap during procedure in one of the patients we did not face any complication during or after the procedure.

CONCLUSION:

CT guided Neurolysis is a highly effective technique to treat pain of infiltrative pelvic malignancies for short term. [7] CT guided chemical lumbar sympathectomy for the management of infiltrative pelvic malignancies producing lower limb pain syndrome. CT guided presacral and precoccygeal sympatholysis in the management of pelvic cancer pain. Neurolytic sympathetic blocks were found to be highly useful for long term benefits and side effects were very minimal or rather negligible. These can be done as outpatient procedures by way of its simplicity, minimal risks and cost effectiveness, which is ideal for our population.

REFERENCES:


ACKNOWLEDGEMENT:

Patients with pain of infiltrative pelvic malignancy who participated in the study.
INTRODUCTION:

Vague abdomen pain is the most commonly encountered symptom in the emergency department at any hospital. The various cause of the abdomen pain may vary from benign to life threatening disease. Time is a very important factor as any delay may lead to grievous consequences like perforation. Appendicitis is one of the common cause of abdomen pain in patients admitted at the emergency department. Diagnosing this in young male patient is mostly straight forward, but the same becomes a problem in premenopausal women with similar clinical history and symptoms.

The timely diagnosis and intervention of acute appendicitis is important due to the fact of its grave complication like perforation. Some surgeons are in favour of early laparotomy even if there is no definite diagnosis of appendicitis, taking into account only the clinical findings. This is done mainly to minimize the risk of appendiceal perforation. So this study is done to prove the role of radiological imaging in early diagnosis of appendicitis and also to prevent negative appendectomy rates and also to compare the accuracy within the imaging modalities.

MATERIALS AND METHODS:

This prospective observational study was carried out after obtaining clearance from the ethical committee in our institution and with written consent from all the patients.

INCLUSION CRITERIA:

Patients who were admitted in the casualty surgical emergency ward within the age of 15-45 who presented with clinical findings and symptoms of acute appendicitis of right iliac fossa pain, fever and vomiting were enrolled in the study. A total study sample of 100 was selected. Patients were subjected to both the investigations USG and CT findings are recorded. Surgical and histopathology findings were noted and compared with the radiological reports. The sensitivity, specificity and the diagnostic accuracy were calculated.

CONCLUSION:

From the study it is concluded that CT is superior in all aspects of sensitivity, specificity, PPV and NPV than USG. Hence the CT investigation is more accurate than USG in diagnosing cases of appendicitis.

Key-words: acute appendicitis, right iliac fossa pain, CT scan, USG scan

Key Message: CT investigation is more accurate than USG in diagnosing cases of appendicitis.
EXCLUSION CRITERIA:
Rest of any not from inclusion criteria.

USG PROTOCOL:
A routine USG was done in SONOSCAPE - S 20 machine for the upper abdomen and pelvis using a 3-5–MHz convex transducer to rule out alternative abnormalities related to solid organs and to rule out free fluid. Then graded compression and color Doppler sonography of the right lower quadrant giving attention to the site of maximal tenderness was performed using a linear transducer.

The normal appendix appeared as a blind ended loop with no peristalsis. The graded compression technique is used to displace the bowel loops, allowing differentiation between an incompressible inflamed appendix and compressible normal bowel loops.

An incompressible blind-ended, and fluid-filled tubular structure that was more than 6 mm in diameter with hyperaemic walls was diagnostic of appendicitis. The presence of an appendicolith, peritoneal fluid, and other additional findings were also recorded.

Total time of 10-15 min on average was taken. The sonography report was positive, negative or inconclusive for acute appendicitis. Alternative diagnoses, when achieved, was also reported.

CT PROTOCOL:
Examinations were performed on a MDCT performed using a 4-slice CT scanner (TOSHIBA - ASTHEION) at 120 kVp and 100 mAs; a pitch of 1 was used. CT of the lower abdomen and pelvis, from the xiphoid to the pubic symphysis, was performed with 80 mL of non-ionic contrast material Iohexol 350 mg (Omnipaque 350) was injected through a 18-gauge cannula placed in the volar aspect in the cubital vein at a flow rate of 4 ml/s and delay of 50 sec.

Axial reconstructions from the raw data were done at representative cases:

Case 1 - a) USG - dilated non compressable tubular structure in right iliac fossa of 11mm in diameter with peripheral vascularity  

b) CT - confirms the findings.

Case 2 - USG - appendix with a rent noted in the wall with adjacent areas of collection that does not show vascularity. Pericaecal wall thickening noted. CT - confirms the findings of USG and in addition shows the the extent of the collection with pericaecal wall thickening. Mural wall enhancement of the appendix and a discontinuity in the appendicular wall noted.
Case 3- 52 Year male patient with abdominal pain 3 days, clinical diagnosis of appendicitis a) USG - rent noted in the wall of appendix with adjacent areas of collection that does not show vascularity b)CT- confirms the findings of USG and in addition shows the the extent of the collection with pericaecal wall thickening.

**HISTOPATHOLOGY:** Perforated appendix

3 mm thick; at 1.5-mm increments were obtained. The second data set was reformatted coronal at a thickness of 3 mm with 3-mm increments. No oral contrast was used. The normal appendix when visualized was reported. Appendicitis was reported based on the presence of a blind-ended tubular structure of more than 6 mm in diameter adjacent to the cecum without intraluminal air or contrast medium and the presence of additional positive findings, such as an appendicolith, cecal wall thickening, periappendicular fat stranding, or periappendicular fluid. An abscess in the right iliac fossa raised suspicion for perforated appendicitis.

**OBSERVATION AND DISCUSSION:**

The common age group under the presentation was 21 - 30 years with 33 of 63(52%) in male and 11 of the 37(29%) in female falling in this age group. The next common age group is < 20 years with 22 of 63(34%) in male and 13 of 37(35%) in female. Considering the overall percentage of age group 44% falls in 21 to 30 year, 35% < 20 years, 15% in 31 to 40 years, 4% in 41 to 50 years and 2% in 51 to 60 years of age. The study did not take in to account the sex of the patient but the sex distribution in the study showed male to be predominant than female patient. Among the total of 100 patient 37 were female and 63 were male. So the study showed that the diagnosis of acute appendicitis was common in 21 to 30 year both in male and female patient.
USG(ULTRASONOGRAM):

As of the USG findings of the 100 patient 86 were found positive which Shows ultrasound finding of acute appendicitis. 14 showed was reported negative .Of the 14 negative cases 7 case shows HPE Finding of acute appendicitis .Of it two patient were obese patient whose appendix was not visualized out and another 2 patient had only tip of appendix inflammation which was not identify. These 4 cases were picked up by CT which reported positive.

Two of the 14 patient had treated with antibiotic outside and the last one case was an early appendicitis and the last 3 cases were also missed by CT which was reported negative. The remaining 7 cases were true negative with HPE findings also negative for the lesion.(fig 1)

The 86 positive findings in USG 84 also showed HPE positive of appendicitis Two case were reported positive in USG which showed negative findings in all CT ,HPE and surgery. Some case showed probe tenderness which was reported as negative but just was mentioned as probe tendernes,

this was decided considering that the pain threshold varies and could not be confidently given positive unless the appendix is visualised ,in view of reducing the reporting false positive cases (fig 1)

COMPUTED TOMOGRAPHY(CT):

Among the 100 patient, CT was found positive for acute appendicitis in 89 patient and negative in 11 patient .Of the 11 patient who had negative findings 8 were also found to have negative histopathology findings .Of the 9 patient negative in HPE one Female patient had CT finding of minimal fat stranding with normal size appendix measuring 6 mm which was given as positive,and three case showed both surgical and Pathological inflamed appendix with negative CT findings.From the history it was found that two of the patient had been treated with IV antibiotic for 3 days outside .Whether this history and intervention had affected the image findings is not known. (fig 2)
SURGICAL:

In the study, patients were taken for surgery based on the clinical findings by the surgeon. Of the 100 patients taken for surgery, 98 cases were reported positively as inflamed appendix. Of the 98 cases positive in surgery, 91 cases were reported positive in HPE also. Hence, on the basis of clinical findings, there is 92.8% probability of correctly diagnosing cases of acute appendicitis. Two cases were reported negative which was also reported negative in HPE. (fig 3)

HISTOPATHOLOGY:

The above algorithm shows an overview of the histopathology report. Of the 100 cases taken for surgery, 91 cases were histopathology proven positive. Of the 91 cases, CT showed positive findings in 88 cases, which comes to about 96.7%. Hence, CT has 96.7% probable of correctly diagnosing a positive case of acute appendicitis with confidence interval of 95%.

With respect to USG, of the 91 cases positive in histopathology ultrasound showed positive findings in 84 patients amounting to about 92.3%, hence USG has 92.3% probable of correctly diagnosing an appendicitis.

Coming to the negative findings in HPE, of the 100 cases, 9 cases were reported negative in histopathology. CT also showed negative findings in 8 cases covering about 88.8% and USG showed negative findings in 7 out of the 9 negative in histopathology.

Hence, the percentage that USG could correctly diagnose a negative case of appendix comes to about 77.7%.

Negative appendectomy as of according to the study is 9% with 9 cases taken for surgery on clinical grounds was found to be negative. If in addition to the clinical acumen, CT and USG findings were to be taken into account, 6 cases out of the 9 negative cases could have been avoided. (fig 4)

<table>
<thead>
<tr>
<th>COMPARING THE ACCURACY OF CT AND USG</th>
<th>CT</th>
<th>USG</th>
</tr>
</thead>
<tbody>
<tr>
<td>SENSITIVITY</td>
<td>0.97</td>
<td>0.92</td>
</tr>
<tr>
<td>SPECIFICITY</td>
<td>0.89</td>
<td>0.78</td>
</tr>
<tr>
<td>PPV</td>
<td>0.99</td>
<td>0.98</td>
</tr>
<tr>
<td>NPV</td>
<td>0.73</td>
<td>0.50</td>
</tr>
</tbody>
</table>

TABLE:1 Comparing the accuracy of CT and USG. From the above table it clearly shows that CT is more sensitive, specificity, PPV, NPV.
STATISICAL REVIEW:

**HISTOPATHOLOGICAL EXAMINATION** is the gold standard and hence the CT findings and the USG findings are compared to the histopathological reports received. **CT study** shows a sensitivity of 97% and specificity of 89%. Positive predictive value of 99% and negative predictive value of 73%. All the value has a confidence interval of 95%.

The study has 95% probability of giving the result if used in a large population. The p value also fall in the significant value of <0.001. Comparing the parameters with the studies done earlier the study shows comparative similar results. Many studies have come up with values of sensitivity -96% and PPV-96%. Yet another study gives a sensitivity of 87-100%, specificity of 83-99% and PPV of 92-99%. Again which is near to our result.

**USG** shows a sensitivity of 92% and specificity of 78%, PPV-98% and NPV-50%. All the value has a confidence interval of 95%. The study has 95% probability of giving the result if used in a large population. The p value also fall in the significant value of <0.001.

Comparing the parameters with the studies done earlier the study shows comparative similar results. Many other studies reviewed in literature shows similar results. Puylar at3 in his studies found the sensitivity and specificity to be 89% and 100% respectively. Terasawa and coworker4 showed 86% of sensitivity, 81% specificity, PPV-84% and NPV-85%. Another Korean meta analysis gave sensitivity and specificity as 86.75 and 90% which is comparable with the study.

CONCLUSION:

From the study it is concluded that CT is more sensitive, specificity, PPV, NPV. Hence the CT investigation is more accurate than USG in diagnosing cases of appendicitis.

REFERENCES:


ACKNOWLEDGEMENT:

The patients, surgical and pathological departments, MMC.
**INTRODUCTION:**

MR is becoming immensely popular in imaging of the abdomen because of the better Spatial resolution in multiple planes. Rapid Acquisition with Relaxation Enhancement Technique (RARE) published in 1987 facilitated the visualization of urinary collecting system without administration of intravenous contrast for the first time. Later in 1994, Kiefer published a new technique for MR urography, which allowed ultrafast acquisition on T2 weighted high resolution images called HASTE (Half Fourier Acquisiton Turbo spin echo). This new technique had the advantage of visualizing renal parenchyma as well as the urinary tract; in a few seconds thus reducing motion artifacts. Dilated urinary collecting system is an important management problem for urologists and frequently encountered finding for the radiologists. The cause and level of dilatation and presence or absence of obstruction are all important problem in which radiologist has a vital role. This study is an attempt to evaluate the diagnostic capability of MR urography and its efficacy in visualization of urinary collecting system.

**AIM OF THE STUDY:**

The aim of study was to evaluate and compare the roles of Static Magnetic Resonance Urography and Intravenous Urography in the assessment of the dilated urinary tract with regard to localizing the level and cause of obstruction.

**MATERIALS AND METHODS:**

The Study was performed on a 1.5 Tesla super conductive whole body MRI scanner MAGNETOM VISION (Siemens Magnetic Vision, Germany). The imaging method is based on the physical principle of magnetic resonance. During the measurement the patient is placed on the strong homogenous magnetic field. The hydrogen nuclei (protons) distributed through the entire body tissue, generate signals when stimulated by a Radiofrequency field. These signals are processed into images by a computer.

**Patient Preparation:**

Patients should be in full bladder and fasting for four hours. In patients with obstructive uropathy no pre-medication is used. In patients with no obstructive urinary tract diseases, diuresis was induced using IV injection of 10mg Furosemide given 20 minutes before imaging done to distend the urinary system. No abdominal compression was used.

This is Prospective study done in Barnard Institute of Radiology, Madras Medical College, Chennai, during September 2013 to September 2014 and approved by local ethics committee.
**Patient selection:**
Patients referred to the radiology department for intravenous urogram, who had dilated renal tract on IVU, Kidneys which failed to opacify after 1 hour of contrast injection and where USG showed hydronephrosis.

**Materials**
Patients were subjected to scanning after excluding MRI contraindications like MR incompatible Cardiac pacemaker, Metallic Implant and cardiac defibrillator.

**MRU Technique:**
MR Urography is performed with heavily T2 weighted pulse sequences. The most commonly used T2 weighted technique, is HASTE (Half Fourier acquisition of single shot turbo spin echo) HASTE is a susceptibility insensitive single shot sequence, allowing ultra fast acquisition of heavily T2W images with single breath-hold. This technique generates images sequentially within 1 to 2 seconds with excellent spatial resolution. Heavily T2-weighted MR urograms can be obtained as single thick slab projection images or MIP views generated from multiple thin section images. Single thick slab projection imaging with a large field of view obtained in coronal and both oblique coronal projections provides a quick survey of the upper tract without requiring any post processing.

**Image Analysis:**
MR urograms were analyzed for image quality and classified as technically accurate or moderate on bases of visualization of urinary tract and presence of artefacts. Dilation was considered to be present if at least two of following were seen (1) fornical blunting or ballooning, (2) prominence of renal pelvis (3) continuous column of signal intensity from renal pelvis and ureter which terminated before or at UVJ (ureter dilation >5mm). Level of obstruction classified as pelvicalyceal, proximal ureter, mid ureter, distal ureter. Renal calculi were diagnosed on MRU when a round, oval or multifaceted area of signal void urinary tract was surrounded by bright signal from urine. Absence of Signal Intensity from urinary tract is due to combination of low mobile proton density and short T2 relaxation values.

As MIP images are projection images which selectively display high Signal intensity pixels’ bright Signal from urine may surround stone and obscure it. Therefore, all Source images must be reviewed for stones. Stricture is defined as area of narrowing in urinary tract proximal to which there was urinary tract dilation. Extrinsic obstruction was diagnosed when a mass or other structure (eg. Uterus) was seen in vicinity of urinary tract associated with gradual tapering, defect or obstruction in proximal dilation.

**RESULTS AND OBSERVATIONS:**
The following table and bar column shows the comparison of the overall accuracy of MRU Vs IVU in determining the cause of obstruction.

<table>
<thead>
<tr>
<th>Modality</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRU</td>
<td>92.1%</td>
</tr>
<tr>
<td>IVU</td>
<td>78%</td>
</tr>
</tbody>
</table>

The following table shows shows the accuracy of MRU Vs IVU in determining the level of obstruction.

<table>
<thead>
<tr>
<th>Modality</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRU</td>
<td>100%</td>
</tr>
<tr>
<td>IVU</td>
<td>83.7%</td>
</tr>
</tbody>
</table>

**DISCUSSION:**
MR urography can be used to evaluate the urinary tract without ionizing radiation and administration of iodinated contrast material. The two major techniques employed were the heavily T2 weighted RARE and HASTE sequences.
REPRESENTATIVE CASES:

**CASE 1.** Postop Ureteric Stricture. Level of stricture well demonstrated in MRU (B)

**CASE 2.** Partial Duplication; Right Upper Moiety Hydronephrosis well demonstrated in MRU (B)

**CASE 3.** Left Hydronephrosis with Urinoma seen in the left retroperitoneal space by MRU (B) not visualized in the IVU (A)
A total of fifty one patients including thirteen normal controls formed the study group. This included twenty-nine males (57%) and twenty-two females (43%). MR urography was done using HASTE sequence (Half Fourier Acquisition of single shot Turbo spin echo). Similar studies using HASTE sequence were done by, Martin et al (12) and Aetrts et al (7). Most of these patients belonged to the 3rd and 4th decade. The commonest complaint in this study was pain followed by dysuria. MR urography images were of relatively good quality. The images of the healthy volunteers showed nondilated collecting systems and ureters after a dose of 20mg iv furosemide was administered. Calyceal, fornical and infundibular anatomy was not seen in same detail as with an intravenous urography. The retroperitoneal anatomy and adjacent organs were reasonably seen. MR urography findings were correlated with findings on intravenous urography / Ultrasound/ Scopy/ Surgery and final diagnosis obtained in 38 patients. The MR images were analyzed on the basis of level of obstruction and cause of obstruction. Six patients were shown to have obstruction at renal pelvis by MR Urography and confirmed on follow up (100% accuracy). Three patients had proximal ureteric obstruction by MR urography confirmed on further follow up (100% accuracy). In contrast IVU was only 83.7% accurate in predicting the level of obstruction. The main reason for the poor performance of IVU was due to failure of contrast medium excretion. MR urography using half Fourier acquisition of single shot Turbo-spin Echo can produce high resolution images of the urinary tract. High accuracy regarding site (100%) can be obtained. For 38 patients the final overall diagnosis was correct by MRU alone in 35 (92.1%) and IVU alone in 30 follow up was correct by MRU alone in 35(78%).

MRU compared to IVU provided clear anatomic depiction of congenital anomalies of renal tract in our study which aided in the diagnosis of these congenital anomalies. MRU depicted the pathologic conditions in all 9 Patients with congenital anomalies. This correlates with the study of Patrick Aerts (7) who were successful in demonstrating the pathological conditions in all their 10 cases. Also in patients with non visualized kidney on one side and bladder irregularity on IVU, suggesting bladder growth, MRU accurately depicted intraluminal growth and a deposit at pelvis causing ballooned out pelvis suggestive of multifocal Transition-al cell carcinoma. This information was of immense benefit to urologist and confirmed at surgery. Kidneys which failed to opacify on IVU one-hour after contrast and where USG showed the presence of dilation(n=6) MRU accurately depicted the level of obstruction in all 6 cases (100%). In 5 of 6 cases (83%) IVU failed to produce nephrogram even on delayed images, so the presence of obstruction was uncertain. MRU showed the cause of obstruction in 5 cases (83%). In similar study by Sung et 31(21), MRU showed the level of obstruction in 5 cases (83%).

CONCLUSION:

MR urography produce high resolution images of the urinary tract. Dilation of urinary tract facilitates diagnosis by MRU as fluid in urinary tract is seen. MRU gives 100% sensitivity in diagnosing urinary obstruction.
MRU provides high sensitivity and accuracy regarding the site and cause of obstruction in comparison with IVU. MRI is also valuable in kidneys while fail to opacify on IVU to demonstrate the level and cause of obstruction.

MRU provides additional important anatomic information not revealed on IVU, which is valuable for the surgeon, before urinary tract intervention.

MRU has a significant role in renal failure patients and patients with allergy to iodinated contrast medium, safe as it involves no radiation and can be use of children and pregnant women.

Although MRU does not currently have a role as a screening test for urinary tract dilation due to its prohibitive cost, it must be used for investigation of dilated renal tract when other techniques are contraindicated or does not provide the information necessary for diagnosis and management.

REFERENCES:

InTR Oduc TIOn:
BACKGROUND:
Chronic renal disease is a world-wide health problem with the overall incidence of the end-stage renal disease is 150 /million populations. Renal dysfunction is a condition defined according to the presence or absence of damage of the kidneys and level of kidney function, not related to the type of kidney damage. Since renal parenchymal disease is accompanied by renal dysfunction, monitoring renal function permits assessment of disease progression, and periodic assessment of renal function is necessary for optimal management of a patient.

Renal function is assessed by means of effective glomerular filtration rate (e-GFR). The normal value of GFR is 90 ml/min or higher. GFR can be measured indirectly from the estimation of creatinine in the blood. So the amount of serum creatinine correlates with level of kidney function. Serum creatinine (S Cr), blood urea (BU), and estimated glomerular filtration rate (eGFR) derived from creatinine clearance are useful for monitoring renal function; however, these indirect measures of renal filtration are imperfect and cannot assess single kidney function.

Imaging may play an important role in the evaluation of renal parenchymal disease. Ultrasonography (USG) and computed tomographic (CT) scan provide good anatomic images but limited functional information. USG may show changes in renal echogenicity, it suffers from subjective variation. CT scan requires radiation and use of

Abstract

Context: Diffusion-weighted magnetic resonance imaging (DW-MRI) in renal diseases is an emerging field and its utility is yet to be fully realized.

Aims: To study the relationship between apparent diffusion coefficient (ADC) values of renal parenchyma, Renal Resistive Index (RI) with serum markers of renal function and stage of chronic kidney disease (CKD).

Settings and Design: A prospective study was performed 100 patients with normal and elevated renal parameters. Patients underwent DW-MRI (at b-values of 0, 250 and 500 s/mm2) and renal Doppler examination.

Methods and Material: Patients underwent DW-MRI (at b-values of 0, 250 and 500 s/mm2) and renal Doppler examination. Of these 25 normal GFR, 26 patient’s stage2, 20patients stage3, 10 patients stage 4, 19 patients stage 5 CKD and were staged depending on disease severity. ADC values were determined for renal parenchyma and compared. Receiver operating characteristic (ROC) curves were drawn to establish cut-off ADC values.

Statistical analysis used: Pearson’s correlation coefficient (R) was calculated between ADC and renal function parameters.

Results: ADC values in patients with renal dysfunction were significantly lower than in patients with normal renal function. ADC values lower than 1.986 x10-3 mm2/sec for right side ,1.97067 x10-3 mm2/sec for left side were seen only with renal dysfunction and higher than 2.49318 x10-3 mm2/sec for right side 2.4706 for left side , were seen only with normal function. Average ADC value for both side: 2.334 x10-3 mm2/sec below which indicates renal dysfunction. There was significant inverse correlation between ADC of renal parenchyma and serum creatinine, blood urea .There is significant linear correlation between the ADC of renal parenchyma and estimated glomerular filtration rate (eGFR). Renal resistive index is not persistently elevation in all the patients with elevated renal parameters and couldn’t be reliable in predicting the renal dysfunction.

Conclusions: ADC values may serve as an additional marker for the presence and degree of renal dysfunction.

INTRODUCTION:

BACKGROUND:
Chronic renal disease is a world-wide health problem with the overall incidence of the end-stage renal disease is 150 /million populations. Renal dysfunction is a condition defined according to the presence or absence of damage of the kidneys and level of kidney function, not related to the type of kidney damage. Since renal parenchymal disease is accompanied by renal dysfunction, monitoring renal function permits assessment of disease progression, and periodic assessment of renal function is necessary for optimal management of a patient.

Renal function is assessed by means of effective glomerular filtration rate (e-GFR). The normal value of GFR is 90 ml/min or higher. GFR can be measured indirectly from the estimation of creatinine in the blood. So the amount of

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iodinated contrast material, which is undesirable in patients with renal dysfunction. Magnetic resonance imaging (MRI) has the ability to show both anatomical and functional information objectively without any radiation exposure to the patient.

Diffusion-weighted MRI (DW-MRI) is a non-invasive modality to characterize tissues based on Brownian motion of water molecules within them. Apparent diffusion coefficient (ADC) is a quantitative parameter calculated from DWI that combines the effects of capillary perfusion and water diffusion. DW-MRI in kidneys makes sense because of the organ’s high blood flow and role in water filtration. DW-MRI in renal diseases is an evolving field and previous investigators have attempted to evaluate its utility in the characterization of focal renal lesions[5-11] renal parenchymal disease,[7,12-16] and renal infections.[17-19] There is less number of studies investigating the relationship between ADC values, Renal resistive index and eGFR as well as with different stages of CKD.

The purpose of this study was to investigate the relationship between ADC values of renal parenchyma, Renal-Resistive Index (RI) and serum markers of renal function and stage of CKD. We also intended to establish cut-off ADC values to identify renal dysfunction. Diffusion weighted imaging in kidneys will be useful in assessing the renal function because it has increased blood flow and regulates water fluid and electrolyte balance.

SUBJECTS AND METHODS:

METHODOLOGY:

Design of study: Prospective observational study
Sample size: 100 patient
Study period: 6 months
Study centre: Barnard institute of radiology, Rajiv Gandhi Government General Hospital, Madras medical college

INCLUSION CRITERIA:

Patients who has elevated renal parameters Serum creatinine>1.5mg/dl, Blood urea>40mg/dl along with patients with normal renal function.
Patient who comes for renal Doppler examination.
Patient who comes for MRI abdomen for renal and non-renal lesions

EXCLUSION CRITERIA:

Non consenting patient • Patient who cannot breath hold

STUDY:

It is a single institutional prospective study in Rajiv Gandhi govt General hospital. Approval got from institutional ethical committee. The informed consent from the patients and controls have been obtained. Patients who came for MRI abdomen and spine both non renal and the renal disorder and to renal Doppler study with normal and elevated renal parameters were identified and included in the study. Diffusion weighted imaging and Renal Doppler study was performed of all patients with elevated renal parameters and in patients with normal renal parameters. The cases are divided based on the presence of renal dysfunction, with cut off value for Serum Creatinine (sr.cr)>1.5 mg/dl. Totally 100 patients with both renal dysfunction and normal serum renal parameters were identified.

Mean Creatinine Level for group with the renal dysfunction group was 3.7 mg/dl (range 1.6-12.4 mg/dl) and mean Blood Urea was 58.4 mg/dl (range 30-140 mg/dl). We have not selected the patients as acute and chronic kidney disease as separate entity. Patients were classified into stages based on the disease severity, as per the level of serum creatinine and blood urea level. Data including age, sex, clinical, and laboratory parameters were collected. eGFR was calculated by using C-G formula. Cockcroft-Gault method: (140-age) x (wt in kg) x(0.85if female) / (72*cr)

TECHNIQUES:

MAGNETIC RESONANCE IMAGING:

All the persons examined under 1.5-Tesla MRI scanner (Siemens-Germany) in supine placing a body coil over the abdomen. Body coils with six element matrix were placed on the abdomen anteriorly in addition with two posterior spine coils for better SNR(signal to noise).

Imaging protocol:
1. Localizer: True (FISP) - True Fast Imaging and Steady Precession in the axial and coronal sequences for planning
3. IN phase opposed phase imaging
4. Diffusion Weighted - MR imaging (DWI) with b values of 0, 250, 500.

DWI IMAGING:

DWI is Respiratory triggered Fat suppressed axial diffusion weighted sequence with b values of 0, 250 and 500 s/mm2. The physical parameters comprises of: TR/TE = 4100/14 Slice thickness = 5mm Receiver Bandwidth =
Field of view  =230
Acquisition time  = 2 min (depends on patient’s respiratory rate).

DWI is Respiratory triggered using the navigator-trigger prospective acquisition correction technique –PACE, the position diaphragm is assessed periodically by the navigator echoes. Apparent Diffusion Coefficient (ADC) maps were derived automatically on a voxel-by-voxel basis. A quality of Diffusion Weighted images and the ADC maps were obtained.

