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Editorial correspondence should be addressed to:
The Chief Editor, JCPSP,
Department of Publications,
College of Physicians and
Surgeons Pakistan (CPSP),
7th Central Street, Phase II, DHA,
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Tel: (92-21) 99266439 (Direct)
(92-21) 99266400
Ext: 224
UAN: (92-21) 111-606-606
Fax: (92-21) 99266450

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EDITORIAL

Paediatric Spinal Cord Injuries in Pakistan

Farooq Azam Rathore

Published research on spinal cord injury (SCI) in Pakistan is scarce; and mostly reports epidemiological pattern and clinical profile of adults with SCI. This article on paediatric SCI is the first attempt at documenting the clinical profile of pediatric SCI in Pakistan. It is based on the data collected from a paraplegic centre, which is the first SCI centre of the country established by the International Committee of the Red Cross in 1984 during the Afghan War.[1]

The epidemiology, clinical profile, and complication patterns of paediatric SCI are unique and different from adult-onset SCIs.[2] Fire arm injuries, fall from height, and motor vehicle accidents are documented as the most common causes of paediatric SCI in this study. Other important causes of paediatric SCI mentioned in the literature include all terrain-vehicles accidents,[3] spinal cord tumors,[4] transverse myelitis,[5] cord compression due to mucopolysaccharidosis,[6] and child abuse.[7]

Spinal cord injuries without radiographic abnormalities are more common in paediatric population.[2,8] This is likely to be due to the greater elasticity of the bony tissue in children, which reduces the likelihood of fractures, but increases the chances of injury to the spinal cord.[8] Therefore, it is important not only to rely on X-rays and CT-scans of the spine to rule out paediatric SCI in the emergency department, but correlate clinically and employ MRI whenever deemed clinically appropriate.

Pressure ulcers were present in half of the patients in this study. Pressure ulcer management is a major issue; in Pakistan. Routine skin inspection is not carried out and to the best of our knowledge, no neurosurgical or rehabilitation unit in the country formally documents the risks of pressure ulcer formation by using a validated pressure ulcer risk assessment tool.[9] There are very few trained rehabilitation nurses in the country; and most of the general nurses do not take active part in pressure ulcer management and only inform the doctors.[10] Pressure ulcer in SCI are associated with prolonged immobilisation, poor functional outcomes, and even mortality. Therefore, it is important to prevent them in the first place and actively treat them, if they occur. Other complications reported in literature in paediatric SCI include scoliosis, hip dysplasia, latex allergies, autonomic dysreflexia, spasticity, deep venous thrombosis, and kidney stones.[2] Deep venous thrombosis in paediatric SCI can occur many years after the initial injury.[2]

Paediatric SCI (especially complete injury) is a devastating and life-changing event, both for the children and their parents. Paediatric SCI patients have rehabilitation needs that are different from adults.[11] They may require prolonged outpatient rehabilitation sometimes for years to achieve optimal functional outcomes. If they are too young, they might not understand the mechanisms of injury and implications of life-long disability after SCI. They are unable to comprehend why they are not able to move around in the community and play with their peers. Therefore, it is important that rehabilitation programmes of paediatric SCI must be developmentally based, and goal-planning must address the changing needs of children as they grow.[12] The child needs assessment checklist has been proposed as a practical tool for planning rehabilitation and assessing rehabilitation outcomes in paediatric SCI cases.

Use of wheelchair as the main means of mobility in paediatric SCI should be started as early as the patient is medically stable and enrolled in rehabilitation. Depending on the level of injury, associated complications and financial status of the family, both manual and powered wheelchairs can be used. Schottler *et al*. reported that even children younger than five years with SCI were capable of independent wheelchair propulsion.[2] It has been recommended that use of manual or powered wheelchairs should be initiated in children with SCI as young as 12-18 months.[2]

Another important issue faced by SCI patients in Pakistan in general and particularly paediatric SCI patients, is of mobility barriers and community re-integration. Half of the patients in this study were either uneducated or not of school-going age. It would be interesting to know how many of them were able to continue their studies or secure admissions in schools after sustaining injury. Discrimination by school administrations towards children with disability is a bitter reality which is neither discussed nor highlighted. Since the healthcare system of Pakistan is mostly geared towards curative medicine, so this essential aspect of community reintegration and education of patients with paediatric SCI remains unaddressed. There is no legislation to support such children and to ensure their

Department of Rehabilitation Medicine, PNS Shifa Hospital, Karachi.

