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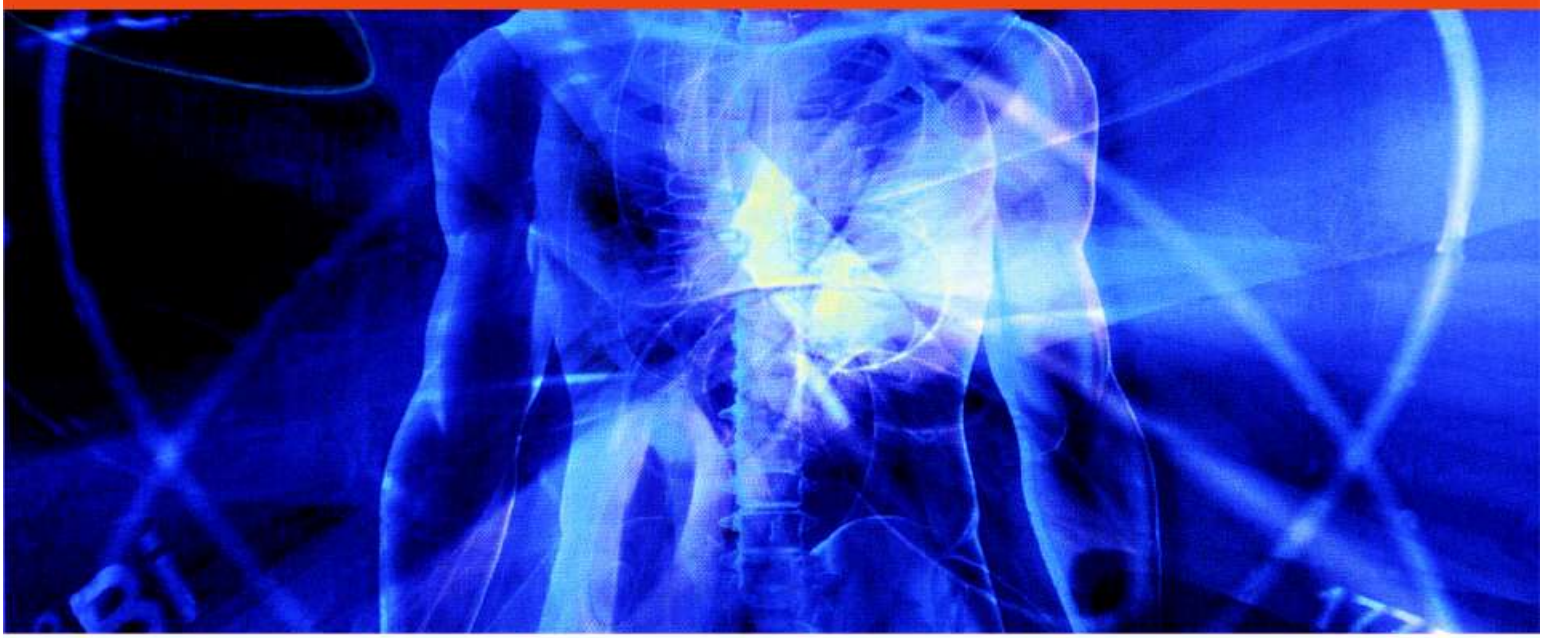

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EDITORIAL

Heat Stroke: Deadly but Preventable

Sajid Abbas Jaffri

A severe wave with temperature as high as 49 ºC(120ºF) struck southern Pakistan in June 2015. It caused deaths of approximately 2000 people from dehydration and heat stroke mostly in Sindh province and its capital city Karachi.Mr.Asif Shuja former DG of Pakistan Environmental Protection Agency claimed that heat wave was a symptom of global climate change, aggravated by de-forestations, expansion asphalt highways and rapid urbanisation[1].Dunya News reported at least 1360 patients died due to heat stroke in different hospitals of Karachi[2].

HEAT EXPOSURE SYNDROME:

Four medical disorders comprise a spectrum of illness that can result from exposure to hot environments (1)Heat Cramps(2)Heat Syncope(3)Heat Exhaustion and (4)Heat Stroke.Health conditions that inhibit sweat production or evaporation and increase susceptibility to heat disorders include Obesity, Skin disorders (Miliaria), Reduced cutaneous blood flow(by use of vasoconstrictors and beta adrenergic blocking agents) ,Dehydration (by use of alcohol and illicit drugs e.g. phencyclidine, LSD, amphetamines and cocaine),Malnutrition,Hypotension and reduced cardiac output,Medications such as anticholinergics, antihistamines, phenothiazines, tricyclic antidepressants, monoamine oxidase inhibitors, diuretics etc.Risk of heat disorder increases with (1) Age (2)Impaired cognition (3) Concurrent illness(4) Reduced physical fitness (5)Insufficient acclimatization etc[3].

HEAT STROKE:

Heat Stroke is a life threatening medical emergency that results from failure of thermo-regulatory mechanism. It is imminent when the core (rectal) temperature approaches 41ºC or 105ºF and presents in one of two forms: (a) Classic heat stroke that occurs in patients with compromised homeostatic mechanisms. (b) Exertional heat stroke that occurs in healthy persons undergoing strenuous exertion in a thermally stressful environment[4]. The hallmarks of heat stroke are cerebral dysfunction with impaired consciousness, high fever and absence of sweating.Morbidity or even death can result from cerebral, cardiovascular, hepatic or renal damage.Persons at greatest risk are the very young, the elderly,and chronically ill and patients receiving medications like anticholinergics, antihistamines, phenothiazines that interfere with heat dissipating mechanism.Laboratory evaluation may reveal dehydration, leucocytosis, elevated BUN, hyperuriceamia, hemoconcentration, lactic acidosis, decreased serum sodium, potassium,calcium and phosphorus. Thrombocytopenia, increased bleeding and clotting times. Urine becomes concentrated with elevated protein, tubular casts and myoglobinuria.

Rhabdomyolysis, myocardial, hepatic or renal damage may be identified by elevated serum creatinine kinase,aminotranseferase levels and BUN and by the presence of anuria, proteinuria and hematuria[5].

TREATMENT OF HEAT STROKE: [6,7,8].

- Treatment is aimed at rapidly reducing the core temperature (within 1 hour) while supporting circulatory and organ system function to prevent irreversible tissue damage and death.
- Intravascular volume status should be assessed and managed early to reduce the risk of hypovolemic shock.
- Central venous or pulmonary artery wedge pressure should be monitored.
- Five percent dextrose in half-normal or normal saline should be administered for fluid replacement.
- IV fluid administration must be provided to ensure a high urinary output (>50 mL/h).
- Mannitol administration (0.25 mg/kg), and alkalinizing the urine (intravenous administration of 250 mL of 4% bicarbonate administration may be needed)
- Cooling methods are evaporative and conductive based. Choice of cooling method depends on which can be instituted the fastest with the least compromise to the overall care of the patient.
- Evaporative cooling is a non-invasive, effective, quick and easy way to reduce temperature. This method is done by placing the undressed patient in lateral recumbent position or supported in hands-and knees position to expose maximum skin surface to the air.Large fans circulate the room air while the entire body is sprayed with lukewarm water (20%) or cold wet sheets are applied to the undressed body. Inhalation of cool air or oxygen is also effective.
- Conductive-based cooling involves immersion into ice-water or cool water. Ice bath (1-5 °C) is effective but usually impractical method due to its limitations (space, patient access and monitoring). Cold water immersion includes cool baths, localized ice or ice slush application (groin, axilla, and neck) and iced gastric lavage and infusion of cool intravenous fluids. Intravascular heat exchange catheter systems as well as hemodialysis using cold dialysate (30-35 °C) have been successful in reducing core temperature.
- Care must be taken to avoid shivering, which will increase internal heat production and inhibit effectiveness of cooling.
- Benzodiazepines may be used to suppress shivering.
- Skin massage is recommended to prevent cutaneous vasoconstriction.

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- Treatment should be continued until the rectal temperature drops to 39°C.
- Antipyretics (aspirin, acetaminophen) have no effect on environmentally induced hypothermia and are contraindicated.
- All patients with suspected heat stroke must be admitted to the hospital for close monitoring.
- Monitoring includes vital signs, temperature and cardiac rhythm and observation for potential complications of electrolyte abnormalities (e.g.hypokalemia), acute kidney injury due to rhabdomyolysis, cardiac arrhythmia, coagulopathy, hepatic failure, acute respiratory distress syndrome (ARDS), hypoglycaemia, seizures and infection.

PROGNOSIS: Multi-organ dysfunction is the usual cause of heat stroke related deaths and it can be predicted by CK >1000 units/L, metabolic acidosis and elevated liver enzymes.Following heat stroke, sensitivity to high environmental temperature may persist for prolonged periods and immediate re-exposure should be avoided.[9]

PREVENTION:

The risk of heat stroke can be reduced by observing precautions to avoid overheating and dehydration. Light, loose-fitting clothes will allow perspiration to evaporate and cool the body. Wide-brimmed hats in light colors help prevent the sun from warming the head and neck. Vents on a hat will help cool the head, as will sweat bands wetted with cool water. Strenuous exercise should be avoided during daylight hours in hot weather; so should remaining in confined spaces (such as automobiles) without air-conditioning or adequate ventilation. In hot weather, people need to drink plenty of cool liquids to replace fluids lost from sweating. Thirst is not a reliable sign that a person needs fluids. A better indicator is the color of urine. A dark yellow colour may indicate dehydration. Thus following aspects must be given due attention:[10,11]

(a) Public education programs to improve prevention and early recognition of heat related disorders.
(b) Proper acclimatization measures must be achieved before heavy physical exertion is performed in hot environments.
(c) All children's athletic programs must set heat-acclimatization guidelines.
(d) Parents, coaches, athletic trainers and athletes must be educated about heat related illness, specifically about prevention, risks, signs and symptoms and treatment.
(e) Those who are physically active in a hot environment should increase fluid consumption before, during and after physical activities
(f) Fluid consumption should include balanced electrolyte fluids and water. Drinking fluids must be often, and before one is thirsty[12].

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REVIEW ARTICLE

Role of MicroRNA in Breast Cancer

Ambreen Usmani[1],Amir Ali Shoro[2]

ABSTRACT:
Breast Cancer is the commonest cancer affecting women worldwide especially in Asia. Several proteinaceous,genetic and epigenetic biomarkers areallied with the disease but their efficacy as vigorous and robust indicators of disease remains uncertain. The need to detectand differentiate aggressive from non-aggressive breast tumors at cellular level is being investigated. MicroRNAs seem to be a promising marker to identify the disease before it reaches aggressive level. MicroRNAs (miRNAs) are small 18-24 nucleotide RNAs which regulate the expression of approximately 30% of human genes. Their expression is frequently deregulated in cancers. .miRNAshave been found in significantly large copy numbers in serum/plasma of cancer patients. The stability of the serum miRNAs is not compromised even if the samples are treated with RNase or incubated at room temperature over prolong periods or subjected to repeated freeze-thaw cycles. miRNAs that are breast cancer-specific can therefore be employed as disease predicting biomarkers.
Keywords: Breast cancer, Micro RNA, Role, Serum, Stability, Biomarkers.

INTRODUCTION:

MicroRNAs (miRNAs) are described as non-coding ribonucleic acids with 18-22 nucleotide bases. Expression of miRNAscan be transformed in breast cancer when compared to healthy breast tissue.There may also be difference in expression in breast cancer subtypes. Their mode of action maybe as either oncogene or tumor suppressors; this shows that their expression is deregulated in cancers. MicroRNAs are also used during development stages and have been found to be involved in processes such as proliferation, differentiation and apoptosis. Breast cancers are controlled by cancer-restricted signaling pathways.[1]Methods to diagnose breast cancer are many, the most common being mammography which is utilized for screening and diagnosing purposes. But scanning is not the gold standard for diagnosis as confirmation of cancers is by means of biopsy which is an invasive procedure. This procedure is performed when the patient complains of lumps in the mammary gland.[1,2] Breast Cancer originates at cellular level but diagnosis can only take place once the signs and symptoms appear. Multiple genetic based procedures have been determined to mark the genetic signatures causing this cancer.In comparison to other continents, Asia has the highest rates of breast cancer; it is considered as the most frequently occurring cancer of origin in women in this region. Pakistan's leading cancer to date in women is also breast cancer.[2,3] Till to date no robust and precise method has been determined to predict the occurrence of this deadly disease. Hence there is a need to identify sensitive biomarkers that will be beneficial for discovering breast cancers and differentiate between aggressive versus non-aggressive tumors.[4,5,6] The association of manifold miRNAs with breast cancer is becoming a promising method for diagnosing this cancer at cellular level which may lead to diminishing prevalence of the disease. Therefore there is a dire need to identify miRNA and label them as diagnostic factors. They may also be useful in prognosis of the disease, as well as possible remedy targets.[7, 8, 9] Literature search was performed by using database of PubMed. The keywords used were microRNA (52 searches) and breast cancer (169 searches). PERN was used by database of Bahria University. This included literature and articles from international sources; local literature on this topic was not available. Out of these, 35 articles were shortlisted which discussed relation of microRNA genetic expression in breast cancer. These articles were consulted for this review.

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LIEERATURE REVIEW:

MicroRNAs (miRNAs) are RNAs of 18-22 nucleotides (nt) in extent which are found profusely in plants, animals and also viruses.These small genes are formed by a sequence of events first in the nucleus and then in the cytoplasm. In the nucleus they are originally transcribed as primary-mi-RNA (pri-miRNA) due to the presence of RNase polymerase II which is 100-1000 nucleotide in length. This is followed by the process of capping and polyadenylation. Further this pri-miRNA is cut by RNase III, DROSHA and its co-factor DGCR8 into smaller70 nucleotide stem loops called as pre-RNA.[7,8] This pre-RNA journey`s from nucleus to cytoplasm by means of exportin-5. The loop region of pre-RNA is removed by DICER (RNase III) and its binding partner TRBP. A mature miRNA-miRNA* duplex is released. [9] The single dominant strand is incorporated with RISC (RNA induced silencing complex) to finally regulate gene expression by complementary-base pair interaction resulting in interference with translational ability and stability of target mRNA or it may result in its degradation.[10,11] Multiple miRNAsare linked with breast cancer and it is a fact now that most of these post transcript structures may transform complex functional

networks of mRNAs. Diagnostic tools are available but more genetic markers which would allow the prevention of the disease are required. This is where the importance of identifying miRNAs as potential biomarkers is of great importance to scientists.An additional advantage related tomiRNAs in oncology is that they are remarkably stable and are notably detectable in serum and plasma. Triple negative breast cancer which is aggressive in nature shows strong linkage to various miRNAs. Five microRNA (miRNA)clusters which include miR-17-92 at 13q 31.3, miR-183-182 at 7q32.2, miR-200-429 at 1p 36.33, miR-301b-130b at 22q 11.21, and miR-532-502 at xp 11.23 were upregulated in triple negative breast cancer. This research is a promising research in clearly identifying global miRNAs regulatory characteristics in ER–ve, PR-ve and HER2 –ve breast cancer.[3]Studies related to gene expression have proven that estrogen and progesterone receptors (positive/-negative) are expressed as distinct disease at molecular level. Human epidermal growth factor receptor 2(HER2) if tested significantly affirmative promotes the growth of cancer cells and is normally involved in functions such as signal transduction pathways influencing cell growth and differentiation.[4] Huang GI et al has reported that ER/ PR negative cancers show high expression of miR-21. ER, PR and HER2 negative (triple negative tissue) have exhibited very high expression of some miRNAs e.g. miR-21, miR-155, miR-145, miR-16.[5] This finding is consistence with several other reports indicating the aggressive nature of tumor with negative receptor proteins. Metastasis of cancer is also linked to triple negative tumors and have poor prognosis and do not respond properly to chemotherapy. Several current studies have shown the importance of detecting blood based miRNAs in breast cancer and this has revealed new biomarkers. A pilot study shows that the presence of urinary miRNAs may also be used to diagnose breast cancer. It was shown that urinary miR-155 levels were significantly higher in breast cancer patients as compared to healthy controls. This urinary miRNA was quantified by real time PCR.[6]

A greater proportion of miRNAs which are around 600 in number, have been identified already which participate in development as well as regulate developmental sequences in a growing fetus.[12,13,14] This includes mechanism such as increase in the cell number of organs, their differentiations to form body structures and these genes may also control the process of apoptosis and cellular metabolism.[15] A substantial number of genes and their expression are controlled by miRNAs impact. It is likely that any changes in their expression or DNA sequence are likely to culminate in a diseased state. A study on Hispanic women showed a different pattern in women after pregnancy who are diagnosed with breast cancer in less than 5 year of pregnancy. This postpartum development of breast cancer showed two-fold or higher difference in expression with miR-138, miR-660, miR-31, miR-135b, miR-135b, miR-17, miR-454 and miR-934 being overexpressed. This study forecasts that miRNAs may have different pattern depending upon the ethnicity and condition of women.[15, 16]The miRNomes of several cancers have been studied and such studies have identified miRNAs whose expression levels are robustly compromised. In biopsies obtained from breast cancer patients such miRNA profiling exercise revealed 29 miRNAs whose expression was down-regulated in tumors.[1] A recent study revealed specific miRNA signatures that were unique for several benign and malignant tumors, some of the common organs include the breast, prostrate, lung and the intestines. In advanced breast cancer, metastasis to the brain is a cause of death in such patients. The phenomena behind this is that cancer cells migrate through blood brain barrier, however the molecular mechanism still remains to be investigated. It has been shown that the delivery of these cancer cells maybe via miRNAs which maybe involved in the breakdown of the blood brain barrier. The identified miRNA which may promote this event is miRNA-181c.This identified miRNA causes destruction of blood brain barrier through abnormal localization acting via down regulations of its target gene PDPK1.[17, 18] Some of the highly expressed miRNAs that were found in this study were miRNAs 155, 17-5p, 20a, 21, 92, and 106a. Functional genomic validation of some of the miRNAs identified through the gene array screens proved that miRNAshave a definite action as oncogenes or suppressor genes implying that any mutations or un-programmed changes in their expression levels has the potential to trigger uncontrolled cellular proliferation miRNAs that are metastasis promoters as well as suppressors have also been identified.[19, 20] In this decade several studies carried out on cell lines derived from breast cancers as well on primary tumors have been performed in an effort to identify miRNAs which are unique to these types of cancers and which are abnormally expressed. Profiles obtained from 76 breast cancer tissues which were primary in nature as compared to 34 non malignant counterparts led to the identification of 5 different miRNAs ,that were deregulated. Among the given cases 3 showed that miR-10b,-125b, and 145 were most significantly down-regulated. In addition 2miRNAs were found to be up-regulated (miR21, and miR155).[1] In another study, miRNA profiles were obtained from primary breast cancers, in which 5were normal breast samples and 21 samples included breast cancer tissue cell lines.On further experimentation of these samples derived from breast cancer individuals,exposed conspicuous variances in miRNA expression when ER-ve and ER+ve tumors were studied. The investigators also showed that they were able to discriminate between HER2+ and HER2– cancers based on miRNA signature.[3]

Recently, Literature search revealed that Mitchell et al has studied the presence of miRNA in human plasma which are unusually stable culminating to the fact that they are able to resist degradation even if exposed to freeze thaw cycles repeatedly. These micro genes also have the capability tosurvive prolonged incubations at room temperature. This experiment demonstrated that miRNAs are secure from endogenous RNase performance in the plasma of human beings thus prposing that they may be considered as a portion of complexes

or may be associated with exosomal vesicles. Although inconclusive, this study also found that mir-141 can serve as a biomarker.[21]

Studies related to gene expression have proven that estrogen and progesterone receptors (positive/negative) are expressed as distinct disease at molecular level. Human epidermal growth factor receptor 2(HER2) if shown to be present promotes the growth of cancer cells and is normally involved in functions such as signal transduction pathways influencing cell growth and differentiation. Correlation between clinico-pathological factors and miRNAs concentration is very important especially for treatment purposes. Multi variant analysis of breast cancer in various stages show very high concentration of some circulating miRNAs but this may be independent of ER, PR and HER2. Henegham reportednumber of miR-21 in a greater quantity in the circulation in ER negative disease as compared to those individuals whose biopsy showed ER positive breast cancer.[22] They also tried to establish a relationship between this circulating gene, type of breast cancer which maybe of in situ type but may also be invasive, the subtype and HER2 status but no significant relation could be established.[2]