**RENAL DOPPLER STUDY:**

Renal Doppler study was done by using 3-5 MZ probe in the sonoscope machine. Resistive -index (RI) of the intra renal parenchymal vessels have been taken in the segmental/interlobar vessels in the upper, mid and lower pole. Good quality wave forms taken and spectral analysis done. Segmental/interlobar arteries were examined using a 2- to 5 mm gate with Doppler angle of 0- 60°. Wave forms were optimized for measurement Resistive Index . Lower pulse repetition frequency (PRF) used without any aliasing to maximize waveform size, high gain with good obscuring background and the lowest wall filter.

At each level 3 to 5 reproducible wave forms from the intra renal arteries were obtained. RIs from these waveforms traced manually and are average value was taken. Mean RI for each kidney were measured. (RI: Peak Systolic Velocity-End Diastolic Velocity / Peak Systolic Velocity)

**OBSERVATIONS AND RESULTS:**

**DWI IMAGING AND ADC MEASUREMENT:**

ADC values are measured quantitatively by placing region of interest of size 1 cm² in the commercial workstation. Region Of Interest(ROI) is placed on renal parenchyma for measuring the ADC was done by drawing a circular over renal parenchyma(without any preference to cortex and medulla). ADC values were not separately measured for the renal cortex and medulla, because it is hard to place the ROI cursor precisely in cortex and medulla especially patients with severely contracted kidneys. ROIs placed one each over the superior, mid polar, and lower polar region of each kidney separately. The mean ADC of these three values were calculated for each kidney separately. The Apparent Diffusion Co efficient were measured as mean ± standard deviation (A × 10−3 mm2/s).

![FIG 1a](image1)

1.ADC: RT :2.570 x10-3mm2/sec LT:2.620x10-3mm2/sec

![FIG 1b](image2)

ADC: RT:1.530 X10-3mm2/sec LT: 2.420X10-3mm2/sec

**RESISTIVE INDEX:**

All the patients who underwent DWI were subjected for renal Doppler examination. Duplex Doppler study done patient in supine or postero lateral position. Renal resistive index of were measured in the intra renal arteries for each kidney separately. Measured RI values were compared with the serum creatinine and blood urea

![FIG 2](image3)
**ANALYSIS:**

**Patient characteristics:**
The population of our study, 100 patients (men, women, mean age 39.5 years), 40 female, 60 male patients. 26 patient had DM, 30 patient present with hypertension, 4 had calculus disease, and 40 had no obvious background clinically.

According to KDOQI-CKD classification using C-G method GFR calculated 25 patients normal, 26 patients in stage -2, 20 patients had stage-3, 10 had stage-4, and 19 had stage-5 disease.

**Age range:**
Population of our study is mixed age distribution with mean age of 40-41 years. Age group representing all the age groups except under 10 year.

**Blood urea:**
45 patients had normal blood urea level and 55 patients had elevated blood urea level. Blood Urea >40 mg/dl considered as elevated < 40 mg/dl considered as normal.
Mean urea level: 58.4 mg/dl

**Serum creatinine:**
55 had raised elevated serum creatinine(>1.5mg/dl) , 45 patients are normal creatinine values. Creatinine level up to 1.4 mg/dl taken as normal above which is taken as elevated. Mean creatinine level: 3.7 mg/dl

**DATA ANALYSIS:**
The collected data was analysed with SPSS 16.0 version. To describe about the data descriptive statistics frequency analysis, percentage analysis were used for categorical variables and for continuous variables the mean and S.D were used. To find the significance difference between the bivariate samples in Independent groups (Normal & Abnormal) Independent t-test was used. For the multivariate analysis the one way ANOVA with Tukey's Post-Hoc test was used. To assess the relationship between the variables Pearson's Correlation was used ROC-Receiver operating characteristic curves were drawn to calculate area under the curve (AUC) to differentiate the two groups and cut off ADC values were calculated so as to achieve the highest average sensitivity and specificity. To find the significance in categorical data Chi-Square test was used. In all the above statistical tools the probability value .05 is considered as significant level.

**COMPARISONS :**

**BLOOD UREA VS ADC:**
(Table 1)

When Comparing the ADC with blood Urea, ADC values more than 2.466 x10-3mm2/sec on right side, 2.431 x10-3mm2/sec on left side seen only in patients with normal blood urea level. ADC below 1.907 x10-3mm2/sec on right side, 1.907 x10-3mm2/sec on left side seen only with elevated urea level. With normal Blood Urea show a high mean ADC (with level more than 2.466 x10-3mm2/sec on right side, 2.431 x10-3mm2/sec on left side), compared with raised Urea level show low ADC value with level (< 1.907 x10-3mm2/sec on right side, 1.9 x10-3mm2/sec on the left side seen).

**TABLE 1**

<table>
<thead>
<tr>
<th>ADC x10-3mm2/sec</th>
<th>RT kidney</th>
<th>LT kidney</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>2.466</td>
<td>2.431</td>
</tr>
<tr>
<td>Abnormal</td>
<td>1.907</td>
<td>1.9078</td>
</tr>
</tbody>
</table>

**INDEPENDENT SAMPLES TEST**
(Table 2)

ADC values more than 2.466 x10-3mm2/sec on right side, 2.431 x10-3mm2/sec seen on left side seen only in patients with normal blood urea level and ADC below 1.907 x10-3mm2/sec on right side, 1.907 x10-3mm2/sec on left side seen only with elevated urea level. Which is significant at 0.004 on right side, 0.002 on left side.
Correlating the ADC values with the urea level there is significant inverse correlation (with p value of <0.05)
SERUM CREATININE WITH ADC:
(Table 3)

With normal serum creatinine show a high mean ADC (with level more than 2.493 x10-3 mm2/sec on right side, 2.470 x10-3 mm2/sec on left side), compared with raised creatinine level show low ADC value with level (< 1.986 x10-3 mm2/sec on right side, 1.970 x10-3 mm2/sec on the left side seen which is significant at .000 (<0.05) on both sides. ADC values above 2.4x10-3 mm2/sec seen with normal creatinine level only. ADC values below 1.72 x10-3 mm2/sec seen with creatinine> 5 mg/dl only. Correlating the ADC values with creatinine level there is significant inverse correlation (with p value of <0.05).

Table 3 – ADC VALUES WITH DIFFERENT RANGE OF CREATININE LEVEL:

<table>
<thead>
<tr>
<th>Creatinine mg/dl</th>
<th>ADC RT</th>
<th>Creatinine mg/dl</th>
<th>ADC LT</th>
</tr>
</thead>
<tbody>
<tr>
<td>UPTO 1.5</td>
<td>2.49</td>
<td>UPTO 1.5</td>
<td>2.47</td>
</tr>
<tr>
<td>1.6-3.0</td>
<td>2.14</td>
<td>1.6-3.0</td>
<td>2.14</td>
</tr>
<tr>
<td>3.1-5.0</td>
<td>1.92</td>
<td>3.1-5.0</td>
<td>1.88</td>
</tr>
<tr>
<td>ABOVE 5</td>
<td>1.72</td>
<td>ABOVE 5</td>
<td>1.70</td>
</tr>
</tbody>
</table>

ROC analysis was performed for ADC in differentiating patients with elevated & normal renal parameters. On right side AUC for a cut off ADC value of 2.343 x10-3 mm2/sec, sensitivity was 85.5%, specificity was 86.7%, and 95% confidence intervals = (0.562, 0.878) on right side, (values lower than cut off indicated renal dysfunction). On left side For a cut off ADC value of 2.326 (x10-3 mm2/sec), sensitivity was 83.6%, specificity was 84.7%, and 95% confidence intervals = (0.562, 0.878) for left side (values below cut off indicated renal dysfunction). Average ADC VALUE FOR BOTH SIDE: 2.334 x10−3 mm2/s. Values of ADC below this cut off will indicate renal dysfunction.
CORRELATIONS : ADC WITH GFR:
(Table 7&8)

Represents a positive linear correlation ADC with GFR level. High ADC level are seen only with patient with normal GFR level on both side. When GFR falls ADC also falls. so we can predict the GFR and stage of kidney disease with parenchymal ADC level.

RI value between 0.58 -0.74.

RI values cannot be reliably correlated with the serum creatinine level. Measuring the RI value perfectly in patients the severely contracted kidneys and those unable to hold breath is difficult which operator dependent and needs patient co-operation. And some cases measuring RI is very difficult(obese persons, severely contracted kidneys, patients who unable to hold breath). Patients with renal dysfunction varied RI values from 0.58 to 0.78 .( p value>0.05) Pearson correlation: There is Positive but weak correlation between RT RI and creatinine: 0.314 (p= 0.06), between LT RI and creatinine: 0.264 ( p=0.06). This necessitates the further study for with known histopathological causes for renal dysfunction.

DISCUSSION:

The Renal parenchyma of the patients with elevated renal parameters has shown significantly low level of ADC compare to those with normal renal serum markers(10,11,19,22). Similar kind of results observed in other studies also. Lower ADC values in renal parenchymal disease which causing rise in the serum creatinine, Blood Urea is probably due to reduced perfusion and reduced water diffusion. The cause for reduction in the ADC level in Glomerulo-sclerosis, tubular atrophy, and interstitial fibrosis is due to reduction in free movement of water molecules both in the intra and extracellular space causing low ADC level. Average ADC value for both side: 2.334 × 10−3 mm2/s. Values of ADC below this cut off will indicate renal dysfunction. Very low level of ADC will be seen only in patient with very much elevated creatinine level and stage 4, 5 CKD patients. There
is a positive linear correlation between renal parenchymal ADC values and Glomerular filtration Rate in renal failure patients. Low ADC values are statistically significant with increasing stage of chronic kidney disease. So the ADC values can be added additionally to assess and monitor the stage of renal dysfunction. Similar to serum creatinine level, if the baseline ADC values are fixed then will be helpful in monitoring of parenchymal disease progression.

In this study ADC values of the asymmetric kidneys of two patients were differing with ADC value of above 2.42 x10^-3 mm2/sec noted in the normal side (LT) and decreased ADC 1.53 x10^-3 mm2/sec was measured in the small sized kidney (RT). So we can assess the ADC values of the individual kidneys by which we can assess the function of each kidney separately.

ADVANTAGES:

DW MRI in monitoring of renal function has following advantages.

- Short acquisition time
- Non invasive character
- Absence of ionizing radiation
- No contrast agents.
- No subjective variation
- Each kidney can be separately examined
- Morphological and functional detail can be obtained together in a single study
- Other associated organ pathology can be detected.
- We can differentiate malignant and benign lesion in case of mass lesion.

DRAWBACKS:

Availability and cost.

We should be aware that Diffusion Weighted MRI is in not alternate to serum markers (Blood Urea, Serum creatinine) or radio nucleotide study for evaluation of renal failure. It will serves as an extra tool, adding of which to the existing protocols will give more functional details.

LIMITATIONS OF THE STUDY:

- Sample size of study group was small.
- Patients with renal dysfunction without known aetiology.
- No Standardized protocol for the renal DWMRI.
- The major limitations for wide-spread use of DWI are regarding the selection of b values for renal imaging. Different studies done with different b values so fixing cut off values will be difficult.
- Detailed works needed in the evaluation of the precision and accuracy of the ADC values obtained with different MRI systems. Final results will allow investigators to reliably fix ADC Values and confidently apply DWI in clinical practice.

CONCLUSION:

Apparent Diffusion Co-efficient value can be implemented as an additional Marker to identify level of the renal function. ADC will be useful especially in patients those who undergoing MRI examination for other reasons we use the ADC value to detect renal dysfunction. It will be helpful known CKD patients to monitor the progression of disease. ADC values can measure each kidney separately and values are individually correlating with the elevated renal parameters. So we can assess the single kidney function separately and the kidney which is most severely deranged can be identified separately.

Cut off values of ADC can be fixed for identifying renal impairment and also to find out the different stages of CKD. The functional and morphological details of renal parenchyma (collecting system-MRI urography, and renal vessels -MRI angiography, DWI- parenchymal diffusion) - will make the MRI as a onestop modality for complete renal evaluation.

Renal resistive index has weak positive correlation(18,21) with the elevated renal serum markers because rise in the RI depends on the pathology (either tubulo-interstitial/glomerular), hence RI cannot be a reliable marker for identifying the stage of renal disease and to identify the progression of the renal dysfunction.

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Acknowledgement:
The patients, medicine and nephrology departments, MMC.
VALUE OF ADDING MR SPECTROSCOPY TO DYNAMIC CONTRAST-ENHANCED MR MAMMOMGRAM IN EVALUATING INDETERMINATE (BIRADS 3,4) BREAST LESIONS.

K. Geetha (1), Beula Emmanuel (2)

Abstract

Aim: The purpose of our study was to evaluate the diagnostic value of adding MR spectroscopy to dynamic contrast-enhanced MRI (DCE-MRI) in patients with indeterminate breast lesions - BIRADS 3 & 4.

Materials & methods: A total of 21 female patients with 27 lesions classified as BIRADS 3 & 4 by sono-mammography were examined by MRI using the multiphase dynamic sequence and proton MR spectroscopy using a high field magnet (3 Tesla). Sensitivity, specificity and accuracy for DCE-MRI, MRS and their combination were calculated and observed that combined contrast enhanced MRI with MRS had higher sensitivity, specificity and accuracy.

Results & Conclusion: Adding MR spectroscopy to conventional dynamic MRI in evaluating probable and indeterminate breast lesions offered additional information that increased the sensitivity and specificity of the conventional dynamic MRI in discriminating benign and malignant lesions and thus avoiding unnecessary intervention.

Key Words: DCE-MRI, MR spectroscopy, MR Mammogram, Indeterminate, breast lesions

INTRODUCTION:

The work-up for indeterminate breast lesions - BI-RADS 3 & 4 categories demands a short term follow up and or biopsy procedure. But most of breast lesions found are benign upon biopsy. New imaging techniques required for more precise evaluation of these indeterminate lesions. MRI of the breast provides a good tool for diagnosis based on the morphological and the kinetic data. In addition to morphologic and kinetic analyses, in vivo proton (1H) MR spectroscopy (MRS) of the breast, provides molecular information obtained in a non-invasive manner, has shown that choline-containing compounds can be detected in most breast cancers (4), whereas choline is generally not detectable in normal breast tissues. Thus MR spectroscopy can be helpful in diagnosis of indeterminate lesions based on the well-established principle that malignant tissues show elevated concentrations of choline, a product of membrane synthesis. So elevated choline is considered as marker for cancer (4). Therefore, in this study, the usefulness of adding MRS to DCE MRI breast as a problem-solving modality in patients with mammographic BI-RADS 3 and 4 lesions is investigated.

AIM:

The purpose of our study was to evaluate the diagnostic value of adding MR spectroscopy to dynamic contrast-enhanced MRI (DCE-MRI) in patients with indeterminate breast lesions - BIRADS 3 & 4 aiming at decreasing the un-necessary breast intervention.

METHODS AND MATERIALS:

This prospective study done in a period of six months from March 2015 to August 2015 was approved by our institutional review board. Twenty one patients (Mean ± S.D.; 50 ± 10 years) with 27 lesions of indeterminate mammograms by X-ray and sono-mammography classified as BIRADS 3 & 4 were included. Lactating mother were excluded as Lactating breasts are metabolically active, and to avoid false positivity in 1H-MRS. All women underwent post contrast 1H-MRS examination after given written consent. Please Scan this QR Code to View this Article Online

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informed consents.

All MRI and 1H-MRS scans were performed in the prone position for minimizing the effect of respiratory motion of the breasts, on a 3T MR scanner (GE, Healthcare, Signa HDx), using a dedicated phased array breast coil. Conventional MRI protocol included axial T2-weighted Fast Spin Echo imaging sequence (T2-FSE, TR/TE = 4260/102 msec, slice thickness = 6mm, spacing = 1.5mm and axial T2 short tau inversion recovery imaging sequence (STIR, TR/TE = 7100/32 msec, slice thickness = 6mm, spacing = 1.5mm). Dynamic contrast enhancement MRI sequence was performed using fat-suppressed three-dimensional T1-weighted vibrant dynamic images (flip angle = 10°, 1 mm3 isotropic voxel, one unenhanced and five contrast-enhanced acquisitions). Gadolinium was automatically injected over 10 seconds approximately. For 1H-MRS performance a single-voxel water and fat-suppressed point-resolved spectroscopy (PRESS) was acquired after contrast administration for evaluating the MR spectra resonances.

The postcontrast localization of the voxel would yield a better consideration of the lesion morphology including as much of the lesion as possible while avoiding surrounding adipose tissue. 1H-MRS sequence was acquired with the following technical parameters: TR/TE = 2,000/155 msec, number of excitations (NEX) NEX = 32 for any voxel size. This relatively long TE was chosen to increase the visibility of tCho resonance because of the longer T2 of tCho (>350 msec) in comparison to that of lipids (~100 msec). For voxel placement, sagittal contrast-enhanced T1-weighted MR images were used as scout images, and a voxel of interest was placed to include the lesion. tCho resonance in breast spectra was qualitatively determined, and the criteria for determining the presence or absence of tCho were that a peak should be clearly identifiable at 3.2 ppm within the lesion. Pathologic correlations were made for all patients.

RESULTS AND DATA ANALYSIS:

Data analysis of DCE has been performed through the evaluation of the ROI signal intensity over the time. The curve of wash-in and washout has been classified as type I, II and III as shown in figure 1. A type I curve shows a continuous signal increasing over the whole time and it is suggestive of benign. A type II curve, after an initial signal increase, flattens out and is related to an intermediate probability for malignancy. A type III curve, after a sharp increase, shows a rapid fallout and it is indicative of malignancy.

Final diagnoses were obtained with histopathologic analysis of the surgically excised specimen in 10 lesions and of core biopsy specimens in 9 lesions. Fine needle aspiration (FNA) cytologic analysis was performed in the remaining 8 lesions. Tissue diagnoses of ductal carcinoma in situ (DCIS) and any type of invasive carcinoma were counted as malignant. Patients with a benign diagnosis at core biopsy and FNA were followed-up within at least 1 year with mammography or ultrasound to ensure the stability of the index lesion. Pathologic correlations were made for all patients. DCE MRI data analysis shows 3 false positive
REPRESENTATIVE CASES:

CASE 1. Fifty-two years-old female with Sagittal MRI after Dynamic contrast (B), Perfusion(A) showing the enhancing mass. (C) The kinetic data obtained from the time intensity curve indicate a highly suspicious pattern, Type 3 curve was obtained (rapid rise followed by wash out). (D) The MR spectroscopy shows positive Choline peak. The lesion was histopathologically proven as invasive lobular carcinoma.

CASE 2. Forty-years female with Sagittal MRI after Dynamic contrast (B), Perfusion(A) showing the enhancing mass. (C) The kinetic data obtained from the time intensity curve indicate Type 1 curve was obtained (continuous signal increasing over the whole time). (D) The MR spectroscopy shows no Choline peak. The lesion was histopathologically proven fibroadenoma.

CASE 3. Forty-three years-old female with Sagittal MRI after Dynamic contrast (B), Perfusion(A) showing the enhancing mass. (C) The kinetic data obtained from the time intensity curve indicate benign Type 1 curve (D) But MR spectroscopy shows positive Choline peak. The lesion was histopathologically proven as Ductal carcinoma in situ.
lesions and 2 false negative lesions, MRS data analysis shows 1 false positive lesions and 3 false negative lesions whereas combined shows no false positive lesions and 1 false negative lesions. Sensitivity, specificity and accuracy of the MRI Parameters - DCE MRI, MRS and their combination were shown in Table 1 and Chart 1.

**DISCUSSION:**

DCE-MRI analysis by assessment of the time-signal intensity curve type (i.e., kinetic curve) and categorizing the washout pattern of a gadolinium contrast agent has been increasingly used to characterize breast lesions into benign and malignant. Breast MR spectroscopy also have just shown great promise in the MR diagnosis of breast lesions and in the therapeutic decision for patients with breast cancers. According to our results, the diagnostic sensitivity, specificity and accuracy of H MRS done using the 3T high field magnet for the 27 lesions in 21 patients were 78.57 % and 92.31% respectively (p <0.001). For the Dynamic MR- Mammography without spectroscopy, the sensitivity and specificity were 85.71 % and 76.92%, respectively (p <0.001). The false-negative lesions by MRS included 3 ductal NOS masses. The negative results could be explained by the tiny lesion and or central necrosis. The histologic diagnoses in the one false-positive mass lesions by MRS was giant fibro adenoma showing small bifid choline peak. The false negative lesions by dynamic MRM were 2 cases and the false positive lesions were 3 cases. The sensitivity and specificity of their combined contrast enhanced MRI with

<table>
<thead>
<tr>
<th>Lesion No</th>
<th>DCE-MRI Type</th>
<th>MRS - increased choline peak</th>
<th>DCE + MRS</th>
<th>Histology Type</th>
<th>Verification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>Absent (FN)</td>
<td>Malignant</td>
<td>Malignant</td>
<td>Biopsy</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>Absent (FN)</td>
<td>Malignant</td>
<td>Malignant</td>
<td>Biopsy</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>present</td>
<td>Malignant</td>
<td>Malignant</td>
<td>Surgery</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>present</td>
<td>Malignant</td>
<td>Malignant</td>
<td>Surgery</td>
</tr>
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<td>Malignant</td>
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<tr>
<td>6</td>
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<td>Malignant</td>
<td>Malignant</td>
<td>Surgery</td>
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<td>7</td>
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<td>Malignant</td>
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</tr>
<tr>
<td>9</td>
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<td>Benign (FN)</td>
<td>Malignant</td>
<td>Surgery</td>
</tr>
<tr>
<td>10</td>
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<td>Malignant</td>
<td>Malignant</td>
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<tr>
<td>11</td>
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<td>Benign</td>
<td>Benign</td>
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</tr>
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<td>Benign</td>
<td>Biopsy</td>
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<td>Benign</td>
<td>Biopsy</td>
</tr>
<tr>
<td>14</td>
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<td>Malignant</td>
<td>Malignant</td>
<td>Surgery</td>
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<tr>
<td>15</td>
<td>3</td>
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<td>Malignant</td>
<td>Malignant</td>
<td>Biopsy</td>
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<td>16</td>
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<td>Malignant</td>
<td>Malignant</td>
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<tr>
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<td>Malignant</td>
<td>Malignant</td>
<td>Biopsy</td>
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<tr>
<td>18</td>
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<td>Benign</td>
<td>Biopsy</td>
</tr>
<tr>
<td>19</td>
<td>1</td>
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<td>Benign</td>
<td>FNAC</td>
</tr>
<tr>
<td>20</td>
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<td>Benign</td>
<td>Benign</td>
<td>Surgery</td>
</tr>
<tr>
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<td>Benign</td>
<td>Benign</td>
<td>FNAC</td>
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<tr>
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<td>Benign</td>
<td>Benign</td>
<td>FNAC</td>
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<tr>
<td>23</td>
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<td>Benign</td>
<td>Benign</td>
<td>FNAC</td>
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<tr>
<td>24</td>
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<td>Benign</td>
<td>Benign</td>
<td>FNAC</td>
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<tr>
<td>25</td>
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<td>Benign</td>
<td>Benign</td>
<td>FNAC</td>
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<tr>
<td>26</td>
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<td>Benign</td>
<td>Benign</td>
<td>FNAC</td>
</tr>
<tr>
<td>27</td>
<td>1</td>
<td>Absent</td>
<td>Benign</td>
<td>Benign</td>
<td>FNAC</td>
</tr>
</tbody>
</table>

Master Chart showing Number of lesions and their findings in DCE-MRI, MR Spectroscopy, verification method and Histology (FN = False Negative; FP = False Positive).
MRS increased to 92.86% and 100%, respectively. These results were comparable to the previously published (1,5–7). Naglaa Mohamed Abdel Razek et al. proved breast cancer detection through the combination of enhancement information from DCE-MRI and MRS.

The results of this study using a 3T MRI suggested that careful referencing and optimizing post acquisition data processing improved the spectral resolution resulting in few false-positive and false negative cases. In this study, H MRS was performed using the residual water signal as a reference. Higher sensitivity of our study compared to previous studies (1) of 1.5-T MRI is attributed to high field magnet. It is difficult to routinely perform H MRS on a 1.5-T MR unit to characterize breast masses smaller than 15 mm but based on our results, the potential availability of higher-field-strength magnets will enable us to characterization of smaller breast lesions by the MRS. Based on our results we found that presence of a high choline peak in MRS yields best for characterizing indeterminate breast lesions. The combined assessment of kinetic data of DCE-MRI together with the MRS allows better characterization of indeterminate breast lesions.

CONCLUSION:

Adding MR spectroscopy to conventional dynamic MRI in evaluating probable and indeterminate breast lesions offered additional information that increased the sensitivity and specificity of the conventional dynamic MRI in discriminating benign and malignant lesions and thus avoiding unnecessary intervention.

REFERENCES:

5. Naglaa Mohamed Abdel Razek, , Amr Osama Azaba, Omar Sherif Ombar, Hussein Osama Solimanc et al., Role of proton MR spectroscopy in the high field magnet (3T) in diagnosis of indeterminate breast masses (BIRDS 3 & 4) The Egyptian Journal of Radiology and Nuclear Medicine, Volume 43, Issue 4, Pg 657-662 (Dec 2012)
INTRODUCTION:

Coronary arterial calcification is a change occurring almost exclusively in atherosclerotic arteries, and is absent in the normal vessel wall. Hence the presence of any coronary arterial calcification is nearly 100% specific for atheromatous coronary plaque. Since both obstructive and non-obstructive lesions can have calcification present in the intima, coronary arterial calcification is not specific for obstructive coronary disease. Patients who have calcified plaque are also more likely to have non-calcified or soft plaque that is prone to rupture and acute coronary thrombosis.

AIM:

The purpose of the study is to compare CAC (coronary artery calcium) score in patients with Obstructive & Non obstructive coronary artery disease CAD and to compare CAC score in patients with single & multivessel disease and between infarct related artery & other vessels in multivessel disease. The study is a prospective observational non interventional study involving 100 patients after the treatment of ST-segment elevation myocardial infarction. Based on coronary angiogram findings the study population is categorized into study group with obstructive coronary artery disease and non obstructive coronary artery disease. The assessment of CAC score was done with no knowledge about the CAG lesions of the patients concerned.

MATERIAL & METHODS:

The study is a prospective observational non interventional study involving 100 patients after the treatment of STEMI (ST-segment elevation myocardial infarction) was conducted in the Barnard Institute of Radiology, Government General Hospital, Chennai, during the year 2011 – 2015 after Ethical committee clearance was obtained. Informed consent obtained for all patients. All patients following STEMI (diagnosed by History, ECG, ECHO & Enzymes) including both recent & old myocardial infarction, irrespective of age & sex are included in the study. All patients with acute coronary syndrome, chronic stable angina, chronic kidney disease, uncontrolled tachycardia were excluded. Based on coronary angiogram (CAG) findings the study population is categorized into study group with obstructive coronary artery disease and non obstructive coronary artery disease.
and must be a single volume. The images selected for scoring must be from the same series, with equal spacing between them, and whose slice thickness is equal to or greater than the spacing. Since the scoring process provides quantitative results, all images from the region being scored must be selected, not just those images with visible calcifications.

**RESULTS:**

The study population included 100 patients (91 males and 9 females) who had undergone CAC scoring after coronary angiography evaluation following STEMI. The results were analyzed by the statistical methods- Chi-square test, Mann Whitney U Wilcoxon Rank Sum test, Correlation coefficient methods & Multiple regression analysis and p values were found. The study showed poor sensitivity, specificity, predictive values and likelihood ratios in detecting Agatston score in Obstructive CAD in comparison to Nonobstructive CAD. The p values show no statistical significance.
DISCUSSION:

Our study showed poor sensitivity, specificity, predictive values and likelihood ratios in using Agatston score to differentiate Obstructive CAD from Nonobstructive CAD. The p values show no statistical significance. There is no correlation between the CAG stenosis and the CAC score of the vessel involved among patients with Non obstructive CAD or obstructive CAD. The CAC score was analyzed between double and triple vessel involvement with single vessel disease. It was found that there is no increase in either the positivity or the degree of CAC score with multivessel involvement when compared to single vessel disease.