Correspondence: Dr. Farooq Azam Rathore, Consultant and Head, Department of Rehabilitation Medicine, PNS Shifa Hospital, DHA II, Karachi.
E-mail: farooqrathore@gmail.com

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inclusion in the educational institutes. The commonest barrier towards education in paediatric SCI is lack of accessible school buildings. A patient with complete paediatric SCI (as with majority of patients in this study) is likely to be wheelchair-bound for life for mobility. Most of the private and public schools in Pakistan do not have ramps to facilitate movement of wheelchair-bound paediatric SCI patients. They also lack accessible toilets. The other barrier is discriminatory attitude of the society towards persons with disability. While an adult patient with SCI might be able to understand this discrimination and cope well, but a child with SCI using wheelchair or orthosis might find it challenging to adjust to such hostile environment.

Multi-disciplinary SCI rehabilitation services are lacking in Pakistan. The SCI services being provided mostly consist of physiotherapy and exercises by a physical therapist. Rehabilitation medicine physicians (physiatrists), with expertise and training in SCI rehabilitation, are either not available or not involved at an early stage. Even major cities like Karachi and Lahore do not have a single SCI rehabilitation centre with a standard multi-disciplinary rehabilitation team. The only comprehensive SCI rehabilitation centre in the country with all members of a SCI rehabilitation team (physiatrist, physiotherapist, occupational therapist, clinical psychologist, orthotist, resettlement officer, and vocational trainer) is located at the Armed Forces Institute of Rehabilitation Medicine, Rawalpindi. The lack of a team approach results in issues like untreated spasticity and contracture formation, neuropathic pain, pressure ulcers, inadequate bladder and bowel management, psychological issues, and a poor community reintegration.

There is a need to establish a Disability Registry in the country to document all forms of disabilities including paediatric SCI. Instead of only physiotherapy, comprehensive rehabilitation services should be developed and offered to all patients with SCI so that they can achieve optimal functional outcome compatible with their disability. This will result in better community re-integration and improved quality of life.

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ORIGINAL ARTICLE

Galactose-induced Aging Model in Rat Testicular Tissue

Seval Aydin[1], Karolin Yanar[1], Bahadir Simsek[2], Tamer Cebe[2], Mustafa Erinc Sitar[1], Ahmet Belce[3] and Ufuk Çakatay[1]

Abstract

Objective: To examine whether the D-galactose induced aging model is an appropriate model for further aging research.
Study Design: Experimental study.
Place and Duration of Study: Aziz Sancar Institute of Experimental Medicine, Istanbul University, Turkey, June 2015-June 2017.
Methodology: The study comprises 3 groups of rats. Group I is young control (YC) 5-month-old rats. Group II is 5-month-old rats, which were mimetically aged (MA) for 6 weeks via intraperitoneal D-galactose (60 mg/kg body weight/day, 0.5 mL) administration. Group III is naturally aged (NA) 24-month-old rats. Group I and III received intraperitoneal saline (0.9% 0.5 mL) for 6 weeks as vehicle. Group I and Group II received injections at 21 weeks age and Group III rats 6 weeks before 24 months age. Tissues were harvested when rats became 6.5-month-old (Group I and Group II) and 24-month-old (Group III). Quantitative biochemical analyses of proteins, lipids, DNA biomarkers and Cu, Zn-SOD were conducted. Statistical analysis of the data was conducted using ANOVA, followed by post-hoc Bonferroni test.
Results: Higher magnitude of oxidative damage and diminished antioxidant defence capacity were found in both mimetically aged and naturally aged testicular tissues. It is observed that D-galactose aging model group shares significant similarities in terms of impaired redox homeostasis with the naturally aged rats.
Conclusion: D-galactose induced testicular aging model successfully mimics aging process. Therefore, D-galactose induced aging model may be used as an accelerated aging model to study the age related alterations and interventions.

Key Words: *Galactose. Natural aging. Mimetic aging. Oxidative stress. Redox homeostasis. Testis.*

INTRODUCTION

Among the various etiologic factors contributing to the occurrence of age-related testicular dysfunction, increased production of reactive oxygen species (ROS) seems to play an important role in the pathogenesis of impaired redox homeostasis. Impaired redox status may lead to oxidative damage in cellular macromolecules.[1,2] Antioxidant systems to scavenge excess ROS are necessary to maintain redox homeostasis. Age-related oxidative modifications in macromolecules of testicular tissue are considered as a sign of the progression of testicular dysfunction. Decreased androgen synthesis rate and impaired spermatogenesis are accepted as inevitable outcomes of reproductive aging.[3] Although all these aforementioned alterations were previously thought to be a part of natural aging, this issue needs to be reconsidered in the light of increasing life expectancy and the wish of humanity to live longer, while maintaining a good quality of life.