In a study on Asian Indians and Pakistani, the receptor status in relation to age was analyzed showing that in ages between 40-50 years an increased percentage of ER/PR negative disease was noted as compared to the younger group. However over time pathologically assessed cancers show that triple negative receptors are more common in this part of the world which may result in recurrences, resistance to treatment and metastasis in brain and spinal cord.[21,23]

Pakistan presently is considered to have the uppermost rates of breast cancer in Asia; it has also been proved that breast cancer is the most common cancer among other gynecological cancers. India and Pakistan have reported a significant rise in the incidence of breast cancer. ER, PR negative breast cancer are more common according to several reported studies.[2] In a tertiary cancer care hospital in Karachi, a study of over a span of nine yearswas conducted which showed that breast cancer was the most frequently occurring cancerin females and consisted of 38.2% of the entirecancer cases inducted in that institution, this was proved to be highest in Asia.[23]

For breast cancer treatment to be attainable we must first identify biomarkers which will robustly reduce universal morbidity and mortality due to this disease. Research also shows that there is a difference in the expression of miRNAs in various diseases. There is indication that there may also be different expression in various populations. Hence the importance of identifying these micro genes in a sample of Pakistani population will be of benefit as we will be able to differentiate it with the western data. [16] This will however be possible with larger sample size studies with participants from all parts of the country. Smaller studies should also be conducted as they may provide cues for further studies.Therefore identification and the quantity of tumor-derived miRNAs in the circulation are an essential methodology for blood based exposure of human cancer which will lead to (1)diagnosis and (2) prognosis of cancer by non-invasive methods and will (3) determine their relation with protein receptors in tissue biopsy of breast cancer and level of aggressiveness of the breast tumor.[24, 25]

As developing confirmations highlight the significance of miRNAs in diagnosis and prognosis, the usefulness of miRNAs based breast cancer therapy is also being explored. Many miRNAs have been associated in numerous cancers, including breast cancer. They are known to control cell cycle and developmental processes. Therefore it is likely that miRNAs are beneficial targets for exploring in anti-cancer treatments.[25,26]The therapeutic strategies based on miRNAs suggest a substitute for targeting multiple gene networks that are controlled by a single miRNA. These approaches can be expressed by either antagonizing or reinstating the functions of miRNAs[27,28,29] Anti-miRNA 2-O-methyl or blocked nucleic acid oligonucleotides used to inactivate oncomiRNAs such as miR-21 in breast cancers may taper down tumor growth. Anti-miR-21induced decrease in cancer growth was revealed to be potentiated by the addition of topotecan (a chemotherapeutic agent), this is an inhibitor of DNA topoisomerase I.[29,30,31] Such novel event highly recommends that suppression of the oncogenic miR-21 could sensitize tumor cells to anti-cancer therapy.This is a promising prospect for patients displaying a poor response to initial stages of chemotherapy.[32,33,34,35] Another point of interest shows the capability of miRNA 34a to inhibit proliferation and migration of breast cancer through down regulation of Bcl-2 and SIRT1[36,37,38,39,40]

CONCLUSION:

It is important to check the contributory factors (genetic and non-genetic) since incidence rates are on such a rapid rise. As with many cancers, early detection of breast cancers has been inadequate and methods for prognosis and diagnosing the disease are limited to invasive procedures. Due to advances in understanding the cancer cell at molecular level, development of several targeted therapies are progressing and have also lead to advancement in the treatment. To achieve such individualized treatment appropriate targets must be identified.

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ORIGINAL ARTICLE

Comparison of Neutrophil Gelatinase Associated Lipocalin with Serum Creatinine for Early Detection of Decrease in Estimated Glomerular Filtration Rate

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ABSTRACT:

Objective: To determine the accuracy of Neutrophil Gelatinase Associated Lipocalin (NGAL) at 2 h compared to serum creatinine at 48 h after Computerized Tomography (CT) scan with contrast medium for early detection of decrease in estimated Glomerular Filtration Rate (eGFR).

Materials and Methods: This Cross Sectional Study was carried out in Departments of Chemical Pathology and Radiology PNS SHIFA Karachi from 1st February 2014 to 31st Jan 2015. One hundred and ten patients undergoing CT scan with contrastwere included. Serum creatinine wasmeasured byJaffé assay using Alkaline Picrate reagent on Modular P800 (Roche) analyzer before and 48 h after CT scan. eGFR was calculated by Modification of Diet in Renal Disease (MDRD) formula. Patients were divided into AKI and non-AKI groups. NGAL was analyzed by NGAL Reagent Kit on Triage meter pro at 2 h after contrast.

Results: Out of 110 patients, 5 (4.54%) developed Acute Kidney Injury (AKI) 2 h after CT scan with contrast in which eGFR was decreased more than 25%. NGAL level in AKI group was 161ng/ml (IQR: 98 to 196) at 2 h after CT contrast was significantly higher than non-AKI group of 63ng/ml (IQR: 42 to 75). Serum creatinine showed significant rise but with delay of 24 – 48h after CT contrast in AKI group. There was a positive correlation between 2 h plasma NGAL and eGFR at 48 h, which was statistically significant.

Conclusion: NGAL is a potential marker for early detection of decrease in eGFR and predictor of AKI.

Keywords: Acute kidney injury, Biomarkers, Creatinine, Estimated Glomerular Filtration Rate, Neutrophil Gelatinase Associated Lipocalin, CT scan with contrast.

INTRODUCTION:

Acute Kidney Injury (AKI) is a variety of severity of stages of kidney dysfunction ranging from a reversible decline in the glomerular filtration rate (GFR) to sustained Acute Renal Failure (ARF) with anuria, which may progress to chronic renal failure[1]. In 2004 the Acute Dialysis Quality Initiative Group developed a new definition for ARF, called the Risk (R), Injury (I), Failure (F), Loss of kidney function (L) and End-stage kidney disease (E) (RIFLE) criteria[2]. Later, for the term ARF, Acute Kidney Injury Network (AKIN) criteria (AKI) was used, reflecting the fact that structural injury most certainly precedes an acute decline in kidney function. The criteria is identical to the first three stages of RIFLE, with the exception of a shorter time frame of AKI within 48 hours, and a lower creatinine threshold of greater

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than 26.4 umol/L from baseline to peak value[3]. Serum creatinine levels and changes in urine output have been used to define AKI for decades. Typically, the serum creatinine level begins to increase 24-72 hours after AKI, peaks at 3-5 days and requires further 3-5 days to return to baseline[4]. Creatinine is now considered as an inadequate marker, as serum creatinine levels rise when more than 50% of kidney functions are lost. Moreover serum creatinine is not specific for AKI[5]. Neutrophil Gelatinase Lipocalin (NGAL), was first purified from the secondary granules of human neutrophils[6]. NGAL is among the most promising biomarker after ischemic AKI in animal models and further experimental studies[7]. As the contrast induced AKI can easily be studied in hospital settings, so we compared accuracy of NGAL and serum creatinine to detect AKI after CT scan with contrast. This study was undertaken to determine the accuracy of Neutrophil Gelatinase Associated Lipocalin (NGAL) at 2 h compared to serum creatinine at 48 h after CT scan with contrast for early detection of decrease in estimated Glomerular Filtration Rate (eGFR).

MATERIALS AND METHODS:

This Cross sectional study was carried out in Department of Chemical Pathology, PNS SHIFA Karachi in collaboration with Department of Radiology, from 1stFebruary 2014 to 31stJan 2015. According to the RIFLE criteria, AKI is an abrupt reduction in kidney function, evidenced by decrease in eGFR of more than 25%[3]. ForNGAL, a cutoff value of 100 ng/ml in serum after 2 h of iodinated contrast medium was taken as AKI[4].

110 subjects of either sex scheduled for contrast enhanced CT of any part of the body, with contrast dose (Iobitridoil) of more than 90ml, ages between 18 to 80 years were selected by non-probability consecutive sampling. Individuals with advanced chronic kidney disease i.e. serum creatinine greater than 300 ìmol/L or patients on chronic hemodialysis, with kidney transplant, with peripheral vascular disease and on nephrotoxic drugs were excluded from the study. The study was conducted after approval by the Ethical Committee of PNS-SHIFA. All subjects fulfilling the inclusion criteria were elaborately apprised about the study to obtain their informed consent. The name, age, gender and contact numbers were noted. Medical history and physical examination was carried out and blood samples were collected. Blood samples of subjects for NGAL and creatinine were drawn from ante cubital vein aseptically before CT scan with contrast, 2 h and 48 h after CT scan. NGAL samples collected in EDTA tubes while serum creatinine samples were collected in plain serum tubes.

NGAL was analyzed by means of NGAL Reagent Kit on Triage meter pro which utilizes a two-step immunoassay for using chemiluminescent micro particle immunoassay (CMIA) technology[5]. Serum creatinine was measured by the Jaffé assay using Alkaline Picrate on Modular P800 fully automated chemistry analyzer (Roche) using Roche calibrator and controls as per manufacturer instructions and specifications[6]. eGFR was calculated by Modification of Diet in Renal Disease (MDRD) formula[7]. Patients were divided into AKI and non-AKI groups on the basis of 25% reduction in eGFR[8]. All the data was entered in a specially designed proforma and analyzed using SPSS version 18. Descriptive statistics for qualitative variables were calculated in percentage. Mean and SD were calculated for all quantitative variables like age, NGAL levels and serum creatinine levels at 2 h and 48 h.

RESULTS:

A total of 110 patients undergoing CT scan with contrast who met the inclusion and exclusion criteria were consecutively included. There were 68 males (61.8%) and 42 females (38.2%). The age of the patients ranged from 18 to 71 years, with mean age of 52 years. Subjects were grouped into AKI and Non AKI group as per patient characteristics of the study based on RIFLE criteria and AKIN criteria. Serum creatinine levels prior to CT contrast and at 2 h after the contrast, did not show any significant difference between two groups (Table 1).Whereas serum creatinine levels at 48 h and plasma NGAL levels at 2 h after the CT contrast showed significant statistical difference between two groups (Table I).

Table: 1

Characteristics of CIN after CT without AKI as compared with the patients who developed AKI within 48 h

Parameter	Non AKI (n = 105) Median (IQR)	AKI (n = 5) Median(IQR)	P value
Gender (number)	Male (65), Female (40)	Male (03), Female (02)	-
Age (years)	48 (36 to 59)	59 (50 to 65)	-
Baseline eGFR ml\min\1.73m^2	81 (90-71)	71 (76-62)	-
eGFR at 48 h ml\min\1.73m^2	77 (83-61)	49 (51-38)	-
Baseline serum creatinine (umol/L) before CT contrast	92 (84 to 103)	99 (94 to 112)	< 0.270
Serum creatinine (umol/L) at 2 h after CT contrast	94 (84 to 103)	102 (94 to 112)	<0.310
NGAL at 2h (ng/ml) after CT contrast	63 (42 to 75)	161 (98 to 196)	<0.0001
Serum creatinine at 48 h (umol/L) after CT contrast	96 (105-117)	137 (132 to 164)	<0.0001

Five patients (4.53%) developed AKI fulfilling the RIFLE criteria and their eGFR decreased by more than 25% as shown in Table 1. Plasma NGAL ability was assessed to predict AKI after CT with contrast. NGAL levels in AKI group of 161ng/ml (IQR: 98 to 196) at 2 h after CT contrast were significantly higher as compared to non-AKI group having a level of 63ng/ml (IQR: 42 to 75), with a p value of < 0.0001. Serum creatinine

showed significant rise with a delay of 24 to 48 h in AKI group (Table 1).

Plasma NGAL ability to predict clinical outcome was assessed using Spearman rank order correlation analysis. There was a positive correlation (Figure 1) between 2 h plasma NGAL and serum creatinine at 48 h after CT contrast, which was statistically significant (rs = 0.33, P = < 0.001). The Independent sample Mann Whitney U Test also showed that plasma NGAL at 2 h and serum creatinine at 48 h after the CT contrast reject the null hypothesis while creatinine at 2 h after CT contrast retains the null hypothesis (Table 2).

Figure: 1

Graph showing comparison between NGAL after 2 h and creatinine at 48h after CT contrast.

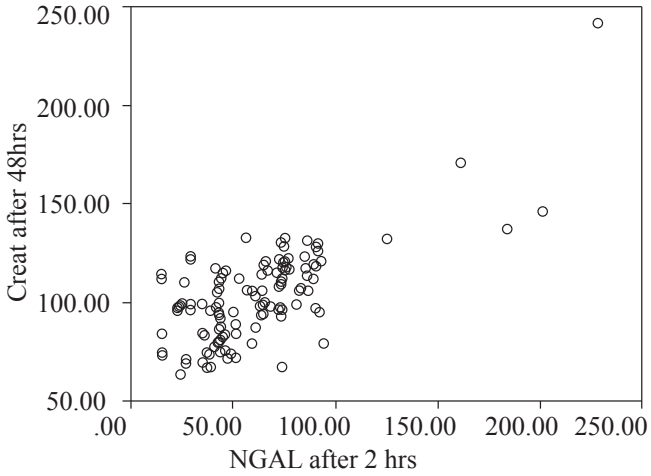

Table: 2

Comparison of NGAL and creatinine at 2 h after CT contrast and creatinine at 48 h after CT contrast by independent sample Mann Whitney U Test

Null Hypothesis	Test	Sig	Decision
The distribution of creatinine at 2 h is same across categories of AKI criteria	Independent sample Mann Whitney U Test	0.119	Retain the null
The distribution of NGAL after 2 h is same across categories of AKI criteria	Independent sample Mann Whitney U Test	0.000	Reject the null hypothesis
The distribution of Creatinine after 48 h is same across categories of AKI criteria	Independent sample Mann Whitney U Test	0.000	Reject the null hypothesis

DISCUSSION:

AKI is characterized by abrupt and sustained decline in GFR. The absence of a uniform definition has, however, delayed the ability to compare preventive strategies, therapies and outcomes in different studies[9,10]. According to the RIFLE criteria AKI is an abrupt reduction in kidney function, evidenced by decreased in GFR of more than 25% within 48 h after the administration of contrast agent. Serial serum creatinine measurements are taken as gold standard for identification and classification of AKI but this may be problematic for a number of reasons such as serum creatininelevels rise when more than 50% of kidney functions are lost, serum creatinine is not specific for kidney injury, serum creatinine level begins to increase 24-72 hours after AKI, it peaks at 3-5 days and requires further 3-5 days to return to baseline etc.[11]. Levels can vary widely depending on non-renal factors such as gender, muscle mass and hydration status. Conventional urine markers such as casts or fractional excretion of sodium are insensitive and non-specific for early recognition of AKI[12]. As in RIFLE criteria AKI is defined on the basis of creatinine which is a poor marker of AKI, so it causes late diagnosis and bad prognosis of AKI. There are several new biochemical markers of tubular damage which include Cystatin C, IL -18, NAG, KIM -1, L- FABP, homocystiene, á1-microglobulin and NGAL[13]. NGAL, also known as human neutrophil lipocalin or lipocalin [2], was first purified from the secondary granules of human neutrophils in the search for ideal biomarkers of AKI. NGAL was among the most promising biomarker of AKI. In our study Plasma NGAL ability to predict clinical outcome was assessed using Spearman rank order correlation analysis. There was a positive correlation between 2 h after CT contrast plasma level of NGAL and serum creatinine at 48 h after CT contrast, which was statistically significant (rs = 0.33, p = 0.001). Our study showed that at cut off level of 99ng/ml NGAL rejected the null hypothesis by Independent Mann Whitney U Test while creatinine at 2 h after CT contrast retained the null hypothesis. These were the properties of early and excellent biomarker in detecting AKI. Documented studies of establishment of NGAL as marker of AKI after contrast medium are scarce to nil in Pakistan. A study was carried out by Usman et al to determine the accuracy of NGAL in early detection of AKI after cardiopulmonary bypass surgery by comparing with serum creatinine[14]. Analysis of urine NGAL at a cutoff value of 87 ng/ml showed area under the curve of 0.91 [95% confidence interval (CI) 0.83 – 0.96] with sensitivity of 90.9% (95% CI 58.7 – 98.5) and specificity of 98.7% (95% CI 92.9-99.8).

The first study evaluating NGAL as an AKI predictor was conducted on children after cardiac surgery. Urinary NGAL rose almost 100-fold and serum NGAL 20-fold up to 48 h (ROC of 0.998) before AKI was detected by creatinine[15]. Siew et al. reported a (ROC) AUC ¼ 0.77 (CI 0.64–0.90) for developing AKI in a subgroup of patients for urine NGAL[16]. The predictive performance was also highlighted in a meta-analysis pooling data from 19 studies and eight countries involving 2,538 patients[17]. The overall AUROC for AKI prediction was 0.815 and was similar in general ICU patients. Several studies such as Liangos et.al, showed that in 103 cardio pulmonary bypass patients 2 h after surgery, AUC for NGAL was ¼ 0.50 with CI 0.33–0.68[18]. Koyner et al. measured both plasma NGAL AUC 0.526 (0.388–0.664) and urinary NGAL AUC ¼ 0.705 (CI 0.581–0.829) at ICU admission[19]. Research articles published have

showed that both urinary NGAL and plasma NGAL are superior to other emerging biomarkers of AKI.[20,21,22,23] It has been documented that among biomarkers for AKI, NGAL is best available biomarker for AKI. These results are quite similar to results of our study.[24,25]

CONCLUSION:

NGAL seems to be a potential marker for early detection of decrease in eGFR and predictor of AKI. As a biomarker of AKI it is far superior in comparison to serum creatinine. It is particularly important in reducing the expenditure of stay in hospital by early diagnosis of AKI. It can fulfill the gap of early biomarker of AKI. Further studies should be done for establishment of role of NGAL in AKI in Pakistan especially in patients with pre-existing decreased eGFR.

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ORIGINAL ARTICLE

Clinical Presentation of Malignant Tumours of Tonsil and its Association with Unilateral Enlarged Tonsil in Different Age Groups

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ABSTRACT:

Objective: To determine different clinical presentations in tonsil malignancy with unilateral enlarged tonsil (UET) in different age groups.

Materials and Methods: This descriptive cross sectional study was carried out from 2007 to 2014 in Social Security Hospital Islamabad (allied with Islamabad Medical and Dental College) and in Holy Family Hospital Rawalpindi.80 patients underwent tonsillectomy suspected of tonsil tumour with tonsil asymmetry. In Group I patients were of 3-12 years and in group II, of 13 and above. Clinical assessment was done for any Regional and systemic disease.After tonsillectomy, difference in tonsil size was recorded on gross examination and then sent for histopathology. Statistical evaluation was done by using SPSS 16.

Results: In group I predominant symptom was bilateral (B/L) cervical lymph node enlargement, 32(82%) along with UET. Majority of patients (82.5%) with clinically enlarged tonsil also showed enlargement in gross. Reactive hyperplasia was seen in 2 and lymphoma in 7 on histopathology. In group II Predominant clinical features were cervical lymphadenopathy, recurrent sore throat, headache, nasal obstruction, cough, earache and postnasal drip. 87.5 % of clinically enlarged tonsil showed enlargement in gross examination.Histopathology revealed lymph adenitis in 30, Squamous cell carcinoma (SCC) in 5 and B cell lymphoma in 2.

Conclusion: Tonsillectomy must be done in UET to rule out malignant tumour of tonsil if accompanied by specific symptoms that could lead to tonsillar malignancy especially in adults.