CONCLUSION:

Sixty four slice MDCT derived Agatston score

<table>
<thead>
<tr>
<th>CAX</th>
<th>LAD</th>
<th>LCX</th>
<th>RCA</th>
<th>TOTAL</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAG</td>
<td>LAD</td>
<td>0.1545</td>
<td>0.0258</td>
<td>0.0161</td>
<td>0.1128</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P=0.284</td>
<td>P=0.859</td>
<td>P=0.912</td>
<td>P=0.436</td>
</tr>
<tr>
<td></td>
<td>LCX</td>
<td>0.0038</td>
<td>0.1617</td>
<td>0.1529</td>
<td>0.0298</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P=0.979</td>
<td>P=0.289</td>
<td>P=0.289</td>
<td>P=0.837</td>
</tr>
<tr>
<td></td>
<td>RCA</td>
<td>0.0893</td>
<td>0.075</td>
<td>0.1718</td>
<td>0.1663</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P=0.538</td>
<td>P=0.605</td>
<td>P=0.233</td>
<td>P=0.248</td>
</tr>
</tbody>
</table>

Table 3 showing the significance of individual vessel involvement and CAC scores in patients in Group I

A detailed analysis of CAG lesions of individual vessel was correlated with the CAC scores of corresponding vessel in patients among Non obstructive CAD. The details of Group II comparing CAG with CAC score were analyzed using the correlation coefficient method and the details revealed no statistical significance (Table 2). A detailed analysis of CAG lesions of individual vessel was correlated with the CAC score of the corresponding vessel of patients among obstructive CAD. The details of Group 1 comparing CAG with CAC score were analyzed using the correlation coefficient method and the details revealed no statistical significance (Table 3).

About 90% of AWMI patients showed LAD involvement whereas LCX & RCA are the predominant culprit vessels among patients with IWMI/RVMI. The significance of correlation of multivessel involvement and total calcium scoring was analyzed by multiple regression analysis (Table 4).

<table>
<thead>
<tr>
<th>S.NO</th>
<th>VESSELS INVOLVED</th>
<th>MULTIPLE R</th>
<th>SIGNIFICANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LAD &amp; LCX</td>
<td>0.112</td>
<td>NO</td>
</tr>
<tr>
<td>2</td>
<td>LAD &amp; RCA</td>
<td>0.245</td>
<td>NO</td>
</tr>
<tr>
<td>3</td>
<td>LCX &amp; RCA</td>
<td>0.166</td>
<td>NO</td>
</tr>
<tr>
<td>4</td>
<td>LAD, LCX &amp; RCA</td>
<td>0.250</td>
<td>NO</td>
</tr>
</tbody>
</table>

Table 4 showing the significance of multivessel involvement and CAC scores in patients in both groups.
shows poor correlation in differentiating the obstructive and non obstructive coronary artery disease following STEMI. CAC score was not useful to identify infarct related artery. There was no linear correlation between CAC score and the number of vessel involvement.

REFERENCES:

A STUDY ON THE CURRENT STATUS OF NEONATAL TRANSPORT TO A SPECIAL NEWBORN CARE UNIT

Punitha P(1), K.S.Kumaravel(2), Pugalendhiraja K V(3), Santhoshkumar(4)

Abstract

Introduction: Neonatal care in India has witnessed a revolution in the last 10 years under the auspices of National Rural Health Mission (NRHM). The major causes of neonatal mortality in developing countries are Prematurity, Birth asphyxia and Sepsis. Institutional delivery and in utero transport of newborn is the safest way to transport a sick neonate. But unfortunately preterm delivery and many other perinatal illnesses cannot be always anticipated. Hence we undertook this study to analyse the profile of newborn babies referred to our SNCU.

Study design: This is a cross sectional study of neonates admitted in SNCU of Govt Dharmapuri Medical College Hospital, Dharmapuri, Tamilnadu from April’2016 to June’2016.

Results: About 75% of neonates were transported by neonatal ambulance service. About 25% of the neonates were transported by self arranged conveyance. On analysis of TOPS scores, about 26% of neonates had hypoglycemia, 14% had low oxygen saturation, 15% had prolonged capillary refill time and 19% had hypoglycemia. In the self arranged transport group, the TOPS score was significantly abnormal. During the study period 23(6.6%) neonates died.

Conclusion: Though almost all the neonates are safely transported in neonatal ambulances in the government sector, there has been a paucity of neonatal ambulances in the private sector. Most of the available ambulances now are not adequately equipped to handle sick new born babies. So extension of neonatal ambulance services to all babies referred to SNCU will improve the survival of neonates.

Keywords: Neonatal transport, Ambulance, Infant Mortality Rate, Special Newborn Care Units

INTRODUCTION:

Neonatal care in India has witnessed a revolution in the last 10 years under the auspices of National Rural Health Mission (NRHM). Under NRHM, Special Newborn Care Units (SNCU) were established across the country. These units helped in a great reduction in Infant Mortality Rate (IMR) in the country. Two-third of IMR is contributed by deaths within the first week of life(1). The major causes of neonatal mortality in developing countries are Prematurity, Birth asphyxia and Sepsis(2). Institutional delivery and in utero transport of newborn is the safest way to transport a sick neonate. But unfortunately preterm delivery and many other perinatal illnesses cannot be always anticipated. This makes the transport of an ailing neonate inevitable. These babies are often critically ill and the outcome is also dependant on the effectiveness of transport system. In most of these newborn babies the ineffective transport system results in hypoglycemia, hypothermia, cyanosis and other complications(3,4,5). These complications further increase the morbidity and mortality among these sick neonates. A further fall in IMR can only be achieved by improving the Neonatal Transport Facilities.

The introduction of Neonatal 108 ambulance services in Tamilnadu has revolutionised the transport of sick neonates to the SNCU. They transport sick neonates from the Primary Health Centres and Govt Hospitals to nearby SNCU. They are equipped with ventilators, warmers and other resuscitation equipments. They are also manned by technicians trained in neonatal resuscitation. But in the private sector the neonatal ambulance services are sparse. They are neither equipped nor manned for transporting neonates. It is well known that the transport of newborn baby by a skilled organised team reduces neonatal mortality and morbidity(6). Navjat shishu suraksha karyakram(NSSK) launched by Government of India also emphasizes the role of safe neonatal transport(7). Hence we undertook this study to analyse the profile of newborn babies referred to our level III NICU.

METHODOLOGY:

This is a cross sectional descriptive study of neonates admitted in SNCU of Govt Dharmapuri Medical...
College Hospital, Dharmapuri, Tamilnadu from April'2016 to June’2016. The inclusion criteria was all neonates born extramurally and referred to our SNCU for care. The exclusion criteria were the neonates having major congenital anomaly, neonates referred for surgical care and neonates who were discharged Against Medical Advice. A Proforma was designed and their case records were scrutinised for Place of birth, Birth weight, Gestational age, Mode of Transport, final diagnosis and outcome. The TOPS score of every neonates was recorded separately. TOPS is a simplified assessment of neonatal acute physiology which gives a very good prediction of mortality in transported neonates(8). It includes Temperature, Oxygenation, Perfusion by capillary refilling time(CRT), Sugar by reagent strip. Hypothermia, hypoxia, prolonged CRT and hypoglycemia were defined as <36.5°C, <90%, ≥ 3 seconds and <45mg/dl respectively (8). Neonatal physiology is adversely affected in TOPS and was shown to predict the mortality in transported neonates by MathurNB et al(8). For birth weight, gestational age and diagnosis standard case definitions were used (9). Outcome was measured as discharged and died. Descriptive statistics was employed used Microsoft Office Excel.

RESULTS:

The demographic profile of neonates transferred to the SNCU during the study period has been depicted in table: 1. About 348 neonates were referred from various centres to this SNCU. The male: female sex ratio is 1.4:1. About 45% of neonates transported were of Low Birth Weight. About 60% of transported babies were preterm. Respiratory distress, Birth asphyxia, Meconium aspiration and Septicemia were the predominant causes for transportation of neonate.

About 75% of neonates were transported by neonatal ambulance service. About 25% of the neonates were transported by self arranged conveyance. On analysis of TOPS scores, about 26% of neonates had hypoglycemia,
14% had low oxygen saturation, 15% had prolonged capillary refill time and 19% had hypoglycemia. During the study period 23(6.6%) neonates died. Respiratory distress syndrome and septicemia were the major causes of mortality.

On analysis of correlation between TOPS score and mode of transport, we observed a significantly higher percentage of neonates having abnormal TOPS scores in the self arranged transport group (Table: 2).

**DISCUSSION:**

Prematurity and low birth weights are the major reasons for referral in the present study and same has been observed in many studies from other developing countries (10,11). So this finding emphasizes the need for safe neonatal transport system to improve the survival on neonates. The neonatal transport in India has taken a giant leap in the last decade. In a study in 2001 by Sehgal Arvind, it was observed that only 5% of neonates were transported in ambulances equipped and manned to resuscitate neonates(10). In the present study we observed about 75% of neonates were transported in ambulances. However a further fall in Infant mortality rate will occur only if universal safe neonatal transport has been achieved. This has become a necessity as India has achieved more than 95% institutional deliveries(12). In the present study hypothermia was observed in 26% of transported neonates and is the commonest deranged neonatal physiology. Similar phenomenon was observed in other studies by Bhoopalam et al, Mathur et al and Rathod et al (8,13,14).

In the present study we observed a significantly higher percentage of deranged TOPS in self arranged transported neonates when compared to neonates transported by neonatal ambulance. A study by Podduttoor Preetham Kumar also observed similar trend(15). Prior stabilization and adequate care during transport are associated with lesser chances of hypoglycemia, acidosis and mortality.

<table>
<thead>
<tr>
<th>Mode of transport</th>
<th>Presence of Hypothermia</th>
<th>Low oxygen saturation</th>
<th>Prolonged Capillary refill time</th>
<th>Hypoglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal ambulance</td>
<td>8(2.3%)</td>
<td>9(2.58%)</td>
<td>12(3.44%)</td>
<td>16(4.59%)</td>
</tr>
<tr>
<td>Self arranged</td>
<td>82(23.5%)</td>
<td>39(11.2%)</td>
<td>40(11.49%)</td>
<td>49(14.08%)</td>
</tr>
</tbody>
</table>

Table: 2 Correlation between mode of transport and TOPS scores

Premature, LBW and sick term babies are at risk for developing these complications. Early recognition of these derangements will improve survival of sick neonates.

**CONCLUSION AND RECOMMENDATIONS:**

Adhering to strict neonatal transport protocol, pre transport stabilisation, increasing the fleet of neonatal ambulances, training the ambulance technicians in care during the transport, and equipping all ambulances with equipments for neonatal care will help in reducing the neonatal morbidity and mortality. Though almost all the neonates are safely transported in neonatal ambulances from government sector, there has been a paucity of neonatal ambulances in the private sector. Most of the available ambulances now are not adequately equipped to handle sick new born babies. So extension of neonatal ambulance services to all babies referred to SNCU will improve the survival of neonates.

**REFERENCES:**

INRODUCTION: Thrombocytopenia is defined as platelet count of less than 1,50,000/µL irrespective of the individual's age. In Neonatal Intensive Care Units (NICU) it is the commonest haematological abnormality encountered except for phlebotomy induced anemia (1). Around 20-40% of neonates admitted to NICU will develop thrombocytopenia and 20% of them will develop severe thrombocytopenia.

OBJECTIVES: 1. To study the etiological profile, clinical spectrum and immediate outcome of neonates admitted with thrombocytopenia in our NICU. 2. To study the predisposing factors associated with neonatal thrombocytopenia.

Keywords: Neonatal Thrombocytopenia, Platelet count, Septicemia

Key message: Septicemia and birth asphyxia are the major causes of neonatal thrombocytopenia.
SUBJECTS AND METHODS:

This is a retrospective study of 100 consecutive thrombocytopenic babies irrespective of their underlying illness admitted in the NICU of Government Dharmapuri Medical College Hospital, Dharmapuri from January’2014. All neonates admitted in the NICU of Government Dharmapuri medical College, Dharmapuri and who had thrombocytopenia with a platelet count of less than 1,50,000 per cubic mm of blood formed the study group.

The case sheets of all the babies admitted in the NICU were scrutinized. Those neonates whose platelet counts were less than or equal to 1,50,000 per cubic mm of blood were included in the study. A proforma was designed to include maternal history, natal history, APGAR score at birth, birth weight, gestational assessment using New Ballard Scoring, presence of birth asphyxia, presence of mucosal bleed, Gastro Intestinal bleed, internal bleeding, platelet count, Hb%, sepsis workup, blood culture and final outcome. After this, the neonates were grouped into two groups based on their platelet counts. Group I included those neonates with a platelet count between 50,000/cu.mm to 1,50,000/cu.mm. Group II included neonates with a platelet count of <50,000/cu.mm. The standard case definitions were used. The outcome was measured as discharged and expired.

STATISTICAL ANALYSIS:

The descriptive data are represented as percentage or number. By means of Chi-square test, the two groups were compared for categorical variables. One way analysis of variance (ANOVA) or unpaired student t test was used for continuous variables. A P value of less than 0.05 was taken as significant.

<table>
<thead>
<tr>
<th></th>
<th>GROUP I</th>
<th>GROUP II</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Percent</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>71</td>
<td>71%</td>
<td>29</td>
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<table>
<thead>
<tr>
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<th>Mean (Standard Deviation)</th>
<th>Mean (Standard Deviation)</th>
</tr>
</thead>
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<tr>
<td></td>
<td>87323.94 (20032.67)</td>
<td>32862.07 (6271.96)</td>
</tr>
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<table>
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<th>MALE</th>
<th>FEMALE</th>
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<tr>
<td></td>
<td>37(52.1%)</td>
<td>34(47.9%)</td>
</tr>
<tr>
<td></td>
<td>17(58.6%)</td>
<td>12(41.4%)</td>
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</table>

<table>
<thead>
<tr>
<th>GESTATIONAL AGE DISTRIBUTION</th>
<th>TERM</th>
<th>PRETERM</th>
<th>28-30WEEKS</th>
<th>30-32WEEKS</th>
<th>32-34WEEKS</th>
<th>34-36WEEKS</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>29(41.8%)</td>
<td>42(59.2%)</td>
<td>2(6.2%)</td>
<td>2(6.2%)</td>
<td>15(35.7%)</td>
<td>18(42.8%)</td>
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</tbody>
</table>

<table>
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<th>PLACE OF DELIVERY</th>
<th>INTRAMURAL</th>
<th>EXTRAMURAL</th>
</tr>
</thead>
<tbody>
<tr>
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<td>25(35.2%)</td>
<td>46(64.8%)</td>
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<table>
<thead>
<tr>
<th>BIRTH WEIGHT DISTRIBUTION</th>
<th>&lt;=1 KG</th>
<th>1-2.5KG</th>
<th>&gt;2.5KG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4(5.6%)</td>
<td>29(40.8%)</td>
<td>38(53.6%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CORRELATION BETWEEN THROMBOCYTOPENIA AND MATERNAL PIH</th>
<th>PIH</th>
<th>NON PIH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>11</td>
<td>60</td>
</tr>
</tbody>
</table>

| TABLE I: PROFILE OF NEONATES WITH THROMBOCYTOPENIA |
|---------------------------------------------------|------|-------|
| P value 0.0001 (significant)                      |      |
| ONSET OF THROMBOCYTOPENIA                         |      |
| EARLY ONSET                                       | 22   | 10    |
| LATE ONSET                                        | 49   | 19    |
| CAUSES OF THROMBOCYTOPENIA                        |      |
| SEPTICEMIA                                        | 29   | 9     |
| BIRTH ASPHYXIA                                    | 17   | 8     |
| PRETERM/BIRTH ASPHYXIA                            | 10   | 2     |
| OTHERS                                            | 1    | 6     |
| PREV ALENCE OF BLEEDING                           |      |
| WITH BLEED                                        | 9    | 26    |
| NO BLEED                                          | 62   | 3     |
| TYPE OF BLEED                                     |      |
| GI BLEED                                          | 6    | 20    |
| SKIN(PETECHIAE/ PURPURA)                          | 2    | 3     |
| GI/PULMONARY                                      | 1    | 1     |
| GI/SKIN                                           | 0    | 6     |
| OUTCOME                                           |      |
| DISCHARGED                                        | 68   | 27    |
| DIED                                              | 3    | 2     |
RESULTS:

The study group was divided into two groups based on the severity of thrombocytopenia. There were 71 babies in group I and 29 babies in group II. The demographic and clinical profile of the study group is shown in Table I.

The male: female sex ratio of the study population was 1.2:1. This table shows a slightly higher incidence of severe thrombocytopenia in male babies. The study group consisted of 42% of term babies and 58% of preterm babies. Among the severely thrombocytopenic babies in the study group, 45% were term babies and 55% were preterm babies. Among the study group, 68 cases were born extramural. The table shows that about three-fourths of the severely thrombocytopenic babies were born extramural. The table shows that nearly half of the preterm babies included in the study group were late preterm. About 31% of preterm babies had severe thrombocytopenia. The table shows that nearly half of the babies were below 2.5 kg.

Maternal PIH was significantly associated with severe thrombocytopenia in group II neonates than in group I neonates with mild to moderate thrombocytopenia. The p-value obtained by Chi-square method was 0.001 which is significantly higher. The association of other maternal factors such as GDM, Mode of delivery, Rh incompatibility, APH and PROM with thrombocytopenia was not statistically significant. About 32 babies had early onset thrombocytopenia (0-3 days) and about 68 babies had late onset thrombocytopenia (onset more than three days). It was observed that a significantly higher proportion of cases presented with thrombocytopenia only after 72 hours. On analysis of the cause for thrombocytopenia, septicemia remained as the predominant cause in both the groups as seen in the table. The second major cause was birth asphyxia in both the groups. NNEC was seen in 4 babies of which 2 had moderate thrombocytopenia and 2 had severe thrombocytopenia. The prevalence of bleeding was significantly high in group II. About 35 neonates had some form of bleeding. In group I the prevalence was 12.6% whereas in group II it was higher 89.7%. This shows that severely thrombocytopenic infants bleed more frequently. P value was calculated by chi square test and found to be 0.001 which was significantly high. Petechiae were less than 1 cm in size, red, circumscribed and non blanchable lesions and purpura are the same lesions when more than 1 cm in size. About 5 neonates had purpura. The table shows that GI bleed was the most common site of bleed in the study group. About 2 neonates had both gastrointestinal and pulmonary bleeding and about 2 neonates had both gastrointestinal and cutaneous bleeding. In the study group 5 neonates died and the proportion of mortality was significantly high in the severely thrombocytopenic infants. The mortality was significantly high in the severely thrombocytopenic infants which was 2(7%) when compared to the group I infants in which it was 3(4%).

The association between gestational age and platelet count was analysed using one way ANOVA and found to be not associated with thrombocytopenia (Table II).

Septicemia as confirmed by blood culture was found to be significantly associated with thrombocytopenia. The prevalence of septicemia was significantly high in both the groups. The incidence of severe thrombocytopenia was significantly high in gram negative sepsis when compared to gram positive sepsis. DIVC was found to be strongly associated with severe thrombocytopenia. In the study group 7 (7%) babies had DIVC of which 4(4%) were due to sepsis and 3(3%) were due to Birth Aphyxia. Babies with DIVC had a significant mortality of 86%.

<table>
<thead>
<tr>
<th>GESTATIONAL AGE</th>
<th>PLATELET COUNT</th>
<th>MEAN</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>28 – 30 weeks</td>
<td>5(5)</td>
<td>66666.67</td>
<td>6261.50</td>
</tr>
<tr>
<td>30 – 32 weeks</td>
<td>12(12)</td>
<td>72631.58</td>
<td>33473.39</td>
</tr>
<tr>
<td>32 – 34 weeks</td>
<td>14(14)</td>
<td>69840.91</td>
<td>28651.02</td>
</tr>
<tr>
<td>34-36 weeks</td>
<td>27(27)</td>
<td>77272.73</td>
<td>34734.62</td>
</tr>
<tr>
<td>&gt;=37 weeks</td>
<td>42(42)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p-value 0.72(not significant)*
A common haematological abnormality encountered in NICU is neonatal thrombocytopenia. There are many predisposing factors for thrombocytopenia and they interact in a complex manner to cause thrombocytopenia. Like other illnesses, the manifestations are variable and the severe form of neonatal thrombocytopenia is very well documented to be associated with poor outcome.

Similar to the other Indian studies, the etiological profile in our study showed septicemia and perinatal asphyxia as the common causes for neonatal thrombocytopenia. In both the groups septicemia was the predominant cause of Thrombocytopenia. Perinatal asphyxia was the next most common cause. DIVC accounted for nearly 7% of all cases. According to Western medical literature, prematurity, IUGR and birth asphyxia were the common causes for neonatal thrombocytopenia whereas in our study septicemia was the common cause. The mechanism by which septicemia leads to thrombocytopenia is by decreased platelet production as well as increased platelet consumption and sequestration in the enlarged spleen usually resulting in severe thrombocytopenia. This difference may be due to the higher incidence of septicemia in our extramural admissions which warrants the need for strict aseptic precautions while conducting deliveries as well as in handling the newborn babies. Intrauterine infection, CMV infection causing thrombocytopenia was found in one neonate. The baby had hepatosplenomegaly, severe thrombocytopenia causing purpuric spots and mucosal bleeding. CT Brain showed diffuse calcifications. The baby died on tenth day of life in spite of platelet and blood transfusions.

Maternal PIH had a significant association with neonatal thrombocytopenia in our study. This is in concordance with the study conducted by Burrows et al (7). In our study maternal PIH was more commonly associated with severe thrombocytopenia whereas in other studies it was associated with mild to moderate forms. This disparity once again can be explained by the fact that these high risk infants would have also acquired infections which led to severe forms of thrombocytopenia. Other factors like GDM, Rh incompatibility, APH, mode of delivery, gestational age were not significantly associated with thrombocytopenia in our study unlike other studies where there is a strong documentation for association for these factors (8).

In our study, 59% infants presented after 72 hours of life. This finding is in concurrence with other studies which also showed a well documented finding that majority of the severely thrombocytopenic infants presented only after 72 hours of life and the most common etiology is the late onset sepsis (9).

There was a strong association between septicemia and thrombocytopenia in both the groups in our study. This is in accordance with other studies where sepsis is a well recognized risk factor for low platelet counts in neonates admitted in NICU (8). According to Western literatures, around 10% of babies with sepsis and severe thrombocytopenia had DIVC (10). In our study 7% of cases had DIVC. The exotoxins and lipopolysaccharide of the bacteria will cause endothelial dysfunction contributing to DIVC. Regarding the incidence of thrombocytopenia, some studies show that there is an association between gram negative sepsis and thrombocytopenia while many other studies fail to show such an association. This may be explained by the pathological variations in the mechanism of sepsis among various organisms. In our study there is a higher incidence of thrombocytopenia and mortality among gram negative sepsis when compared to gram positive sepsis. Around 50% of group I and 40% of group II babies had gram negative sepsis.

In our study there was a significant association between birth asphyxia and thrombocytopenia. The P value was found to be 0.01. It is in concordance with most other studies showing a significant association of perinatal asphyxia with low platelet counts (4). A study done in 1976 showed that thrombocytopenia may be found in 90% of cases with NNEC, with a platelet count of less than 50,000/µL (11). Among the 4 babies with radiological evidence of NNEC in our study, 2 had severe thrombocytopenia. This

<table>
<thead>
<tr>
<th>SEPSIS WORKUP</th>
<th>GROUP-I</th>
<th>GROUP- II</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO. OF BABIES</td>
<td>PERCENTAGE</td>
<td>NO. OF BABIES</td>
</tr>
<tr>
<td>CULTURE POSITIVE</td>
<td>60</td>
<td>84.5</td>
</tr>
<tr>
<td>CULTURE NEGATIVE</td>
<td>11</td>
<td>15.5</td>
</tr>
<tr>
<td>TOTAL</td>
<td>71</td>
<td>100</td>
</tr>
</tbody>
</table>

Chi square 7.79
p-value 0.01(significant)

Table:III CORRELATION BETWEEN THROMBOCYTOPENIA AND SEPTICEMIA
is in agreement with the well known factor that low platelet count is one of the reliable laboratory markers for NNEC. Other factors such as exchange transfusion, hyperbilirubinemia, RDS, MAS were not significantly associated with thrombocytopenia. Exchange transfusion done using non fresh blood can lead to thrombocytopenia. Since in our study only fresh whole blood was used for exchange transfusion there was no significant association of exchange transfusion with thrombocytopenia.

Several studies showed severely thrombocytopenic infants bleed more frequently than their normal counterparts(2,4). In our study mucosal bleed was significantly associated with thrombocytopenia. While 13% of group I infants had bleed, 90% of group II infants had bleed like G.I. bleed, pulmonary hemorrhage, skin bleed. The mortality rate was significantly high in the severely thrombocytopenic infants which were around 7% when compared to the group I infants in which it was 4% it may be due to the severity of the underlying illness or the incidence of higher complications in severely thrombocytopenic infants.

**CONCLUSION:**

Septicemia was the major cause associated with both mild to moderate and severe thrombocytopenia. The predisposing factors associated with neonatal thrombocytopenia were maternal PIH, age at presentation, place of delivery, septicemia, NNEC, DIVC and perinatal asphyxia. Bleeding of any sort either mucosal or skin was significantly associated with severe thrombocytopenia. Mortality rate was far more common among the severely thrombocytopenic infants.

Hence it can be concluded that septicemia and birth asphyxia are the most common and most important cause of neonatal thrombocytopenia. Various maternal and neonatal factors contribute to it. Extramural cases contributed a higher percentage for these sepsis cases. Hence it will be easier and cost effective to prevent thrombocytopenia and its death by preventing the occurrence of sepsis and birth asphyxia rather than by treating these infections with higher antibiotics later in the course of illness.

**REFERENCES:**

ABUSE PATTERN, PERPETUATING FACTORS AND CO-MORBIDITY ISSUES AMONG SUBSTANCE USERS AND PATIENTS WITH PSYCHOSIS

P. Natarajan (1), Venkatesh Madhan Kumar (2), T.V. Asokan (3), G.S. Chandralekha (4)

Abstract

Context: Substance Abuse is a common comorbidity with psychotic illnesses. Although several theories exist to explain this link, individual reasons for use may differ.
Aims: The aim of this study was to evaluate abuse, perpetuating factors and comorbidity issues among substance users and patients with psychotic illness.
Settings and Design: The study was done in the Psychiatry Department, Govt. Stanley Medical College Hospital, Chennai using a cross-sectional study design.
Methods and Material: Patients were divided into two groups viz (1) Psychotic illness with substance use and (2) substance use individuals without psychosis. Individuals are diagnosed with Psychotic disorders using ICD-10 Diagnostic Criteria. They were analyzed by semi structured proforma, Inventory of Drug Taking Situations, (IDTS) and Global assessment of functioning (GAF) and comparative analysis between these groups was done.
Statistical analysis used: the student-t test was used for continuous variables and Pearson’s chi-square test was used for categorical variables.
Results: There were significant differences between the two groups for the pattern and perpetuating factors for substance use and there was family history of substance use more with substance use disorders and less with psychotic patients. The causes of maintenance of substance use were internal factors in psychotic patients and external factors for substance use disorder patients.
Conclusions: In psychotic patients with substance use identifying the internal factors would definitely help in compliance, treatment and prognosis of these patients.
Key-words: abuse, perpetuating factors, comorbidity, substance users, psychosis.

INTRODUCTION:

Substance use by people with mental illness is much higher than in general population (1) . A study by Spencer et al shows lifetime rate of alcohol abuse in patients with schizophrenia related disorders and/or bipolar disorder to be 36.3% for males and 15.7% for females as opposed to the general population estimate of 3.1% for males and 1.3% for females. The study also showed the rate of illicit substance use to be 38.7% for males and 17% for females among psychotics as opposed to 9.4% and 3.7% respectively in the general population.

Among psychotics, substance use is an increasing problem that affects the course and outcome of psychotic illnesses. (2) The renowned Epidemiologic Catchment Area study, revealed a lifetime prevalence of 47% for substance misuse in patients with schizophrenia [33.7% - alcohol abuse and dependence, 27.5% other drug misuse] and 56% prevalence of substance use in Bipolar illness.