[1] *Department of Medical Biochemistry, Cerrahpasa Faculty of Medicine, Istanbul University, Istanbul, Turkey.*
[2] *Cerrahpasa Faculty of Medicine, Medical Program, Istanbul University, Istanbul, Turkey.*
[3] *Faculty of Health Sciences, Bezmialem Vakif University, Istanbul, Turkey.*

Correspondence: Dr. Ufuk Çakatay, Department of Medical Biochemistry, Cerrahpasa Faculty of Medicine Istanbul, Turkey.
E-mail: cakatay@yahoo.com

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Experimental aging research frequently utilises aged rodents. D-galactose induced aging model offers many advantages including easy application, low experimental cost, high survival and low attrition throughout the aging period.[4] Recent experimental studies have shown that D-galactose induced mimetic aging model is increasingly being used to study age-related oxidative alterations in various tissues.[4,6] Recently, D-galactose was shown to increase lipid peroxidation, reduce thiol groups, and cause deterioration in redox homeostasis.[5]

D-galactose has wide ranging effects on various organ systems, but comprehensive research into how testicular tissue is affected from oxidative stress markers point of view remains scarce. There are no experimental data investigating the effects of D-galactose on the redox homeostasis markers of testicular tissue of rodents in a comprehensive manner. In the current literature, no comprehensive research is performed examining the damage in protein, lipid and DNA content of testicle tissue caused by impaired redox homeostasis. In addition, the extent of oxidative damage on these macromolecules has not been previously compared with naturally aged (NA) rodents in any research.

Hence, the aim was to clarify whether the D-galactose mimetic aging (MA) model is a reliable model for further aging research on testicular tissue. Because of the absence of comprehensive data related to macromolecular oxidative process in testicular tissue, this study was conducted to assess macromolecular redox homeostasis biomarkers to reveal whether D-galactose

induced mimetic aging model in rats is applicable to mimic natural aging process to facilitate further research in this field.

METHODOLOGY

This experimental research was carried out on male Sprague-Dawley rats (n=24). Animals were followed up at the Institute of Aziz Sancar Experimental Medical Research, Istanbul University, Turkey. The study was conducted between June 2015 and June 2017. All experimental protocols were approved by the Animal Care and Ethics Committee of Istanbul University. Animals were housed in a temperature controlled room (21 ±2°C) with 12-hour light-dark cycles. All rats (n=24) were fed with a standard laboratory diet and had free access to tap water. After one week of acclimatisation period, when they were 21 weeks old, they were divided into three groups. Group I included young control (YC) rats (n=8; 5-month-old, body weight average 404 g), which were given saline (0.9%, 0.5 mL) intraperitoneally for 6 weeks. Group II included mimetically aged (MA) rats (n=8; 5-month-old, body weight average 421 g), which were given D-galactose (60 mg/kg body weight/daily, 0.5 mL) intraperitoneally for 6 weeks. Group III included naturally aged (NA) rats (n=8; 24-month-old, body weight average 513 g), which were given saline (0.9%, 0.5 mL) for 6 weeks before they reached 24-month age. Interventions to Group I and Group II were started when mice were 21 weeks old.

Testicles were immediately extracted from the rats under ketamine (44 mg/kg)-xylazine (33 mg/kg) anesthesia and were washed in cooled 0.9% NaCl. The extracted tissue samples were then immediately frozen in liquid N_2 until they were homogenised.

Analysis was carried out spectrophotometrically as previously described by Hanasand et al method.[7] Supernatant and citric acid were mixed. One minute later, potassium iodide was added. AOPP concentration was expressed as micromoles per liter of chloramine-T equivalents. The absorbance of chloramine-T standards was recorded at 340 nm.

PCO assay was performed as previously described by Reznick and Packer.[8] PCO groups react with 2,4 Dinitrophenylhydrazine (DNPH) reagent to form chromophoric dinitrophenylhydrazones. The final absorbance values were recorded at 360 nm, using the molar extinction coefficient of dinitrophenylhydrazine reagent. PCO-BSA positive control were both prepared according to the method of Lenarczyk *et al*.[9]

LHP levels were determined spectrophotomerically with the method using oxidation of ferrous ions with xylenol orange FOX2 (Ferrous Oxidation with Xylenol Orange, version 2).[10] LHPs oxidize ferrous to ferric ion selectively in dilute acid and the resultant ferric ions bind xylenol orange, forming a blue-purple complex. Absorbance was recorded at 560 nm against reagent blank.