Keywords: Unilateral tonsil enlargement, Hyperplasia,Neoplasm ,Clinical presentation , Prevalence

INTRODUCTION:

Palatine tonsils (PTs) are importantlymphoid tissue of Waldeyer's ring, symmetrically located in the tonsillar fossae in oropharynx.[1,2]Unilateral enlarged tonsils(UET) is a common clinical finding in otorhinology caused by repeated tonsillitis, chronic tuberculosis, actinomycosis, anatomical variations in the tonsillar fossa depth, benign and malignant tumors.[3,4,5] Lymphomas are the most common malignant tumors of the head and neck in the pediatric population[6]and non-Hodgkin lymphoma (NHL) is the most common type among lymphomas.[6,7] The most common presentation of NHL is painful cervical lymphadenopathy along with UET. Extra nodal involvement is more common in NHL[8]. In adults squamous cell carcinoma is found to be commonest type that usually presents with non-healing ulcer over the tonsil[9]. It has been standard practice to perform encountered and it is one of the definite indications for surgery especially when UET is associated with leading diagnostic tonsillectomy for histopathological purposes to exclude malignancy when tonsillar asymmetry is symptoms.[2,10,11] It is rare to find malignancy in enlarged tonsil if UET has been the only indication for tonsillectomy without any leading symptom especially in children[12,13].Tonsillectomy when indication is asymmetry accompanied by leading symptoms, could be an important and beneficial step in the management of such cases.This study aims to assess the frequency of malignancy in patients with UET having different clinical symptoms leading to suspicious of tonsillar malignancy both in children and this may lead to early diagnosis of malignancies and start of early treatment and will have positive impact on the progression and survival rates.[3,11,12]

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MATERIALS AND METHODS:

This descriptive cross sectional study was carried out from 2007 to 2014 in Social Security Hospital Islamabad (allied with Islamabad Medical and Dental College) and in Holy Family Hospital Rawalpindi.A total of 80 patients were studied with UET along with specific symptoms; recurrent throat infections, nasal obstruction, post nasal drip(PND), Odynophagia, ear ache, headache, cervical lymphadenopathy, lump in neck and ulcer over tonsil leading to suspicious of malignancy.They underwent tonsillectomy for purpose of histological examination from 2007 to 2014 in above mentioned institutes.Sampling was done by non-probability convenient sampling technique. Patients were dividedinto two groups according to their age.In group I, pediatric group; included patients between age group 3-12 years

and in group II, adult group; were of age 13 years and above. All the patients were assessed clinically for chronic sinusitis, recurrent tonsillitis, and ulcers over the tonsils, chronic nasal obstruction, dysphagia, PND, neck swelling, significant cervical lymphadenopathy and systemically like long standing fever, enlarged inguinal lymphnodes and hepatosplenomegaly.Only those patients presented with above mentioned symptoms with UET were included in study for biopsy purposes. Exclusion criteria included patients with no preoperative notes, where histological reports were not available, and patients having no clinical feature except UET, immune compromised patients, who had malignancy at other sites already diagnosed and patients who had received radiotherapy.

Any difference noticed between right and left sides was considered asymmetric. Patients' age, gender, right (R) and left (L) tonsil asymmetry in size, all clinical features, pathological results; gross pathology (width, depth, volume and height) and histopathology were recorded. Clinically enlarged tonsils were kept in three levels; mild difference (+1), moderate difference (+2) and marked difference (+3).

After doing bilateral tonsillectomy, difference was divided in three categories, +1; when difference in gross and clinical was<5mm, +2; was between 5-10mm, and in +3cases was >10mm. t test was applied for clinically enlarged tonsils and actual tonsil size in gross pathology, P value was considered significant when it was< 0.05. Tonsils were sent for histopathology. In retrospective cases data was collected from record. All the data was recorded on a preformed Proforma.Statistical evaluation of results was done by using Window SPSS 16 and descriptive analysis was done.

RESULTS:

In group I number of patients were 40, age ranged from 3- 12 years, mean age was 7.5. 30 (75%) were male, 10 (25%) were female. Mild difference (+1) was noticed in 15(37%), 5 on right(R) and 10 on left(L) side, moderate (+2) in 10 (25%) 5 on R side and 5 on L side; marked difference (+3) was in 15(37.5%), 6 were of L side and 9 were on R side (Table I).

Table: 1
Average of difference between clinical and pathological enlarged tonsil

Size of tonsil	Hypertrophy assessed clinically		Hypertrophy in gross pathology		Average	
	Group I	Group II	Group I	Group II	Group I	Group II
Mild (+1)	15	25	8	21		
Moderate (+2)	10	10	10	10	82.5%	87.5%
Marked (+3)	15	5	15	4		

In gross pathology, difference was noticed in volume, height, width and length in32 out of 40(80%), 8(53%) out of 15 cases of mild (+). All cases (100%) of moderate (+2) and marked (+3) enlargement showed valuable difference in size. Total average of difference in size in all cases was 82.5% (Table 1). t test was applied for clinically enlarged tonsils and actual tonsil size in gross pathology, P value <0.05.Predominant clinical feature was bilateral (B/L) cervical lymphadenopathy (32=80%). Other clinical features with average are shown in Table 2.

Table: 2
Clinical features in group I and II

Clinical features	Group I	Group II
B/L cervical lymphadenopathy	32(80%)	2(5%)
Recurrent sore throat	27(67%)	25(62%)
U/L cervical lymphadenopathy	20(50%)	30(75%)
Nasal obstruction(due to DNS or Adenoids)	17(42%)	1(2.5%)
PND	9(22%)	22(55%)
Abdominal symptoms	5(12.5%)	2(5%)
Headache	---------	9(22%)
Cough	---------	9(22%)
Earache	----------	10(25%)
Swelling neck	----------	4(45%)
Ulcer over tonsil	…….	4(10%)

Results of histopathology are shown in Figure 1. Only 4 out of 40 enlarged tonsil diagnosed as tumour, average was 10% (Figure 2). Chi-square test was applied for frequency, p value <.05, results were significant.

Figure: 1
Histopathology results in group I

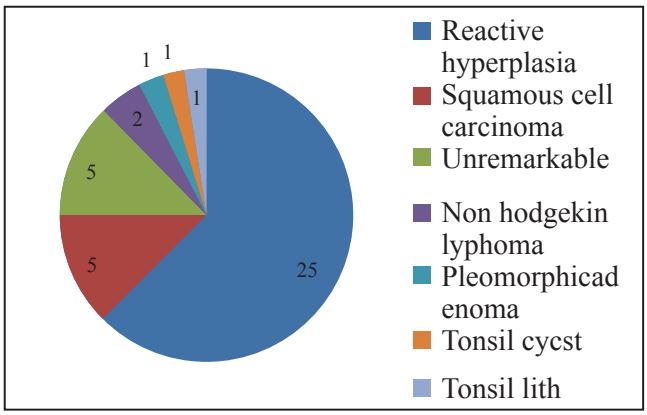
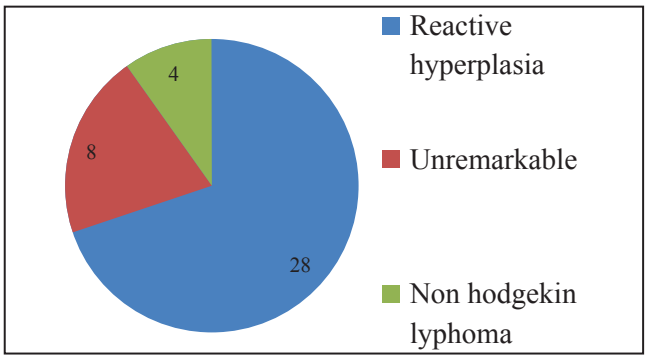


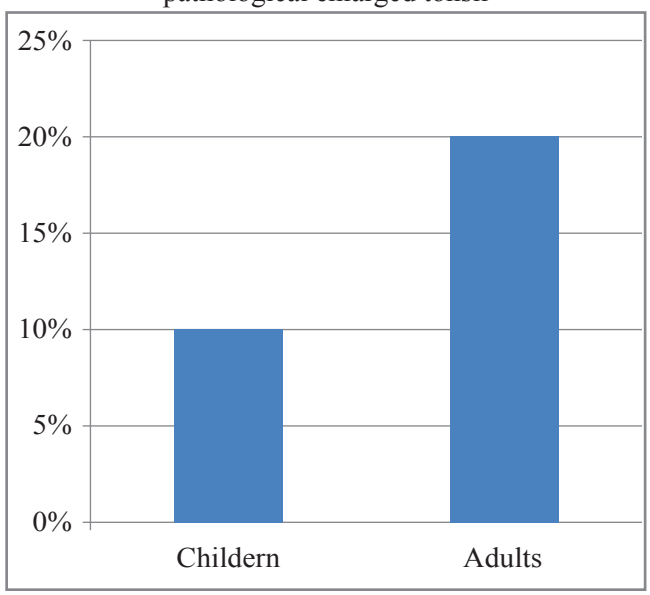
Figure: 2
Histopathology results in group II



In group II number of patients were 40, age ranged from 13- 60 years, mean age was 36, 27 (75%) were male, 25 (67.5%) were female. Mild difference (+1) was noticed in 25(62.5%), 10 on right (R) and 15 on left (L) side, moderate (+2) in 10 (25%) 6 on R side and 4 on Lside; marked difference (+3) was in 5(12.5%), 1 on L side and 4 on R side (Table 1). In gross pathology after doing tonsillectomy, difference was noticed in volume, height, width and length in35 out of 40(87.5%), 21 out of 25 cases (84%)of mild(+1) and all cases(100%) of moderate (+2) showed valuable difference in size. 4 cases (80%) of markedly enlarged tonsil (+3) showed difference in size. Total average of difference in size in all cases was 87.5% (35/40 as seen in Table 1). t test was applied for clinically enlarged tonsils and actual tonsil size in gross pathology, significant P value < 0.05.Predominant clinical feature was unilateral (U/L) cervical lymphadenopathy (30=75%).Combination of symptoms were seen. Other clinical features with average are shown in Table 2.

Histopathology of 25 (62.5%) tonsil specimens showed reactive hyperplasia, 5(12.5%) were diagnosed as squamous cell carcinoma, Non Hodgkin lymphoma in 2 (5%) and pleomorphic adenoma, tonsil cyst and tonsillith in each case (2.5%) as shown in figure 2.Histopathology of only 5(12.5%) enlarged tonsil was unremarkable, these were mainly from +1 group. 8 out of 40 (20%) enlarged tonsils were diagnosed as tumour (figure 3). Chi-square test was applied for frequency, p value <.05, results are significant.

Figure: 3
Frequency of malignancy in different age groups in pathological enlarged tonsil



DISCUSSION:

Although unilateral enlargement may be due to anatomical variations, but may result from repeated tonsillitis, chronic tuberculosis, benign and malignant tumours of tonsil particularly if the patient presents with suspicious symptoms such as sore throat, ulcer or membrane over the tonsils, painful cervical lymphadenopathy, or fever.[4,5,11]

If tonsillectomy is being done to rule out malignancy in enlarged tonsil, these clinical features are important [12]. Present study determines the frequency of malignancy in clinically UET accompanied by other clinical features.

In our study, 32 out of 40(80%) children and 35 out of 40(87.5%) adults with UET clinically showed actual enlargement in gross pathology after doing tonsillectomy. Most of the patients were from moderate to severely enlarged group.

Our study is comparable with one study performed in adults above 18 years of age with UET. 46 patients were assessed for UET, 28 out of 46(57.14%) showed actual difference in size when measured in gross specimens. It was noticed that pathological enlargement was usually seen in+2 and +3. Difference was seen only in few cases of +1 cases.[6,13]

In another study, 47 children with tonsil asymmetry were studied, no statistical difference in degree of asymmetry was found on clinical and pathological examination (p=0.5). A difference in depth of tonsillar fossa was identified. More accurate method to assess the size of tonsil is CT scan. After confirming the size of tonsil with CT scan clinician will be better able to council the patients regarding need to undergo tonsillectomy.[14,15]Actual tonsillar hypertrophy in gross after tonsillectomy was significant in both adults and children if there are leading clinical features such as enlarged cervical lymph nodes, nasal obstruction, PND, recurrent sore throat as compared to if UET has been the incidental finding. False results due to anatomical variation in depth of tonsillar fossa are more common if UET is not accompanied by other clinical features.[9,12]

In our study Predominant clinical feature in children with reactive hyperplasia were bilateral cervical lymphadenopathy, recurrent sore throat, adenoid hypertrophy, deflected nasal septum (DNS), postnasal drip (PND) along with UET. Abdominal symptoms (pain, inguinal lymph nodes and splenomegaly were seen with UET where tonsillectomy specimen showed lymphomas.

In adults predominant symptoms with UET due to reactive hyperplasia were post nasal drip, U/L cervical lymphadenopathy. In patients with malignancy predominant symptoms were U/L cervical lymph node, earache, ulcer over tonsil and abdominal symptoms along with UET. We can compare our study with retrospective studies in which predominant symptoms in children with malignancy were UET with change in voice (muffled) nocturnal snoring, some episodes of apnea, nighttime awakenings, reduced appetite, weight loss, cervical lymphadenopathy and cough.[9,16,17,18]Tonsillar asymmetry, visible lesion or hard consistency upon palpation of the tonsil, unexplained loss of weight and the presence of cervical mass had been common

symptoms in adults with squamous cell carcinoma.[9,18] Symptoms of infection of the pharynx and tonsils, such as exudate in the tonsils, painful cervical adenopathy, PND or fever were common in UET with reactive hyperplasia in both adults and children [9,16,19]. Asymmetrical tonsils and suspicion of malignancy is one of the indications for tonsillectomy. The incidence of malignancy in patients undergoing tonsillectomy is low (approximately 2.5:10,000) if not associated with other important clinical symptoms.[15,20,21] Incidence increases if tonsil asymmetry is associated with suspicious clinical symptoms.[2,20,21]In a previous study, children undergoing surgery because of tonsillar asymmetry where the presence of enlarged cervical lymph nodes and abnormal appearance of the tonsils were additional risks factors, incidence was 20%. In one of previous study incidence of lymphoma in patients with UET without any other clinical symptom was 4%.[13,22]In our study frequency of malignancy in children was 10% and in adults was 20%. All of the patients presented with UET and different clinical features.While considering frequency we can compare our results with these previous studies.[23,24,25] The tonsillectomy is one of the most common surgeries in the world and a malignancy is generally connected to other clinical findings along with UET that may be confirmed by histopathology of all tonsillectomy specimens. This study proposes thattonsillectomy must be reserved for cases of suspicionand the tonsillar asymmetry is undoubtedly the main one.

CONCLUSION:

Although a few patients with palatine tonsil asymmetry have malignancy but most of the patients with tonsillar malignancy have tonsillar asymmetry. Detailed examination of the oral cavity and neck is essential and only those patients of UET with other important clinical symptoms suggestive of malignancy should undergo tonsillectomy.

The histopathological review of all pieces of tonsillectomy is crucial especially where the patient has other associated symptoms that suggest a malignancy. A large scale multicenter study should be carried out to determine the frequency of malignancy in uneven enlarged tonsil.

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ORIGINAL ARTICLE

Maternal and Fetal Outcomes in Pregnancies Conceived with In-Vitro Fertilization

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ABSTRACT:
Objective: To assess the outcome of pregnancies conceived by in vitro fertilization.
Materials and Methods: A retrospective study utilizing case notes of 110 cases of in vitro fertilization (IVF) delivered in East Sussex Hospital Trust (ESHT)was carried out from 2010 to 2011 in two district general hospitals, Eastbourne and Conquest hospital that come under ESHT. All cases with IVF during these two years were included. Demographic details, predisposing risk factors, body mass index, causes of infertility, antenatal care, onset of labour, mode of delivery and details of baby were collected and analysed.
Results: Infertility was female related in 46% and male related in 38%. In females tubal factor was the main cause. 18% had pre-existing medical conditions, polycystic ovaries being the commonest. 75% had singleton pregnancy and 25% twin's .Nearly 6% had antepartum haemorrhage, twins having higher (11%) rates compared to singleton pregnancy (3.6%). The incidence of pregnancy induced hypertension and diabetes were the same being more in twin compared to singleton pregnancy .There were 8.4% singleton preterm deliveries. The singleton babies born with weight of less than 2500 gms were 4.8%. There were 2 (1.8%) stillbirths. 3.6% babies had congenital abnormality. In 42 % mode of delivery was caesarean section.
Conclusion: Majority ofchildren born following IVF had a good outcome but increased risk of obstetrics and fetal complications was found when compared to spontaneously conceived pregnancies. Multiple births remain a major cause of morbidity among infertility patients
Keywords:Infertility, Assisted reproduction, In vitro fertilization, Maternal outcome, Fetal outcome.

INTRODUCTION:

It is estimated that infertility affects 15-20% of the couples in the UK at some stage in their reproductive life. [1, 2]Assisted reproduction techniques have developed to improve chances of achieving pregnancy in subfertile couples. Assisted reproduction techniques have subsequently become an effective and widely used therapy for such couples. In vitro fertilisation (IVF) is one of these techniques. Most (80 %) of the sub fertile couples conceive with assisted reproductive technology (ART), but still 20% will not be able to conceive [3]. In women aged 40 years treatment of infertility is difficult and controversial [4]. Reasons for the increasing infertility are delaying the childbearing, increased pelvic infections and deteriorating sperm quality [5]. The reasons for infertility are related to both females and males. The most common causes for infertility are ovulatory disorder or anovulation, tubal factor, endometriosis, abnormal semen parameters. Infertility in many couples can have multiple causes. In about 15-17% of couples, no reason for infertility is found.[6] IVF is the treatment of choice for infertility that has not been successfully treated by other modalities.[5, 7, 8] Most of the pregnancies after IVF have good outcomes, but there is also an increased risk of obstetric and neonatal complications, compared to naturally conceived pregnancies [9]. Pregnancies from IVF has increased risk of perinatal mortality , congenital anomalies and is associated with higher rates of preterm deliveries , prematurity , antepartum haemorrhage , caesarean sections, , fetal malpresentation ,small for gestational age ,low birth weight and admission to neonatal intensive care unit . The risk of pregnancy-induced hypertension, pre-eclampsia, placenta previa and non-insulin-dependent gestational diabetes increases in IVF-pregnancies as well. [10, 11, 12,13] It is not clear whether these increased risks are related to infertility, or use of assisted reproductive techniques [14]. The causes of infertility influence the outcome of ART treatment. The prognosis with unexplained infertility is better than tubal infertility or endometriosis. The duration of infertility and parity of women also have influence on pregnancy rates achieved by ART. An increase in duration of infertility will decrease the chance of successful IVF treatmen.t[15]A previous pregnancy and delivery with IVF treatment, increases the chance of success in a subsequent IVF treatment [16] .Couples with secondary infertility have double pregnancy rates compared to primary infertility.[17,

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[18] There is significant risk of multiple pregnancies with ART. The rate of multiple pregnancies being approximately 25-35% [19, 20] compared with only 1% in naturally conceived pregnancies. Multiple pregnancies increase the risk of foetal and maternal complications. The Dichorionic twins are most common, but the incidence of monochorionic twins is also increasing [14]. In vitro fertilization increases the risk of monozygotic twins by two folds compared with natural conception. Malformation rates in IVF multiple pregnancies are higher than in IVF singletons [21, 22]. Multiple births are a leading cause of long-term child morbidity among infertility couples.[23](Table 1). Present study was undertaken to assess the outcome of pregnancies conceived by in vitro fertilization.

MATERIALS AND METHODS:

This retrospective study utilizing case notes of 110 cases of in vitro fertilization (IVF) delivered in East Sussex Hospital Trust (ESHT) was carried out from 2010 to 2011 in two district general hospitals, Eastbourne and Conquest hospital that come under ESHT. All cases with IVF during these two years were included. Demographic details, predisposing risk factors, body mass index, causes of infertility, antenatal care, onset of labour, mode of delivery and details of baby were collected and analysed.

RESULTS:

110 cases were studied. Most of these pregnancies had consultant lead care except 4 cases which had only midwifery care. Those who had assisted reproduction with primary infertility were 68 %. About 35% who had treatment were of ages 31-35 years and 29% were aged 36-40 year. 40.9% had BMI 25-30 and 5.46% had BMI 31 and above (Table 2). In 46% subfertility was female related and 38% cases male related. In females 23% tubal factor and 13% endometriosis were responsible. In 13% cases cause was unexplained and in 7.2% there were more than one cause of infertility. 18% had pre-existing medical condition, the incidence of polycystic ovaries were 75% (Table 3). In our study 75% had singleton pregnancy and 25% twins. Those who suffered from pregnancy induced hypertension (PIH) were around 5%. Singleton 4% and 8% twin pregnancy suffered from pregnancy induced hypertension. The numbers of patients with diabetes were the same as PIH (5%) and the distribution were the same as in PIH, about 4% in singleton and 8% in twins. There was antepartum haemorrhage in nearly 6% of cases. It occurred in about 4% in singleton and 11% in twin pregnancy. There were 16% cases which had no scan in the third trimester. There were 8.4% singleton preterm deliveries and 15% twin pregnancy. Thesingleton babies born with weight of less than 2500gms were 4.8% .There were 1.8% stillbirths, one singleton at 41+ weeks and one DCDA twin at 33 weeks. About 3.6% babies had congenital abnormalities. Induction of labour was done in 33% of the cases. In 42% , mode of delivery were spontaneous vaginal ,16% had instrumental deliveries and around 42% were delivered by caesarean section There were 59% emergency and 41% elective caesarean sections (Table 4) .