Prevalence of substance use disorders varies between 24-50% (3). By SUD, we refer to use, harmful use and dependence of alcohol with or without other substances.

Substance use is a common comorbidity with psychotic illness. In spite of increased frequency of substance use disorder among patients with psychotic illness, very less is known about biological mechanisms and the clinical epidemiology.
Though multiple hypotheses have emanated, the widely accepted theories were:
1. Substance use increases the risk of schizophrenia, especially in vulnerable individuals.
2. Substances have been used by psychotics to alleviate their symptoms (e.g. negative symptoms) or to get high or to tide over the debilitating side effects of antipsychotics.

PURPOSE:

As compared to previous studies, our study also attempted to evaluate these hypotheses by exploring the reasons for substance use in patients with psychosis (group - 1) and comparing them with the reasons for substance use in those SUD with out psychosis (group - 2). The main aim of our study were to:
1. To compare the above two groups on clinical and socio demographic variables.
2. Pattern of substance use, perpetuating factors, but this study was done in a tertiary care hospital, with an established referral system and the study done in patients attending the out patient department in contrast to previous study (1,3,4).

SUBJECTS AND METHODS:

STUDY SETTING:
This study was conducted at department of psychiatry, at Stanley Medical College and Hospital, Chennai. The patients included in this study were those referred from medical OutPatient Department (OPD) and Inpatient Wards of the same hospital. Patients from urban, semi urban and rural areas were included. Patients attending the psychiatry OPD, after registration and clinical examination, and after obtaining consent were placed into one of the two groups: 1. psychotic illnesses with substance use as first use and 2. substance users without psychosis as second group. This study was conducted from May 2011 to November 2011 and the study was approved by the Ethical Committee of the institute.

STUDY DESIGN:
The patients with age between 18 – 60 were included in the study. Patients fulfilling the ICD-10 diagnostic criteria for psychotic illnesses, and using substance were included in the first group. Of the 69 patients with psychotic illnesses screened, 32 patients who were primarily diagnosed to have psychotic illnesses like schizophrenia, bipolar disorder etc, with current use of substance were enrolled for the study (n=32).

Patients with substance use, fulfilling the ICD-10 criteria for F1x.1 harmful use to F1x.2 dependence were included in the second group (n=42). The number difference in the groups were due to the number of patients attending for deaddiction being more than those of psychotic patients. Patients aged less than 18 years and more than 60 years, females and those with organic mental disorders were excluded from the study. All the participants were male patients as patients attending deaddiction clinic were mostly males, hence female subject were not included.

INSTRUMENTS:
In this study, demographical and clinical information were recorded for each patient by using a semi structured proforma, the first part of which included age, residential area, education, socio economic status, occupation, care giver and marital status. The second part of the proforma included age of onset, mode of consumption, pattern of use, perpetuating factors. The latter had two domains:
1. internal locus e.g low self esteem, to enhance positive mood and to alleviate negative moods etc.
2. external locus e.g. work discomfort, peer pressure and social pressure, duration of use, family history, initiating factors, type of substance used and associated physical

<table>
<thead>
<tr>
<th>Type</th>
<th>N</th>
<th>Mean</th>
<th>Std. Deviation</th>
<th>Std. Error Mean</th>
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</thead>
<tbody>
<tr>
<td>age of onset in yrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>32</td>
<td>25.13</td>
<td>8.435</td>
<td>1.491</td>
</tr>
<tr>
<td>2</td>
<td>42</td>
<td>24.21</td>
<td>5.546</td>
<td>.856</td>
</tr>
</tbody>
</table>

*Table 1: Table showing the age of onset between the two groups.*
illnesses were recorded. Scales of Inventory of drug taking situations (IDTS-8) and Global assessment of functioning scale (GAF) were administered to both the groups. In IDTS patients, the first, second and third frequent causes were recorded. GAF scale assessed clinical presentation and present functioning level of patients.

**STATISTICS:**
When comparing the two groups, the student-t test was used for continuous variables and Pearson's chi-square test was used for categorical variables.

**RESULTS:**
Of the total 74 patients, 32 patients belonged to psychotic illness with substance use group (group-1) and 42 patients belonged to substance use disorders group (group-2).

**SOCIODEMographic FINDINGS:**
In this study, the sociodemographic findings showed no significant difference age and education wise. Occupation wise, more number of patients with substance use disorders (group-2) are skilled workers (52%) compared to 34% in psychotic patients (group-1).
The spouses are the major caregivers in both the groups about 62% in first group and 85% in second group, but there was an increased number of parents as care givers about 34% in psychotic group compared to 11% in substance users.

Most of the substance users were married, 85% in the second group, compared to 59% in first group, but there is an increase in unmarried status in first group about 34% compared to 14% in the second. Socioeconomic status of most patients was in the Rs.1000-5000 per month income range, in both the groups.

### Table 3: Comparison between the substance variables of the two groups.

<table>
<thead>
<tr>
<th>Pattern of use</th>
<th>Psychotic patients</th>
<th>SUD</th>
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<tbody>
<tr>
<td>Use-1</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Harmful use-2</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Dependence-3</td>
<td>10</td>
<td>41</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Perpetuating factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internal locus-1</td>
</tr>
<tr>
<td>External locus-2</td>
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<table>
<thead>
<tr>
<th>Mode of sub use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alone-1</td>
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<tr>
<td>Peer group-2</td>
</tr>
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<table>
<thead>
<tr>
<th>Family history</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes-1</td>
</tr>
<tr>
<td>No-2</td>
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<table>
<thead>
<tr>
<th>Type of alcohol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Others-1</td>
</tr>
<tr>
<td>Arrack,others-2</td>
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<table>
<thead>
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<tr>
<td>Enjoyment-2</td>
</tr>
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<td>Experiment-3</td>
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<td>Stress &amp; others-4</td>
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<table>
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<tr>
<td>Endocrine -3</td>
</tr>
<tr>
<td>Hematology-4</td>
</tr>
<tr>
<td>Neurological-5</td>
</tr>
<tr>
<td>Hypertension-6</td>
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</table>

<table>
<thead>
<tr>
<th>Duration of sub use(years)</th>
</tr>
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<tr>
<td>1-20</td>
</tr>
<tr>
<td>21-40</td>
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<table>
<thead>
<tr>
<th>Care giver</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wife-1</td>
</tr>
<tr>
<td>Parents-2</td>
</tr>
<tr>
<td>Others-3</td>
</tr>
</tbody>
</table>

**SUBSTANCE USE RELATED FINDINGS:**

In our study, the substance use pattern in psychotic patients (group-1) were more of harmful use i.e, about 15(46%) patients and 10(31%) patients were found to have dependence pattern. But in substance using patients (group-2), 41(97%) patients were in dependant pattern and just 1 patient was having harmful use pattern.

In psychotic patients common substance use is alcohol in about 19 patients, alcohol and other substance use was seen in 5 patients. In substance users 14 patients were using alcohol and another substances.
There were significant differences in the perpetuating factors of substance use. In psychotic patients about 31 of 32 (96%) were found to have internal locus for perpetuating factors whereas in substance use disorders about 35(97%) patients having external locus for perpetuating factors.

It was also found that family history of substance use was more in substance use disorder group, about 31 of 42 patients compared to 19 of 32 psychotic patients. The outcome of IDTS-8 scale showed unpleasant emotions as the most frequently occurring cause for using the substance in psychotics (group-1) in about 19 of 32 patients. While in SUD patients (group-2) the causes of substances use were unpleasant emotions, physical discomfort and urge and temptations, (1,2,5 of IDTS Scales), were equally found, 13 in each.

In initiating factors for substance use, there were stress and other factors more in 71% of psychotic patients, compared to peer pressure in 71% of group 2 patients. Mode of consumption of substance use in psychotic group 24 (75%) compared to group-2 where it was equal (50%) using both alone and with peer group.

The duration of substance use was less in psychotic patients compared to substance use disorders. The mean age of onset of substance use in 1st group is 25 years and 24 years in 2nd group. Age of onset of substance use did not show much significance in our study.

**ASSOCIATED FINDINGS:**

In our study, more number of patients referred from Out Patient Department for both the groups about 87% in first group and 76% in 2nd group, but there is an increase in referral from wards for 2nd group 23% as compared to 12% for 1st group.

In this study, we found associated comorbid physical illnesses in group-2, in about 12 of 42 (28%) patients, but none in group-1.

**DISCUSSION:**

Previous studies have examined about the reasons for substance use psychotic patients (5,6). Many studies have focused on substance use in schizophrenia and affective psychosis. Compared to previous out patient and community studies (5,6,23), this study was conducted in tertiary care hospital with established liaison psychiatry, and the comparison groups, the group-1 and group-2 in this study, could be well matched for correlating and comparison.

Our study has also confirmed the pattern and perpetuating factors as shown in other previous study (1). In this study, more number of group-1 patients were in harmful use compared to the previous study (1) and the perpetuating factors were mainly internal locus in psychotic patients and more of patients in group-2 were having external locus similar to the previous study (1).

In this study, the duration of substance use was generally less than SUDs and the type of main substance use in psychotic patients were of alcohol, compared to the other group having more than one substance use and this could be correlated positively with IDTS scores. The mode of consumption of alcohol alone in psychotic patients may be due to the internal factors.

The initiating factors for substance use, most of the group-1 patients have stressors to initiate substance use, in group-2 it was peer pressure. From the IDTS-8 scale results, the causes for maintaining substance in group-1, were frequently the disturbed emotions, urge and temptations and conflict with others which match with internal locus of perpetuating factors and in group-2 the frequent causes were physical discomfort, urges and temptations and social pressures which match with external locus of perpetuating factors.

In our study, even though the dependent pattern is more in group-2, they were able to maintain some job for earning. In group-2, most patients reported with wives, it showed stable marital life, similar to the previous studies (24,25,26,27) and this could be due to more tolerability in the spouses of Indian culture.

In our study, the frequency of referrals from ward in group-2 was a little higher, because patients used to get admitted with comorbid physical illnesses and then referred.

The findings of pattern and perpetuating factors and with IDTS results suggest the area for future research and the possibility to find out the exact cause related to the internal factors for substance use in psychotic patients.

There are limitations in our study
1. the small sample size
2. exclusion of female patients, so we could not generalize our findings beyond a point.

**CONCLUSION:**

To conclude, understanding the internal factors would help us in prevention of initiation and main-
tainence of substance use, in psychotic patients because it has a definite negative impact on compliance and prognosis.

The present study has paved way in identifying and differentiating the substance use pattern and perpetuating factors in psychotic patients and substance use disorders. Our liaison psychiatry in tertiary care hospitals could develop multimodal treatment in management of such patients.

REFERENCES:

1. Sahoo . Saddichha , BA, MBBS, DPM, MD, etal, Dept of Psychiatry, NIMHANS, Bangalore. (saddichha@gmail.com). Perceived reasons for and consequences of substance abuse among patients with psychotics.


23. Batra L, Gautam S. Psychiatric morbidity and

The Slide

A.Gomathy (1), Chandramoouleshwari (2), Arunalatha (3)

45/male came with complaints of joint swelling and synovial fluid was aspirated and sent for cytology.

FIG.1.40X VIEW – SHOWING NEEDLE SHAPE CRYSTALS IN GOUT

1,2,3. Department of pathology, Government Stanley Medical college, Chennai
INTRODUCTION:

UTI is defined by the presence of bacteria within the urine and is confirmed by a urine culture of at least 5 x 10^4 colony-forming units (cfu)/mL of the same bacterial species on a catheterized specimen or 10^5 cfu/mL on a voided specimen. UTI in paediatric age group is an important clinical issue. Renal scarring, which occurs in a small proportion of children is the most important outcome of infection as it is associated with significant future complications and ultimately with end stage renal disease. Identification of VUR is associated with increased risk of renal scarring. However, not all children with renal scarring have VUR. The aim of our study is to identify urinary tract abnormalities by IVU and MCU and correct it to avoid future complications.

EXCLUSION:

Neonates
Children with contrast allergy
Uncooperative and unwilling patients

RESULTS AND DISCUSSION:

50 children (30 female & 20 male) having both febrile and afebrile UTIs in various age group under 10 years are subjected to MCU followed by IVU and urinary tract abnormalities1,2 are diagnosed and treated. Out of 50 patients 34 patients had febrile UTI and 16 patients with afebrile UTI. Out of 34 patients 13 have VUR of varying grades3, 6 patients with PUV, 3 with neurogenic bladder, 2 with double moiety, 2 with megaureter, 1 patient with horse shoe kidney, 7 patients have no urinary abnormality. Out of 16 afebrile UTI patients 4 have VUR, 3 with duplex collecting system, 1 with urachal diverticulum, 1 with neurogenic bladder, 1 with paravesical diverticulum, 1 with PUJ obstruction, 1 with polymegecalycosis, 4 patients without renal abnormality. There are many studies focussing on
VUR and radiological evaluation but few studies about UTI and IVU evaluation of congenital anomalies. In our study about 42% of patients had congenital abnormalities of the urinary tract, considering that the hospital is a large referral centre. The greater incidence of correctable congenital abnormalities warrants investigation of all UTIs. In our study 38% of patients had VUR comparable to a similar study and setting. 5 Out of 50 patients UTI is common in male under 6 months (12 out of 20 patients), and in all other age groups females outnumber male. This is the usual situation. 6,7

**CONCLUSION:**

Conventional radiological procedures like IVU and MCU are cheap and effective ways of diagnosing and evaluating most urinary tract abnormalities. Though radiation concerns are there in conventional MCU, still it is the best method to depict VUR and ureteric anomalies. Modern upcoming methods like CT urogram and MR urogram and nuclear scan are increasingly used. However, conventional methods are technically easier and cost effective and has its own role even in advanced tertiary care centres. Early detection of the anomalies leads to better treatment and avoids future complications.

**FIGURE 1:** Agewise distribution of UTI in children

**FIGURE 2**

**FIGURE 3**

CASES 1 & 2:
1) 2 month old baby showing urachal diverticulum
2) month old boy MCU showing dilated posterior urethra with increased bladder trabeculation

CASES 3 & 4:
3) 6 year old female child MCU showing horse shoe kidney with gross right VUR
4) 2 year old female patient showing bilateral gross VUR
CASES 5 & 6:
5) 9 year old boy IVU showing left double moiety with cyst in lower pole with ureterocoele in the lower end of upper moiety ureter with cobra head appearance
6) 4 month old male child showing rectovesical fistula and left VUR

CASES 7 & 8:
7) 10 year old male child IVU showing left primary megaureter
8) 1 year old female child MCU showing left paravesical diverticulum and gross VUR left side

CASES 9 & 10:
9) 5 year old female child IVU showing left PUJ obstruction
10) 8 year old female child IVU showing left polycalyx and left megaureter

REFERENCES:

ABBREVIATIONS USED:
IVU - Intavenous Urogram
MCU - Micturating cystourethrogram
CFU - Colony forming units
VUR - Vesico ureteric reflux
UTI - Urinary tract infection
CT - Computed Tomogram
MR - Magnetic resonance
PUV - Posterior urethral valve
PUJ - Pelvic ureteric obstruction

Conflict of interest: None
‘THE IMPACT OF ALTERED MATERNAL LIPID PROFILE LEVELS ON MATERNAL AND PERINATAL OUTCOME IN WOMEN WITH GESTATIONAL DIABETES MELLITUS’

Vijaya.S(1), Sudha.S(2)

Abstract

Context: Gestational Diabetes Mellitus is associated with an increased risk of various short- and long-term adverse maternal outcomes and perinatal outcomes.

Aims: To identify the impact of altered lipid levels on maternal outcome and neonatal outcomes in women with gestational diabetes mellitus.

Settings and Design: Institutional based study and a prospective case control study.

Methods and Material: The fasting lipid profile was taken for about 200 women with Gestational diabetes diagnosed by DIPSI criteria. The patients were divided into two groups based on their lipid profile values. The patient were then followed throughout the antenatal period and the occurrence of maternal complications and neonatal complications were studied.

Statistical analysis used: Statistical analysis was performed by the student t-test.

Results: Among the altered lipid profile group 78.2% of the patients were in age group above 25 years, 66.7% of patients were in BMI of range 25 to 29 kg/m². About 41.7% of the patients with altered lipid profile developed Preeclampsia, 15.4% had Gestational hypertension, 43.6% had polyhydramnios, 55.4% had caesarean section. There was about 11.5% macrosomic babies, 30.8% babies had respiratory distress syndrome, 12.2% babies had hypoglycemia, 14.1% of babies had hyperbilirubinemia, 2.6% babies had anomalies, 23.7% babies had NICU admissions more than 3 days among the babies born to GDM patients with altered lipid profile.

Conclusions: In our study, lipid profile alterations detected were increased total cholesterol, serum triglycerides in GDM patients and lower HDL levels. There was increased incidence of adverse maternal outcome and perinatal outcomes among GDM cases with altered lipid profile.

Key-words: Gestational Diabetes, Total cholesterol, Serum triglycerides, maternal outcome, perinatal outcome.

INTRODUCTION:

Gestational Diabetes Mellitus (GDM) is one of the most common metabolic disorders of pregnancy which is characterized by glucose intolerance detected for the first time during pregnancy due to decreased insulin sensitivity combined with insufficient insulin secretion (1). The incidence of GDM has been increasing due to the increased age of pregnant women and the rising rates of obesity in population. India being capital of Diabetes, there is increased prevalence of GDM in south Indian population. It is reported to be about 16% (2).

During pregnancy, the metabolism of carbohydrates and lipid undergoes adaptations to ensure a continuous input of energy and nutrients to the fetus which are mediated by placental hormones mainly estrogen and placental lactogen and by altered insulin levels and changes in insulin sensitivity (3). The maternal serum lipid levels are elevated during mid to late gestation in normal pregnancy which is a part of maternal adaptation to maintain stable fuel distribution to fetus. The triglyceride levels increase continuously from early pregnancy and by term there is two- to threefold elevation (4).
These metabolic changes that occur in normal pregnant women are progressive and are accentuated in GDM patients(2). There are alterations in fasting, postprandial, and integrated 24-hour plasma concentrations of amino acids, glucose, and lipids. There is three-fold elevation of plasma triacylglycerol concentrations towards term, elevation of plasma fatty acids, delayed postprandial clearance of fatty acids and elevation of branched-chain amino acids(7). In GDM there is a state of dyslipidemia consistent with insulin resistance. The lipid abnormalities in GDM are elevated triglycerides, elevated LDL cholesterol and low HDL cholesterol(8).

GDM is associated with adverse maternal and perinatal outcome, which includes increased likelihood of birth defects, preterm birth, caesarean delivery, macrosomia, preeclampsia and gestational hypertension(10). It is found that even with strict glycemic control there is higher incidence of complications. The abnormalities in carbohydrate metabolism occurring in GDM may lead to abnormalities in insulin resistance and metabolism of lipid(9). The insulin resistance causes inflammation, endothelial dysfunction and formation of reactive oxygen species. During pregnancy there is imbalance of HDL and LDL cholesterol due to oxidative stress, which is more enhanced in GDM where excess glucose acts as principle oxidative substrate used for fetal growth(16).

SUBJECTS AND METHODS:

Study place:
The study was conducted at the Institute of Social Obstetrics, Government Kasturba Gandhi Hospital, Madras Medical College, Chennai.

Study Design:
This was an prospective case control study.

Study Period:
The study was conducted for a period of two years.

Participants:
The study group consisted of 200 patients after considering

| Table 1-Mean comparison of Age and BMI between two groups: |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | Mean            | Standard Deviation | Std Error | P value |
| AGE             |                 |                  |           |        |
| Altered Lipid   | 28.4615         | 4.5314            | 0.3628    | <0.0001 |
| Normal Lipid    | 24.6136         | 4.2274            | 0.6373    |        |
| BMI             |                 |                  |           |        |
| Altered Lipid   | 26.0369         | 2.54944           | 0.20543   | <0.0001 |
| Normal Lipid    | 22.5899         | 2.80753           | 0.4433    |        |
The patients are divided as,

- Group A: GDM Women with altered lipid profile taken as cases
- Group B: GDM Women with normal lipid profile taken as controls

Fasting blood samples (4ml) were collected from these patients on the next day and subjected to lipid profile analysis. Total Cholesterol calculated by CHOD POD method, HDL by Enzymatic selective protection method ,Triglycerides levels by Enzymatic Calorimetric method and LDL levels were estimated by Homogenous Enzymatic Calorimetric assay and the levels of VLDL was calculated indirectly from serum triglyceride values. OGCT is repeated at 24 – 28 weeks when the first test is negative and repeated again at 32-34 weeks and fasting lipid profile was done in patients diagnosed as GDM on the next day. GDM mothers attending antenatal clinics during study period were tested with fasting and postprandial blood sugar [2 hours] to know their glycemic control and manage with medical nutrition therapy and Insulin depending on their blood glucose levels. The maternal and perinatal outcome were studied.

**Statistical analysis**

Statistical analysis between two groups was performed by the student t-test.

**RESULTS:**

Among the altered lipid profile group multiparous women constitute 59%,78.2% of the patients were in age group above 25 years, 66.7% of patients were in BMI of range 25 to 29kg/m² and family history of diabetes was present in 46% of the patients. About 86% of GDM were detected in 2nd trimester and 14% in third trimester in the altered lipid profile group. About 41.7% of the patients with altered lipid profile developed Preeclampsia,15.4% had Gestational hypertension, 43.6% had polyhydramnios, 46.2% of patients required Inj. Insulin therapy, 11% had preterm delivery, 55.4% had caesarean section out of which CPD was the most common indication for caesarean section. There was about 11.5% macrosomic babies, 30.8% babies had respiratory distress syndrome, 12.2% babies had hypoglycemia, 14.1% of babies had hyperbilirubinemia, 2.6% babies had anomalies, 23.7% babies had NICU admissions more

**TABLE 2- Mean comparison of lipid profile between two groups:**

<table>
<thead>
<tr>
<th>Lipid profile</th>
<th>Groups</th>
<th>Mean</th>
<th>Standard Deviation(SD)</th>
<th>Significant (P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol(TC)</td>
<td>Altered lipid</td>
<td>220.6</td>
<td>26.71</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>Normal lipid</td>
<td>165.25</td>
<td>19.04</td>
<td></td>
</tr>
<tr>
<td>Triglycerides(TGL)</td>
<td>Altered lipid</td>
<td>265.37</td>
<td>66.96</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>Normal lipid</td>
<td>138.99</td>
<td>38.94</td>
<td></td>
</tr>
<tr>
<td>Very Low Density Lipoprotein(VLDL)</td>
<td>Altered lipid</td>
<td>42.28</td>
<td>21.65</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>Normal lipid</td>
<td>27.84</td>
<td>7.73</td>
<td></td>
</tr>
<tr>
<td>Low Density Lipoprotein(LDL)</td>
<td>Altered lipid</td>
<td>112.58</td>
<td>41.25</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>Normal lipid</td>
<td>88.61</td>
<td>18.95</td>
<td></td>
</tr>
<tr>
<td>High density lipoprotein (HDL)Cholesterol</td>
<td>Altered lipid</td>
<td>49.34</td>
<td>9.58</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>Normal lipid</td>
<td>52.34</td>
<td>9.15</td>
<td></td>
</tr>
</tbody>
</table>
than 3 days, 2.6% IUD, 1.9% perinatal mortality among the babies born to GDM patients with altered lipid profile.

**DISCUSSION:**

Our study included 200 pregnant women diagnosed with Gestational Diabetes Mellitus. Among them about 156 patients had altered lipid profile and were grouped as altered lipid profile group and the remaining 44 women with normal lipid profile were taken as normal lipid profile group.

In our study about 78.2% of the GDM mothers with altered lipid profile are above 25 years. It was concluded that there was significant association between age with GDM with altered lipid profile since P value < 0.0001. In our study about 59% of GDM cases with altered lipid profile were multiparous women. Since P value < 0.001 there was significant association between parity and GDM cases with altered lipid profile. In our study about 66.7% of GDM cases with altered lipid profile group had pre-pregnant BMI between 25-29 kg/m² which is statistically significant as p value is < 0.0001.

| TABLE- 1 | In our study family history was present in 46% of GDM cases. Since P value 0.547, there was no significant association between family history of diabetes and the occurrence of GDM in cases with altered lipid profile. In our study the mean fasting total cholesterol and triglyceride levels were 220.6±26.71 and 265.37± 66.94 mg/dl respectively. (TABLE-2). The mean values were 216.8±55.1 mg/dl for fasting triglyceride and 223.2±45.9 mg/dl for cholesterol in the study by Kustagi et al from southwest India in 2009 (18). In another study from Iran, mid pregnancy Fasting serum triglyceride (mg/dl) was 213.9 ± 77.7 mg/dl (17). In our study 86% GDM cases were detected in 2nd trimester, 14% of GDM cases were detected in 3rd trimester. In the present study, Total cholesterol, serum triglycerides were higher in GDM patients and there was lower HDL levels.

**MATERNAL OUTCOME:**

Among the altered lipid profile group the incidence of preeclampsia in GDM cases was 41.7%. Wiznitzer et al reported that elevated serum level of triglycerides are associated with Gestational hypertension and pre-eclampsia, compared to women with low TG levels (14). Llurba et al showed that 16 of 34 women with pre-eclampsia, had TG levels > 250 mg/dl (p < 0.001) (16). Donovan McGrowder et al (19) showed, Gestational diabetes mellitus is associated with increased risk of Gestational hypertension, preeclampsia and other maternal and fetal complications of pregnancy. The GDM patients had significantly increased total cholesterol and triglyceride concentrations and the study concluded that the GDM cases with dyslipidemia were at risk of developing preeclampsia. Arnon Wiznitzer et al (22), in their study compared and the lipid profile of pregnant women with and without GDM and or Preeclampsia. The abnormal lipid levels are associated with increased pregnancy complications.

In our study, polyhydramnios occurred in about 43.6% of

| TABLE 3-Comparison of maternal outcome between altered lipid profile and normal lipid profile group: |

<table>
<thead>
<tr>
<th>Gestational hypertension</th>
<th>Altered Lipid Profile % within group (count)</th>
<th>Normal Lipid Profile % within group (count)</th>
<th>Pearson Chi-Square</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>15.4%(24)</td>
<td>2.3%(1)</td>
<td>5.395</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>No</td>
<td>84.6%(132)</td>
<td>97.7%(43)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>Yes</td>
<td>41.7%(65)</td>
<td>9.1%(4)</td>
<td>16.117</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>58.3%(91)</td>
<td>90.9%(131)</td>
<td></td>
</tr>
<tr>
<td>Polyhydramnios</td>
<td>Yes</td>
<td>43.6%(68)</td>
<td>11.4%(5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>56.4%(88)</td>
<td>88.6%(39)</td>
<td></td>
</tr>
<tr>
<td>Mode of delivery</td>
<td>Labour Natural</td>
<td>39.1%(61)</td>
<td>65.9%(29)</td>
<td>11.171</td>
</tr>
<tr>
<td></td>
<td>Instrumental delivery</td>
<td>4.5%(7)</td>
<td>0%(0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LSCS</td>
<td>41.0%(64)</td>
<td>29.5%(13)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Repeat LSCS</td>
<td>15.4%(24)</td>
<td>4.5%(2)</td>
<td></td>
</tr>
</tbody>
</table>
GDM patients with altered lipid profile. About 46.2% of GDM patients in altered lipid profile group required Inj. Insulin for optimal control of blood sugar. Preterm deliveries occurred in about 11% of GDM patients with altered lipid profile. Evers et al (20) reported about 44% of caesarean section. Yoge v et al (21) reported about 30%. The percentage of patients who had caesarean section was 55.4% (Both LSCS and repeat LSCS), the most common indication being CPD which is about 44% and previous about 27%. (TABLE-3).

Ga Hyun Son et al (24), showed that maternal hypertriglyceridemia is a predictor of large for date babies born to GDM mothers. Ute M. Schaefer-Graf et al (23), explained that the association of maternal lipids as determinants of fetal growth and fetal environment in GDM patients. In the present study, the incidence of macrosomia was 11.5%, RDS 30.8%, hypoglycemia 12.2%, hyperbilirubinemia 14.1%, Anomaly 2.6%, IUD 2.6%, perinatal mortality 1.9%, NICU admission requiring more than 3 days of admission was 23.7%.

There was a significant association between altered lipid profile in GDM cases and the occurrence of macrosomia, Respiratory distress syndrome hypoglycemia, hyperbilirubinemia and NICU admission > 3 days in neonates. (TABLE-4). There was no significant association between altered lipid profile in GDM cases and the occurrence of anomaly, IUD, perinatal mortality.

**TABLE 4-Comparison of perinatal outcome between altered lipid profile and normal lipid profile group:**

<table>
<thead>
<tr>
<th></th>
<th>Altered Lipid Profile %within group (count)</th>
<th>Normal Lipid Profile %within group (count)</th>
<th>Pearson Chi-Square</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 2.5 kg</td>
<td>5.8%(9)</td>
<td>0.0%(0)</td>
<td>14.617</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2.5-3.5 kg</td>
<td>66.7%(104)</td>
<td>95.5%(42)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 3.5 kg</td>
<td>27.6%(43)</td>
<td>4.5%(2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 min Apgar</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 7</td>
<td>28.2%(44)</td>
<td>4.5%(2)</td>
<td>10.848</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥ 7</td>
<td>71.8%(112)</td>
<td>95.5%(42)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory distress</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>30.8%(48)</td>
<td>11.4%(5)</td>
<td>6.635</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>69.2%(108)</td>
<td>88.6%(39)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>12.2%(19)</td>
<td>2.3%(1)</td>
<td>3.743</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>No</td>
<td>87.8%(137)</td>
<td>97.7%(43)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>14.1%(22)</td>
<td>2.3%(1)</td>
<td>4.179</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>No</td>
<td>85.9%(134)</td>
<td>97.7%(43)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NICU Admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>23.7%(37)</td>
<td>0%(0)</td>
<td>12.805</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>76.3%(119)</td>
<td>100%(44)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**CONCLUSION:**

In the present study, lipid profile alterations detected were increased total cholesterol, serum triglycerides in GDM patients and lower HDL levels. There was increased incidence of adverse maternal outcome such as preeclampsia, gestational hypertension, polyhydramnios, preterm labour and increased caesarean section rate and adverse perinatal outcome such as macrosomia, RDS, hypoglycemia, hyperbilirubinemia, NICU admissions and increased perinatal morbidity among GDM cases with altered lipid profile.

**REFERENCES:**

4. Coustan DR, Carpenter M W, O’Sullivan PS, SR. Gestational diabetes: predictors of subsequent disordered...


ACKNOWLEDGEMENT:
All the GDM patients who participated in the study
INTRODUCTION:

100 years ago, Bassini described the first herniorrhaphy. They believed immobilization and bed rest enhanced wound healing. But it turned out to be the culprit for genesis of fatal pulmonary embolism. Hence early ambulation was suggested.

This study is done to prove the fact that Trans Inguinal Preperitoneal (TIPP) Hernia Repair (using prolene mesh) resulted in greater patient comfort with reduced post operative pain and also decreases the number of complications and recurrence rate and that it can be recommended for all primary unilateral Inguinal Hernias.

More than 7 lakh inguinal hernia repairs were performed each year in US in 1980. More than 70,000 patients developed recurrent hernia due to excessive tension repair
which was then replaced with Lichtenstein's tension free mesh repair. But due to chronic post operative pain, sensory loss, cord oedema, Trans Inguinal Pre Peritoneal repair was tried which proved to be useful.

**SUBJECTS AND METHODS:**

About 25 cases of transinguinal pre peritoneal mesh repair was done in the period 2014 to 2015 at Kilpauk medical college hospital and compared with 25 cases of Lichenstein repair. Cases were selected at random irrespective of the type of inguinal hernia, the age of the patient and the size of the defect. The material used for repair is monofilament polypropylene clear non absorbable synthetic knitted surgical mesh available in our hospital as SURUMESH manufactured by SURU INTERNATIONAL PVT. LTD. These cases were followed up in the immediate and post operative periods. Post operative pain, scrotal collection, seroma, cord oedema and wound infection were looked for. They were asked to come for regular follow-up visit after discharge. During each follow-up visit, the patients were assessed for pain, surgical site infection and recurrence.

**TRANSINGUINAL PRE PERITONEAL MESH REPAIR:**

Under spinal anesthesia, aseptic precaution, parts painted and draped, classical inguinal incision made between the anterior superior iliac spine and the pubic tubercle. Then external oblique fascia is divided, cord structure and sac identified, ilio inguinal nerve is isolated from the posterior inguinal wall. In a case of indirect hernia, sac is separated from the cord well beyond the deep ring, content reduced and then sac is transfixed and excised. In case of congenital hernia, firm adhesion with the tunica vaginalis, sac may be transected in the middle part, leaving open the distal sac. In case of direct hernia, is reduced into the peritoneal cavity, transversalis fascia is opened from the deep ring to the pubic tubercle, safe-guarding the epigastric vessels. Preperitoneal space is defined, dissection is extended laterally beyond the deep ring, inferiorly to the Cooper's ligament and medially to the outer border of the rectus sheath. A synthetic polypropylene mesh, rectangular in shape, 15x7 cm in size, is prepared to cover Bogros's space and the Fruchaud's Myopectineal orifice. A slit is made at the lateral end of the mesh, to create a new deep ring and allow free passage of the cord. The mesh is anchored inferiorly to the ilio Pectineal ligament medially to the rectus sheath. The two tails of the newly created deep ring are crossed behind the cord and laterally sutured to the internal oblique muscle. External oblique fascia is sutured. Skin is closed. Compressive dressing to be done at the end of the procedure. Post operatively analgesic and antibiotics given. Each patient discharged at 7th post operative days.

**FIGURE 1: Lichenstein repair**

**FIGURE 2: Polypropylene mesh**

**FIGURE 3: TIPP**
RESULTS:

Among the 50 patients taken for the study, 25 patients were subjected to lichenstein’s hernia repair and 25 for the TIPP procedure. The mean age of the patients subjected to lichenstein repair was 53.84±12.44 yrs and for TIPP it was 48.8±14.17yrs.

Operation length was 49.16 ± 8.74min in the Lichenstein group and 82.36 ± 8.34min in the TIPP group. The duration of operation was more in the TIPP group and this was statistically significant. (p < .05)

The per operative complications encountered were injury to peritoneum, vessels and nerves. Injury to peritoneum was encountered in(n=0) none of the patients in Lichenstein group whereas injury to peritoneum was encountered 3 (n=3)patients of TIPP group. Injury to nerves was encountered in (n=0) none of the patients in TIPP group whereas injury to nerves was encountered in 6 patients (n=6) in Lichenstein group.

None of the patients developed urinary retention in the early post operative period. The various early post operative complications encountered among the patients subjected to Lichenstein repair were seroma (n=8), surgical site infection(n=2), scrotal collection(n=0) and cord edema(n=8). Among the patients who underwent TIPP procedure the early post operative complications seen was surgical site infection(n=1) with only one patient experiencing it.

During the first follow up of patients at one month it was noticed that 24% of patients who underwent linchenstein repair had complications. SSI(n=2), cord edema (n=2), recurrence (n=0), loss of sensation(n=5). On the other hand none of the patients who underwent TIPP had complications.

At second follow up (3rd month) it was noticed that no patient who underwent TIPP had complication like chronic pain,cord oedema,sensory loss and recurrence in my observation. On the other hand one patient who underwent LR had chronic pain and 2 patient who underwent LR had sensory loss.

<table>
<thead>
<tr>
<th>TABLE 1: The comparison of the patient demographics, early and late complications, and cost effectivity among two groups.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VA S Lichenstein (n=25) Mean+ SD</strong></td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Time</td>
</tr>
<tr>
<td>Hospitalization time</td>
</tr>
<tr>
<td>Early complication</td>
</tr>
<tr>
<td>NO</td>
</tr>
<tr>
<td>Late complication</td>
</tr>
<tr>
<td>NO</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>FEMALE</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TABLE 2: The comparison of the VAS score among the two groups.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VAS</strong></td>
</tr>
<tr>
<td>DAY 1</td>
</tr>
<tr>
<td>DAY 7</td>
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<tr>
<td>3rd month</td>
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Visual analog scales at day 1 were 2.44 + 1.44 for Lichtenstein group and 0.8 + 1.08 for TIPP group, whereas visual analog scale values at day 7 were 0.96 + 1.42 for Lichtenstein group and 0.32 + 0.55 for TIPP group. Visual analog scale results at 3rd month were 0.12 + 0.63 in the Lichtenstein group and 0.00 in the TIPP group.

**DISCUSSION:**

Of the 25 transinguinal pre peritoneal mesh repair was done, 12 were indirect hernia versus 13 were direct hernia. Most of them were European hernia society classification PM1. Maximum number of patients belonged to 45-55 year age group. From the observation, it is clear that post-operative pain is very much less with transinguinal pre peritoneal mesh repair using prolene mesh with most of the patients having minimal or no pain after 2 days. The majority of patients required only oral analgesic. Most of them required sedation only on the day of their surgery. One patient developed wound infection at the end of 1st week, no patient developed wound infection, cord oedema, recurrence at the end of 1st month and one patient who developed chronic pain at the end of 1 month in this group of patients. Unrestricted activity was encouraged in these patients after discharge.

Out of 25 patients for transinguinal pre peritoneal mesh repair, 23 patients came for regular follow-up, the average follow-up period was 3 month. During each follow-up visit, patients were assessed for pain, any restriction of physical activity, surgical site infection, mesh rejection and recurrences. 25 patients underwent lichtensteins repair experienced more pain in the early post operative period. The intensity of pain was more in the early post operative period, the intensity of pain was even more increased during coughing and during ambulation. Although these patients experienced minimal pain at rest after 5 days the intensity was increased during coughing and ambulation. These patients needed larger doses of analgesics and sedatives and most of them had restricted physical activities up to 1 month post operatively. 5 patients developed wound infection. 8 patients developed cord oedema, at the end of 1st week 9 patients developed pain over surgical site. Although no recurrence was noted in these group, 1 patient developed pain at 3rd month.

In the study conducted by JF Maillar, P. Vantournhoudt, G. Piler – Gerard, E. Mauel, Pelissier et al [1] using a Preperitoneal mesh performed with a permanent memory ring for groin hernia TIPP found to be a good alternative to LR (2006-2008), no infection of mesh, no clinical recurrence. There was an ultrasound recurrence in < 2% (n=3) of the asymptomatic patients and chronic pain in 4.8% of the patients. Benefits of the anterior approach (easy technique, short learning curve, low cost) and the Preperitoneal placement of the mesh (less recurrence, less pain). This procedure is a good alternative to LR. Frederik Berrevoet UGent, Leander Maes UGent, Koen Reynjens UGent, Xavier Rogiers UGent, Roberto Trouser UGent and Bernard de hemptinne UGent [2010] [2] did study to compare TIPP versus lichtensteins in relation to acute and chronic pain, post operative complication and recurrence rate. Duration of study was 18 months. They observed mean operative time for TIPP is less than Lichtenstein, 33 versus 44 min, respectively (p=0.04). Less post-operative pain observed in the TIPP than Lichtensteins. Recurrence were observed less in TIPP than LICHENSTEIN group respectively 2.8% versus 5.1%. Pelissier and colleagues (2007) [3] described that recurrence rate is 2% and rate of chronic pain is 5-7% in TIPP groups. More recently Berrevoet and his team [4] described a recurrence rate of 1-3% and visual analogue pain scale of 0.2 1yr after TIPP. Reason for lower rate of post operative pain were found to be minimal dissection around the ilioinguinal and iliohypogastric nerve and also due to no fibrosis of the mesh in contact with the inguinal nerve. Koning GG, Schipper HJP, Oostvogel HJM, Verhofstad MHJ, Gerritsen PG, Larrhoven KCJHM, Vriens PWHI [5] double blind RCT comparing Lichtensteins and TIPP (2009-10). Studied in 496 patients: 225 TIPP and 271 LICHENSTEINS. This study revealed no significantly better result for the TIPP as compared to lichtensteins. Moldoon RL, Marchant k, J Ohnson dd, Yoder GG, Read RC, Hauer-Jensen M, RCT study of lichtensten and TIPP Trial (2004) [6], described recurrence in the lichtenstein is 4.3% and in less than 1% recurrence in THE PREPERITONEAL Read Rives. Both anterior repairs are associate with low post operative morbidity and recurrence rates (p=0.21). Giel G Koning: Patrick W.H.E Vriens 2011 [7], St Elizabeth hospital, did study on Anterior PPR of extremely large hernias. In extremely large hernias, the lateral side of the mesh can be insufficient to fully embrace the hernia sac. They describe the use of 2 preperitoneal placed meshes (Butterfly technique) to repair extremely large hernias. 2 inverted meshes to cover the deep ring both medial and lateral. Recurrence did not occur after repair. Chronic pain was not reported. In a study by Muldoon RL, Marchant K, Johnson DD, Yoder GG, Read RL, Haver- [8] Jeni M PPR (n=121); LR (n=126) Read Rive’s repair was 9min longer than LR. No wound infection. Jamal
Akhavan Moghaddan, Shaban Mehrvarz, Hassan ali Mohabbi [9] did comparison of Read Rive's and LR for treatment of unilateral inguinal hernia. Early postoperative complications, duration of surgery and hospital stay, return to normal activity, recurrence was found to be equal in both the groups. G.G. Koning, C.S. Andeweg, F. Keus, M.W.A. Van Tilburg, C.J.H.M. Van Larrhova, W.L. Akkersdijk [10] popularized the Preperitoneal mesh position due to promising result of less chronic pain. However, considering the proportions of severe adverse events, learning curve, added cost, Performed trans rectus sheath preperitoneal repair in 50 patients. They observed no technical problems in surgery, no recurrence and chronic pain after a mean follow up of 2 years.

CONCLUSION:

In our experience, the repair of groin hernias with Preperitoneal mesh (Prolene mesh through an inguinal incision) has resulted in greater patient comfort with reduced post operative pain and also decreased number of complications. Although there was no recurrence observed in my study, the follow up period was only minimal (average 3 month). The duration of stay in the hospital was reduced and the patients had a rapid return to work. Hence the transinguinal pre peritoneal mesh repair is an amazing simplistic technique which gives an approach to inguinal, femoral and obturator hernias and bears the same anatomical relationship in TEP and TAPP approaches which gives a better understanding of the TEP and TAPP procedures. It is an easy technique with short learning curve. The risk of vessel injury is less in the hands of an expert. The contact of mesh with the cord structures and nerve is minimal which reduces the postoperative cord oedema, pain (Inguinodynia), orchitis and sensory loss.

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Comparison of USG guided Transverse Abdominis Plane block (TAP block) with Epidural Analgesia for Postoperative Pain Relief following Inguinal Hernia Surgery.

S.Ponnambala Namasivayam(1), Senthil Kumar (2), S. Saravanakumar(3)

Abstract

The aim of the study is to compare the analgesic efficacy of USG guided TAP block with the epidural analgesia, in patients undergoing inguinal hernia surgery. 120 patients were randomly allocated into two groups, Group T and Group E (n = 60 each). Primary outcome measured was postoperative pain by VAS score and secondary outcome measures were haemodynamic variations, rescue analgesic requirements, PONV, patient satisfaction and failure rates. Data was analysed using students – t test. Demographic profile was comparable in both the groups. USG guided TAP block was found to be comparable to epidural analgesia in terms of analgesic efficacy. TAP block is less invasive and devoid of the side effects of epidural analgesia.

INTRODUCTION:

Inguinal hernia repair is one of the most commonly performed surgical procedures. Open inguinal hernia repair is associated with moderate postoperative pain and postoperative analgesia is an issue to be addressed. Optimal postoperative analgesia is important to prevent negative outcomes such as systemic hypertension, myocardial ischemia, arrhythmias, respiratory impairment, postoperative ileus and poor wound healing. There is an increased evidence of an association between severity of acute pain and risk of developing chronic postsurgical pain. Pain after hernia repair is more pronounced in the first two postoperative days. Pain is aggravated during mobilisation or coughing, than during rest.

Epidural analgesia is a well-established technique that has been commonly regarded as the gold standard in postoperative pain management. However, epidural analgesia is not devoid of complications which may include accidental post-dural puncture head ache, total spinal anaesthesia, seizures due to intra-vascular injections, epidural hematoma and epidural abscess. The physiological side effects include hypotension, motor blockade, and urinary retention.

Although epidural techniques can provide excellent analgesia following major surgeries, there is increasing evidence that less invasive regional techniques can be as effective. Transverse abdominis plane block (TAP block) is now being used for postoperative pain relief in surgical procedures like inguinal hernia repair. Initially "anatomical landmark based" single shot transverse abdominis block was used for postoperative analgesia. To increase the success rate, transverse abdominis plane block was performed under "USG guidance". To extend the benefit of postoperative pain relief for a period of 2-3 days, TAP catheters are used. Postoperative analgesia with TAP block is achieved using continuous infusion or intermittent boluses.

Taking all these into consideration we decided to conduct a prospective randomized controlled study comparing the analgesic efficacy of USG guided TAP block with epidural analgesia for postoperative pain relief in patients undergoing inguinal hernia surgery under spinal anaesthesia.
AIM OF THE STUDY:

The aim of the study is to compare the analgesic efficacy of USG guided Transverse Abdominis plane block with epidural analgesia for postoperative pain relief following inguinal hernia surgery. Primary outcome measure includes assessment of the postoperative pain by Visual Analogue Score. Secondary outcome measures include haemodynamic parameters, Rescue Analgesic requirement, Post-Operative Nausea and vomiting (PONV), Therapeutic/Technical failure rate and Patient Satisfaction.

MATERIALS AND METHODS:

This randomized, prospective, interventional clinical trial was conducted on 120 patients (n=120) who underwent elective surgery for inguinal hernia. Institutional ethical committee approval was obtained. Patients were explained about the procedure in detail and informed written consent was obtained. Patients were randomised into 2 groups of 60 each. Transverse abdominis plane group (Group T) (n=60) patients received transverse abdominis plane block; Epidural group (Group E) (n=60) patients received epidural block.

All the patients subjected to the study were assessed in the pre-anaesthetic assessment clinic. Patients were given premedication with injection midazolam IM (0.5 mg/kg). Patients were connected to the monitors NIBP, ECG, SpO2 after shifting to the operation theatre. All the baseline hemodynamic parameters were noted. Patients from both the groups underwent inguinal hernia surgery, under spinal anaesthesia with 3.2 ml of injection 0.5% hyperbaric bupivacaine at L3 – L4 interspace using 25 G Quincke's spinal needle.

GROUP E patients received epidural catheter at the time of spinal anaesthesia pre operatively. Group T patients received USG guided TAP catheter at the end of the procedure.

In GROUP E, midline approach epidural was used. Epidural space was identified by loss of resistance technique with air filled syringe, using the Bromage grip. Tuohy needle (18 G) is introduced at L1 – L2 interspace with intermittent compression of the syringe plunger attached to the Tuohy needle. Epidural space was identified at 3 – 5cm from skin level. An epidural catheter was threaded into the epidural space via the epidural needle and catheter was fixed so that 5 cm of the catheter was in the epidural space. Then, patient was given spinal anaesthesia using midline approach with 3.2 ml of injection 0.5% hyperbaric bupivacaine, at L3 – L4 interspace using 25 G Quincke's spinal needle.

GROUP T patients were given spinal anaesthesia with 3.2 ml of injection 0.5% hyperbaric bupivacaine at L3-L4 interspace using 25 G Quincke's spinal needle after local infiltration with injection 2% Lignocaine. At the end of the surgical procedure, patients received USG guided transverse abdominis plane block via posterior approach3. Patient was placed in the supine position. After preparation of skin with povidone iodine, sterile drapes applied. A sterile high frequency linear array USG probe (6-12 MHz) was placed on the anterolateral abdominal wall, just cephalad to the iliac crest level where the 3 muscle layers (External Oblique, Internal Oblique and Transverse Abdominis) are most distinct4. After identification of TAP neurofascial plane between internal oblique and transversus abdominis, probe was moved postero-laterally to lie between costal margin and iliac crest across mid-axillary line. Appropriate depth and frequency are adjusted to optimize the image of the abdominal wall muscle and underlying peritoneal cav-
ity. The image is further optimised by transducer manipulation consisting of pressure, alignment, rotation and tilt angulation (PART) on the abdominal wall. Depth and quality of image may vary with respiratory excursions. The fascial planes separating the muscular layers are specular reflections. Thus they appear as very visible, bright hyperechoic linear lines located between hypoechoic abdominal wall muscles. After local infiltration with 2ml of 2% lignocaine, 18 G Tuohy needle was introduced in an "In-Plane" approach with respect to the USG probe. Needle entry point was 3-4cm medial to the edge of the transducer. This allows for a decreased needle angle trajectory to TAP plane, which optimizes the angle of incidence of the USG beam relative to the needle.

The Tuohy needle is advanced in a postero-lateral direction with the hub of the needle directed towards the USG probe. The needle is advanced and observed penetrating the external oblique – internal oblique fascial plane and subsequently into TAP plane between internal oblique and transverse abdominis muscles. Needle passage through the fascial planes may be accompanied by tactile and visual pops as the fascia tents as needle contacts the fascia followed by recoil as the needle passes into the fascial plane. Once the needle enters the TAP plane, 4-5ml of 0.9% saline is injected to confirm correct needle placement. Optimal needle location is indicated by the appearance of an 'anechoic' fluid collection separating the internal oblique from transverse abdominis and visibly expands the TAP plane. The TAP plane is reached at an average depth of 5-8cm from skin level.

Then the epidural catheter is inserted 4-6cm beyond the needle tip into the TAP plane. The correct location of the catheter tip may be confirmed by either direct visualisation via USG or local anaesthetic accumulation in TAP plane. 15ml of injection 0.25% bupivacaine is injected via the TAP catheter. As the local anaesthetic is injected, the TAP plane expands due to hydro dissection. This will result in gradual separation of internal oblique and transverse abdominis.

The Tuohy needle is withdrawn over the TAP catheter and the catheter was tapped along ipsilateral posterior flank and secured to the lower ipsilateral chest. In the post-operative room, patients from Group T were given 15 ml of injection 0.25% plain bupivacaine via TAP catheter. 15 ml of 0.25% bupivacaine was given as 8 hourly boluses during the first 48 hours after surgery. The TAP catheter was activated immediately after catheter placement. In Group E patients, epidural catheter was activated 150 minutes from the start of surgery. They received 10 ml of injection 0.125% bupivacaine via epidural catheter as 8 hourly boluses during the first 48 hours after surgery.

Visual analogue pain scores were measured on a 0-10 cm scale. VAS score of “0” indicates “no pain”, at a score of 4 patient will be uncomfortable and at a score of 10 indicates unbearable pain. VAS scores were measured at 15, 30 and 60 minutes and 2, 4, 8, 16, 24, 30, 36, 48 hours after surgery. When VAS scores are greater than or equal to four, Injection tramadol 100 mg was given intravenously preceded by Injection Ondansetron 4mg IV. Number of patients who required rescue analgesics was noted.

Haemodynamic parameters like systolic pressure, diastolic pressure, mean arterial pressure and pulse rate were recorded at 15, 30, 60 minutes and 2, 4, 8, 16, 24, 30, 36, 48 hours after surgery. Hypotension is defined as mean arterial pressure < 20% from baseline. Episodes of hypotension were treated with fluid boluses of normal saline or ringer lactate. Patients not responding to crystalloids were to be given injection ephedrine.

Patients were assessed for post-operative nausea and vomiting by nausea scores, None = 0; Mild = 1; Moderate = 2; Vomiting = 3. Rescue antiemetic (Injection Ondansetron 4mg) was given to patients with nausea score greater than or equal to 2.

Therapeutic failure is defined as inadequate pain relief from surgical wound and drains. Technical Failure is the inability to insert TAP catheter/epidural catheter as a result of poor tissue planes.

Patient satisfaction about post-operative analgesia was assessed at the end of 48 hours, Poor = 1; Fair = 2; Good = 3; Excellent = 4.

**OBSERVATIONS AND RESULTS:**

The demographic profile in both the groups are comparable. Mean age in group T was 42.83 years and the mean age in Group E was 45.22 years (P value = 0.3253: statistically not significant). The number of male patients in Group T were 56 and the number of female patients were 4. The number of male patients in Group E were 54 and the number of female patients were 6. The two failed P-value equals 0.7412, which is not statistically significant. Mean weight in Group T was 59.76 kg and in Group E it was 60.967 kg (P-value = 0.4283, not statistically significant). Mean height in Group T and Group E were 161.01cm and 160.88 cm respectively.
(P-value = 0.4283, not statistically significant). In Group T, the number of patients who had Left inguinal hernia were 33 (55%) whereas patients with Right Inguinal Hernia were 27 (45%). In Group E, patients diagnosed with Left inguinal hernia were 32 (53.3%), whereas patients with Right Inguinal Hernia were 28 (46.7%). The average duration of surgery (Group T: 129.19 minutes & Group E: 130.83 minutes) in both groups were comparable (p value= 0.3134, not statistically significant). The Level of block in Group T patients at the end of the surgical procedure, was T10 in 22 patients, T9 in 11 patients, T8 in 19 patients and T7 in 8 patients. The level of blockade in Group E patients at the end of the surgical procedure was T10 in 12 patients, T9 in 21 patients, T8 in 19 patients and T7 in 8 patients.

**VAS SCORING:**

The average VAS scores at 15 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 8 hours, 16 hours, 24 hours, 36 hours and 48 hours for both Group T and Group E are enumerated in figure 3. The visual analogue scores over the entire 48 hours were comparable between the two groups. The p-value between the two groups over the entire 48 hours in the post-operative period was not statistically significant.

**RESCUE ANALGESIC REQUIREMENT:**

Out of 60 patients in Group T, 12 of them required rescue analgesic and in Group E also 12 patients required rescue analgesic.

**PULSE RATE:**

Pulse rate was monitored over a period of 48 hours, in the postoperative period at intervals of 15 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 8 hours, 16 hours, 24 hours, 30 hours, 36 hours and 48 hours (Fig:4). There was a decrease in pulse rate in Group E at all time intervals, except at 30 hours. The p-value was significant at all time intervals except at 30 hours.

**SYSTOLIC BLOOD PRESSURE:**

Systolic BP was monitored over a period of 48 hours. There was a significant fall in systolic BP over the entire 48 hours in Group E as depicted in figure 5. The p-value was found to be statistically significantly at all time intervals.

**DIASTOLIC BLOOD PRESSURE:**

Diastolic BP was measured over the 48 hours post-operative period, at specified time intervals. The mean diastolic blood pressure was found to be lower in Group E than Group T at all time intervals as depicted in figure 6. The P value was found to be statistically significant at all time intervals.

**MEAN ARTERIAL PRESSURE:**

The mean arterial pressure was lower in Group E than Group T at all time intervals as depicted in figure 7. The P value was found to be statistically significant, at all time intervals.
HYPOTENSION:
In Group T, there was no incidence of hypotension in the 60 patients. Whereas in Group E, there was significant hypotension in 15 out of 60 patients. The P value was 0.0001, which is statistically significant (Fig 8).

POST OPERATIVE NAUSEA AND VOMITING:
Nausea score was 2 in 19 patients in group T. Vomiting was present in 6 patients in Group T. Nausea score was 2 in 13 patients in Group E. Only 1 patient had vomiting in Group E (Fig: 9).

FAILURE RATE:
In group T patients, therapeutic failure rate was found in 12 out of 60 patients. In Group E therapeutic failure rate was found in 8 out of 60 patients. Technical Failure was not seen in any patient in both groups.

POST-OPERATIVE PATIENT SATISFACTION:
In group T, 13 patients recorded 0 score and 15 patients scored 4. In Group E, 6 patients recorded score 0 and 21 patients recorded score of 4 (Fig: 10).
DISCUSSION:

Elective inguinal hernia repair is one of the most common surgical procedures performed. In many centres, inguinal hernia repair is performed as a day case procedure. A good postoperative analgesic regimen is critically important to improve postoperative outcome. Adequate postoperative analgesia facilitates earlier patient mobilisation and earlier fulfilment of discharge criteria from postoperative wards. Pain after inguinal hernia repair is more pronounced in the first two postoperative days. The pain is aggravated during mobilisation or coughing. Patients undergoing inguinal hernia repair commonly receive intravenous opioids for postoperative analgesia. However, systemic opioids provide only static analgesia; but do not alleviate the dynamic component of pain. Dynamic analgesia is provided mainly by regional anaesthetic techniques in the postoperative period. The gold standard technique that has been used for postoperative pain relief is epidural analgesia. With the advent of truncal nerve blocks there seem to be an alternative to epidural analgesia. However, failure rate is high in truncal nerve blocks in anatomic landmark based approaches. With the introduction of ultra-sonogram, truncal nerve blocks have gained popularity. One of the most common truncal nerve blocks used for postoperative pain relief is USG guided Transverse abdominis plane block (TAP).