Table: 1
Comparison of IVF & natural conception outcomes
RCOG data

	IVF pregnancy	Natural Conception	Comments
Miscarriage	14-30%	15-20%	Slight increase, due to older age.
Ectopic pregnancy	1-11%	0.2-1.4%	Increase due to many factors
Preterm delivery	24-30%	6-7%	Four-fold increase.
Small birth weight	27-32%	5-7%	Five-fold increase.
Stillbirth rate	1.2%	0.6%	Two-fold increase.
Perinatal death	2.7%	1.0%	Two-fold to four-fold increased risk.
Congenital abnormalities	1.0-5.4%	0.8-4.5%	30-40% increase. However, the absolute risk is nevertheless low. The increase is partly attributable to the underlying infertility as couples who take longer than 12 months to conceive also have an increased risk of abnormalities.
Caesarean section	33-58%	10-25%	Increase mainly because of multiple pregnancy and woman's age.
Multiple pregnancy			
twins	24-31%	1.2-4.5%	Increase due to higher number of embryos transferred.
triplets	0.5-5.2%	0.012%	
quadruplets	0.5%	0.0001%	

Table: 2
N=110

Parameter	IVF Pregnancy	Percentage (%)
Age in years	31-35	35%
	36-40	29%
BMI	25-30	40.9%
	31 & above	5.46%

Table: 3
N=110
Causes of Infertility

Causes	Percentage (%)
Tubal factor	23%
Endometriosis	13%
polycystic ovaries	75%.
Unexplained	13%
More than 1 cause	7.2%

Table: 4
N=110
Pregnancy Outcomes

Outcome	Percentage (%)
PIH	5%
Gestational Diabetes	5%
APH	6%
Preterm delivery	8%
Induction of labor	33%
Mode of Delivery	
Spontaneous vaginal	42%
Instrumental	16%
Caesarean section	42%
(i) Emergency	59%
(ii) Elective	41%
Baby weight	
Less than 2500 gm	4.8%
Still births	1.8%
Congenital Abnormalities	3.6%

DISCUSSION:

The findings of our study showed that maternal, obstetric and foetal complications increase in IVF pregnancies. In our study 75% had singleton pregnancy and 25% twins which is comparable to the United Kingdom (HFEA patient's guide 2002), 25% of deliveries after IVF were twins. The stillbirth rate in our study is 1.8% compared to 0.6% in naturally conceived pregnancy. Two fold increase risk in stillbirth by IVF has been reported but in our study threefold increase was noted compared to naturally conceived pregnancies. There is two-fold to four-fold increased risk of perinatal death with IVF pregnancy compared to spontaneously conceived pregnancy [24] however there was no perinatal death in our study. The incidence of pregnancy induced hypertension and diabetes were the same in IVF pregnancies. It is concerning that the incidence was twice in twins as compared to singleton pregnancy. This study also confirmed that polycystic ovaries have a significant role in infertility. The preterm delivery of singleton pregnancy with IVF is 12-14%, our study showed 8.4% compared to 6-7 % in naturally conceived. This study also confirmed increased risk of preterm delivery compared to naturally conceived pregnancy. However the risk of preterm delivery is increased two fold in twins. Babies who had congenital abnormalities were 3.6%, whereas in naturally conceived pregnancy it is 0.8- 4.5%. However the absolute risk is low. The increase in congenital abnormality may be partly attributable to the underlying infertility. There are evidences that couples who took longer than 12 months to conceive have an increased risk of structural chromosomal abnormalities. The IVF techniques themselves could be involved. Another possible cause is that babies conceived through fertility treatments are monitored more closely than other babies We found an increased risk of Caesarean sections with IVF pregnancy, 42% compared to 10-25% naturally conceived pregnancy. The increased risk can be because of maternal age and the risks associated with IVF pregnancy.[25] The success of assisted reproductive technology should not only be in terms of live birth rates, but also in terms of reduction of multiple births to singleton babies. Efforts should be made to limit multiple pregnancies resulting from ART. Women receiving in vitro fertilisation should be counselled about the increase obstetrical risks and interventions. They need to be made aware of psychosocial implications of assisted conception techniques. Clear information in different languages of choice and patient information leaflets should be available. Close surveillance during pregnancy is required in pregnancies conceived with IVF. Evidence from randomized controlled trials, have shown significant reduction in the probability of live birth and multiple birth, when comparing double embryo transfer with single embryo transfer. These trials suggests that increasing the number of attempts of single embryo transfer results in a cumulative live birth rate similar to that of two embryo transfer. The live birth from single embryo has less complications as well financial burden than two embryo transfer [26]Our study confirmed that maternal, obstetric and foetal complications increase in IVF pregnancies as seen by many other studies in literature.[27,28,29]This study also showed that multiple pregnancies is the most powerful predictive factor for adverse maternal, obstetrical, and perinatal outcomes as concluded by many other studies[23.]

The limitations of our study are, our model was based on data from a single centre .It was a retrospective study, our analysis depended on previously recorded data from the notes, therefore some data was missing. We did not have comparable data from the same trust on women of the same age who conceived naturally regarding maternal background such as body mass index, medical complications and mode of delivery .Other limitation was the sample size and the ethnicity. This study was conducted mainly on Caucasians so there was no ethnic diversity.There were however some inconsistencies in relation to management of IVF pregnancies, particularly in relation to singleton pregnancies .Some women were not assessed in consultant clinics .There was no agreement on timing of birth. All the women did not have the regular growth scans in third trimester .In the future there should be a reduction of the multiple pregnancies and a higher rate of singletons after adoption of a single embryo transfer policy. This will reduce the cost of the trust in providing care for these pregnancies. Trusts should have regular review and audits on the management effectiveness of in vitro conceived pregnancies. The increased rate of congenital abnormalities may be due to the fact that children conceived with artificial reproduction techniques have more vigilant follow up as compared to general populations. The strengths of the study are that majority of the women had treatment for primary infertility and had good outcome. We also found that data was comparable to national level for demographic and pregnancy outcome with IVF pregnancy.

CONCLUSION:

Majority of children born following IVF had a good outcome but increased risk of obstetrics and fetal complications was found when compared to spontaneously conceived pregnancies. Multiple births remain a major cause of morbidity among infertility patients. It is recommended that there should be a policyof trust for the management of IVF/ICSI singleton pregnancies, to improve compliance to recognised standards; ensuring community midwives refer IVF pregnancies for consultant-led antenatal care. These pregnancies should have at least two third trimester growth scans due to high risk nature of IVF pregnanciesThere is need to develop consensus agreement regarding timing of birth for singleton IVF babies.

Further research is required to determine the cause and increased risks to children as well as cancer associated with artificial reproduction technique. There is no research on the long-term health outcomes in women and children after IVF .This is because of the confidentiality affected by Human Fertilization and Embryology Act in the United Kingdom to the parents

and children resulted from ART has meant that follow up of these children has not been possible.

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ORIGINAL ARTICLE

Obstetric Restless Legs Syndrome in Industrialized Area of Pakistan

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ABSTRACT:

Objective:To determine the frequency of obstetrics Restless legs syndrome(RLS) in industrialized area of Karachi and to identify possible risk factors of RLS in Pakistani population.

Materials and Methods: This cross-sectional study was carried out in a Teaching Hospital from 1st January 2013 to 31st January 2014.All pregnant women of 20- 44 years old in first trimester without peripheral vascular disease, painful legs, peripheral neuropathy, nocturnal leg cramps and moving toes were enrolled in the study. A close-ended questionnaire developed from International RLS Study Group was used.The diagnosis of RLS was then ascertained by the obstetrician by using the criteria of the International RLS Study Group and they were labeled as "RLS sufferers and were kept in RLS group while others that is non RLS sufferers were kept in the healthy group. Descriptive and comparative statistical analyses were performed using SPSS Statistical Software 17.

Results: During a period of thirteen months, 900 pregnant women were interviewed and examined out of these 85.7% fulfilled the criteria and constituted the study population. Out of these 31.90 % were RLS suffers. Among RLS suffers 55% were resident of industrialized area. The majority of RLS suffers were multigravida and in their advance pregnancies.

Conclusion: The frequency of obstetrics Restless legs syndrome (RLS) in industrialized area of Karachi is 31.90 % Possible risk factors of RLS in Pakistani population are multigravidity, advance pregnancy, industrialized area etc.

Keywords: Obstetrics restless legs syndrome**,** Frequency, Industrialized area, Risk factors

INTRODUCTION:

Restless legs syndrome (RLS) is a neurologic movement disorder that is often associated with a sleep complaint. Suffers of RLS have an irresistible urge to move their legs, which is usually due to displeasing feelings that are worse during periods of inactivity and often affect sleep specially at night.Patient often has unpleasant sensation or pain in limbs. Restless Legs Syndrome (RLS) is very common during pregnancy especially in advance pregnancy. Unfortunately its etiology[1] is poorly understood that is why it is under-diagnosed and so poorly treated.

The frequency of RLS upsurges as the age advances. There is a significantly higher prevalence of RLS in female gender, gravid women, end-stage renal disease and in patients with diabetes.

The negative impact of RLS on quality of life is enormous.The discomfort of RLS and periodic limb movements interfere with the initiation and continuation of sleep resulting in inadequate and insufficient sleep and imprecise daytime functioning.Alterations in sleep are also commonly reported during pregnancy.[2]An association between the two disturbances can be suspected as ingravid women the risk of RLS is greater than the general population[3]. Several studies have been done on RLS during pregnancy[4, 5] but none has been documented in industrialized area and on the probable predictors of RLS in entire pregnancy. Some have focused on mid trimester and others on last trimester. The diagnosis of RLS is based primarily on the patient's history. Often, patients do not bring RLS symptoms to the physician's attention; therefore, it can be helpful to include general sleep questions in the review of systems (Table 1a). When RLS is suspected, more specific questions should be asked.[6,7] (Table 1b)

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Table: 1a Sleep/Wake Profile

1. How has the patient been sleeping recently? (Ask the patient and bed partner.)

Suggested questions following a sleep complaint:

1. When did the problem begin? (To determine acute vs. chronic insomnia).
2. Does the patient have a psychiatric or medical condition that may cause insomnia?
3. Is the sleep environment conducive to sleep? (Relates to noise, interruptions,temperature, light).
4. Does the patient report "creeping, crawling or uncomfortable, difficult- to-describe feelings" in the legs or arms that are relieved by moving them? (Relates to restless legs syndrome).
5. Does the bed partner report that the patient's legs or arms jerk during sleep? (Relates to periodic limb movements of sleep).
6. Does the patient snore loudly, gasp, choke or stop breathing during sleep? (Relates to obstructive sleep apnea).
7. Is the patient a shift worker? What are the work hours? (Relates to circadian sleep disorders/sleep deprivation).
8. What times does the patient go to bed and get up on

Table: 1a Sleep/Wake Profile (continued)

breathing during sleep? weekdays and weekends? (Relates to poor sleep hygiene and sleep deprivation).
9. Does the patient use caffeine, tobacco or alcohol? Does the patient take over-the-counter or prescription medications, such as stimulating antidepressants, steroids, decongestants or beta-blockers? (Relates to substance-induced insomnia)

Signs of sleepiness:

1. What day time consequences, such as fatigue, sleepiness, confusion or difficulty concentrating, does the patient report?
2. Does the patient report dozing off or have difficulty staying awake during routine tasks, especially while driving?

Table: 1b
Essential diagnostic criteria (all must be met)

1. An urge to move the legs usually but not always accompanied by, or felt to be caused by, uncomfortable and unpleasant sensations in the legs.
2. The urge to move the legs and any accompanying unpleasant sensations begin or worsen during periods of rest or inactivity such as lying down or sitting.
3. The urge to move the legs and any accompanying unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.
4. The urge to move the legs and any accompanying unpleasant sensations during rest or inactivity only occur or are worse in the evening or night than during the day.
5. The occurrence of the above features is not solely accounted for as symptoms primary to another medical or a behavioral condition (e.g. myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping).

Present study was designed to determine the frequency of RLS in pregnancy in industrialized area of Karachi and to formulate promising risk factors of RLS in a Pakistani pregnant population.

MATERIALS AND METHODS:

This cross sectional study of pregnant women aged 20 to 44 years was carried out in the Gynecology and Obstetrics Department of Jinnah Medical and Dental College, Karachi for a period of 13-month from 1st January 2013 to 31st January 2014. Pregnant women with neurological disorders,the patients with peripheral vascular disease, the patients with painful legs, patients with peripheral neuropathy, patients with sleep disorders, patients with akathisia, patients with nocturnal leg cramps and moving toes were excluded. The included population was studied by means ofa close-ended questionnaire being filled by one to one interview by the medical staff of the Obstetrics and Gynecology Department. The study and its aims were explained to the participating women and their verbal consent was obtained before conducting the interview. The questionnaire designed to assess the patient's characteristics had two parts. The first part was about subject identification (woman's name, initials, date of birth) and demographic characteristics of the woman (age, marital status (married, separated, widow), professional status, number of previous pregnancies and type of pregnancy (single, twin or multiple pregnancies). In the second part, the participants were requested to reply the questions as defined by the International RLS Study Group[8], the trimester of the RLS apparition during pregnancy, its eventual presence before this pregnancy or during previous pregnancy. If RLS was already present before the pregnancy, additional data were gathered: its frequency (less frequent, the same, more frequent than actually) and its severity (less severe, the same, more severe than actually). The diagnosis of RLS was then ascertained by the obstetrician by using the criteria of the International RLS Study Group. For the confirmed diagnosis of RLS, all these criteria must be present ina participant so as to symbolize her as "RLS sufferer" group whereas four or less than four criteria represented a "healthy group".There was no selection prior to giving the questionnaire, meaning that the two groups with and without RLS were constituted in an independent manner Descriptive and comparative statistical analyses were performed using SPSS Statistical Software 17.

RESULTS:

During this 13-month period, a total of 900 women were interviewed and questionnaires were filled. 771 questionnaires (85.66 %) were satisfactorily filled in and constituted study population. Out of 771 participants, 246 (31.90%) had fulfilled all the criteria and were diagnosed as "RLS sufferers" group and the remaining constituted the "healthy group".

Among the 246 RLS suffers 136 patients were found to be residents of industrialized area of Karachi that constitute 55.28% of RLS suffers group.35% of RLS suffers were in their first pregnancy and 65% were in their second or more gravidity. Out of all multigravida 21.13% patients were in their second, third or fourth pregnancies while 43.90 were in their fifth or more pregnancy(Table 2) Among the 160 multigravidae, RLS suffers who had one or more than one pregnancy in past 38% of them had the same complaint in previous pregnancy and 35% had the same complaint in past without pregnancy.

Among the women who developed RLS during pregnancy only 8.5% complained of these symptoms during their first trimester, 31.4% during second trimester and more than half of them (60.1%) during the last trimester (Table 3).

Table: 2
Characteristics of RLS and Healthy groups

	RLS Group		Healthy Group	
	Number	Percentage	Number	Percentage
Total number of patients	246	31.90	525	68.09
Resident of industrial area	136	55.28	282	53.71
Primigravida	86	34.95	202	38.4
Multi-gravida	52	21.13	124	23.6
Grand multigravida	108	43.90	199	38.0
Positive past obstetrics RLS history	61	38	111	21
Positive past RLS history	67	42	131	25

Table: 3
Duration of pregnancy in RLS Patients

	Number(246)	Percentage (%)
Trimester		
First trimester	21	8.5
Second trimester	77	31.4
Third trimester	148	60.1

DISCUSSION:

The relationship between RLS and pregnancy was first reported by Ekbom[9] in his original publication in 1945 and confirmed later by a number of surveys and systematic studies [10,11,12,13,14] but none focused on obstetric RLS in industrialized area. Our study is devoted to obstetric RLS in this particular area.

Prevalence of RLS in general population is ranging from 5% to 10%. [9] As we know that gravidity is a significant risk factor and the stated dincidence of RLS among pregnant women is 20–26%[15,16,17,18] and in some studies even to 30%.[19,20,21] This indicates thatgravid women have a two to three time greater risk of suffering from RLS than in the overall. Our study validates the great occurrence of RLS during gravidity. The prevalence of obstetrics RLS in our patients was (31.90%). This comparatively greater occurrence of obstetric RLS in our study might be owing to environmental (air and noise) pollution and chemical pollution in industrialized area and top of this low socioeconomic status of pregnant women and high parity in this area. However, this relatively high prevalence of RLS could be due to our evaluation which was assessed through a performa which was filled by asking the patients themselves[22]. The risk of false positivity might be pertinent, since mimic symptoms are frequent during pregnancy. In fact, in a previous study[14], only women at 32–34 weeks' gestation were assessed as having RLS, but the four RLS criteria were not used.

Factors associated with RLS are numerous, but positive RLS past history and obstetric RLS in previous pregnancies increase the risk of RLS [15, 16, 23, 24] in the index pregnancy. In RLS sufferers with positive past history, the prevalence of RLS was significantly higher for multigravida women than for primigravida. This shows that pregnancy could be a major non-genetic factor which increases the risk of developing RLS, [22] but only for those with positive past history of RLS [24]. Thus, the fact that women with RLS affected history have a higher chance of developing it during pregnancy means that a particular genetic background is probably necessary in order to develop RLS during pregnancy. Pregnancy could increase the RLS risk in all women, but clinical symptoms could only appear in some predisposed women. Another possibility could be to verify the frequency of the already known allelic variants for RLS in these women. Beside genetic factors, RLS in prior pregnancies or RLS in the past without pregnancy are also important risk factors for RLS during pregnancy [16, 19]. In our study 80% RLS suffers had positive RLS history with or without pregnancy and only 20% experienced RLS for the first time during the current pregnancy. As we have seen in other studies RLS seems to be more frequent and more severe among women with previous pregnancies than women without children [25]. This could suggest that only one pregnancy is sufficient to generate ongoingmodification in organicelements which later leads to RLS [24]. Although the obstetric RLS prevalence increases throughout the pregnancy it is highest during the third trimester which is the most critical[9, 10, 14, 19,20,21] as with 8.5% of expectant in our study were affected during the first trimester, reaching 60.1% during the third trimester. Other studies also confirm increasing prevalence with advance pregnancy.[1, 8, 10, 14,15,16 18] This may be because of gravidityassociated hormonal changes, i.e., rise in prolactin, placental lactogen, progesterone and estrogen levels. These chemicals upsurge dramatically during the latter half of pregnancy and associates well with commencement of RLS symptom in gravid women in advance pregnancy.

Our study has some constraints. Primarily, this is a solitary study in an industrialized area tertiary care center in non-governmental sector, and therefore it may not be a true illustration of the population. Secondly, we did not follow-up the patients afterwardso we cannot say anything about the sequence of obstetric RLS in Pakistani society. Thirdly, we used reputable diagnostic standards of RLS which were translated in our native language Urdu without any authentication study.

CONCLUSION:

The frequency of obstetrics Restless legs syndrome (RLS) in industrialized area of Karachi is 31.90 % Possible risk factors of RLS in Pakistani population are multigravidity, advance pregnancy, industrialized area etc.

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ORIGINAL ARTICLE

Awareness among the Patients of Chronic Suppurative Otitis Media about the Disease and its Complications

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ABSTRACT

Objective: To assess the level of awareness among patients of chronic suppurative otitis media (CSOM) about disease and its complications.

Materials and Methods: This cross-sectional study was carried out in Combined Military Hospital Rawalpindi, Cantonment General Hospital Rawalpindi and Pakistan Institute of Medical Sciences Islamabad from April to September 2014.Diagnosed out-patients of CSOM after history and clinical examination were included in the study and interviewed with the help of structured questionnaireto assess the knowledge about their disease and its complications. The data was analyzed using SPSS 18.

Results: Majority(48.8 %) patients were 15 to 30 years of age. Male to female ratio was 3:2. Only 49.6 % patients knew they had a perforation in their ear drum and 30.4% understood perforation as the cause of continued discharge from the ear. Only 33.6% patients had knowledge about entry of water in the ear as a cause of recurrence of discharge. Most patients (71.2%) did not know they had either the safe or the unsafe type of disease and only 48.8% patients knew that this disease could cause serious complications.58.4% knew that it can cause permanent hearing loss, 19.2% were aware that infection could spread to brain, 11.2% knew it could cause facial paralysis. Only 0.8% knew it could cause giddiness and vertigo. 27.2% were aware that their disease could be cured by surgery and 26.4% thought early surgery is necessary.

Conclusion: Awareness among patients of CSOM about their disease and its complications is very low.

Keywords: Chronic suppurative otitis media, Awareness, complications, Perforation, Vertigo

INTRODUCTION:

Chronic suppurative otitis media (CSOM) is defined as persistent inflammation of the middle ear and mastoid air cells[1]characterized by a perforated tympanic membrane with persistent drainage from the middle ear (i.e., lasting >6-12 week)[2].The WHO definition requires only 2 weeks of otorrhoea, but otolaryngologists tend to adopt a longer duration, e.g. more than 3 months of active disease[3].The disease usually occurs after upper respiratory viral infections followed by invasion of pyogenic organisms[4]. The organisms responsible for most cases of CSOM include Pseudomonas aeruginosa, Staphylococcus aureus, Klebsiella pneumonia, Escherichia coli, and anaerobes[5].There are two types of CSOM, depending on pathology, tubotympanicor safe type and the atticoantralor unsafe type. Later is often associated with life-threatening complications[6]. The complications of CSOM can be classified as extracranialor intracranial[7]. Extracranial complications include mastoid abscess, petrositis, labyrinthitis, and fascial nerve paralysis.Intracranial complications comprise intracranial abscesses including extradural, subdural, and brain abscess; lateral sinus thrombophlebitis, meningitis and otitic hydrocephalus[8]. Chronic suppurative otitis media is the most common cause of hearing impairment in the developing world, although it is infrequently seen in the developed world[9]. According to the 2004 WHO report, the prevalence of CSOM ranges from less than 1% in developed countries to as high as 30% to 46% among certain developing countries. This burden falls disproportionately on children in developing countries[10]. Majority of the patients with chronic ear disease come from poor communities living in subsistence agricultural or slum areas of the cities[11]. The main reason behind mortality and disability due to CSOM is the lack of awareness among patients about the disease and its possible complications. People consider ear discharge as merely a nuisance rather than a potentially dangerous condition and thus do not seek help till they reach critical stages. Scarcity of qualified ENT practitioners forces patients to take medical advice from local unqualified persons or sometimes they resort to self-medication which makes them vulnerable to develop complications. Ignorance and lack of awareness is so grave that many patients present to the clinics with severe intracranial complications. Hence there is a need to study the level of awareness among OPD patients about CSOM and its complications. This could help in planning interventional measures.

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MATERIALS AND METHODS:

This cross-sectional study was carried out in the

Combined Military Hospital Rawalpindi, Cantonment General Hospital Rawalpindi, Pakistan Institute of Medical Sciences (PIMS) Islamabad for a period of 6 months from April to September 2014.Permission was taken from hospital authorities and an informed consent was obtained from the patients.A total of 125 Patients diagnosed as CSOM in outpatient department were included in this study by utilizing convenient sampling technique. A close ended questionnaire was used to collect the information regarding the disease and its complications.Patients not able to give correct information due to any reason were excluded from the study.Data was analyzed by SPSS-18. Chi-square was applied between the variables and p value of less than 0.05 was considered significant.

RESULTS:

Most of our patients (48.8%) were 15 to 30 years of age (Figure 1a).The male to female ratio was 3:2. Majority of the patients i.e. 61.6% had a monthly income below 15,000 rupees. Education status of the patients (Figure 1b) and duration of the disease of the study group is shown (Figure 2).Only 49.6 % patients knew that they had a perforation in their ear drum and 30.4% understood perforation in the ear drum as the cause of continued discharge from the ear.Ear cleaning practice of the patients is shown (Table 1). When enquired about previous treatment, 51.2% patients said they had consulted qualifieddoctors or ENT specialists.Treatment seeking pattern of patientsis shown (Figure 3).Only 33.6% patients had knowledge about entry of water in the ear as a cause of recurrence of discharge.Practice of preventing water entry in the earis mentioned (Table 2).When asked about the type of disease, 71.2% patients did not know they had either the safe or the unsafe type of disease and only 38.4% patients recognized foul smelling discharge and bleeding from ear as indicators of unsafe disease. When knowledge of complications of the disease was questioned, 48.8% patients said that this disease could cause serious complications. Among the complications, 58.4% knew that it can cause permanent hearing loss, 19.2% said infection could spread to brain, 11.2% said it could cause facial paralysis, 8 % knew that it can result in accumulation of pus in mastoid area. Only 0.8% knew it could cause giddiness and vertigo and 0.8% said that diplopia or squintcould be caused by the disease. Those who said that their disease could be cured by surgery were 27.2% and 26.4% thought early surgery is necessary. Table-3 tells about the source of most of the information about the disease among patients.

DISCUSSION:

Most of the patients of CSOM have very little awareness about their disease, despite the disease being highly prevalent in our community and contributing to a great portion of the Otolaryngology practice nationwide. The CSOM patients constitute an average of 25.3% (13.1) of ENT patient load, with an average of 31 (15.3) % having significant hearing loss[12].

Figure: 1a
Age distribution of patients

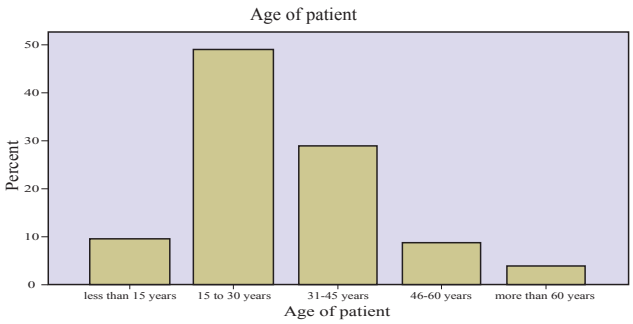

Figure: 1b
Education status of study group

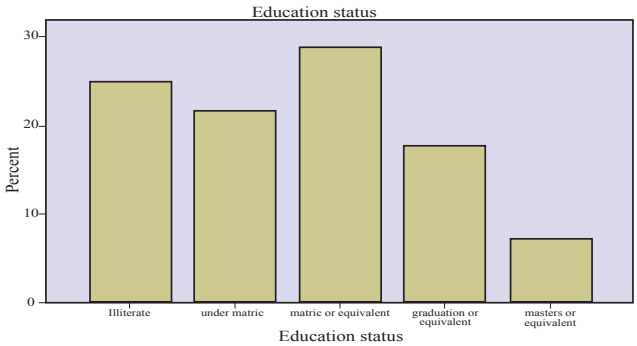

Figure:2
Duration of disease in patients

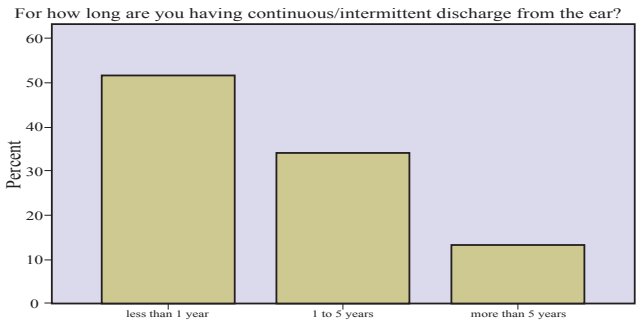

Figure: 3
Treatment seeking pattern of patients

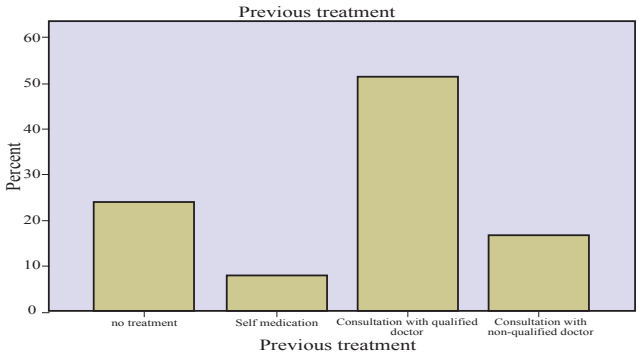

Table:1
Ear cleaning practice of patients

Practice	Frequency	Percent (%)
With match stick	14	11.2
With tissue paper	19	15.2
With cotton bud	90	72.0
With water	2	1.6
Total	125	100.0

Table: 2
Practice of preventing water entry in the ear

	Frequency	Percent (%)
None	61	48.8
Cotton soaked in oil	21	16.8
Cotton with vaseline	30	24.0
Ear plugs	13	10.4
Total	125	100.0

Table: 3
Source of information for the patients

Source	Frequency	Percent (%)
Treating doctors	91	72.8
Internet/literature	4	3.2
General public	29	23.2
Total	124	99.2

The 125 patients included in our study had very limited knowledge about the underlying cause of their symptoms, the cause of recurrence of the symptoms, preventive measures against recurrence of the symptoms and the complications that can occur if the disease is left untreated.Majority of our patients (75.2%) were either illiterate or educated only up to the level of matriculation. Lack of education shows out to be a major factor associated with low awareness about such a common disease. Most of our patients were from low socio-economic status group (61.6%). Poor living conditions, poor access to medical care, inadequate medical treatment, bad status of hygiene and recurrent upper respiratory tract infections can be considered as predisposing factors in this group of population. Our findings are quite similar to the findings of a previous similar study, conducted to assess the level of awareness about complications of chronic suppurative otitis media (CSOM) in CSOM patients, by Chandrashekharayya in a tertiary care teaching hospital of Bagalkot, India[13]. In this study too, the majority (77.6%) of the patients belonged to low socio-economic status group. The results obtained about knowledge of association between perforation in ear drum and the discharge from ear, entry of water in ear as a cause of recurrence of discharge, differentiation into safe and unsafe type of disease, possibility of serious complications, surgery as a cure for the disease and the need for early surgery were more or less comparable to those of our study and indicated little awareness in patients. However the study differed from ours in some aspects. Majority of patients in this study were from 3rd and 4th decade of life whereas in our study majority were between 15 to 30 years of age. Unlike our study, a very small percentage (16.4%) of the patients had ever consulted an MBBS or ENT doctor. This finding, and that the majority of patients (52.23%)were using match sticks to clean their discharging ears unlike cotton buds mostly being used in our study group, show a worse picture of awareness in their study group than in ours .

Another study conducted by Neogi revealed that 31.2% patients were from 0-10 years of age group and were males (58.8%). Majority of them (96%) lived in slums, 76.8% practiced unhygienic ear pricking, 36.8% poured oil in their ears, 70.8% bathed in ponds/rivers, 52.8% had ear discharge for more than 1 year. 17.2% knew that CSOM was contagious, 24% thought CSOM ran in family, 20% knew CSOM is preventable[14]. Complications of CSOM are common among untreated cases and include meningitis, brain abscess, lateral sinus thrombosis mastoid fistula and facial nerve paralysis. These complications have significant morbidity[15,16,17]. Only 30.4% patients understood perforation in the ear drum as the cause of continued discharge from ear.These figures include the patients who had the disease for more than 5 years and many of them had been consulting doctors before but were never properly educated. Only 33.6% patients had knowledge about entry of water in the ear as a cause of recurrence of discharge and yet 48.8% were not taking any measures to prevent water to enter the ear while taking a shower despite many of them being taking consultation from general practitioners and ENT specialists before. So it would not be wrong to blame the treating doctors for improper counseling of their patients[18]. Most of the patients (71.2%) did not know or were never told whether they had the safe or the unsafe type of disease and only 38.4% patients recognized foul smelling discharge and bleeding from ear as indicators of unsafe disease. This lack of knowledge about how to recognize the disease being dangerous may be the cause of failure of many patients to consult a doctor at the right time before occurrence of serious complications[19,20].

Knowledge about the potential complications of CSOM among the patients was very poor. Less than half i.e. 48.8% patients said that this disease could cause serious complications. Many of the patients, due to lack of education, could not think of a disease causing symptoms in the ear to cause problems elsewhere like in the eyes, the face or the brain [21,22,23]. This is why many patients as well as their families neglect the disease and often present to the doctors too late sometimes with life threatening intracranial complications. Only 27.2% patients thought that their disease could be cured by surgery and only 26.4%, because most patients being unaware of the possibility of the disease to progress to serious complications, thought early surgery is necessary [24,25,26].

The limitations in our study were that it only included patients of tertiary care hospitals and that too only of Rawalpindi and Islamabad which are among the most advanced cities of Pakistan with better literacy rate and health care facilities. The level of awareness among patients in smaller cities and rural areas is expected to be much lower than that shown by our study. We suggest such areas to be included in future studies so that the results can be applied to the whole country. Besides this,

since our study group was small, we recommend for large scale studies on this topic which would be helpful in planning interventions for health education.

CONCLUSION:

Awareness among patients of CSOM about their disease and its complications is very low despite living in the age dominated by media and technological revolutions like mobiles and internet.This is leading to ignorance of the disease making it potentially life threatening and demanding serious interventions regarding health education.Wide implementation of mass educational programs aimed at imparting the knowledge about the nature of the disease and the complications caused by it can drastically lower the disease burden. A large number of people can be targeted through media campaigns to spread the basic knowledge about the disease and the preventive measures that can be adopted to avoid complications.

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ORIGINAL ARTICLE

Immediate Post-Placental Insertion versus Interval Insertion of Intrauterine Devices for Contraception

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ABSTRACT:

Objective: To compare the frequency of uterine perforation, expulsion and pelvic infection rate of multiload 375 in women of immediate post-placental (IPP) insertion versus interval insertion (I).

Materials and Methods: This Quasi-experimental study was carried out in the Department of Obstetrics & Gynecology, PNS SHIFA Hospital Karachi from 6th October 2008 to 5th October 2009. Fifty patients were selected by consecutive sampling technique for Group A (immediate post-placental insertion of multiload 375). Fifty women for group B (interval insertion of multiload 375) were selected by simple random sampling during their postnatal follow-up visit. Post- insertion follow up visit was done within six weeks. The results were analyzed by SPSS version 12 and expressed in frequencies and percentages. Pearson's Chi-square test was used as the test of significance.

Results: Mean age of women in group A was 29.02 ± 2.97 and in group B it was 31.24 ± 5.59 years. Multiparous women opted for IUD in both groups (48% in group A versus 44% in group B). IUD expulsion was 14% & 18% in group A & B respectively. While infection rate was 4% in group A and 2% in group B. Statistically non significant (P>0.05) results were found. No case of uterine perforation was noted in both the groups.

Conclusion: Although both methods have almost same complication rate but for non compliant women IPP insertion of an IUD is a convenient selection for contraception.

Keywords: Intrauterine device (IUD), Immediate post-placental insertion (IPP), Interval insertion (I), IUD expulsion, Uterine perforation, Pelvic infection

INTRODUCTION:

The role of family planning in preventing maternal deaths and improving the quality of women's lives is one of the strategies of the safe motherhood initiative. Post-partum period is one of the critical times when both woman and newborn need a special and integrated package of health services as morbidity and mortality rates are quite high during this period and also the women are vulnerable to unintended pregnancy. Intrauterine contraceptive device (IUD) is a convenient, effective reversible contraceptive and relatively safe method with failure rates only slightly higher than those for oral contraceptives. Approximately 85 million women are using it all over the world. In Pakistan, especially in rural areas, it is acceptable to most of the couples due to its safety, cost effectiveness and convenience of use.[1]

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Pakistan has annual growth rate of 2.8% and family planning services reach just a quarter of people. According to reproductive health and family planning survey, 40% of Pakistani women use contraceptives and IUD is used by 3.5% of women after pills and Injectables.[2,3] Intrauterine devices have been used for more than three decades as an effective method of reversible contraception. Newly introduced copper IUD's have pregnancy rate of 0.8% along with lower expulsion and perforation risk.[4]

In many family planning centers interval insertion of IUD is practiced after 6 weeks of delivery but lack of client information about IUD's, unskilled health care workers and poor sterilization techniques during its insertion have made it less successful method of contraception.[5]

Immediate post-placental insertion of intrauterine device is a method of early post-partum contraception. Insertion of an intrauterine device immediately after delivery is appealing for several reasons. The woman is known not to be pregnant and her motivation for contraception may be high. In contrast, women waiting for IUD may experience an unintended pregnancy or never return for the insertion.[6]

The concept of immediate post-placental insertion of IUD was introduced in Pakistan in 70's and few trials were conducted but were discontinued due to high expulsion rate. Recently it is not practiced for early post-partum contraception in population welfare programs. This technique is being widely used in Mexico and China and latest studies revealed that use of newly copper bearing IUD's i.emultiload 375, insertion within 10 minutes of delivery of placenta and by especially trained health personnel produced expected results.[7]

In this study future contraception was discussed with the couples as part of antenatal care and they were informed about immediate post-placental multiload 375

insertion as an option for contraception. Study was conducted by especially trained doctors to overcome the problem of expulsion which was cause of its failure in previous trials. The study compared the frequency of uterine perforation, expulsion and pelvic infection rate of multiload 375 in group A (inserted within 10 minutes of delivery of placenta) with group B (inserted 6 weeks after delivery).

MATERIALS AND METHODS:

This Quasi-experimental study was carried out in the Department of Obstetrics & Gynecology, PNS SHIFA Hospital Karachi from 6th October 2008 to 5th October 2009. One hundred women were included in the study. Fifty women were selected by consecutive sampling technique for Group A (immediate post-placental insertion of multiload 375) with inclusion criteria of women delivering vaginally or by caesarian section, counseled for IUD insertion in pre- natal period or in labor and willing to participate in the study. Women having anemia (hemoglobin <10 g/dl), PPH, pre-labor rupture of membranes >18 hours, obstructed labor or distorted uterine cavity were excluded.

For group B (interval insertion of multiload 375), fifty women were selected by simple random sampling during their postnatal follow-up visit in the outpatient Department. Women who were delivered vaginally were included in the study and willing for spacing by IUD insertion. Those who had distorted uterine cavity, pelvic infection or abnormal vaginal bleeding during puerperium were excluded.

In group A the multiload IUD was placed within 10 minutes of delivery of placentain the uterine cavity (fundus) of women delivered vaginally. In case of caesarean section, IUD was placed through the lower segment incision and uterine incision was then closed routinely. In group B IUD was placed as an outdoor procedure 6 weeks after delivery. Post insertion follow up was done within six weeks for history of expulsion of IUD, abnormal vaginal bleeding or discharge and lower abdominal pain. Abdominal & pelvic examination was performed. Ultrasound was done for suspected misplaced IUD.

The results were recorded in proforma and analyzed using software SPSS version 12. Results of variables were expressed in frequencies and percentages. Pearson's Chi-square test was used as the test of significance. P value less than 0.05 was taken as significant.

RESULTS:

Mean age of women in group A was 29.02 ± 2.97 and in group B it was 31.24 ± 5.59 years. Women having 2-5 children opted for multiload IUD for contraception, 48% in group A and 44% in group B (Table 1). Comparison of uterine perforation, expulsion and pelvic infection rate in both the groups is mentioned (Table 2). IUD expulsion was 14% in group A and 18% in group B. However infection rate was 4% and 2% in group A and B respectively. No uterine perforation was noted in both the groups.

Table: 1
Parity distribution in both groups

Parity	Group A (n=50)		Group B (n=50)	
	Frequency	Percentge(%)	Frequency	Percentage (%)
P1	17	34.0	16	32.0
P2-5	24	48.0	22	44.0
P>5	9	18.0	12	24.0

Table: 2
Comparison of post-insertion complications at follow-up (n=100)

Post-insertion complications	Group A (n=50)		Group B (n=50)		Total (n=100)		Chi Square test	P- value
	No.	%	No.	%	No.	%		
IUD expulsion	7	14.0	9	18.0	16	32.0	0.298	0.585
Uterine perforation	-	-	-	-	-	-	-	-
Pelvic infection	2	4.0	1	2.0	3	6.0	0.344	0.558

DISCUSSION:

Current contraceptive prevalence rate in Pakistani married women from 15-49 years of age is 27% in 2008.Immediate post-placental insertion of IUD has been recommended by the WHO, as one of the safe and effective methods of temporary contraception.It is increasingly included in many postpartum family planning programs.[8]For the women, the only opportunity to receive information about contraceptives is during childbirth when they are in contact with medical personals. Hence, it is suggested that family planning should be integrated with maternal and child-care services in order to effectively promote the use of contraceptive devices in these women who otherwise would not seek the use of such a device.[9]

Regarding the complications of IUD, the present study showed expulsion rates in both groups (Group A- 14%, Group B- 18%) which are similar to other studies.[10,11] However in comparison a study showed higher expulsion rate in the IPP group compared to delayed insertion of IUD.[12]While another study showed contrast results.[13] Two studies conducted in India revealed lower expulsion rateof 10.8% and 3.6% in the immediate post-placental insertion of IUD as compared to present study.[14,15]The expulsion rate for different IUCD's are different, we used Multiload that had lower expulsion rate as shown in a study.[16]However the benefits of providing highly effective contraception immediately after delivery outweigh the disadvantage of expulsion, particularly in country like Pakistan where women have limited access to medical care.