TAP block is used as a part of multi modal analgesic regimen for post-operative pain relief for a wide variety of indications ranging from caesarean section, hysterectomy, appendicectomy, renal transplant, colon resection and inguinal hernia repairs.

While there are various studies comparing epidural analgesia with conventional systemic analgesia and USG guided TAP block with systemic opioids for post-operative pain relief, there are only very few studies comparing epidural analgesia with USG guided TAP blocks.

In this study we tested the hypothesis that USG guided TAP block would provide post-operative analgesia that will be comparable to epidural analgesia. A previous study 7 evaluated analgesic efficacy of USG guided subcostal TAP block with epidural analgesia, following upper abdominal surgery. In that study pain scores were evaluated between the 2 groups. Postoperative nausea and vomiting, patient satisfaction at the end of 72 hours, rescue analgesia with tramadol and success rate were the other parameters evaluated. However, the hemodynamic parameters were not compared between the 2 groups in that study. In this study, we have included the hemodynamic parameters, in addition to pains scores, post-operative nausea and vomiting, patient satisfaction at 48 hours, requirement of rescue analgesia and the complications associated with the procedure.

The success rate observed for epidural procedure is 78% and for TAP catheter procedure is 63%. Based on these proportion for these two groups and assuming the significance level of 5% with power of 80%, the required minimum sample size for the study is 112. i.e. for each group 56 cases are needed. Hence, a sample size of 120 patients with 60 patients in each group was decided.

18G Tuohy needle was used in an ‘in plane approach’ under USG guidance to locate the TAP neuro-fascial plane between the Internal oblique and Transversus abdominis muscles. 18G Tuohy was chosen based on a study by Justin W. Hail and his colleagues8. 18G Tuohy needles are clearly defined under real time USG. Visualisation of the needle tip is the most important factor determining the success of the block.

Real time visualisation of the expansion of TAP plane, was done by injecting via the Tuohy needle 4-5ml of normal saline. This was defined as hydro dissection of the TAP neuro-fascial plane. This was based on a previous study by Hebbard and his colleagues4, while demonstrating the posterior approach to transversus abdominis plane block (TAP Block) under USG guidance.

Optimal needle location is indicated by the appearance of an “anechoic” fluid collection. Then the epidural catheter is inserted 4-6cm beyond the needle tip into the TAP neuro-fascial plane. 15 ml of Inj. 0.25% bupivacaine via TAP catheter was given as intermittent boluses. Bilateral TAP block with 15 ml of Inj.0.25% Bupivacaine on either side by TAP block provided adequate analgesia in patients undergoing mid line incision surgery like abdominal hysterectomy9. In this study, since it was a non-midline incision only unilateral TAP block was performed. 15 ml of injection 0.25 % bupivacaine was repeated every 8 hours. 10 ml of injection 0.25% bupivacaine was used in epidural group and was repeated every 8 hours.

In group E, epidural catheter was activated at 140 minutes from the skin incision time, whereas in Group T, Tap catheter was activated immediately after insertion in the post-operative period. Since the mean duration of the inguinal hernia repair was approximately 140 minutes, the groups were comparable in terms of time of activation of TAP catheter and epidural catheter.

The mean VAS scores at all the time intervals, measured were comparable between the TAP group and the epidural group. The p-value computed was statistically not sig-
significant. So the analgesic efficacy of USG guided TAP block as measured by visual analogue scores were comparable with epidural analgesia. Visual analogue pain scores were used for grading postoperative pain scores based on previous studies by Avelin.C, H.L.e.Hetat on patients undergoing open inguinal hernia repair10 and by John G.McDonald, John carney on patients undergoing caesarean section9. In both these studies, patient received USG guided TAP block for postoperative pain relief.

Rescue analgesia was given as per the patient requirement and on patients demand. Rescue analgesia was given if VAS scores were greater than or equal to 4. Injection ondansetron 4 mg was given before administering tramadol. Rescue analgesia was required in 12 of the 60 patients in the TAP group and 11 of the 60 patients in the epidural group. Hence, requirement of rescue analgesia was comparable in both the groups.

The average post-operative nausea scores were similar in both groups. Rescue anti-emetics were given with Inj. Ondansetron 4 mg intravenously, when the PONV scores were ≥ 2. Average PONV scores were similar in both the groups. Incidence of vomiting would have been higher if Epidural narcotics were used. However in our study, only 0.125% bupivacaine was used for epidural analgesia as intermittent boluses every 8 hours.

In the TAP group, therapeutic failure rate was 20%. In the epidural group the therapeutic failure rate was 12%. Out of the 7 patients in the epidural group who had therapeutic failure 3 patients had bloody aspirate 24 hours after surgery. 2 patients had block in the epidural catheter and 2 patients had inadequate pain relief probably due to catheter migration. As far as the TAP catheter group was concerned, out of 12 patients who had therapeutic failure 7 patients had inadequate pain relief probably due to either catheter migration or block in the catheter. In other 5 patients there was bloody aspirate in the TAP catheter. In all the patients who had bloody aspirate in both the groups catheter was re-sited. Then post-operative analgesia was continued with the same analgesic regimen. The re-sited catheters were effective in 75% of the patients.

A score of 4 which means excellent postoperative patient satisfaction was recorded in 19 patients in Group E compared to 11 patients in group T. The mean postoperative satisfaction was shade better in the Epidural group (3.04±0.96) than the TAP group (2.52±1.07). This may be because of the vague underlying dull visceral pain in the TAP group. There was no incidence of bradycardia, respiratory depression, urinary retention in both the groups, since the surgical repair done was an infra umbilical procedure. The analgesic levels required were well below T10 levels. 14 of the 60 patients had hypotension in Epidural group. However, all patients responded to fluid boluses. Physiological effect of sympathetic blockade was the reason behind this hypotension in epidural group. But there was no incidence of hypotension in the TAP group.

In epidural analgesia intermittent bolus dosing of bupivacaine has been shown to minimize block regression and marginally improve analgesia compared to the continuous infusion of the same hourly dose in patients undergoing infra-umbilical surgery 11.

Adverse effects of epidural analgesia include dural puncture, transient neuropathy, spinal hematoma, neur-axial infections, and catheter migration. Catheter migration can be intrathecal or intravascular. Both can present with catastrophic complications. Lower limb motor block is uncommon when using low concentrations of bupivacaine. Urinary retention is seen when sacral segments S2 to S4 are blocked by epidural analgesia. Post-operative respiratory depression and nausea and vomiting are more pronounced in patients receiving epidural narcotics.

Use of USG guided sensory block of anterior abdominal wall with bupivacaine for post-operative pain relief is an attractive method because of its simplicity and safety. The USG guided posterior approach of TAP block has been mainly used for infra-umbilical surgeries. The dermatomal levels covered were T9-L1 whereas oblique subcostal approach has been mainly used for surgeries above the umbilicus12. Posterior approach of USG guided TAP block used for inguinal hernia repair in our study provided both static and dynamic analgesia.

One of the advantages of TAP block include unilateral analgesia on the side of surgery, a potential advantage in patients undergoing non-midline abdominal incisions. USG guided TAP block is devoid of the side effects of epidural analgesia such as hypotension, postoperative nausea and vomiting, urinary retention and motor blockade.

**CONCLUSION:**

USG guided TAP blocks are comparable to epidural analgesia in relieving the post-operative pain after open inguinal hernia surgery. USG guided TAP block can be an effective alternative and a less invasive approach compared to epidural analgesia, because of its relative simplicity. USG guided TAP block holds considerable promise as a part of postoperative analgesia regimen, devoid of the side effects.
of epidural anaesthesia, such as hypotension, respiratory depression and vomiting.

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For most diagnoses all that is needed is an ounce of knowledge, an ounce of intelligence, and a pound of thoroughness
CASE REPORT - ANATOMY

A CASE REPORT OF BILATERAL LUMBAR RIBS

K. Sujatha (1), K. Dhamodaran(2)

Abstract

A 32 year old female who had undergone double value replacement at JIPMER, Pondicherry, had come to Stanley Cardiothoracic OP for productive cough and fever. After examination a chest X-ray PA view and plain x-ray abdomen PA view was taken which showed bilateral super numery ribs below T12 Thoracic vertebra. Lumbar ribs are a very rare anomaly characterized by extra rib arising from Lumbar vertebr.a. Lumbar ribs arising from vertebr.a may be mistaken for kissing osteophytes, transverse process anomalies or abdominal vessel anomalies. Adequate knowledge of this condition is therefore important for further research.

Key words: Bilateral lumbar ribs, gorilla ribs, supernumerary ribs, accessory ribs.

INTRODUCTION :

Variation in the ribs can be supernumerary or sub-numerary. Extra ribs are formed in cervical or lumbar regions. The lumbar ribs are less common than cervical ribs and carry a great clinical importance in that they confuse the identification of vertebral level in diagnostic images. The first case of bilateral lumbar ribs was reported by John cumming in 19263.

Lumbar ribs are a very rare anatomical variant and represents the transition of vertebra at the thoracolumbar junction with the prevalence of 1% and it represents as an additional ribs coming off from T13/L1 depending on numbering classification and may be unilateral or bilateral.

Lumbar (Gorilla) ribs develops from the costal elements of L1 vertebra but remains undiagnosed as it usually does not cause symptoms.

CASE REPORT :

A 32 years old female came to Stanley Cardio Thoracic OP for productive cough and fever for the past 15 days. She gave a past history of double valve (Aortic & Mitral) replacement done at JIPMER Pondicherry on taking a chest x-ray PA view, clavicle appeared normal on both sides, Sternal angle corresponds to 2nd costal cartilage and there were 13 pairs of ribs. 12 pairs from corresponding thoracic vertebra. And the last pair from lumbar vertebra. The first 7 pairs of ribs were attached to the sternum directly, 8, 9, 10th pair were attached to the 7th rib and there were 3 floating ribs on either side. So x-ray spine -thoracolumbar region PA view was taken which demonstrates linear radio – opaque outgrowths (upright black arrow) resembling ribs on either side. Plain radiograph of entire spine was taken to confirm the location of L1 vertebra and to rule out the possibility of any rib arising from transitional vertebra. The length of the ribs were much shorter than the T11 & T12 ribs and it terminates upwards. Thus these additional rod like radio opacities were confirmed to be extra floating ribs at L1 vertebra which is a very rare anomaly.

The other lumbar vertebra and 5 sacral vertebra were normal. First 2 pairs from T11 and T12 the last pair from L1. The bilateral lumbar ribs were much smaller than the other floating ribs.

DISCUSSION :

Extra ribs are formed usually in the lumbar are cervical regions. The costal element of the L1 vertebra may form a short lumbar rib. Which articulates with the transverse process but not usually with the body of vertebra. The costal element of 1st lumbar vertebra may grow and to form a rudimentary or complete rib.

According to Deepak anap et.al. A lumbar ribs can be differentiated from the thoracic rib by noting its length which is usually nearly half or less than half of the adjacent thoracic rib and its course is more horizontal to begin with.
and tapers upwards as it terminates distally. Contrary to this thoracic ribs are slanting downwards to begin with and continue this downward slant until their termination which very well coincides with my study8.

Embryology: Lumbar ribs are a common finding in standard developmental toxicology bioassays that are performed globally. Apart from physical and chemical agents that can induce lumbar ribs formation. Maternal factors like stress can also play a role. During embryogenesis the development of lumbar ribs is attributed to the changes in the axial skeleton and are intrigued due to developmental changes in gene expression9.

Whatever the cause the patient with extra ribs may prove a surgical challenge at the operating table because of the possibility of ending up in different/wrong sites. Bone grafting using the twelfth rib may be significantly affected if there were more than 12 or less than 12 pairs of ribs. Location of the kidney using the angle of T12 and L1 for percutaneous renal biopsy or nephrectomy can be a nightmare. Hence the availability of such knowledge helps the surgeon to devise an alternate approach to nephrectomy or renal biopsy procedures. Interpretation of radiological examination might be confusing because it depends on numbers and site of vertebra and ribs present. However there is extra protection for spleen, kidneys and other viscera. Thereby reducing the effect of direct blow to these organs.

**CONCLUSION:**

Super numerary lumbar ribs are used clinically important in radiological diagnosis, therapeutic procedures forensic and medicolegal identification. Knowledge of such variation is essential to students of radiology, anatomy, pathology, surgery, Uro surgery because each variation would have unique features different from others.

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InTr Oduc TIOn:
Subcutaneous mycoses are characterised by a heterogenous group of infection that often result from direct penetration of fungus into the dermis and subcutaneous tissue through traumatic injury [1]. Subcutaneous mycoses are much less common than superficial fungal infection. The fungus spreads by local deep tissue invasion from the inoculation site. The disease usually remains localized and then slowly spreads to adjacent tissue and eventually to the lymphatics.

CAsE hISTOry:
A 45 years female came to fnac room with complaints of swelling in left foot for the past one year. History of trauma 1 year back following which the swelling developed. It started as a small swelling in size and gradually increased to the present size. On examination, the swelling was visualised on the medial side of left foot, 6x5cm in size, surface was nodular and smooth. Consistency was firm. The swelling was not tender and not mobile. FNAC was done and 0.5ml of pus aspirated.

The smear was moderately cellular and showed fungal hyphae admixed with sheets of neutrophils, lymphocytes and multinucleated giant cells in a necrotic background. The fungal elements were broad, septate and not pigmented.

Subcutaneous fungal infection was considered as the diagnosis. Culture for typing of the fungus was suggested. Patient lost for follow up.

Abstract
The incidence of fungal infections are on the rise and at present they are the 4th most common cause of dermatological diseases. Here we present a case of subcutaneous swelling in the foot following injury which was diagnosed as subcutaneous mycosis by fnac and culture suggested for subtyping. This is to highlight the importance of considering this as a diagnostic possibility in posttraumatic subcutaneous swelling.

Key-words: Subcutaneous mycosis, hyphae.

Key Messages: This is to highlight the importance of considering this as a diagnostic possibility in posttraumatic subcutaneous swelling.

INTRODUCTION:
Subcutaneous mycoses are characterised by a heterogenous group of infection that often result from direct penetration of fungus into the dermis and subcutaneous tissue through traumatic injury [1]. Subcutaneous mycoses are much less common than superficial fungal infection. The fungus spreads by local deep tissue invasion from the inoculation site. The disease usually remains localized and then slowly spreads to adjacent tissue and eventually to the lymphatics.

CASE HISTORY:
A 45 years female came to fnac room with complaints of swelling in left foot for the past one year. History of trauma 1 year back following which the swelling developed. It started as a small swelling in size and gradually increased to the present size. On examination, the swelling was visualised on the medial side of left foot, 6x5cm in size, surface was nodular and smooth. Consistency was firm. The swelling was not tender and not mobile. FNAC was done and 0.5ml of pus aspirated.

The smear was moderately cellular and showed fungal hyphae admixed with sheets of neutrophils, lymphocytes and multinucleated giant cells in a necrotic background. The fungal elements were broad, septate and not pigmented.

Subcutaneous fungal infection was considered as the diagnosis. Culture for typing of the fungus was suggested. Patient lost for follow up.
DISCUSSION:

Subcutaneous mycoses are generally caused by fungi that are normally saprophytic inhabitants of soil, particularly in tropical and subtropical areas of Africa, India, and South America. Wounds of the skin. Most infections involve people who normally walk barefoot. This condition involves the dermis, subcutaneous tissue, muscle, and fascia. These infections are chronic and can be initiated by piercing trauma to the skin which allows the fungi to enter. These infections are difficult to treat and may require surgical intervention.

Differential diagnosis for subcutaneous fungal infection are given in Table.1.

Subcutaneous mycoses are less common than superficial mycoses and spread by direct injury and hence when a patient walks into the OPD/FNA room with a subcutaneous swelling following injury this condition should also be entertained in the differential diagnosis. Fungal hyphae should be examined for in the FNA smear showing features of an infective etiology. Culture is the ideal methodology for subtyping the organism and should be suggested. This case is presented for its rarity and to highlight the importance of considering fungal infection as a differential diagnosis for soft tissue swelling following trauma as it has definite implications on therapy.

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Vitamins used in clinical practice as food supplements sometimes act as cofactors for catalysis of many metabolic processes in the body. A few neurological disorders, including seizures, have been associated with vitamins. Progressive bulbar palsy in children is a severe and debilitating illness with high morbidity. Many of the aetiologies of the disorder seem to be mostly neurodegenerative and have poor outcomes. Fazio Londae disease, a similar rare disorder with progressive bulbar paralysis and respiratory failure, is found to be due to mutation of SLC52A3 gene which encodes the intestinal riboflavin transporter in few children. They respond very well to prompt riboflavin therapy as we described and thus emphasizing this entity of riboflavin responsive neurological disorder as a unique vitamin responsive problem.

Case History:

A 7 months old female infant presented with swallowing difficulty, poor cry and pooling of secretions of the throat as progressive bulbar palsy. She responded to riboflavin treatment and continued to improve.

Key Words: bulbar palsy, riboflavin, hypotonia, respiratory distress

Key Messages: riboflavin responsive bulbar palsy.

Abstract

A seven months old infant presented with swallowing difficulty, poor cry and pooling of secretions of the throat as progressive bulbar palsy. She responded to riboflavin treatment and continued to improve.

Reference:

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investigations. MR brain and cervical spine were normal and metabolic screening with tandem mass spectroscopy, vitamin B12 levels, survival motor neuron gene PCR (SMN gene) for spinal muscular atrophy were all negative. Detailed nerve conduction study revealed normal conduction velocities and F waves, normal sensory potentials; needle electromyography (EMG) showed fibrillation potentials over deltoid, biceps and triceps on both sides revealing axonal neuropathy (anterior horn cell). Parents refused for muscle biopsy and CSF study to this child. With the limited available clinical picture and electro-physiological investigations she was diagnosed as neurogenic bulbospinal amyotrophy probably due to anterior horn cell disease. Following possibilities were put forth: spinal muscular atrophy (SMN gene mutation negative), hereditary motor sensory neuropathy type 1 (nerve conduction study normal), Brown- Vialetto -Van Laere syndrome (normal hearing), Tay Sach’s disease (absent startle myoclonus, cherry red spot) Fazio Londe disease. With the above differential diagnosis, she child could be suffering from progressive bulbar palsy of Fazio Londe disease; a trial of riboflavin treatment at a dose of 15 mg per Kg body weight was given. Surprisingly, she showed dramatic improvement in 2 weeks time and successful extubation was done on the 25th day. Riboflavin was then continued on 10 mg per Kg weight of the child and discharged from hospital with the same medication. She was reviewed after 3 months; she started to swallow liquids as well semi solid food with no nasal regurgitation, could hold the neck and could sit and stand with support. She is still on the above treatment and advised regular follow up.

**DISCUSSION:**

Fazio Londe disease is a rare neurological disorder presenting with progressive bulbar palsy with respiratory failure. (1) It was once considered to have an unrelenting course, is now found to be due to mutations in the SLC52A3 gene which encodes the intestinal (hRFT2) riboflavin transporter in some children (2). Brown-Vialetto-Van Laere syndrome is similar rare neurological disorder with sensory-neural deafness, presenting at all ages with bulbar palsy and respiratory compromise and Fazio-Londe syndrome is considered to be the same disease entity presenting in children with normal hearing. (3) Appropriate diagnosis requires mutation analysis of all the related three transporter genes of the above. (4) Because of the striking and often lifesaving effects of riboflavin supplementation it is highly advisable to start treatment immediately without awaiting results of mutation analysis. Thus despite lack of availability of genetic analysis, a trial riboflavin therapy, administered to our child, on the basis of clinical symptoms resulted in a life saving effect.

**CONCLUSION:**

This case illustrates the rarity of presentation of progressive bulbar palsy of Fazio Londe disease in this child on clinical and limited electrophysiological investigation and the beneficial life saving role of riboflavin treatment for this disorder. The point of philosophy is to start with something so simple and to end with something so surprising that no one will believe it. Points to ponder!

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**ACKNOWLEDGEMENT:**

The above presentation is not assisted by any financial support and parents did not object for the publication of their child’s condition.
Opsoclonus ataxia syndrome also known as dancing eye dancing leg syndrome is a very rare neurological disorder affecting 1 in 1000000 people worldwide. In children, it is commonly associated with neuroblastoma. It can also be consequent to ingestion of toxic dose of medications like haloperidol and amitryptilin. It can be associated with infections like West Nile virus, Epstein Barr Virus (EBV), Varicella zoster virus, Mycoplasma pneumoniae and listeriosis.

INTRODUCTION:

Opsoclonus ataxia syndrome is a rare neurological disorder in children and is commonly associated with neuroblastoma. It can be associated with other malignancies, infections, metabolic disorders, toxic medications or autoimmune causes. Here we report a rare case of postinfectious opsoclonus ataxia syndrome secondary to Epstein Barr Virus infection.

CASE REPORT:

2 years old male child with normal birth and development history had fever of 2 days duration. 5 days after subsidence of fever, child was not able to get up from bed. When made to stand or sit, child had severe truncal ataxia. Child had tremulousness and was not able to hold objects, not able to speak but was able to recognize mother. Child also had difficulty in swallowing, for which he was tube fed. After admission child had fast chaotic eye movements suggestive of opsoclonus. He had incoordination of both upper limbs. Tone was reduced, deep tendon reflexes were present and fundus was normal. Apart from routine investigations which were normal, the child was screened for occult malignancies like neuroblastoma. CT thorax and CT abdomen were normal. Urine metabolic screening, blood Tandem Mass Spectrometry for metabolic disorders were negative. Urine Vanillyl Mandelic Acid estimation was within normal limit. Vasculitic workup was negative. Serum vitamin B12 and serum lactate were normal. CSF analysis showed elevated cell count-135cells/cu.mm (predominantly neutrophils), CSF biochemistry was normal (protein-10mg/dl, sugar-110mg/dl, lactate-13.4mg/dl) CSF EBV Ig G was positive. Screening for HIV, Japanese encephalitis, Hepatitis C virus, Enterovirus, Cytomegalovirus and Herpes simplex virus were negative. Nerve conduction study was normal. He was treated with a course of IV methyl prednisolone followed by IV Immunoglobulin. Ataxia improved much and he became ambulant and opsoclonus disappeared. 2 months later, child presented with increased unsteadiness and was treated with a course of IV methyl prednisolone followed by oral steroid. Ataxia improved partially.

DISCUSSION:

In children opsoclonus ataxia syndrome may be accompanied by myoclonus and typically presents as paraneoplastic syndrome that is usually related to neuroblastoma, which has been excluded in our case as CT thorax and abdomen, urine Vanillyl Mandelic Acid were normal. Metabolic screening for Maple Syrup Urine Disease and Mitochondrial disorders which can present with intermittent ataxia were negative. Other etiologies are infections, multiple sclerosis and SLE. In our case, MRI brain was normal. CSF showed positive EBV IgG. EBV infection is associated with a polyclonal B lym-
phocyte proliferation and a spectrum of neutrophilic and non specific antibody response. On occasion EBV infection can give rise to autoimmune / lymphoproliferative disorders. Autoantibodies will be directed against cerebellar purkinji cells as well as peripheral nerve axons\textsuperscript{4,5}. Thus IV immunoglobulin can be used for treatment\textsuperscript{7}. Although symptoms are typically steroid responsive, children experience relapse and often suffer cognitive and behavioural problem as long term outcome\textsuperscript{8}. Rituximab can be used as an adjunctive therapy\textsuperscript{8}. Plasmapheresis may be useful\textsuperscript{9}.

**CONCLUSION:**

In a child presenting with opsoclonus and ataxia, apart from neuroblastoma one should also consider infectious etiologies like EBV.

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CASE REPORT - PAEDIATRIC NEUROLOGY

VERTICAL GAZE PALSY- A CLUE TO DIAGNOSE A RARE NEUROMETABOLIC DISORDER

S.Velusamy (1), Uday Srinivas (2), B.Krishna Kumar(3)

Abstract

Nieman Pick disease Type C (NPC) is an autosomal recessive neurometabolic disorder associated with cognitive decline and extrapyramidal features. It is due to abnormalities of intracellular cholesterol metabolism. Sea blue histiocytes in bone marrow aspirate is suggestive. Genetic tests to identify gene mutation and Filipin staining of skin fibroblast are being used to confirm diagnosis. Here we report a child who presented with cognitive decline, seizures and extrapyramidal features where the clinical finding of vertical gaze palsy lead us to diagnose this rare neurometabolic disorder.

Key-words: Vertical Gaze Palsy, Neiman pick disease, sea blue histiocyte

Key Messages: This case is reported for its rarity. Supranuclear vertical gaze palsy in a child with extrapyramidal features, one should consider possibility of NPC.

INTRODUCTION:

Nieman Pick disease Type C (NPC) is an autosomal recessive neurometabolic disorder associated with cognitive decline and movement disorders. Incidence is 1:150,000. Its caused by mutations predominantly in the lysosomal integral membrane protein NPC1 &2. Progressive neurological disease is the hallmark of Nieman–Pick type C disease, and is responsible for disability and premature death. The cellular trafficking of endocytosed LDL-derived cholesterol is impaired and results in accumulation of unesterified cholesterol and other lipids in perinuclear lysosomes. The prognosis correlates with age at onset of neurological signs; patients with early onset form progress faster.

CASE HISTORY:

5 year old boy of consanguineous parents with uneventful birth history and normal milestones except for delayed language development (started speaking a few words at 2 1/2 years of age) presented with frequent falls (20 times per day, no loss of consciousness and no precipitating factors for fall) and progressive difficulty in walking since 3 1/2 years of age. 2 months later, child started having frequent brief episodes of GTGs (1-2 per day) controlled with sodium valproate and lamotrigine. Child began to walk with support. For the past 6 months, child was not speaking even a few words which he used to speak and started having involuntary movements in the upper limbs. Family history was negative. On examination, head circumference was 50 cm. Child was able to obey simple commands, visually follow objects and was not able to speak. Fundus was normal. Horizontal eye movements were normal. Eye movement in vertical direction (for upward gaze) was impaired but normal with oculocephalic maneuver suggestive of supranuclear vertical gaze palsy. Other cranial nerves normal. Bulk, power were normal and tone was varying with normal deep tendon reflexes. He had striatal toes, choreic movements in upper limbs and frequent eyebrow movements.

Figure 1: MRI brain T2 Weighted image showing periventricular hyperintensity

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of sphingomyelin in monocyte macrophage system. Type A presents with developmental regression, hepatosplenomegaly and death by 2-3 years of age. Type B is nonneuronopathic form. Type C is due to defective cholesterol transport and presents with developmental delay or regression, cataplexy, seizures, ataxia, extrapyramidal features, vertical gaze palsy with hepatosplenomegaly. Frequent falls in this case would be due to cataplexy or atonic seizures. Presence of a vertical gaze palsy in a progressive neurological disorder narrows the diagnostic possibilities considerably to Wilson’s disease, neuroacanthocytosis, and NPC6. Sphingomyelinase activity is normal in NPC unlike in other types. Mere presence of Sea blue histiocytes (lipid laden foamy macrophage) is not specific for NPC, but in the appropriate clinical setting, its presence is very much diagnostic of NPC. Diagnostic confirmation is by skin fibroblast culture and filipin staining7 for intralysosomal storage of unesterified cholesterol and by identification of gene mutation (not done in our case due to financial constraints). No specific treatment is available. Miglustat, a glucosylceramide synthase inhibitor has been tried8.

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ACKNOWLEDGEMENT:

We acknowledge the Department of Pathology, Stanley Medical College for bone marrow aspiration study.
INTRODUCTION:

Hydatid disease is endemic in farming areas but occurs worldwide. The most common site of disease is the liver, followed by the lungs, kidney, bones and brain. Other sites such as the heart, spleen, pancreas and muscles are very rarely affected. Splenic hydatid disease has been reported to constitute up to 4% of cases of abdominal hydatid disease.1 The rarity of splenic hydatid disease may pose a diagnostic challenge for clinicians, especially in nonendemic areas.2 In this report, we present the case of a elderly male with concomitant splenic Hydatid cyst which was managed surgically by splenectomy.

Key-words: Hydatid Cyst, spleen

CASE REPORT:

A 52-years-old male came with chief complaints of abdominal distension in left upper quadrant of his abdomen. The patient reported the distension had been increasing rapidly over past 3 months. Patient was admitted under surgical department. On physical examination he showed an asymmetric abdomen and a growing mass on left side. Abdominopelvic computed tomography(CT) showed mildly thick walled septated cyst with multiple daughter cyst like appearance measuring approximately 101x94x130mm in left hypochondrium at splenic hilar region and medical aspect of spleen between tail of pancreas and splenic parenchyma suggestive of Hydatid cyst of spleen. The spleen was displacing intestines to right. A CT of chest was done to rule out any other cysts. CT chest was normal. Exploration was done, found a huge Hydatid cyst in spleen filling the entire left side abdomen and pushing intestines to right. Aspiration of contents of splenic Hydatid cyst was done and then instilled with 10% hypertrophic saline. Opened the cyst and removed all endocysts. Performed a splenectomy aspiration, cystostomy capitonage and omentopexy to the cyst in left lateral segment of liver. The postoperative period of patient was uneventful and he was discharged with advised on taking Tablet. Albendazole.

DISCUSSION:

Splenic hydatid cysts are generally asymptomatic. Diagnosis is usually established incidentally during investigation of unrelated symptoms. When the cyst reaches an advanced size, the patient presents with a painful mass in the left hypochondrium.1,2 Other initial presentations include renal arterial compression and systemic hypertension or rupture of the splenic hydatid cyst to the other organs.1 Our patient was admitted to hospital for pain and a rapidly enlarging mass in the left upper quadrant of his abdomen. The imaging characteristics of splenic hydatid cysts are
similar to those of hydatid cysts:3 calcification of the cyst wall, the presence of daughter cysts and membrane detachment. The differential diagnosis for splenic hydatid cysts includes other splenic cystic lesions such as epidermoid cysts, pseudocysts, splenic abscesses, hematomas and cystic neoplasms of the spleen.3,4

Owing to the risk of spontaneous or traumatic rupture, splenic hydatid cysts are usually treated surgically.1,4 The standard treatment is total or partial splenectomy. Cyst fluid can be drained with puncture and aspiration to reduce the intracystic pressure, but splenectomy without puncturing the cyst is preferable.4,5 We drained the splenic cyst in our patient before splenectomy. Albendazol therapy is the mainstay of treatment in the postoperative follow-up period.

**FIGURE 1:** Abdominopelvic computed tomography (CT) showed mildly thick walled septated cyst with multiple daughter cyst like appearance measuring approximately 101x94x130mm in left hypochondrium at splenic hilar region and medical aspect of spleen between tail of pancreas and splenic parenchyma suggestive of Hydatid cyst of spleen.

**FIGURE 2:** Showing Splenic Hydatid Cyst.

**FIGURE 3:** CT scan showing a slice section of splenic Hydatid cyst with measurements.
FIGURE 4: Showing Splenic Hydatid cyst after splenectomy, the spleen in this image is kept in formalin solution

REFERENCE:

Oesophageal duplication cysts account for a very small percentage of benign oesophageal tumours and are infrequently symptomatic. Chest pain and dysphagia were the most common complaints in symptomatic patients affected by the duplication cysts. Patients with oesophageal cysts seek treatment when a complication such as bleeding or infection causes these cysts to enlarge.

Methods: We report a patient who reported to the Medical Gastroenterology department of Stanley medical college hospital with complains of dyspepsia

Clinical Picture: An otherwise healthy 35-year-old man presented with a 3-week history of dyspepsia. He reported no history of respiratory symptoms or weight loss. The physical examination was normal and his blood pressure was 110/80. Laboratory data were within normal limits. The electrocardiogram did not show any abnormality. Endoscopy revealed oesophageal sub mucosal lesion. MRI scan of the thorax further demonstrated a cystic structure continuous with the oesophageal wall. We performed Endoscopic ultra sound imaging (EUS) which confirmed duplication cysts, described as round, anechoic lesions arising from the third hyper echoic layer. His symptoms were improved with proton pump inhibitors. We advised annual endoscopic follow up.

Result: In our case, upper GI endoscopy revealed the sub mucosal lesion of the oesophagus, confirmed by endoscopic ultrasound. Asymptomatic oesophageal cyst patient could be regularly followed up.

Key-words: Oesophageal cyst, duplication of foregut, EUS: endoscopic ultrasonography

Key Messages: Oesophageal duplication cysts

INTRODUCTION:

Oesophageal duplication cysts are congenital anomalies of the foregut resulting from aberration of the posterior division of the embryonic foregut at 3-4 wk gestation(1). Oesophageal duplication cysts are 1 0%-1 5% of all alimentary tract duplications, occurring at any level from mouth to anus (2,3). Most are discovered in children, but 25%-30% are found in adults(2). Of the duplication cysts, 60% are located in the lower oesophagus. The rest are distributed equally between the upper and middle thirds of the oesophagus (3-5). They represent either simple epithelial-lined cysts, or true oesophageal duplication, which is a duplication of the muscularis mucosa and externa without epithelial duplication (6,7).
Endoscopy revealed sub mucosal lesions covered with normal mucosa and localized in the middle third of the oesophagus (Fig 1).

MRI scan of the thorax demonstrated a cystic structure continuous with the oesophageal wall (Fig.2). The oesophagus was compressed and shifted to the left. The structure had a tubular morphology and occupied the posterior mediastinum.

Endoscopic ultra sound imaging confirmed these data and also showed a round, anechoic lesions arising from the third hyper echoic layer. (Fig.3).

DISCUSSION:

Oesophageal duplication cysts account for a very small percentage of benign oesophageal tumors and are infrequently symptomatic(2,3). Oesophageal duplication cyst usually is diagnosed in childhood, but it also may be unrecognized in the absence of complications. Most of them are found in the mediastinum and manifest themselves as separate masses along or in continuity with the native oesophagus (8). Oesophageal cysts do not usually communicate with the oesophageal wall but occur as a separate malformation along or in continuity with the native oesophagus. The clinical presentation of oesophageal duplication cysts is variable. Most patients are seen early in life, although some remain asymptomatic until adulthood, when a common presentation is an asymptomatic mediastinal mass (8,9).

When symptoms occur, they may include dysphagia, nausea, vomiting, weight loss, anorexia, dyspnoea, wheezing or coughing episodes, and recurrent pneumonitis(10-11). Epigastric or substernal pain or fullness can occur. Bleeding or infection may cause the cyst to enlarge, exacerbating symptoms(10-12). Patients with oesophageal cysts seek treatment when a complication such as bleeding or infection causes these cysts to enlarge (8). In the presented
cases they were localized intramurally as a mass pressing on the oesophageal lumen and this is why they resembled oesophageal varices or sub mucosal tumours (9). The diagnosis may be made with barium swallow and oesophagoscopy although the exact histopathology is not defined until surgery. Surgical excision is recommended at the time of cyst discovery whether symptoms are present or not. In the present case, the patient has dyspeptic symptoms and they are treated either surgically or endoscopically. Surgery is the treatment of choice for bronchogenic and oesophageal duplication cysts (16, 17). Video-assisted thoracoscopy should represent the first-line approach in these patients (16-18). In this report we describe a adult patients in whom oesophageal duplication cysts were localised intramurally as masses pressing on the oesophageal lumen and who were diagnosed with oesophageal duplication cyst by endoscopic ultrasonography. The patient was initially referred to our centre for upper gastroduodenoscopy due to non-specific dyspeptic symptoms. Patients had no symptoms suggesting disease of the oesophagus and required no treatment. As the true prevalence of oesophageal cysts is unknown, it is very likely that in many patients, like the one described by us, they may cause no symptoms, remain undetected and require no intervention. Increasing availability of new diagnostic modalities such as endoscopic ultrasonography may change the current view regarding the prevalence of oesophageal duplication cysts and prove that they may, in fact, not be such rare findings.

Treatment of oesophageal duplication cysts in asymptomatic patients is controversial with no clear clinical guidelines. In our patient, we arbitrarily decided to schedule them for follow up annual gastroduodenoscopy. An earlier intervention will be performed if they become symptomatic.

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ACKNOWLEDGEMENT:

We extend our gratitude and thanks to our patient and siblings for their cooperation to participate in the study. We sincerely acknowledge Dr Piramanayagam P, Consultant Gastroenterologist, Apollo hospitals, Chennai and Dr S.Jeswanth, Professor of Surgical Gastroenterology, Stanley Medical College for their support and encouragement to conduct this study.

Conflict of interest: Authors report no conflicts of interest.
InTraining:
Liver or kidney transplant recipients are at a higher risk of developing tuberculosis (TB) than the general population (1). Tuberculosis (TB) remains a major global health problem. Mycobacterium tuberculosis affects 0.47-2.3% of adults with liver transplantation (1). The overall incidence of tuberculosis in liver transplant patient is three times more than the general population (2). Because of the difficulty of accurately diagnosing symptomatic TB, these figures most likely underestimate the burden of the disease.

Post-transplant TB is more frequent in Asia and Africa (3). It can be reactivation of a latent or primary post-transplant infection (4). Post-liver transplant TB can be either pulmonary or extra pulmonary such as lymph node, meninges and genitourinary (5). Post-liver transplant tuberculosis affecting transplanted liver has been rarely reported, most of which have been part of disseminated diseases. However, isolated hepatic tuberculosis in a transplanted liver is extremely rare and only few cases have been reported (6-8). The RESITRA (Spanish Network of Infection in Transplantation) cohort documented a relative risk of 4.3 for the development of symptomatic TB when the purified protein derivative (PPD) test was positive instead of negative.

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A systematic review of 139 cases of active TB infection after liver transplantation, 37% had a positive tuberculin skin test (TST), 23% had abnormal pre-transplant chest imaging, and 13% had a history of untreated/improperly treated TB (5). The number of pre-transplant patients with a positive TST underestimates the number of patients infected with TB because end-stage liver disease may result in coetaneous anergy, which decreases the sensitivity of the TST. Chest radiography findings consistent with TB (ie, a military pattern, cavitary lesions, and upper lobe focal infiltrates) appear to be the single most important risk factor associated with the development of early-onset TB (9). TB in solid organ transplant (SOT) recipients is a challenge because of its atypical and extra pulmonary presentations, metabolic interactions between the immunosuppressive drugs and the drugs used to treat TB, the side effects from long-term treatment of TB, as well as a high mortality rate (10-12).

**CASE HISTORY:**

A 42 year-old woman underwent OLT in January 2009 for cryptogenic cirrhosis. Her pre-transplant work-up including, PPD test (purified protein derivative test) and chest X-ray were negative. In her past medical history, she had no diabetes (DM), and hypertension (HT). She had no past or contact history of TB. Her pre-transplant chest X-ray and computed tomography scan of the thorax revealed no abnormalities. The patient received a liver from a cadaveric, blood group identical young 27 year old man, victim of a car accident. According to his medical records, the cadaver had completely been healthy, with no prior disease. Patient's post-transplant period was unremarkable and left the hospital in 30 days. Immunosuppressant regimes consisted of Intravenous Methyl prednisolone, followed by tapering dose of prednisolone starting from 20 mg, and Tacrolimus from 0.1 mg/kg/day dose adjusted according to the trough levels around 10. Her immediate post-transplant course was complicated by episode of diarrhoea and upper respiratory tract infection, which resolved with parenteral antibiotics, and he was eventually discharged 30 days post-transplant with a clear chest X-ray (Fig. 1).

Four years post-transplant, the patient was again admitted on August 2012, for fever and cough, anorexia, easy fatigability, malaise, night sweat and low grade fever. Physical examination showed: BP = 150/70, PR = 80/min, RR = 16/min, and T = 37.7°C. The laboratory examination findings: WBC = 6900 cells/cumm, and Hb = 9 gms/dl. Liver function tests (LFT) showed elevated ALT (60 IU/L, normal < 40) and AST (55 IU/L, normal < 40). Alkaline phosphatase was also mildly elevated (385 IU/L, normal 65-300). Chest X-ray, however, showed an acute onset of middle lobe pneumonia (Fig. 2). Sputum smears for acid-fast bacilli (AFB). The patient became afebrile 10 days after starting antituberculous therapy. The patient's fever settled and she was discharged 14 days after admission. Patient was discharged home with referral to start anti-TB therapy at the directly observed Therapy (DOT) centre. The individualized regime was composed of Inj Streptomycin 750 mg IM ethambutol 800 mg/day, and isoniazid (INH) 300 mg/day. With intensive phase of streptomycin, isoniazide and ethambutol for two months and continuous phase of ethambutol and isoniazide for 10 months. Meanwhile tacrolimus dose was reduced to 5 mg/day and maintain the trough level around 6. After a short period sustained reduction of liver enzymes was noticed and also the patient's general condition showed significant recovery. After the 6-month course of therapy, her right middle lobe infiltrates resolved and she remained well with no respiratory symptoms. After 12 months of anti-TB therapy she is completely well, laboratory findings are normal and drugs are gradually decreased to be followed for any further problem until her last review, 40 months after the cessation of anti-TB treatment. She is still on the previous immunosuppressive regimen and there has been no episode of rejection during the last 12 months of the follow up.

**DISCUSSION:**

Tuberculosis (TB) has important implications in the care of transplant recipients. It causes significant mortality in transplant recipients as compared to the general (1). TB is
one of the most important opportunistic infections affecting solid-organ transplant (SOT) recipients because of the high associated morbidity and mortality (1,2). A thorough history documenting TB risk factors, exposures, and infections should be obtained from all transplant candidates (3,4). Previous infections with TB, latent or active, should be recorded along with details about the treatment (or lack of treatment), medications, and length of therapy (3). This may include previous travel to endemic areas, institutional exposure, and contact with individuals with active TB (i.e., household or workplace contacts) (3,4).

In SOT recipients, TB usually develops from a site of latent infection in the recipient. Ideally, treatment of latent TB infection should start before transplantation. If treatment cannot be completed before the procedure, it should be completed after the procedure. Treatment of latent TB infection should be provided for all patients on the waiting list for a transplantation or for recipients who have ≥1 of the following conditions: a PPD skin test (initial or after a booster effect) with an induration ≥5 mm, a history of untreated TB, or a history of contact with a patient with active TB (i.e., household or workplace contacts) (3,4).

The American Thoracic Society, the Centers for Disease Control and Prevention, and the Infectious and Diseases Society of America recommend four regimens for the treatment of pulmonary TB (14). These regimens include a 2-month intensive phase followed by a continuation phase of 4 to 7 months. In the liver transplant population, recommendations for treating active TB differ, because of the known risk of drug-drug interactions between antituberculous medications and immunosuppressive agents and the potential for hepatotoxicity associated with first-line TB therapy. In the liver transplant population, recommendations for treating active TB differ because of the known risk of drug-drug interactions between antituberculous medications and immunosuppressive agents and the potential for hepatotoxicity associated with first-line TB therapy (3,4). These differences also have an impact on the suggested length of treatment (3,4). Isoniazid, rifampicin, and pyrazinamide can all cause hepatotoxicity (14, 15). The deleterious effect on the liver is increased when these agents are used in combination rather than alone (3,4). In a large Spanish series, 12 of 24 liver transplant recipients with TB (50%) developed hepatotoxicity during treatment (16). Another major challenge in treating TB in transplant patients is the use of rifampicin, which can significantly decrease serum levels of calcineurin inhibitors and mammalian target of rapamycin and alter corticosteroid metabolism (3,4,15,17). For this reason, rifamycins must be used with extreme caution in transplant recipients. Cyclosporine and tacrolimus doses should be increased 3- to 5-fold at the outset of therapy, and levels should be monitored closely (4,18). However, even with this adjustment and careful monitoring, combining rifampicin and calcineurin inhibitors can lead to increased graft rejection, graft loss, and TB-related mortality (4). Rifabutin appears to be as effective as rifampicin, but it is a weaker inducer of cytochrome P3A4 and therefore results in less intense drug interactions (4,5,14,19). Little data exist on its use in the transplant population, but it appears to be just as efficacious as rifampicin in human immunodeficiency virus–infected patients and may be considered an alternative in situations in which the use of a rifamycin is mandatory (4). If rifabutin is used, cyclosporine and tacrolimus doses should be increased upon the initiation of therapy, and calcineurin inhibitor levels should be monitored closely. Because of the risks of administering rifamycins in transplant recipients, many clinicians opt to avoid these medications.
in transplant recipients for whom alternative regimens are feasible. As these risk were taken into consideration we had avoided use of rifampicin and pyrazinamide in our patient. Fluoroquinolones and aminoglycosides are other agents used in the treatment of TB; they are primarily used in cases of multidrug resistance or intolerance of first-line medications. Patients on aminoglycosides, such as streptomycin, amikacin, and kanamycin, should be monitored closely for nephrotoxicity (especially with calcineurin inhibitors) and otoxicity (14). Fluoroquinolones, notably levofloxacin and moxifloxacin, are frequently used in the treatment of drug-resistant TB (14). The prolonged use of these agents may result in arthralgias, which typically resolve once the drug has been discontinued (17). Because of a more favourable side-effect profile versus rifampicin and aminoglycosides, fluoroquinolones have been increasingly considered in transplant recipients (14,17). The ideal length of therapy remains controversial, and it is affected by the extent of the disease, choice of regimen, response to therapy, and resistance profile of the organism. Some experts suggest that bone and joint involvement, central nervous system disease, and disseminated TB require longer treatment (3). In addition, patients with cavitary pulmonary TB who remain culture-positive after 2 months of therapy require longer treatment. In general, many providers recommend 12 to 18 months of anti-TB treatment (4,15,17,20). Possible drug interactions are considered as the main problem in rifampicin therapy (24,25). Follow-up of liver functions is mandatory for isoniazid therapy after liver transplantation (21-26). Susceptibility of the new graft to isoniazid toxicity may be determined with genotype testing of liver cytochrome P450 and N-acetyl transferase (14). However, other states associated with deterioration of liver functions (eg, biliary problems or recurrence of original disease) should be mentioned during follow-up. Discontinuation of the anti-tuberculosis therapy, determination, and treatment of the cause of deterioration are considered rational. Despite the well-known adverse effects of isoniazid and rifampicin therapy, it may be inevitable to use both drugs to achieve effective control of active, pulmonary tuberculosis after transplant. Close follow-up and timely distinguishing of drug toxicity from other post transplant problems are most important issues during treatment.

TB can seriously affect the outcome of liver transplantation, preventive measures such as screening and contact avoidance should be considered as part of the post transplant care. Pulmonary TB is a rare post-transplant infection with high rates of mortality and morbidity. Its seriousness warrants a high level of suspicion. Early diagnosis and treatment are crucial for this rapidly progressive disease. Screening of latent TB is generally performed by tuberculin testing or screening chest X-ray. However, tuberculin testing for latent TB infection is not applicable in our local population as it lacks the sensitivity to distinguish between BCG-vaccinated and TB-infected populations (27). As chest X-ray is routine in patients evaluated for liver transplant, this can effectively diagnose any radiological evidence of past pulmonary TB. Sputum examination should be done if the chest X-ray is suspicious (28). New diagnostic tests including enzyme-linked immunosorbent assay, the Gen-Probe Amplified Mycobacterium tuberculosis Direct Test, DNA hybridisation, the Mycobacterium Growth Indicator tubes System and the strand displacement amplification system are currently being used in the diagnosis and drug resistance in Multi drug resistant TB(MDR-TB) in a programme setting, but their applicability in pre and post transplant evaluation and screening for transplant recipients can be made mandatory (29). Avoidance of exposure to TB-infected persons should be strictly observed by the patient and family members (30). Early diagnosis and treatment are crucial for this rapidly progressive disease and awareness of drug-induced hepatotoxicity and drug-drug interaction in anti-TB treatment ensures better prognosis.

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The art of medicine consists of amusing the patient while nature cures the disease.

It is much more important to know what sort of a patient has a disease than what sort of a disease a patient has.
Clinician’s perspective for personalized medicine and genetic testing as the future of cancer diagnosis

Anita Ramesh (1), Subbu Apparsundaram (2), Karthikeyan Rajamani (3), Ramesh K Goyal (4)

Abstract

Molecular diagnostics offer a promise of reducing the length, cost and uncertainty of new molecular entities and potentially unlocking targets for precision medicine through: patient susceptibility to disease; patient respond to treatment or any adverse events; disease progression; proof-of-concept targets correct pathway and success of treatment. Molecular diagnostic tests have emerged as one of the successful means for providing critical insights about disease diagnostics and treatment. The personalized medicine is becoming a reality not only for precise diagnosis but also providing targets towards development of successful therapy for cancer patients. To ensure that new therapies are delivered to the right patients through accurate diagnosis, it is essential to adopt the recommendations for molecular diagnostics as well as therapeutics. Molecular biomarkers can not only serve as predictive for clinical management of cancer but also provide a hope for targeted therapy. With the cost of genomic technologies coming down and results are more clinically relevant, it is possible to predict precise genetic variations that occur in cancer patients. However, awareness is required to reduce cost phenomenally altering cancer management in a better way. To make it reality consortium of oncologists is recommended for development of Indian patient specific biomarker study.

Key words: cancer, biomarker, molecular diagnosis, targeted therapy, personalized medicine

Key Message: When cancer patients at metastasis stage seek medical care clinicians can consider the possibility of molecular diagnosis. If it is delayed or overlooked, the patient remains ill for a prolonged period. A major challenge in cancer management is reflected in the high cost of diagnosis and treatment.

INTRODUCTION:

The cancer mortality a serious health disease worldwide with the highest prevalence in African American men (261.5/100,000) and the lowest in Asian/Pacific women (91.2/100,000) (1). In USA, ~455 per 100,000 men and women per year new cases are diagnosed (2). In India the incidence of cancer is 70-90 per 100,000 population with over 800,000 new cases are diagnosed and 5,50,000 deaths occur each year (3). About 6% of all deaths in India are due to cancers which contribute to 8% of global cancer mortality. The treatment options for cancer before 2000, other than surgery, by and large have been chemotherapy, radiotherapy, and hormone therapy. However, all of these options are known to produce significant side effects. During the last decade many treatment options especially monoclonal antibodies therapy have emerged based on identification of specific gene biomarkers in their tumors. Every patient has a unique set of factors driving their cancer. Decades of advances in basic science, technology, therapeutics, and the understanding of the genetic causes of cancer have coalesced in recent years to make individualized treatment for cancer care possible (4). Targeted therapy took off in early 2000s, with the advent of drugs that interfere with the essential functions of cancer cells in order to get them to die off and keeping tumors from making the new blood vessels to grow. Patients now can get better and specific treatments, with fewer side effects. Further it was found by oncologists that like radiation and chemotherapies aren’t one size fits all. This has given rise to emergence of ‘Personalized medicine or Precision medicine in cancer’.

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If one looks at the current practice for diagnostics for cancer in USA, usage of imaging techniques for guidance for the therapy is approx. 15 % that includes CT scan, MRI and PET. Approximately 50 % oncologists rely on molecular diagnostic techniques like microarray and mutation studies using PCR and ELISA. There is emergence of newer options like Circulating tumor cells and circulating nucleic acids and Next-Generation sequencing (NGS) (5). However, to look at the genetic makeup of a person’s tumor in a relatively quick and low-cost manner has been the great

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<th>Biomarker</th>
<th>Molecular Compart-ment</th>
<th>Purpose</th>
<th>Analytic assay in use</th>
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<tbody>
<tr>
<td>KRAS mutations [except c.38G&gt;A 9p.G13D)]</td>
<td>Tumor DNA</td>
<td>Predictive (-ve for anti-EGFR therapy); negative prognostic marker for several first-line randomized studies</td>
<td>PCR, multiplex assays, direct sequencing</td>
<td>Sanger sequencing and NGS</td>
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<td>Screening (Lynch Syndrome), Prognostic (recurrence overall survival), Predictive (lack of benefit)</td>
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<td>CEACAMS (CEA)</td>
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<td>BRAF c.1799T&gt;A 9p.V600E) mutation</td>
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<tr>
<td>Oncotype Dx Colon</td>
<td>Tumor mRNA</td>
<td>Prognostic stage II</td>
<td>RT-PCR in FFPE samples with recurrence score</td>
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<tr>
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<td>Prognostic</td>
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<td></td>
</tr>
<tr>
<td>LINE-1 hypomethylation</td>
<td>Tumor DNA</td>
<td>Prognostic</td>
<td>Yes</td>
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challenges in developed countries wherein there is a provision of insurance.

In India, 60.80% cancer cases are diagnosed late and 60% patients do not have access to quality treatment. The number of people living beyond a cancer diagnosis reached nearly 14.5 million in 2014 and is expected to rise to almost 19 million by 2024. In India, there are only about 300 cancer centers and 600 more are required to meet the demand. About 400 radiotherapy machines are available against about 1600 required to cover the cancer population adequately. Further, about 40% centers not equipped with all modern facilities. It is estimated that India needs 500 PET-CTs and 1000 cancer units by year 2020. Doctor patient ratio is 1 in 2000 and currently aim is to achieve 1 in 1000 by 2021. There is a need to bring awareness about personalized medicine both to general practitioners and patients in general.

The major goal of personalized medicine is to give treatments for cancer patients that are most likely to work on their particular cancer with fewer harmful side effects. This however, requires wealth of knowledge about the specific molecular and genetic makeup of their patient’s tumor. For personalized medicine in cancer one requires testing a person’s genetics and conducting a genetic test to determine if the patient has certain genetic mutations and thereby to find out if specific targeted treatment will work on it or not or otherwise may put them at a higher risk for developing cancer (6). Screening with advanced technologies have improved for few cancers; however, early detection and prevention is not yet possible for most challenging malignancies. The proliferation marker Ki67 was first identified by Gerdes et al (1983) in 1980s through mouse model of monoclonal antibody against a nuclear antigen from Hodgkin’s lymphoma cells (7, 8). Ki67 turned out to be universal marker for cell proliferation during G1, S, and G2 phases of cell cycle with a peak during mitosis and absence in G0 stage. This has led to boom in development of biomarkers in personalized medicine.

**APPLICATION OF BIOMARKERS IN THERAPEUTICS AND DRUG DEVELOPMENT:**

For personalized medicine in cancer one requires testing a person’s genetics and conducting a genetic test to determine if the patient has certain genetic mutations and thereby to find out if specific targeted treatment will work on it or not or otherwise may put them at a higher risk for developing cancer (6). Screening with advanced technologies have improved for few cancers; however, early detection and prevention is not yet possible for most challenging malignancies. The proliferation marker Ki67 was first identified by Gerdes et al (1983) in 1980s through mouse model of monoclonal antibody against a nuclear antigen from Hodgkin’s lymphoma cells (7, 8). Ki67 turned out to be universal marker for cell proliferation during G1, S, and G2 phases of cell cycle with a peak during mitosis and absence in G0 stage. This has led to boom in development of biomarkers in personalized medicine.

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<tr>
<td>EGFR mutation</td>
<td>Tumor DNA</td>
<td>Predictive</td>
<td>Histology, IHC, PCR, multiplex assays</td>
<td>Sanger sequencing and NGS</td>
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<tr>
<td>ALK gene fusion</td>
<td>Tumor DNA</td>
<td>Predictive (Crizotinib)</td>
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</tr>
<tr>
<td>KRAS mutation</td>
<td>Tumor DNA</td>
<td>Predictive</td>
<td>PCR, multiplex assays, IHC</td>
<td>Sanger sequencing and NGS*</td>
</tr>
<tr>
<td>ERCC1</td>
<td>Tumor DNA</td>
<td>Predictive (poor response to chemotherapy)</td>
<td>IHC, FISH</td>
<td>Sanger sequencing and NGS*</td>
</tr>
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* HER2 (also known as ERBB2) and BRAF V600E mutations, ROS1 and RET gene rearrangements, and MET amplification.