Insertion complications of perforation and infection are not increased by IUD placement at any time during the post-partum period. In this study no case of uterine perforation was noted in both the groups and no statistically significant difference was found for pelvic infection in both the groups similar to a study conducted in Turkey in 2006 that also reported no statistically significant difference for uterine perforation and infection (p>.001) in immediate versus interval insertion of IUD.[17]Our results are supported by another study. [18] While pelvic infection was seen in 4% and 2% of women in group A and B respectively in contrast to a study by

shukla.[14]Another study showed similar rate of infection with immediate insertion and interval insertion.[19]Similar results were observed in a study regarding complications of menstrual complaints, excessive vaginal discharge and persistent pelvic pain.[20]Malpositioning of IUCD is associated with expulsions, menstrual irregularities and pain in a study, so ultrasonographic assessment of the placement of IUCD should be done immediately after insertion.[21]However in contrast to present study another study did not find any instance of infection due to post-partum IUD insertion.[22]

Our study proves that there is no significant complication rate in both groups, so women should be counseled for use of IUD immediately after delivery. Advantages of immediate post-partum insertion include high motivation, assurance that the woman is not pregnant, and convenience. The popularity of immediate post-partum IUD insertion in countries as diverse as China, Mexico, and Egypt supports the feasibility of this approach.[13] Similarly another study of Pakistan stated that there were no serious complications associated with immediate postpartum IUCD insertion considering it safe and effective method.[23]

There are reports of high incidence of infections in developing countries which may affect the risk of pelvic infection. Aseptic techniques and use of prophylactic antibiotics may be considered to reduce the incidence of postpartum sepsis in developing countries as compared to developed countries. A study conducted on postpartum insertion of IUCD at caesarean section supported the view that women, who are desirous of, and suitable for using this method, should be given the option of IUCD insertion at the same time. [24]

This was the first study in this hospital so limitations were lack of skilled operator and poor patient compliance for follow up. As in this study we collected the data of follow-up whenever they visited within six weeks because of non- compliance for follow-up at one, four & six weeks. With the high level of acceptance despite low level of awareness, the government needs to develop strategies to increase public awareness of postpartum insertion through different media sources. It is important to arrange training on post partum insertion of IUCD in order to increase knowledge and skills among healthcare providers.[25]Special kit for the same should be provided to the health centers where deliveries are conducted.Early follow up may be important in identifying spontaneous IUD expulsions.

CONCLUSION:

Although both methods have almost same complication rate but for non compliant women immediate post-placental insertion of an intrauterine contraceptive device is a convenient selection for effective contraception during puerperium as resumption of ovulation is unpredictable after delivery.

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ORIGINAL ARTICLE

Diagnostic Utility of Ultrasound in Acute Appendicitis in Correlation with Total Leukocyte Count

Muhammad Adeel Azhar[1], AtifLatif[2],Mashkoor Ahmad[3], Faisal Mahmood[4]

ABSTRACT:
Objective: To evaluate the diagnostic utility of ultrasound (US) in the diagnosis of acute appendicitis in correlation with total leukocyte count (TLC).
Materials and Methods: This cross sectional comparative study was conducted at the Radiology and Pathology Departments of CMH Lahore from 1st February 2007 to 31st January 2008. A total of 125 suspectedpatientsof appendicitis were included in the study through non-probability purposive sampling. They all underwent US evaluation and laboratory assessment (TLC). Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of US findings and TLC were calculated keeping surgical findings and histopathology of the removed appendix as gold standard whenever appendecectomy was carried out.
Results: Among 62 patients finally proven to be suffering from acute appendicitis US correctly diagnosed the same in 55 (89%), whereas a normal appendix was visualized in 30 (48%) out of the remaining 63 non – appendicitis patients. The most accurate appendiceal finding for appendicitis was adiameter of 6 mm or larger, with a sensitivity of 96%, specificity of 97%,NPV of 98%, and PPV of 98%.The lack of visualization of the appendixwith US had a NPV of 82%. An increase in TLC had a PPV of 66%, whereas normal TLC had a NPV of 73% whereas those of US were 96% and 90% respectively. By utilizing US as an adjunct to clinical evaluation, negative appendectomy rate was lessened to 3.2%.
Conclusion: US have better diagnostic utility than TLC in the diagnosis of acute appendicitis.
Keywords: Ultrasonography, Appendix. Appendicitis, Appendicectomy.

INTRODUCTION:

Acute appendicitis is a common clinical problem, which needs early surgical decision[1,2]. More than 250,000 appendicectomies are being carried out in the UnitedStates each year [3]. Possibility of suffering from appendicitis in the lifetime is approximately 12 percent in men and 25 percent in women [4]. The diagnosis of acute appendicitis traditionally has been based on clinical features found primarily in the patient's history and physical examination. However, this diagnosis not infrequently becomes difficult and results in unnecessary appendicectomies[5],delays in treatment or needless hospital admissions for observation. Removal rate of a normal appendix (negative appendectomy) up to 20% has been widely reported [6,7,8,9]. To improve the diagnostic accuracy and to curb down negative appendicectomies, the importance oflaboratory findings(both white blood cell counts and C-reactive protein values)[10] and the use of US have been widely evaluated.

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The purpose of this study was to evaluate the sensitivity, specificity, PPV, and NPV of the US (in general and its different acute appendicitis – specific findings) and that of TLC in the final diagnosis of appendicitis.

MATERIALS AND METHODS:

This cross sectional comparative study was carried out in the Radiology and Pathology Departments of CMH Lahore from 1st February 2007 to 31st January 2008.125 cases of clinically suspected acute appendicitis were included in the study through Non-probability purposive sampling**.** Inclusion criteria was:
(1)Patient`s referred by surgeons, with strong clinical suspicion of acute appendicitis (2)any gender (3)any age.Exclusion criteria was(1) patients in whom ultrasound could not be performed (e.g., very obese patients, tense ascites, severe pain)(2)patients with clinical signs of appendicular lump / abscess requiring conservative management or drainage(3)patients with already known abdominal disease(4)history of appendectomy(5)history of any leukocyte disorder.
DATA COLLECTION PROCEDURE: After initial clinical evaluation by the surgeons, patients fulfilling inclusion and exclusion criteria were referred to the radiology department for US. In each patient, the abdomen was initially examined by using a 3.5 / 5.0 MHzconvex-array transducer. Sonographic evaluation of appendix was done by a 7.5 MHz linear-array transducer with graded-compression technique in transverse as well as longitudinal planes. Using psoas major muscle, iliac vessels and cecum as landmarks, visualized appendix was identified as a blind-ended, a-peristaltic tubular structure. Color Doppler US to detect blood flow in appendiceal wall was performed at the end of the grey-scaleultrasound by using a low-velocity scale (pulse repetitionfrequency, 1,500 Hz) and a low wall filter (100 Hz) to detect slow blood flow.US criteria for diagnosing acute appendicitis were grouped into two categories.

(a)Appendiceal findings: These findings were noted for their presence or absence in both normal as well as inflamed appendices.

i. Outer diameter: Appendix was considered inflamed when its outer antero-posterior diameter under compression, measured in transverse plane, was 6 mm or greater.
ii. Lack of compressibility
iii. Fluid in the appendix
iv. Appendicolith
v. Blood flow in appendiceal wall on colour Doppler

(b)Peri-appendiceal findings: These were noted in all patients irrespective of visualization of appendix.

i. Hyperechoic peri-enteric fat in RLQ
ii. Lymph node in RLQ measuring at least 5 mm
iii. Cecal wall thickness of 5 mm or more
iv. Peritoneal fluid

In general, US was considered positive when at least two or more criteria for acute appendicitis were met and negative if a normal looking appendix was visualized or if it was not visualized and / or a definite non-appendicular pathology was noted. The laboratory investigation included total leukocyte count, which was given importance for appendicitis when greater than 10 x 10^9/L. The final decision to operate upon was made by the attending surgeon who was in picture of laboratory as well as US findings. Removed appendices were sent to Pathology Department of CMH Lahore for histopathology. US and TLC findings were compared with those of preoperative surgical findings and histopathology of the removed appendix, the later being the gold standards of diagnosis of acute appendicitis in this study.Patients with negative US findings and those who did not undergo surgery at first place were followed up in respect of clinical and surgical outcomes.Sensitivity, specificity, PPV, NPV and diagnostic accuracy of TLC, US and individual US findings were calculated keeping surgical findings and histopathology of the removed appendices as gold standard.

STATISTICAL ANALYSIS: The McNemar's chi-square test for paired data was applied to analyze the differences between the diagnostic values of US and TLC in the diagnosis of acute appendicitis. Differences were considered statically significant if P values were < 0.05.

RESULTS:

Out of 125patients 73 (58%) were males and 52 (42%) females. Gender wise distribution in 10-year age brackets(Figure1).

US diagnosis of acute appendicitis was made in 57 patients who underwent surgery. Histopathology of the resected appendices showed signs of acute appendicitis in 55, whereas 2 appendices turned out normal, thus making 2 FP US results.

In 68 US negative patients a normal appendix was observed in 30 patients (44% of US negative patients) and in the remaining 38 (56%); it was not seen sonographically. Seven patients, among these 38 US negative patients, persisted to have clinical signs and symptoms of acute appendicitis. Surgical intervention was carried out within 24 h of US examination. These patients had inflamed appendices on surgery and histopathology (thus giving the non-visualizationof the appendix at US a NPV of 82%).These were the FN results of US. Two out of these seven patients had perfoated appendicitis and the other five had Pretrocecal appendices.

In the 63 patients without acute appendicitis, diagnosis was confirmed on US in 30 patients, on surgery in 6 patients (including 2 US false positive cases), at endoscopy in one patient and at clinical follow up in 26 patients. Table1 lists the final diagnoses in these 63 patients.

The number of positive or negative US examinations in respect of acute appendicitis, its TP, TN, FPand FN results and diagnostic accuracy are shown in Table 2.Appendiceal US findings were evaluated in 87 patients. Table3a shows (a) the frequency with which each appendiceal finding was interpreted as positive or negative, (b) the number of TP, TN, FP, and FN results, and (c) the sensitivity, specificity, accuracy, PPV, NPV and diagnostic accuracy of each appendiceal finding. The two most consistentappendiceal findings for appendicitis were a diameter of at least 6 mm or larger and incompressibility. In the non-appendicitis group, the appendiceal diameter was 6 mm or larger in one patient only who had a final diagnosis of pyelonephritis. The periappendiceal US findings were looked for in the entire study group(Table3b). Combining the non-appendiceal findingswith appendiceal findings did not increase the NPV or PPV ofindividualappendiceal findings, such as an appendix 6 mm orlarger in diameter or non-compressibility of the appendix.

The number of TP, TN, FP and FN results and the sensitivity, specificity,accuracy, PPV, NPV and diagnostic accuracy of TLC are shown in Table4. A TLC level above 10 x 10^9/L had a sensitivity of 77% and a specificity of 60% for acute appendicitis in appropriate clinical settings.

US showed more diagnostic utility in comparison to TLC in the diagnosis of acute appendicitis. There was a significant difference between the specificity (97% vs 60%; p value: 0.000), PPV (96% vs 66%; p value: 0.016), NPV (90% vs 73%; p value: 0.016) and diagnostic accuracy (93% vs 69%; p value: 0.009) of US and TLC respectively. However, difference between the sensitivity of both was not much significant (89% vs 77%; p value: 0.189).

Figure: 1
Age and gender distribution of patients with suspected acute appendicitis

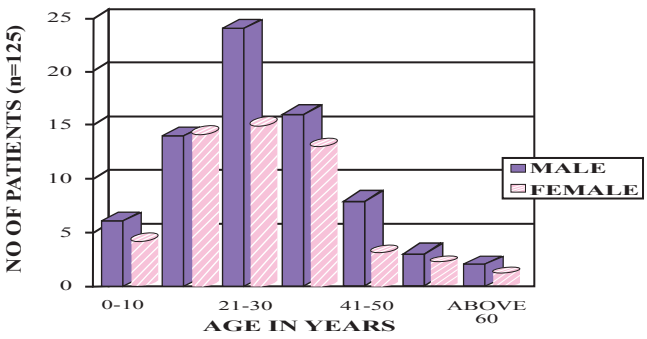

Table:1
Final diagnosis in patients without acute appendicitis

Diagnosis	No of Patients (N= 63)
Non specific abdominal pain	24
Mesenteric adenitis	13
Gynecologic disease	10
Renal and ureteral calculi	8
Ileocolic TB	2
Gastroenteritis	2
Cystitis / UTI	2
Pyelonephritis	1
Duodenal ulcer	1

Table: 2
US results for acute appendicitis

Findings and values	US
Finding at US (n)	
Positive	57
negative	68
Final diagnosis finding (n)	
TP	55
TN	61
FP	2
FN	7
Value (%)	
Sensitivity	89
Specificity	97
PPV	96
NPV	90
Accuracy	93

n = number of patients. Total n = 125
Positive finding mean identification of an inflamed appendix on US. Negative finding means visualization of a normal appendix ornon-visualization of appendix on US

Table: 3a
Appendiceal US signs of acute appendicitis

Finding and value	Diameter > 6 mm	Lack of compress-ibility	Intra-luminal fluid	Appendi-colith	Flow in wall
Finding at US (n)					
Positive	55	55	20	25	28
Negative	32	32	67	62	59
Final diagnosis finding (n)					
TP	54	53	16	15	25
TN	30	29	37	33	30
FP	1	2	4	10	3
FN	2	3	30	29	29
Value(%)					
Sensitivity	96	95	35	34	46
Specificity	97	94	90	77	91
PPV	98	96	80	60	89
NPV	94	90	55	53	51
Accuracy	97	94	61	55	63

n = number of patients. Total n = 87 (in whom appendix was visualized irrespective of its disease status)

Table:3b
Periappendiceal US signs of acute appendicitis

Finding and value	Inflamm-atory fat changes	Cecal wall thickening	Periileal lymph node	Peritoneal fluid
Finding at US (n)				
Positive	65	26	48	55
negative	60	99	77	70
Final diagnosis finding (n)				
TP	50	11	19	31
TN	54	56	40	45
FP	15	15	29	24
FN	6	43	37	25
Value (%)				
Sensitivity	89	20	34	55
Specificity	78	79	52	65
PPV	77	42	40	56
NPV	90	56	52	64
Accuracy	83	54	47	61

n = number of patients. Total n = 125 patients

Table:4
TLC in acute appendicitis

Findings and values	TLC
Finding (n)	
Positive	73
Negative	52
Final diagnosis finding (n)	
TP	48
TN	38
FP	25
FN	14
Value(%)	
Sensitivity	77
Specificity	60
PPV	66
NPV	73
Accuracy	69

n = number of patients. Total n = 125

DISCUSSION:

In our study of 125 patients, US diagnosis of acute appendicitis was made in 57 patients based upon at least 2 of the US criteria of acute appendicitis. Out of these 57 patients, two patients turned out to be having normal appendices on surgery and histopathology. One of these patients was a female in whom a hydrosalpinx was mistaken as a non-compressible pelvic appendix. The other patient had the final diagnosis of non-specific

abdominal pain. Thus the negative appendectomy rate was 3.2%, which is much less as compared to that when diagnosis was made solely on clinical evaluation (10-30% and as high as 47% in women of childbearing age)[6,7,8,9,11,12]. False negative cases were seven. Two out of these seven patients had perforated appendicitis. Perforation of the appendix leads to luminal decompression and reduction in its diameter so that appendix is no longer seen on US.[13,14,15] A non-compressible appendix may be identified in only 38%–55% of patients with perforation.[16] Majority of patients with false negative US results in our study were due to the retrocecal position of the appendix, making it invisible due to overlying cecal gas shadows. False negative US diagnosis of appendicitis owing to its retrocecal position is a commonly reported pitfall in literature [14, 17].

According to our study, identification of an appendix with less than 6 mm diameter was an accurate indication to exclude appendicitis, with a NPV of 94%. Similarly Rettenbacher et al [18]mentioned a NPV of 100%, whereas Rioux[19]reported a NPV of 98%. The appendicular diameter of 6 mm or above for diagnosis of acute appendicitis had high PPV (98%) in our study. The high PPV is out of line with the data obtained by Rettenbacher et al [18], who reported an appendiceal diameter of 6 mm or larger in 32% of symptomatic patients without appendicitis in whom the appendix was identified. Yabunaka[20] had reported the same in 3.6%. We assume that this discrepancy is due to differences in measurement of appendiceal diameter. We thus performed measurements under maximal compression to standardize the measurement because the relevant anteroposterior diameter of a compressible appendix may vary according to the graded compression applied to the abdominal wall, and we hypothesize that we may have compressed some loose feces or air out of the normal patent lumen. However, as mentioned we do have a false positive result based on this criterion. It necessitates the need for addition of at least another US criterion for diagnosing acute appendicitis. In this context, lack of compressibility of appendix was another finding with high PPV (96%) and NPV (90%).

Another finding in our study was Doppler detectable hyperemia in the appendiceal wall was a specific finding for appendicitis that was observed in only three of the patients not having acute appendicitis. Similar high specificity has been reported in already published studies that seldom identified flow in the normal appendiceal wall[21].

Among right lower abdominal quadrant changes, echogenic fat has been observed to be 100% sensitive but not specific to appendicitis at CT[22]. Echogenic fat depicting inflammation in the right lower quadrant may be present in number of differential diagnoses other than appendicitis [23], and we found inflamed fat in 24% of the patients without appendicitis. We did not observe inflamed echogenic periappendicealfat in every patient with appendicitis, which is contrary to known data from CT studies. Right iliac fossa lymphadenopathywas present in 31% of appendicitis positive patients of our study. It is a common finding related to ileal, cecal, or appendiceal inflammatory diseases which may be seen in patients with appendicitis or and also otherwise. We concur with published studies [22, 24]that the much helpful method to differentiate an appendicitis adenopathy from mesenteric adenitis is to identifysonographically either an enlarged inflamed appendix or a normal looking appendix. Cecal wall changes seen on CT include focal cecal apical thickening, arrowhead and cecal bar signs which are suggestive of appendicitis;however, circumferential diffuse wall thickening may also be seen in colitis[22]. However, these observations require adequate cecal distention using the CT technique described by Rao et al [22]. Therefore, we limited our evaluation with US to the identification of cecal wall thickening but did not obtain sufficient predictive values to differentiate appendicitis from non-appendicitis.

Earlier in Pakistan Khan [25]have conducted a prospective study to determine the value of various investigations in the same patient of acute appendicitis including TLC (sensitivity 73%, specificity 80%) and US (sensitivity 86.2%, specificity 91.8%). In our study, TLC and US demonstrated a similar sensitivity of 77% and 89% but specificity of 60% vs 97% respectively for the diagnosis of acute appendicitis. Our study also established that US examinations were superior to TLC for affirming appendicitis (PPV 96% vs 66%; and diagnostic accuracy 93% vs 69%). In addition, more strikingly, US examinations were superior to TLC for excluding appendicitis (NPV 90% vs 73%). Therefore, we do not recommend using TLC as part of an algorithm to restrict imaging indications for patients with increased TLC only. On the other hand, in patients whose appendix is not visualized at US, laboratory tests could be performed to strengthen the NPV of non-visualization of the appendix. However, further studies that include more patients in whom the appendix is not identified at US are necessary to confirm the importance of TLC. Our study faced a number of limitations. First, there was no reliable way to confirm that all patients without appendicitis would have had a normal appendix at histopathologic analysis if surgery had been performed. Second, our study design was based on a prospective evaluation of several US and biologic criteria. We are aware that some additional criteria not included in our protocol may have been interesting to evaluate, especially the thickness of the appendiceal wall, the presence of air in the appendiceal lumen, and the non-compressibility of the periappendiceal fat.

CONCLUSION:

US has better diagnostic utility than TLC in the diagnosis of acute appendicitis. A threshold 6-mm diameter of the appendix under compression is the most accurate US finding with high PPV and NPV for the diagnosis of acute appendicitis. Keeping in view the increasingly high diagnostic accuracy of US for acute appendicitis and its advantages we recommend that US should be carried out more frequently in suspicious patients of acute appendicitis to avoid unnecessary surgical procedures. An US negative patient can be closely

monitored in the hospital instead of being taken straight on to the operation table.

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ORIGINAL ARTICLE

Mortality Associated with Neck Compression Deaths –An Autopsy Based Study

Syed Zubair Ahmed Tirmizi[1], Khurshid Nadir[2], Syed Sanwer Ali[3], Syed Mukarram Ali[4]

ABSTRACT:

Objective: To determine the frequency of deaths due to compression of neck autopsied in three major mortuaries of Karachi and to evaluate the association of cause of neck compression deaths with the age and gender.

Materials and Methods: This autopsy- based descriptive cross-sectional study was conducted from 1st March 2008 to 28th February 2009 in the mortuaries at Civil Hospital, Jinnah Postgraduate Medical Center and Abbasi Shaheed Hospital Karachi. The study included 90 cases of deaths due to hanging and strangulation, brought to mortuaries of public sector hospitals of Karachi. Details of findings from autopsy reports and police papers were entered in a performa under the heading of cause, causative agent, manner, age and gender.

Results: 90 out of 2090 unnatural deaths were due to hanging and strangulation. Hanging was the most frequent cause among the deaths due to neck compression. Male to female ratio was 1.7:1. Male dominated in hanging and ligature strangulation while female dominated in manual strangulation. Age group ranging from 15 to 35years was chiefly involved. 100 % suicidal and homicidal manner of death was seen in hanging and strangulation respectively. Cause of neck compression death was significantly associated with gender (P value <0.036) but not with the age (P value <0.732).

Conclusion: Hanging is the most frequent neck compression death involving males of young age group. Hanging and strangulation are still used to commit suicide and homicide respectively. Such deaths indicate frustrated and stressful condition of young population necessitating comprehensive program of counseling for healthy environment.

Keywords: Neck compression**,** Hanging, Strangulation, Manner, Suicide, Homicide.

INTRODUCTION:

Violence in the society has increased the rate of un-natural deaths and contributed a major part of medico legal autopsies. Violent asphyxial deaths make a significant part of un-natural deaths and are common in occurrence. Asphyxia is defined in simple words as interference with the process of respiration or impairment in the supply of oxygen to the inspired air. In forensic field it is restricted to those forms of oxygen lack (anoxia) resulting from mechanical interference with the process of respiration.[1] Generally in medico legal work asphyxial deaths are associated with some form of mechanical obstruction and classified into hanging, strangulation, suffocation and drowning depending upon the level of obstruction from the nose and mouth to the alveolar membrane.[2] Among the violent asphyxial deaths, those resulting from compression of neck are due to sudden pressure over the sensitive neck structures. Two most commonly encountered causes of death due to neck compression are hanging and strangulation. Hanging in the adults is mostly suicidal although it may occur accidently in children and persons practicing masochistic exercises. Homicidal hanging is difficult unless the victim is intoxicated or unconscious. Toxicological analysis of the victim of homicidal hanging is mandatory because this is not an easy way of homicide. Accused try to make the victim power less before applying noose. Hanging and drowning are generally considered suicidal manner of death while strangulation particularly manual is homicidal. Traumatic asphyxia and other asphyxial deaths resulting from suffocation are accidental.[3] Deaths due to ligature or hand induced compression of neck which include hanging and strangulation are now considered as one of the preferred method either to take away the life of self or other.[4]Hanging is a form of asphyxia resulting from the suspension of the body by a ligature compressing the neck externally, the constricting force being the weight of the body.[5] Globally hanging is considered among the most common methods of suicide, accounting for about more than 50% of all suicide in Saudi Arabia and Hungry and 31.5% of suicide in India.[6, 7] Hanging accounts for about 2000 deaths annually in England and Wales and considered the most common method of suicide.[8] Studies from Canada has also reported hanging as the second most common method of suicide following suffocation.[9] In strangulation compression of the neck is effected by

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a force other than the body's own weight, such as ligature, hands when it is known as throttling, elbow (mugging) and bamboos (bansdola). Apart from the accidental strangulation seen in cases where the law enforcers use choke hold to control criminals, in wrestling and choking games, strangulation is always considered homicidal and will be treated as such by medical examiners and police, in the absence of clear evidence to the contrary. Choking games to achieve euphoric state amongst the youth have been reported in United States of America during 1995 – 2007.[10]

The ligature mark on neck of the body is the only available vital piece of evidence in the absence of actual ligature but on many occasions it creates an element of doubt especially when one has to differentiate ligature mark of homicidal hanging from that seen in strangulation.

Violent asphyxial deaths by the use of ligature or hand to compress the sensitive and delicate structures of neck have increased and contributed significantly to unnatural deaths. Hanging has been reported as the leading cause of suicide in a study from Faisalabad and Karachi on suicidal deaths.[11-12]Present study is therefore aimed to determine, the frequency, manner and associated factors of neck compression deaths autopsied in three major mortuaries of Karachi along with age and gender vulnerability.

MATERIALS AND METHODS:

Jinnah post graduate medical center, Civil hospital and Abbasi Shaheed hospitals being the busiest and authorized public sector centers to conduct autopsies on bodies of un-natural deaths, were selected for the present descriptive cross-sectional study on 90 cases of death as a result of neck compression. A total of 2090 cases of un-natural deaths were brought for autopsy during the study period of one year from 1st March 2008 to 28th February 2009, out of which details were collected for those resulting from the fatal compression of neck. All findings from autopsy reports and police papers were recorded in a purpose built performa under the headings of cause, causative agent, manner, age and gender. Manner of death was concluded from the police papers who investigated the deaths according to the legal provision under section 174 of Criminal Procedure Code. All cases of death that resulted from fatal compression of neck, whose medico legal autopsy was performed at mortuaries of Civil Hospital, Jinnah Postgraduate Medical Center and Abbasi Shaheed Hospital Karachi, were included in the study. Medico legal deaths in Karachi in which the cause of death was other than hanging and strangulation, or the dead bodies submitted for the partial/ external examination or dead bodies handed over to the relatives without proper and complete autopsy were excluded from the study. Microsoft Excel spread sheet and SPSS version 15 were utilized to analyze the data. The frequencies and percentages were calculated for all categorical variables.

RESULTS:

Out of the total 2090 autopsies conducted during the study period, 54 cases were hanging and 36 were due to strangulation making incidence rate of hanging and strangulation 2.58 and 1.72 respectively (Table 1).

Table: 1
Incidence of violent asphyxial death and death due to hanging and strangulation

Total No. of Autopsies	Neck Compression Deaths (90)	
	Deaths due to hanging	Deaths due to strangulation
2090	54 (2.58 %)	36 (1.72 %)

Hanging (60%) is the most frequent cause among 90 cases of neck compression deaths. Out of the 90 cases of death due to neck compression 57 (63.33%) were male while 33(36.37%) were female making male to female ratio 1.7:1. Male out-numbered female in hanging and ligature strangulation while female out-numbered male in manual strangulation.(Table 2a).

Table: 2a
Frequency of deaths due to hanging and strangulation in relation to gender

S.No.	Cause Of Death	Male	Female	Total
1	Hanging	39	15	54 (60 %)
2	Ligature Strangulation	14	10	24 (26.67%)
3	Manual Strangulation	04	08	12 (13.33%)
		57 (63.33%)	33 (36.67%)	90 (100%)

The age group ranging from 15 to 35 years was most commonly involved in deaths due to hanging and strangulation. Hanging and strangulation were less common below 15 year and after 55 year (Table 2b)

Table: 2b
Frequency of deaths due to hanging and strangulation in relation to age

Age	Hanging	Strangulation	Total
< 1 year	-	-	
1 - <15 Year	02	-	02 (2.2%)
15 - <25 year	20	16	36 (40%)
25 - < 35 year	16	08	24 (26.67%)
35 - < 45 year	08	06	14 (15.56%)
45 - < 55 Year	05	03	08 (8.9%)
55 year	03	03	06 (6.67%)
Total	54 (60%)	36 (40%)	90 (100%)

All hanging cases (100 %) were suicidal while all ligature and manual strangulation cases (100 %) were homicidal. Hanging was the leading cause of deaths due to compression of neck (Table 3)

Table: 3
Frequency of asphyxial death in relation to Manner of death

S. No	Cause of Death	Manner of Death			Total
		A	H	S	
1	Hanging	-	-	54	54
2	Ligature Strangulation	-	24	-	24
3	Manual Strangulation	-	12	-	12
			36	54	90 (100%)

A=Accidental, H= Homicidal, S= Suicidal

Cause of neck compression deaths was significantly associated with gender (P value <0.036) but no such association is found with two groups of age of the victim when divided into above and below 25 year of age (P value <0.732). Hanging is significantly common in male. (Table 4)

Table: 4
Relationship of cause of neck compression deaths

Relationship of cause of neck compression deaths with gender			
	Hanging	Strangulation	P-value
Male	39	18	
Female	15	18	0.036
	54	36	
Relationship of cause of neck compression deaths with age			
	Hanging	Strangulation	P-value
≤25 years	22	16	
>25 years	32	20	0.732
	54	36	

DISCUSSION:

Our study shows 90 cases of death resulting from the compression of neck among 2090 unnatural deaths giving 4.30% incidence of neck compression deaths. The similar trend has also been reported in a study conducted at Lahore, Pakistan showing 3.05% incidence of neck compression deaths.[13]

In the present study mostly deaths (54 cases; 60%) were related to hanging followed by ligature strangulation (24 cases; 26.66%) and manual strangulation (12 cases; 13.33%). Hanging has also been reported by most of the authors as the most frequent type of violent asphyxial death.[14,15]The type of the violent asphyxial death occurring most frequently depend upon the area and environment. A report from India has shown drowning as the most frequent type of violent asphyxial death because of the bhakra canal in the near vicinity of the studied area.[16]

The male – female ratio of all deaths resulting from compression of neck in our study is 1.7:1. Patel has also reported male – female ratio 1.69:1 of total violent asphyxial deaths.[14] In the present study male to female ratio is 2.6:1 for hanging, 1.4:1 for ligature strangulation and 1:2 for manual strangulation. Studies from other parts of Pakistan have reported male to female ratio 2.25:1 and 2.7:1 for hanging, while 2.05:1 and 1.4:1 for ligature strangulation which is comparable to our present sudy.[17,18]Author from India has reported higher incidence of ligature strangulation and throttling in female compared to male.[19]Our study has also reported higher incidence of throttling in females. This is due to the fact that females are weak, offer less resistance particularly when female is a child. It is easier for the assailant to throttle when his physical size and strength exceeds that of the victim. Several studies from India[7,20,21] has shown higher number of hanging deaths in the age group ranging from 21-30 years followed by 31-40 years which is similar to our study reporting higher involvement of victims of age group ranging from 15 to less than 25 year followed by 25 to less than 35 year. This is the period of life when a person is exposed to various stresses and anxiety in adverse circumstances.

Our study has reported suicidal manner of death in all hanging cases and homicidal manner of death in all strangulation cases. It is generally considered and described in most of forensic medicine textbooks that hanging is suicidal and strangulation is homicidal in nature until the contrary is proved otherwise. Patel has demonstrated 80.41% suicidal manner of death in hanging and 100% homicidal manner of death in strangulation.[14]Retrospective study from Turkey has reported not even a single case of homicidal hanging.[15]Higher incidence of strangulation for homicidal purposes in females has been reported in a five year retrospective study of India.[22] Studies have reported that hanging is the most common violent asphyxial death which based on opinion were suicide in manner while all strangulation deaths were homicide in nature.[23,24,25]

Our study of neck compression deaths has also shown a significant association of cause of neck compression deaths with gender but not with the age when two groups of victims that is above and below 25 years were compared. Many of the studies have shown male predominance in hanging cases and female dominance in strangulation cases.[17,18,19] Most of the studies have reported that young age group ranging from 15-35 years is mainly involved in asphyxial death that is why the victims of neck compression deaths are evenly distributed around 25 year and showing no significance of age with the cause. Not a single study has shown such significance even on extensive search.

It is required that a medical examiner should perform a meticulous post mortem examination and interpret the manner of death in the light of thorough death scene investigation along with the past history of the deceased in all cases of hanging and strangulation. Doctors generally do not visit the crime scene in our set up and there by miss relevant photographs and trace evidences. We have limitation that not all unnatural deaths were reported and even the reported autopsies are avoided due to religion, political and racial influences. Family honor is also a big hurdle in performing autopsies of unnatural death.

CONCLUSION:

Hanging is the leading cause of death resulting from

the neck compression. Male of age group ranging from 15 to 35 years are the major victims of neck compression death except manual strangulation where females are the major victims. Hanging to commit suicide and strangulation as a mean of homicide continues to be the preferred manner of deaths. Such a picture indicates frustrated environment for the youngsters in our society and demands attention from those who handle and investigate these cases to rectify familial and financial disputes in order to reduce the frequency of violent asphyxial deaths.

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COMMENTARY

Health Promoting Schools: A Powerful Means of Improving Community Oral Health for Future Generations of Pakistan

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ABSTRACT:
Public health has shifted its focus towards social conditions that are responsible for achievement of oral health and prevention of oral diseases like dental caries, periodontal disease and oral cancer. The oral health burden on Pakistani population is alarming with children being the most common victim of oral dental diseases. At present knowledge and attitudes of influential professionals such as school teachers on oral health and school based preventive programs is poor. Health promoting school is a place where institutional policies, physical and social environment, relation with the community, curriculum and personal skills makes it a healthy setting for living, learning and working. School serves as a powerful setting for learning of children and healthy behaviors. Lifestyle developed within a school environment are said to be more sustainable. Dental professionals need to work in partnership with school teachers to change attitudes, beliefs and behavior along with provision of knowledge
Keywords: Oral health, Community, Health promoting schools, Future generations, Pakistan.

INTRODUCTION:

The major aspect of dental public health is concerned with principles of prevention and oral health promotion. For maintenance of oral health it is important to broadly understand the epidemiology of oral diseases and identify social, economic and environmental factors in prevention of dental caries, periodontal disease and oral cancer. The social determinants of health inequalities have been acknowledged worldwide for an individual's overall health outcomes and it is now said that the health is not only achieved by individual's own actions but wide range of social, economic and environmental factors are also responsible for it. WHO states health promotion is the process of enabling people to increase control over, and to improve their health and outlined five key action areas; building healthy public policies, creating supportive environment, strengthening community actions, develop personal skills and reorient health services.[1] Health promoting school (HPS) been defined as 'A school that constantly strengthens its capacity as a healthy setting for living, learning and working.[2] Key components of a health promoting school as outlined by Kwan [3] include:

1. Institutional Health Policies – Reinforcing healthy eating programs, availability of healthy food and assessment of nutrition status, school health team working in collaboration with healthcare professional for health education and referral.
2. Personal Health Skills – curricular activities promoting positive attitudes and healthy behavior, oral health issues incorporated in the curriculum or taught as a subject, teachers and peer educators training on health promotion and the use of health resources in partnerships with dental health centres.
3. Physical Environment – Appropriate actions to avoid accidents at school and enable environmental care such as use of mouth guards to reduce risk of oral trauma, shaded playgrounds, tobacco-free school environment safety of the school's equipment and materials.
4. Social Environment – provision of counseling and support services for students and staff to avoid stress, interpersonal conflict, peer pressure and other social forces.
5. Ties with the Community – participation of family to become part of school community and facilitate children, involvement of parents and community in planning and decision making process, community advisory committee and media promoting oral health message e.g clear food labeling, water fluoridation, restrict tobacco advertisement.

The oral health burden on Pakistani population is indicating an alarming situation with limited healthcare resources which are mainly focused on treatment rather than prevention. Majority of people belonging to low socioeconomic class with low literacy rate acts as a barrier to access care. Many of the oral diseases are first experienced during young age with caries being the most common chronic disease of children. A review article on oral health challenges in Pakistan have reported 12 year Decayed Missing Filled Teeth (DMFT) to be 1.38 which is not too dramatic but the majority of lesions remain untreated with filled teeth ratio of 0.08 that shows the treatment available is too low.[4] Less than 28% of 12 year old children have healthy gingiva making periodontal disease most common oral disease in Pakistan.[5] Oral cancer is the second most common form of cancer among men and women and comprises about 10% of all malignant cancers and the use of areca nut is found in 74% of primary school children. Environmental influences play a major role in molding practices as majority of the children commence the habits from their family[6]. Poor oral hygiene is also a major public health problem. Approximately 8% of population never cleans their teeth while 36% clean

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their teeth every day.[4]The school serves a powerful forum for promoting oral health as it provides access to a large number of children in most influential stages of child's life and through them, the school staff, families and community as a whole. There is a definite need for promoting oral health in schools in our community. In Pakistan school-based Oral Health Education (OHE) has so far been undertaken mainly in urban schools as a sporadic activity.[7] Government school system in our society does not place health upon their priority. Most private schools may have health policies but are deficient in specific dental health policies and few would fulfill all the dimensions of a health promoting school. There is no sufficient data available on level of implementation of health promoting activities. These problems combined with socioeconomic and environmental factors such as poverty, gender inequalities with girls having limited access to education, poor infrastructure of schools and surroundings making the health goals difficult to achieve. The dentists, though sufficient in number, cannot be held responsible for OHE to school children because of their uneven distribution and secondly OHE work in general is not considered to be very rewarding by dentists.[8] Health promotion involves interventions at different levels encompassing actions from different organizations with health professionals playing a central role. People demonstrate a wide variety of attitude towards oral health influenced by their own experience, cultural perceptions, familial beliefs and other life situations which strongly relates to their overall health behaviors.[9,10,11,12]Therefore dental professionals need to work in partnership with a range of other influential organizations such as government policy makers, school authority and educators in this situation and apply a holistic approach to change attitudes, beliefs and behavior along with provision of knowledge.

Knowledge and attitudes of other influential professionals such as school teachers on oral health and school based preventive programs can also be disappointingly poor.[13,]A study conducted in Pakistanon knowledge, attitude and practice of public school teachers reported that they had poor knowledge regarding dental decay and its etiology. The majority of teachers had poor awareness concerning gum diseases which they pointed out could be due to failure of dissemination of knowledge related to oral health issues in our teacher population. Their attitude towards regular dental visit was also not satisfactory and they were found negligent towards importance of routine dental visits hence, their capability to disseminate oral health education to students in schools needs consideration[14].

Hence, health promotion program aimed at school children are of great importance in combating overall oral disease burden in our community. Also, healthy behaviors and lifestyle developed within a school environment are said to be more sustainable and cost-effective. This underlines the need for a comprehensive plan of implementing HPS which is acceptable to the customs of society. Adequate support from health authorities should be provided with respect to manpower, cost and material so that it does not impose extra burden on the schools and result in a sustainable change. Also, there is a need for greater public health efforts directed toward improving knowledge and opinions of teachers and dentists' responsibility to provide them correct information on oral health. A subsequent plan must be made to develop bodies for undertaking program analysis and evaluation. Several practical frameworksand models to guide the development of comprehensive and systemic approach to evaluation planning, including process and outcome evaluation for multi-sectorial community initiatives have been developed[15].This will allow the monitoring of program success at all levels for validity, acceptability and changes in health status.

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STUDENTS CORNER
COMMENTARY

Trauma Management: Should it be a part of Medical Curriculum?

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ABSTRACT:
Trauma management is an approach to assess and treat multiply injured patients. Casualties that present within the first two hours of injury are deaths that can be prevented. Medical professionals need to be trained to appraise and manage these patients during this period. A variety of courses are available, designed entirely to teach medical professionals to treat trauma patients. Many counties have adopted these programs and now they are being taught in over 60 countries worldwide. In developing countries, injuries due to trauma are regrettably neglected, and accounts for more than five million deaths each year. This is nearly equal to combined number of deaths from tuberculosis, malaria and HIV/AIDS. Medical graduates are supposed to be able to handle all types of emergencies, common or traumatic. Lack of ATLS, BCLS and ACLS certified doctors in emergency departments lead to improper and un-necessary delay in provision of medical care to patients.
Keywords: Trauma management, Medical students, Medical curriculum.