### Table 2. Biomarkers targeted for diagnosis and prognosis in lung cancer
mode of action. Due to this there was failure of therapy with some getting more complications and adverse effects whereas others responding to the therapy. The baseline evidence of molecular diagnosis could be integrated with therapeutics, thereby monitoring therapeutic effects for the prognosis possible. Two types of tests emerged as a part of personalized medicine: 1. Pharmacogenomics that was intended to understand single nucleotide polymorphism (SNP) maps, haplotypes, and alterations in gene expression (or) inactivation correlated with therapeutic response. 2. Pharmacogenetics to study the interindividual variations in DNA sequence related to drug absorption and disposition, including polymorphic variations in genes that defines functions of transporters involved in absorption and disposition and metabolizing enzymes/proteins.

Both pharmacogenetics and pharmacogenomics play an important role in personalized medicine for the development of population based targeted therapies to improve the benefit/risk ratios of individuals. They provide ability to offer the right drug to the right patient for the right disease at the right time with right dosage. The technical advancements of customized screening can eliminate life threatening adverse reactions. They also reduce the cost of clinical trials by identifying failures due to genomic variation responsible for drug efficacy (6,7).

The precision medicine utilizes molecular biomarkers like genes or proteins that respond to disease can be measured precisely to diagnose the disease. Genetic aspect of disease diagnosis was first discovered in 1960 for cancer patients with chronic myelogenous leukemia (CML) who had specific alterations in chromosome 22 (shortened) called Philadelphia chromosome. It occurred because of translocation between chromosome 9 and 22. The consequence of this translocation was BCR-ABL oncogene development with high tyrosine kinase activity (8). Another oncogene identified for the prediction of disease was HER2 that was first identified as indicator of patient's prognosis (9). It was reported that if HER2 is overexpressed, the patient is likely to suffer from relapse and tend to have shorter overall survival. About 15% of all breast cancer patients have overexpression of HER2 and they could benefit of anti-HER2 therapies (10). Thus, HER-2 served as predictive biomarker to those who are likely to have favorable outcome based on targeted therapy with improved survival rate (11).

<table>
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<tr>
<td>ER-α/PgR (ESR1/PR)</td>
<td>Tumor Protein</td>
<td>Diagnostic (weak) predictive</td>
<td>IHC</td>
</tr>
<tr>
<td>HER2 (ERBB2)</td>
<td>Tumor Protein</td>
<td>Diagnostic (classification) Prognostic (favorable) Predictive for anti-HER2 therapy</td>
<td>FISH, IHC</td>
</tr>
<tr>
<td>Oncotype Dx</td>
<td>Tumor RNA</td>
<td>Prognostic predictive</td>
<td>21-gene RT-PCR expression assay of FFPE samples</td>
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<td>IDH2 codon 140 mutation</td>
<td>Tumor DNA</td>
<td>Prognostic relevance of IDH2 codon 140 mutation in controversial</td>
<td>PCR, multiplex assays, direct sequencing</td>
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<tr>
<td>MammaPrint</td>
<td>Tumor RNA</td>
<td>Not clear</td>
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<td>CTCs</td>
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<td>Monitor patients with metastatic disease</td>
<td>Cell surface staining and magnetic separation</td>
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</table>
CHANGING TRENDS IN MOLECULAR AND GENOMIC DIAGNOSTICS FOR CANCER:

Evidence for the involvement of cancer genomics was first came up in 1914, when the German cytologist Boveri proposed that chromosomal defects cause a cell to proliferate abnormally (12). Familiarity of chromosome translocations and structural rearrangements coupled with copy number alterations in solid tumors became diagnostic features in cancer. Most cancer cells show cytogenetic abnormalities like chromosomal instability (CIN) which occurs as a consequence of DNA double strand break (DSB). It is important threat to genome integrity because it can result in chromosomal translocations, gene mutations for the characteristic feature of cancer (13). Fluorescent in situ hybridization (FISH) is an excellent technique for detecting chromosomal translocations in cancer. CIN is the ubiquitous of genomic instability and occurs in almost all cancers other than there is a considerable variations among the cancer genomes based on genomic instability they harbor in an individual (14). It is of major importance in predicting these instability phenotype among the individuals which have implications in patient prognosis for the choice of therapeutic targets. Microsatellite instability (MSI) a characteristic feature of genomic change has been reported widely in gastric, endometrial, ovarian, lung and colon cancer (14). These genome instability can be analyzed through advanced technologies in understanding from single-cell approaches to high-throughput multicellular assays, in which each techniques have application of detecting genomic changes. Such methods are karyotyping, flow cytometry, single nucleotide polymorphism (SNP) arrays, polymerase chain reaction (PCR) and genome sequencing.

Cancer genome analysis provide vast information on health risks and susceptibility through predicting phenotype of gene susceptibility (15). Mutation analysis through PCR is becoming standard of care for many cancers where the cell type has a unique molecular phenotype like specific mutations in few subtypes of cancer. Although these advanced techniques cannot accurately measure nucleotide changes throughout the genome. Sequencing technique like Sanger and Next Generation sequencing (NGS) could enable identification of specific alterations within a single cell for successful personalized treatment (16). Jones et al. published an example of clinical treatment decision making based on whole genome analysis (WGA) of a rare tumor (17). The human era heralded a fundamental shift toward global views of genomes and transcriptomes in human biology and disease.

EXPERIENCES WITH ‘PERSONALIZED MEDICINE’ IN COLORECTAL CANCER (CRC)

Colorectal cancer is the fourth most common cancer in men and the third most common cancer in women worldwide with estimated annual incidence of 1.3 million
(18). There is increase in incidence of CRC in low-income countries. The high incidence of CRC in young adults from diverse geographic and ethnic backgrounds can be linked to environmental pollution, lifestyle factors, and diet rich in processed foods. In the Western world, there have been major advances in knowledge of molecular mechanisms involved in CRC carcinogenesis, particularly regarding cytogenetic and epigenetic events.

Biomarker analysis in patient samples can now be used to deliver more personalized medicine for patients with metastatic colorectal cancer (mCRC). National Comprehensive Cancer Network (NCCN) and European Society of Pathology (ESP) have recommended KRAS/NRAS genotyping of tumor tissue in mCRC patients (19).

The molecular genetic testing can differentiate Lynch Syndrome (LS) from sporadic colorectal cancer by chromosomal instability (CIN), microsatellite instability (MSI) and epigenetic gene silencing (Fig. 1A). CIN is used for the diagnosis of 80–85% of mCRC since it can ravel mutation in tumor suppressor genes such as APC, TP53 and activation of KRAS oncogenes. MSI with monomorphic mononucleotide repeat markers are characterized as highly unstable MSI-H, if ≥2 markers are unstable (Fig. 1B), when 1 marker is unstable (MSI-L). LS is characterized as MSI-H, while 15% accounts for sporadic CRC (20).

The mutation in KRAS, NRAS oncogenes occur about 37% of CRC, likewise the mutation in BRAF accounts for 12% of all CRC and it mutually exclusive of KRAS mutation (Fig. 2A). Similarly, NRAS oncogene accounts for 3-5% of all CRC (20). Thus, the presence of BRAF V600E mutation and/or hypermethylation of the MLH1 promoter can further differentiate sporadic CRC from Lynch syndrome (Fig. 2B).

The diagnostic tests CIN or MSI may be sufficient for diagnosis of CRC and LS but from therapeutic point of view, further tests are required for targeted therapy. The first approval of anti-EGFR therapy was made on 2004. Subsequent to this newer understanding of biomarkers and additional approvals with respect to EGFR mutation analysis during 2007 incorporating comprehensive understanding on the status of KRAS mutation and impact of understanding on adaptation of targeted therapies. This was in fact the beginning of the era of personalized medicine. NCCN emphasized the impact of RAS on clinical practice for the presence RASwt before initiating treatment with anti-EGFR therapy (19). It was recommended that considering Based
on the case history in box 1, it was recommended that geno-
typed for mutations (EGFR, KRAS and NRAS) and the sta-
tus of exon2 mutation should be done for molecular diag-
nosis in mCRC patients using the tissue.

Table 1 illustrates various biomarkers targeted for diagno-
sis and prognosis in colorectal cancer. In clinical practice,
usually sequence based diagnostics is not carried out. It is
accepted for a better understanding of cancer genome ad-
vanced techniques like Sanger sequencing and next gen-
eration sequencing (NGS) could be utilized for molecular
diagnosis in precision medicine.

EXPERIENCES WITH ‘PERSONALIZED MEDICINE’ IN NON SQUAMOUS CELL LUNG CARCINOMA (NSCLC)

Lung cancer is one of the most common can-
cer and it accounts for 13 to 19 % of cancer related deaths
worldwide. In India, it constitutes about 9.3 per cent of all
cancer related deaths in either of sexes (5). For lung car-
cinoma the EGFR is widely used as diagnostic and prog-
nostic marker. EGFR and KRAS mutations is the hall mark
of transcriptional genes being activated during metastatic
condition (21). EGFR-TK1 resistance has been reported
as the mechanism of mesenchymal epithelial transition
(MET). Rearrangement of Anaplastic Lymphoma Linase
(ALK) occurs in lung adenocarcinoma with interstitial de-
letion and inversion of chromosome 2p. This may results in
EML4-ALK fusion gene product. KRAS mutations are also
reported to account for 30% of adenocarcinomas and 5% in
squamous cell carcinomas.

Selected biomarkers known for their application in
diagnosis and prognosis of lung cancer are given in Table
2. Earlier, IHC was distinguished between malignant me-
sothelioma and lung adenocarcinoma through positive re-
sponses from carcinoembryonic antigen (CEA), Ber-EP4,
MOC-31, CD15, claudin-4 and TTF-1 (22). KRAS muta-
tions, ROS1 rearrangements were first seen in 2007 with
around 1-2% of NSCLC harbouring different ROS1 fusion
variants (17). It is now reported that the Next-generation
sequencing (NGS) can detect panels of mutations and gene
rearrangements. EGFR mutation is a validated predictive
marker for response, where the tumours with an EGFR mu-
tation have been associated with a more indolent course.
Likewise it is considered that EGFR and KRAS mutations
are virtually mutually exclusive (19). There is evidences for
the presence of exon 19 deletion and exon 21 L858R gene
substitution positive in about 10% of Caucasian patients
and 20-40% in Asian patients with non-small cell lung can-
cer (24). A molecular diagnostic test using FISH for detect-
ing ALK rearrangements is a prerequisite before treatment
with crizotinib (25). The targeted therapy is not currently
available for patients with KRAS mutations, although MEK
inhibitors are under clinical trials.

The EGFR and KRAS analysis should be done in
all patients with lung adenocarcinoma or mixed lung can-
cers with an adenocarcinoma component, regardless of
characteristics such as smoking status, gender or race. It is
also recommended to consider for testing ALK rearrange-
ments and EGFR mutations in patients with squamous cell
histology and non-smoker in addition to biopsy and cytology
testing.

EXPERIENCES WITH ‘PERSONALIZED MEDICINE’ IN BREAST CANCER

Breast cancer is a complex disease it is the second
most common cancer among women in India and accounts
for 7% of global burden and 1/5th of all cancers among
women in India (26, 27). Breast cancer results from dereg-
ulation of a number of molecular signalling cascades. The
molecular markers associated with breast carcinoma are
estrogen receptor (ER), progesterone receptor (PR), HER2/
NEU, Ki-67, TP53, CK5/6 based epithelial markers (keratin
5 and 17), EGFR and androgen receptor (AR) (10). Based
on NCCN guidelines, the status of estrogen receptor (ER)
in all samples of ductal carcinoma in situ (DCIS), invasive
breast cancer (28) should be analyzed. Retesting on sites of
first recurrence is also strongly recommended. The ER sta-
tus and the progesterone receptor (PR) level should also be
determined for all samples of invasive breast cancer, and at
least 1% of cells staining positive for ER should be consid-
ered ER-positive.

Molecular markers like HER2 status can be as-
essed by measuring the number of HER2 gene copies using
in situ hybridization [ISH] techniques, or by a compelement-
tary method in which the quantity of HER2 cell surface re-
ceptors is assessed by IHC (29). However, the gene expres-
sion of HER2 status based on mRNA assays or multigene
arrays is not recommended, where the accuracy of HER2
assays used in clinical practice is a major concern. Breast
cancer tumours are classified as HER2-positive if they are
scored as 3+ by an IHC method. In uniform membrane
staining for HER2 in 10% or more of tumor cells or dem-
onstrate HER2 gene amplification by an ISH method. HER2
can dimerize with any of the HER family receptors to drive
downstream signaling. Pertuzumab and Trastuzumab bind to different regions on HER2 and have synergistic activity. Cellular proliferation marker, Ki-67 is also used at a cut-off of 14% to differentiate between luminal A and B breast cancers (12). A high Ki-67 expression is probably related to a poorer prognosis but also a better response to neoadjuvant chemo and/or targeted therapy. Ki-67 is also interesting in predicting histological response to neoadjuvant chemo and hormone therapy.

The proliferation marker Ki67 expression assessed through IHC, early absence of Ki-67 suppression by hormone therapy is predictive of therapeutic failure. The importance of HER2 testing by IHC, FISH, chromogenic in-situ hybridization (CISH) was most likely to benefit from targeted therapies (table 3). Recent report on glutathione s-transferase pi1 (GSTP1) as a novel triple-negative breast cancer specific target, which impairs cancer pathogenicity through GSTP1inhibitor.

Molecular diagnosis targeting BRCA, HER2, Ki67 through genome grading could better classify the molecular subtypes to determine breast cancer prognosis in adjuvant and neoadjuvant setting. Molecular phenotypes for targeted treatment in advanced breast cancer (ABC) are as follows:

HER2+: The anti-HER2+ agents could be extremely effective.
- Grant access to new target drugs.
- TNBC : (Triple negative breast cancer)
- Cytotoxic therapy as the only option.
- While, limited benefits for the effective chemotherapy and dismal prognosis.
- Promote translational research.
- ER/PR+ HER2–: It could focus on endocrine and cytotoxic therapies which are effective.
- Wide range of options with (apparent) low impact on OS
- Individualize strategies based on scenarios

CONCLUSION:

To ensure that new therapies are delivered to the right patients through accurate diagnosis, it is essential to adopt the recommendations for molecular diagnostics as well as therapeutics. With the cost of genomic technologies coming down and results are more clinically relevant, it is possible to predict precise genetic variations that occur in cancer patients. However, awareness is required to reduce cost phenomenally altering cancer management and consortium of oncologists is recommended for development of Indian patient specific biomarker study.

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REFERENCES:

Non functioning Extra Adrenal Pheochromocytoma is an Abdominal Incidentaloma- A Review.

Varun Arunagiri (1), M.Parimala (2), Ragumani.P (3), Kothai. A (4)

Abstract

Incidentaloma is a lesion identified by imaging unexpectedly while evaluating for other diseases. The incidence of Incidentaloma is increasing with advent of multidetector CT scans. The common Incidentalomas are from Adrenal, Thyroid, Pituitary, Renal, Lung and Lumbosacral. Extra Adrenal Pheochromocytoma (EAP) is not always diagnosed by imaging. It is a diagnosis of suspicion by imaging. Adrenal Incidentaloma (AI) is a mass lesion of >1cm which are serendipitously found by imaging in the adrenal glands. But sometimes a huge Incidentaloma is missed as pheochromocytoma has varied imaging characteristics like a chameleon. Careful history, vital signs and Metastatic spread are some features which can give clue to the radiologist about the malignant adrenal pheochromocytoma. About 10% to 30% of the Pheochromocytoma is extra adrenal of which 40% of the Extra Adrenal Pheochromocytoma is malignant. The standard of care for treating EAP is difficult to formulate as there is lack of evidences. This review explores the diagnostic dilemma of EAP and reviews the literature for a better standard of care. Definition of non functioning EAP must include anatomical and pathological aspects in this era where interventional radiologist have imperative role in accurate pre operative diagnosis.

Key-words: Incidentaloma; extra Adrenal Pheochromocytoma; Abdominal Incidentaloma;

INTRODUCTION:

Non functioning Extra Adrenal Pheochromocytoma (EAP) is a rare disease and clinically it is a diagnosis of suspicion. [1] In the year 1912, Pick coined the name Pheochromocytoma [2] and in the year 1908 Alezais and Peyron, first described them as paraganglioma and presently they are widely called as EAP. [3] ‘Phaios’ means dark and dusky in Greek, ‘chroma’ represents the color produced by the chromaffin reaction. In 1974, Glenner and Grimley classified EAP into four types with respect to anatomical location. Pheochromocytoma arises from adrenal medulla. Paraganglia are chromaffin tissues which secrete catecholamine. The tumour arising from paraganglion system is paraganglioma. They either secrete sympathetic neurotransmitters or parasympathetic. Composite Pheochromocytoma/Paraganglioma is a rare condition where the tumors arise both from parasympathetic ganglia and from chromaffin tissues, secreting both parasympathetic and sympathetic neurotransmitters. According to Vitaly Kantorovich and Karel Pacak, Paragangliomas arise from parasympathetic associated tissues and EAPs arise from extra adrenal sympathetic associated chromaffin tissues. [4] MeSH (Medical Subject Heading) search for terminology pertaining to Paraganglioma, Pheochromocytoma was done. According to Pubmed MeSH, Paragangliomas are Pheochromocytoma arising extra Adrenal apart from Adrenal Medulla and are also called as Extra Adrenal Paraganglioma or Extra Adrenal Pheochromocytoma. EAP is a disease of childhood and 15% occurs in adults. EAPs arise along the sympathetic chains and organs of Zuckerkandl. They are commonly seen below the diaphragm and above the inferior poles of the kidney in close proximity to the caval vein and aorta. [5] They arise from the paraganglion system which extends from head and neck to genitalia. In the head and neck, most of the paragangliomas are non functioning lesions. Non functioning EAPs in the abdomen are usually abdominal Incidentaloma as their preoperative diagnosis is very difficult with just a mass in the abdomen.
with no clinical symptoms apart from pressure symptoms due to huge mass compressing the vital structures in the retroperitoneum. [1]

METHODS:

A retrospective tertiary care institutional analysis of number of Adrenalectomies performed in the Institute of General Surgery, Department of endocrinology, Institute of Urology Madras Medical College was done from January 2015 to May 2016. There were seven Adrenalectomies done of which three were diagnosed as Pheochromocytoma and four were diagnosed as Adrenal Cortical tumors. Another retrospective analysis of pathological specimens diagnosed as Paraganglioma was done in the Institute of Pathology, Madras Medical College. In the year 2015 in Madras Medical College, there were seven specimens diagnosed as paraganglioma. Of these, this is the first case of EAP occurring in the abdomen apart from those occurring in head and neck. This was a specimen considered to be a retroperitoneal sarcoma which had histological and Immunohistological features suggestive of pheochromocytoma. This patient is a 34 year old gentleman who came with complaints of swelling in the left side of the abdomen which he noticed six months back. He was asymptomatic apart from swelling with occasional constipation. He denied history of headache, palpitation, dyspnoea and syncope. His vitals, blood pressure and his general examination were normal. His abdominal examination revealed a huge mass of size 12x10cm occupying left hypochondrium and left loin approaching the midline. The retroperitoneal mass was irregular in surface and had restricted mobility. We had a provisional diagnosis of a retroperitoneal sarcoma. The radiologist reported the CT abdomen (Fig 1) as a Jejunal Gastrointestinal stromal tumour and the CT guided biopsy revealed it as a mesenchymal tumour but Immunohistochemistry was negative for mesenchymal tumor. The patient was assessed for an exploratory laparotomy under ASA-I. Laparotomy was done with left hypochondrial incision extending to right hypochondrium. The mass was found retroperitoneum near the inferior pole of the left kidney abutting the left renal vein, aorta and inferior vena cava. (Fig 2) The mass had its blood supply from left renal artery and drained to renal vein. Care was taken while handling the mass and the specimen was removed without breaching the capsule of the mass. The histopathology of the specimen showed neoplasm arranged as lobules, clusters and sheets of polyhedral and occasional spindle cells with bizarre nuclei and prominent nucleoli. (Fig 3) The chromogranin A stain was positive. There was vascular invasion with 4 mitotic figures per 10 High power fields. The pathologist gave a PASS score of 12 with a diagnosis of pheochromocytoma with high malignant potential. The final diagnosis was non functioning EAP. Post operative urinary catecholamines were normal and 131I- MIBG scan was done with no remnant lesions. The patient is followed up with urinary catecholamine.
EPIDEMIOLOGY:

There are no literatures with exact incidence of non-functioning EAP. But EAPs occur most commonly in 20-30s in men and 30-40s in women. The 10% rule about Pheochromocytoma (10% of the Pheochromocytoma is bilateral, 10% are malignant, 10% are EAP, 10% are extra abdominal) is still imparted universally. But a single review says that EAPs are underestimated and the real projections of EAPs are 30% among the children and 15% among the adults. [6, 7] Pheochromocytoma has slight preponderance towards males than females [8] and the left side is more commonly involved than right side. [9] 0.2% of childhood hypertension is due to pheochromocytoma. [10] As non functioning EAP won't produce hypertension, its manifestation is delayed and goes unnoticed till the mass is felt per abdomen. Of 0.05 to 0.1% pheochromocytoma, 50% of the patients are normotensives or can express paroxysmal hypertension and the rest have uncontrolled childhood hypertension. [4] Usually EAP presents with size less than five cm.

PATHOPHYSIOLOGY:

The reason for symptoms in functioning EAP is because of secretion of catecholamines into the systemic circulation. But non functioning EAP though they harbor catecholamines the secretions which enter the systemic circulation is not sufficient to produce symptoms. The major catecholamines in the EAP are Epinephrine, Norepinephrine and Dopamine. They are formed from the amino acids phenylalanine and tyrosine which are hydroxylated to form DOPA. DOPA is then decarboxylated to form Dopamine. Eventually Dopamine gets converted into Norepinephrine and Epinephrine. The catecholamines get metabolized by monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT) to from Vanillylmandelic acid (3-methoxy 4-hydroxy mandelic acid or VMA), normetanephrine and metanephrine. These metabolites are elevated in pheochromocytoma and get excreted in urine. Free metanephrines and free normetanephrines are preferable for the diagnosis because they are formed extraneuronally. [11] Assessing urinary VMA is less sensitive than HPLC (High Performance Liquid Chromatography) measurement of 24hrs urinary normetanephrine and metanephrine. Non functioning EAP may not produce excess catecholamines to make biochemical circulatory changes.

CLINICAL SIGNS AND SYMPTOMS:

Non functioning EAPs presents as mass abdomen. In general Pheochromocytoma presents with variable symptoms ranging from headache, syncope, anxiety, tremors, palpitation and chest pain. The classical signs of Pheochromocytoma vary from sustained hypertension and paroxysmal hypertension to hypotension in par with the hormones secreted by the tumour. Hypotension is seen in tumors secreting epinephrine. [4] Functioning EAP can manifest cardiac changes due to catecholamines. But non functioning EAPs may manifest with pressure symptoms due to compression of tumour over Inferior vena Cava, ureter and renal vessels. EAP is associated with inherited endocrine syndromes. There are seventeen genes associated with Pheochromocytoma and paragangliomas. The normotensive patients with malignant extra adrenal pheochromocytoma had mutation of the B subunits of SDHB due to decreased expression of tyrosine hydroxylase. [12] Also there is a heterogenous G>A transversion at position +1 of intron 4 of SDHB (Succinate Dehydrogenase Complex- B subunit) gene. [13] But non functioning Pheochromocytoma is associated with mutation in subunit C of the SDHC (Succinate Dehydrogenase Complex- C subunit) gene. [14] EAPs are rarely familial and commonly sporadic. The sporadic form is called as non syndromic EAPs. But Carneys Stratakis syndrome or Carney’s triad is associated with EAP, Pulmonary chondroma, Gastric Epithelioid Leiomyosarcoma. Carney’s triad should not be confused with Carney’s complex which is otherwise

FIGURE 2: Intra operative mass lesion being dissected and excised
called LAMB syndrome or NAME syndrome in which there is a mutation of PRKAR1A gene. EAPs usually secrete Nor-epinephrine.

**HISTOPATHOLOGY OF THE EAP:**

Histologically Pheochromocytoma cannot be differentiated from EAP as both arise from sympathetic parts of paranglion or chromaffin tissues. The site of occurrence of pheochromocytoma is adrenal medulla rather EAP occurs in varied places either in the organ of Zuckerkandl or along paraganglion system or both, which can be made out by imaging. They are highly vascular and microscopically they show polygonal or spindle shaped cells in a rich vascular background. Pheochromocytoma is usually benign. PASS score (Pheochromocytoma of the Adrenal gland Scaled Score) is a valid tool to assess the malignant potential of the Pheochromocytoma. The criteria included in PASS score are blood vessel invasion, nuclear pleomorphism, capsular invasion, peridrenal tissue invasion, tumour size, presence of necrosis and mitotic figures or atypical mitotic figures. Few pathological findings are given 1 point and few are given with 2 points. 0-3 points indicate benign lesion and 4+ lesions are prone for malignancy. [15] Even though PASS score is less sensitive, it has got more prognostic implication. Studies with large sample size have to be undertaken to use PASS score to improve the level of evidence. Pheochromocytoma has no stains to distinguish benign from malignant variant. [16] Immunohistological stains for Pheochromocytoma are Chromogranin A, Synatophysin, S-100 and Tenascin but Chromogranin sensitive and specific to Pheochromocytoma as Synatophysin stain is positive in Adrenal Cortical tumors too. Tenascin is positive in malignant lesions.

**INVESTIGATIONS AND TREATMENT:**

Non functioning EAP is mostly an abdominal Incidentaloma. EAP on ultra sonogram have mixed solid to cystic variations. In CT Abdomen they are large heterogenous mass with areas of necrosis and cystic degeneration. On triphasic CECT abdomen; there is a portal phasic enhancement of the mass than arterial with washout in the venous phase. In the washout phase when the CT intensity is greater than 10HU, the lesion is more likely a Pheochromocytoma. [17] Malignancy is made out by direct invasion of the tumour into the adjacent tissues and metastasis to lung and bones. [18] The sensitivity of MRI abdomen for diagnosing EAP is 98% when compared to CECT which is 89% sensitive. In T2 weighted image there is a hyperintensity which gives it light bulb sign. The most commonly used 123I or 131I MIBG (MetaIodoBenzylGuanidine) is 100% specific but it has low sensitivity of 24% because EAP and pheochromocytoma shares same chromaffin tissues which has similar biochemical qualities. Potassium iodide is given before 131I or 123I-MIBG to block the thyroid uptake of radioactive iodine. 18-FDG-PET is non-specific and 18-F (Dopamine) PET, 18-F (DOPA) and Carbon-11 Hydroxyephidrine PET is more sensitive and specific in localizing the metastatic Pheochromocytoma. [19] The American association of clinical endocrinologists and American association of endocrine surgeons (AACE/ AAES) submitted the guidelines for the treatment of AI. The treatment of adrenal Incidentaloma depends on the size of the tumor, radiological characteristics and biochemical hormonal activity. EAP of >4cm has to be excised irrespective of its hormonal activity with 5 years follow up as it has high chances of malignancy. AI of size 4-6 cm has 6% risk and lesion >6cm has 25% of malignancy [20] Tumors <4cm which are hormonally active needs adrenalec-tomy. [21] Recently in this era of key hole surgery, there are reports of surgical excision of EAP done by laparoscopy. [22]
GENETIC COUNSELING AND FOLLOW UP:

Genetic screening in all patients diagnosed with EAPs is not mandatory. [20] Patients diagnosed with EAP can be screened for RET oncogene mutation to identify MEN2B symptoms, VHL gene mutation to identify Von Hippel Lindau Syndrome and SDHB/SDHC gene mutation when there is recurrence, metastatic lesion and multifocal. Follow up is done for all patients who underwent surgery for recurrence, to diagnose metastatic lesions by imaging every 3-6 months and then after annually for 5 years. [23]

CONCLUSION:

Non functioning EAP is still a diagnosis of suspicion before histopathological confirmation. There are better evidences to treat Pheochromocytoma which can be used to treat EAP which are either functioning or non functioning.

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REFERENCES:


The Grid

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