INTRODUCTION:
Trauma management is an approach to assess and treat multiply injured patients.Casualties that present within the first 2 hours of injury are deaths that can be prevented, therefore, medical professionals need to be trained to appraise and manage these patients during this period, if they are not frequently exposed to trauma casualties.[1]
A variety of courses are available, designed entirely to teach medical professionals a systematic and condensed approach to treat trauma patients. Advanced Trauma Life Support (ATLS), Basic Life Support (BLS) and Advanced Life Support (ALS) are examples of such courses; certification of these courses is acquired by medical health professionals in both developed and developing countries.Advanced Trauma Life Support (ATLS) is progressively becoming the basis of care for traumatically injured patients. ATLS was developed by the American College of Surgeons (ACS) Committee on Trauma (COT) and was first introduced in the United States and internationally in 1980.As its impact grew globally, many counties adopted this program and now it is being taught in over 60 countries worldwide.[2]The basic principles of the course are: "treat first what kills first" and "do no further harm". Rapid assessment of the injuries and treatment is given systematically. In patients who are severely injured, an overall patient assessment has to be made so that logical sequential priorities can be established[3]. This process is known as primary survey and constitutes the "ABCDEs" of trauma care.[4]
The sequence is as follows:-
(A) Airway maintenance with cervical spine protection
(B) Breathing and ventilation
(C) Circulation with hemorrhage control
(D) Disability: neurologic status
(E) Exposure/environmental control
In developing countries, injuries due to trauma are regrettably neglected[5]and account for more than five million deaths each year, which is nearly equal to the combined number of deaths from tuberculosis, malaria and HIV/AIDS.[6]Pakistan is facing unprecedented and repeated attacks of terrorism, which claim large number of lives and leave scores injured. This puts an enormous load on an almost non-existent pre-hospital medical care system.[7]Although Karachi, the largest city of Pakistan has a few organized private ambulance response systems, yet the medical treatment imparted by the first responders to trauma patients at the scene or in the ambulance during transfer to a hospital is minimal or un scientific at best.In majority of the situations, patients are taken to the nearest hospital by relatives or by standers; this may lead to an even poorer outcome as transport of the trauma patient is by an untrained person. Moreover, the absence of trauma centers in every major city is a major disincentive to provision of timely definitive care.[8]Therefore, there is a dire need of implementation of standardized trauma management training, as well as the presence of trauma centers to cater to the increasing numbers of trauma patients. If the person at the scene of disaster or accident is a medical student trained in trauma management, he or she will definitely perform better than the first responder (stretcher bearer of an ambulance).
Trauma is the second leading cause of death in the age group of 15-44 years.[9]WHO estimates that till 2030, a further 40% increase will result in trauma fatalities.Therefore, paramedics and first responders play a pivotal role in decreasing trauma mortality, especially in case of long prehospital transit

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times.[10]Mortality rate escalates by 3 times for every 30 minute increase from time of injury to conclusive care[11]. One principle in medicine is the ''golden hour'' of trauma, which specifies that patient outcomes are improved when patient is transported to a trauma center within an hour of injury as trauma patients have significantly better survival rates if their injuries are treated within 60 minutes[12].

This expectation is quite different from reality in developing countries such as Pakistan. According to a study in Karachi, 58% patients die before they even reach a hospital[13]. A study was conducted to evaluate prehospital care in low to middle income countries of Asia, Africa and Latin America[14]. All sites had some measure of training available for first responders, with the exception of Pakistan and Gujarat State of India. Access to services within 1 hour varied exceedingly, despite availability of an emergency number, and was found to be very low in Pakistan.This indicates that despite there being a system for the provision of emergency medical services, it is barely functioning. Possible causes of this could be inadequate funding, absence of legislation to establish standards, lack of assimilation of multiple systems as well as absence of standardization of emergency procedures among medical personnel[15]. The problem cannot be resolved just by constructing isolated trauma centers. Instead these trauma centers need to have an integrated system of prevention, prehospital evacuation of injured, hospital care and rehabilitation. The proclaimed 7 minute response time of the ambulance service becomes irrelevant when medical facilities are not equipped for the definitive care of the injured[16]. Little can be hoped to be achieved unless the government takes the initiative and grants trauma management its due importance, which as yet has not happened. National health policy of Pakistan 2009 does not acknowledge injury prevention and control[17].Even in medical curricula, Emergency Medicine as a specialty has not received recognition in Pakistan, which affects not only undergraduate training but also the quality of care provided in emergency rooms[17],[18]. Medical graduates are supposed to be able to handle all types of emergencies, common or traumatic but little has been done to ensure that this competence can be achieved[19].In a nutshell, lack of ATLS, BCLS and ACLS certified doctors in emergency departments leads to improper and delayed medical care.

American College of Surgeons developed Advanced Trauma Life Support (ATLS) with a purpose to train the doctors to evaluate, and manage injured patients systematically. An ATLS program for physicians was carried out in Trinidad and Tobago which resulted in a significant augmentation of in-hospital trauma patient outcome.A study has demonstrated that senior medical students perform better in trauma simulation scenarios after completion of the ATLS training. Even attendance at only lectures about ATLS results in an increase in trauma management knowledge among medical students.Another study showed that medical staff who had either undertaken either full ATLS course or a contracted form of the course was more effective in their management of trauma cases[20].

In order to significantly lower mortality rates due to trauma, widespread implementation of standardized trauma training is necessary. This need not be ATLS, but could be a locally introduced program based on the same principles. Society of emergency medicine in Pakistan provides these courses in different cities of Punjab, Sindh and KPK with same policies and procedure as provided by level 1 trauma centers in USA. Educational training is given to 1st responders and to doctors and nurses in Emergency Departments[6]. There are certain hurdles in acquiring ATLS training. One problem commonly associated with ATLS is that there are far more applicants for ATLS programs than available places, resulting in long waiting lists. It is quite evident that the funding for ATLS-type programs in developing countries is grossly inadequate, making it financially inaccessible for quite a few candidates who would like to get trained. These problems could be addressed by implementing alternate programs based on ATLS but conceptualized, developed and validated by trained instructors.

Moreover, knowledge and skills gained through ATLS participation decline after 6 months, with a maximum decline after 2 years if skills learnt are not put to use[2]. Numerous studies have verified that the ATLS course is an effective teaching program despite its limitations.A study evaluated the effects of a trauma training course on medical students in Taiwan. It concluded the confidence of final year medical students after completion of their training was improved by the course.Based on these results, the study recommends that trauma training be taught to final-year medical students before they practice in hospital.A similar study was performed on senior medical students at the University of Toronto. Comparison was made between medical students who received ATLS training with those who did not receive ATLS training. The ATLS-trained students had higher scores than the control group. The study suggests that consideration should be given for including ATLS in the medical curriculum[20].

CONCLUSION:

Trauma management training should be made compulsory for all medical students so that an adequate number of properly trained individuals are available to rapidly assess and stabilize severely injured patients in emergency situations.

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CASE REPORT

Pulmonary Alveolar Microlithiasis with Klippel-Feil Syndrome: The Eye Does Not See What The Mind Does Not Know

Muhammad Tahir Khadim[1], Nisar Ahmed[2], Asif Asghar[3], Rahat Rao[4], Kiran Nauman[5], Syed Raza Jaffar[6]

ABSTRACT:
Pulmonary alveolar microlithiasis is a rare idiopathic disorder characterized by multiple microliths in the alveoli. Chest X-ray examination show miliary mottling mimicking Tuberculosis. Klippel-Feilsyndromeinclude short neck, low hairline and decreased cervical spine movements. It is a congenital anomaly characterized by the fusion of cervical vertebrae and various congenital defects. The present case report is about a 12-years old girl whose Chest X- ray, CT scanand clinical examination revealed KlippelFeil syndrome and Pulmonary alveolar microlithiasis. Open lung biopsy confirmed the pulmonary alveolar microlithiasis. To the best of our knowledge combination ofPulmonary alveolar microlithiasisandKlippel-Feil syndrome has never been reported before.

Keywords: Pulmonary alveolar microlithiasis, misdiagnosis, Klippel-Feil syndrome

INTRODUCTION:

Pulmonary Alveolar Microlithiasis(PAM) was first described by Friedrich in 1856 and by HarbitzIn 1918.[1]

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It has been reported as an uncommon idiopathic disease characterized bymultiplemicroliths in the alveoli. Few familial cases have also been reported. It is regarded as an autosomal recessive lung disease.From clinical point of view it is important as pulmonary tuberculosis hasbeen reported to be the most common misdiagnosis in these cases. About 576 cases of PAM have been reported from Europe and Asia.[2,3]

Klippel-Feil syndrome was described in detail by Mauric Klippel and AndreFeil In 1912. The syndrome is characterized by three signs including short neck, low hairline and decreased cervical spine movements. The syndrome is associated with multiple congenital anomalies including fusion of 2 vertebrae or fusion of complete cervical spine, congenital scoliosis, Sprengel's deformity, renal aplasia, synkinesis, congenital heart defects , brain stem abnormalities, congenital cervical stenosis, syndactyly, and hearing loss. It has been mentioned that about 50% of the cases with congenital defects of cervical spine have all the three signs[4]. Pulmonary alveolar microlithiasis with Klippel-Feil syndrome has never been reported before. In this report of rare combination we aim to emphasize a high index of suspicion for uncommon disordersto avoid misdiagnosis and inappropriate management.

Case Report:

A twelve year old girl with the history of,off and on cough and repeated chest infections since birth was investigated at PNS-Shifa, Karachi- Pakistan. She was previously given a short trial of antituberculous therapy without any clinical improvement or changes in chest X-Ray findings. HRCT Chest showed randomly distributed micro-nodules with the evidence of calcification in both the lungs along bronchovascular fissures and alveoli.

Block vertebrae C2-3 and C5-6 with Omovertebral bone extending from left pedicle of C5 vertebrae to elevated inferior medial border of Scapula was seen. Spina bifida of TV12 was seen. Rudimentry right cervical rib was present.She was labeled as case of Springel deformity of scapula with omovertebral bone,block cervical vertebrae C2-3 and C5-6 as part of Klipper-Feil syndrome (Figure1a,1b,2a). On Further investigations Ultrasound KUB/Pelvis showed congenitally absent left kidney.The laboratory investigations including hematological profile,

biochemical profile including serum calcium and electrolytes were unremarkable.Mantoux Tuberculin skin test was negative. Echocardiography did not reveal any abnormality and spirometry was also within normal limits. The histopathological examination of open lung biopsy revealed chronic inflammatory changes with

Figure: 1a
Omovertebral bone on left with raised left scapula.Multiple fine pulmonary nodules in both lungs mainly in middle and lower zones.

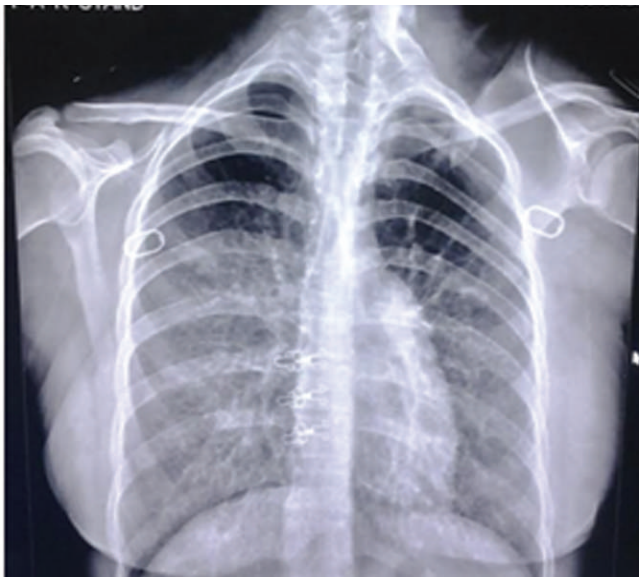


Figure: 1b
Micronodules and calcifications along bronchovascular bundles.

of any calcium metabolism disorder. The cases have multiple calcipheritesof variable sizes within the alveoli and along bronchovascular fissures. The final diagnosis of Pulmonary Alveolar Microlithiasis was made (Figure 2b). The detailed examination of her siblings did not reveal any abnormality.

Figure: 2a
Subpleural calcification giving "Black pleura sign"

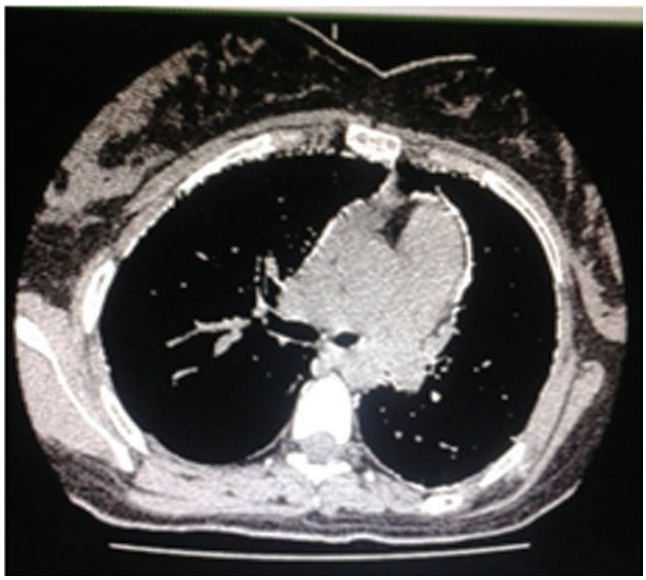
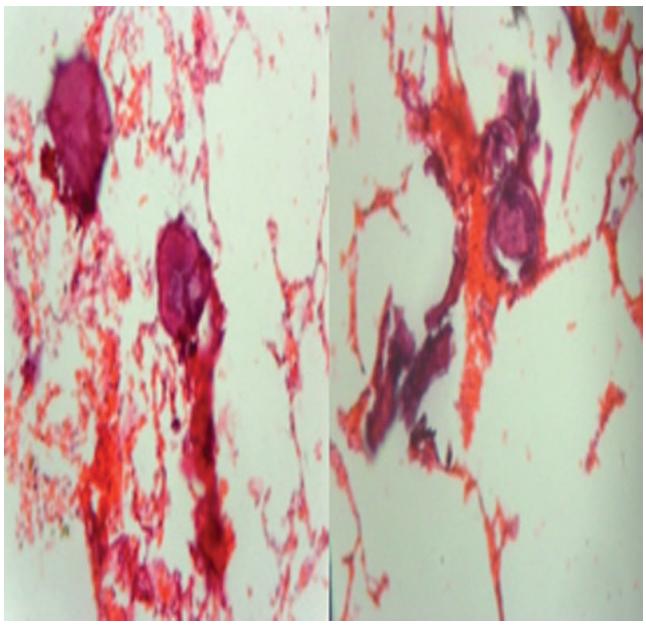


Figure: 2b
Histopathology section showing multiple calcispherites within the alveoli of lung parenchyma. H and E 100×



DISCUSSION:

Pulmonary Alveolar Microlithiasis (PAM) is an uncommon disease presenting as multiple calcipherites within the lung parenchyma and alveoli in the absence

been reported worldwide with significant number from Europe, Turkey and Asia. Cases can be seen in any age but usually present at younger age. There is no specific gender predisposition. Friedrich in 1856, Sosman in 1957 and Harbitz described this condition in 1918.

Recently it has been studied that gene SLC 34A2 coding for type IIb sodium-dependent phosphate transporter and its function is associated with the condition and it has provided some insight to the pathogenesis of this disorder. The Confirmation of diagnosis of PAM can be done by demonstrating the mutation in the SLC34A2 gene[5]. The disorder is slowly progressive. Most of the cases remain asymptomatic[6,7].Progressive dyspenea and respiratory failurehas been observed after 4th decade. Plain X Ray chest interpreted in the light of cough is misdiagnosed as Tuberculosis and treated without any improvement. At present there is no definitive treatment to reduce or halt the progression of the disease process. Systemic corticosteroids, calcium-chelating agents and serial bronchopulmonary lavage have been tried with some improvement [8].Symptomatic treatment and appropriate antibiotic therapy with regular follow up is the only choice presently available. In our case the history of chronic cough and repeated chest infection was present. The patient was empirically given a trial of anti tuberculous therapy also. Her CT chest and X-Ray findings did not show any improvement. Her biochemical profile and test for tuberculosis were also negative.

Maurice Klippel and Andre Feil first described Klippel-Feilsyndrome in 1912. The patients classically had short neck, low hairline and decreased movements of cervical spine. There is congenital failure of segmentation of cervical vertebrae resulting due to failure of normal segmentation of cervical somites at 3-8 weeks gestation. This leads to fused cervical vertebrae at multiple levels[9]. There is a whole spectrum of deformity from fusion of 2 vertebrae to fusion of complete cervical spine. Fusion of C-2 & C-3 is most common. The syndrome can be associated with other deformities such as and Sprengel's deformity.Sprengel's deformity is a complex congenital deformity of shoulder. It is characterized by the congenital elevation of scapula and is the most common congenital shoulder abnormality. Definitive diagnosis can be made on radiography, but CT or MRI is required for the confirmation. This deformity was present in our case along with other deformities including block vertebrae C2-3 and C5-6, Omovertebral bone extending from left pedicle of C5 vertebrae to elevated inferior medial border of Scapula. Our case also showed spina bifida of TV12, rudimentary right cervical rib was present. The ultrasound KUB/Pelvis of this case showed congenitally absent left kidney. Klippel- Feilsyndrome with renal aplasia has been reported as a common finding. Other congenital defects including, synkinesis, congenital heart defects, brain stem abnormalities, congenital cervical stenosis, syndact and hypoplastic thumb and some degree of hearing loss has been reported with different frequency[10,11,12]. The CT scan or MRI is important to evaluate such cases. Recent studies have confirmed that syndrome develops as a result ofmutations in the GDF6 and GDF3 genes. Familial Klippel-Feil-syndrome gene locus has been studied on the long arm of chromosome [8]. These genes provide instructions for protein synthesis that belong to the bone morphogenetic protein family, which in turn are involved in regulating the growth and maturation of bone and cartilage.The condition is inherited in an autosomal dominant pattern.The deformities are usually painless and many patients are not diagnosed until adolescence. The non-surgical management in cases with significant movement restrictions is usually un-successful. Surgical managementis indicated for children between 3-8 yrs of age with significant deformities only[14].

CONCLUSION:

PAM can easily be misdiagnosed as Miliary Tuberculosis. Klippel-Feil syndrome can be seen associated with multiple congenital defects. PAM with Klippel-Feil syndrome has never been reported before. By reporting this rare combination we aim to emphasize a high index of suspicion for uncommon disorders to avoid misdiagnosis and inappropriate management.

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LETTER TO EDITOR

Alarming Scarcity of Blood Donations

Aamir Hussain

To,
Editor,

Human blood is a unique and specialized tissue. Screening of blood donation products have been increasing in the community before usage. However, on the con side "Blood Donation Practices" are decreasing in the society. WHO blood donations recommendationfor low-income countriesare 20/1000 population, at minimum level. Currently, this rate ishigh in high-income countries (38/1000 population) and low in low-income countries(4/1000 population). According to WHO recent report, out of about 100 million blood donations, nearly more than half donations are duly needed by children under the age of five years,among low-income populations. On the contrary, among the high-income populations, this ratio(approximate 75%) is shifted to older than 65 years of age.[1]There is clear trend of boost in the demand of blood donations as the number of surgeries, neurological and blood carcinomas related palliative treatments as well as old age population are growing day by day.To cope up these, there is very scarce supply of blood donations in the healthcare market.[2]Even unethical blood donations like paid donors not able to cut these high demands down. Drastically they are increasing the burden of infections risks of transfusion related serious transmitted infections for instance HIV, Syphilis. [3, 4]There should not be remuneration nor unwillingness regarding blood donations in any respect. It is an urgent need of reform and formulation of the strategic planning regarding hundred percent regular volunteer and unpaid "Blood Donation Practices". It should be highlighted and included in the SDGs (Sustainable Development Goals) as well.Safe blood supply and storage is another burning issue in Pakistan. At present, there is no comprehensive data available regarding "Blood Donation Practices"in Pakistan. It is estimated that Pakistan has been facing a constantstress and challenge to collect enough blood to meet the needs. Nobody actually wants to own the child. No doubt it is the prime responsibility of the political leaders and government to make accessible the provision of evidence based high quality and least costly blood and its products. However, it is neither justified nor acceptable to blame the government solely. Each one of us and everybody is a stakeholder including the donors, doctors, nurses, blood bank staff and paramedical staffabout the safety and availability of blood and blood products. [5]Moreover common mind set of the common man should be reshaped in this regard. Community participation should be enhanced and communication gap should be eliminated from the society as well.

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The Cardiac Society of Australia and New Zealand. Clinical exercise stress testing. Safety and performance guidelines. Med J Aust 1996; 164: 282-4.

c) No author given

Cancer in South Africa [editorial]. S Afr Med J 1994;84:15.

d) Chapter in a book

Phillips SJ, Whisnant JP. Hypertension and stroke. In: Laragh JH, Brenner BM, editors. Hypertension: pathophysiology, diagnosis, and management. 2nd ed. New York: Raven Press; 1995. p. 465-78.

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