The rate of lipid peroxidation was assessed by the procedure of Buege and Aust.[11] Pretreatment of supernatant samples was performed as by Lykkesfeldt.[12] MDA reacts with thiobarbituric acid to generate a colored product. The concentration of MDA was calculated using molar extinction coefficient and was expressed as μmol/mg protein. After reaction with thiobarbituric acid to generate a colored mixture, absorbance was recorded at 535 nm.

8-OHdG levels were assessed using an enzyme-linked immunosorbent assay (ELISA) detection kit (OXIS, Bioxytech, EIA, USA). ELISA method allows the quantification of 8-OHdG utilising 8-OHdG coated plate and horseradish peroxidase (HRP) conjugated antibody.

Cu, Zn-SOD (EC 1.15.1.1) activity was assessed by using the method of Sun *et al*.[13] The rationale in this method is the inhibition of nitrobluetetrazolium (NBT) reduction with xanthine oxidase, which is used as a superoxide anion generator. One unit of Cu, Zn-SOD was defined as the amount of enzyme needed to exhibit 50% dismutation of superoxide radical anion. Final absorbance was recorded at 560 nm against reagent blank.

Statistical calculations were performed with IBM SPSS Statistics 24. Data are expressed as the mean ± SD for each group. All the parameters of the groups were normally distributed. Analysis of variance (ANOVA) was performed in order to observe the differences among groups. Significance was found and this was followed with a Bonferroni post-hoc test. Confidence interval was determined to be 95% and p-values <0.05 were considered as statistically significant.

RESULTS

All biomarker profiles of Young Control (YC), Mimetic Aging (MA), and Natural Aging (NA) rats are given in Table I.

As a sign of extensive protein oxidation, both AOPP and PCO concentrations in MA and NA rats were found to be significantly higher compared to those of the YC. AOPP and PCO levels were found to be similar in MA and NA groups.

As a sign of more oxidative damage to lipids, both MA and NA groups showed significantly higher LHP levels compared to YC rats. NA group also had statistically significantly increased LHP levels compared to MA group. Although D-galactose administration caused significantly elevated LHP levels compared to YC, LHP increase in MA group was not as high as the increase in NA group.

NA group showed significantly more tissue MDA levels compared to YC group, representing more oxidative damage to lipids. Although statistically significant increase was not detected between YC and MA, MDA levels were elevated comparable to MDA levels of NA.

Table I: Comparison of parameters between young control (YC), mimetically aged (MA), and naturally aged (NA) rats.

Parameters	YC (n=8)	MA (n=8)	NA (n=8)	Confidence Interval, 95%	p-values
AOPP	22.56±9.36	32.95±7.09	36.60±6.60	YC, 14.73-30.39	YC vs MA, 0.043
				MA, 27.01-38.81	YC vs NA, 0.005
				NA, 31.07-42.15	MA vs NA, 1.000
PCO	5.11±1.21	8.36±1.84	8.70±1.91	YC, 4.09-6.13	YC vs MA, 0.003
				MA, 6.82-9.90	YC vs NA, 0.001
				NA, 7.09-10.3	MA vs NA, 1.000
LHP	1.06±0.05	1.27±0.04	1.47±0.08	YC, 1.01-1.10	YC vs MA, 0.000
				MA, 1.23-1.31	YC vs NA, 0.000
				NA, 1.40-1.54	MA vs NA, 0.000
MDA	3.47±0.51	4.45±0.98	5.40±0.94	YC, 3.04-3.90	YC vs MA, 0.093
				MA, 3.62-5.27	YC vs NA, 0.001
				NA, 4.60-6.19	MA vs NA, 0.105
Cu, Zn-SOD	6.98±1.01	3.85±0.59	4.46±0.78	YC, 6.13-7.83	YC vs MA, 0.000
				MA, 3.35-4.34	YC vs NA, 0.000
				NA, 3.80-5.11	MA vs NA, 0.445

Values are given as Mean ± SD.

Both MA and NA rats showed significantly higher 8-OHdG concentrations compared to YC rats. MA and NA rats had more oxidative damage to their DNA than YC group. Testicular 8-OHdG levels were found to be similarly elevated in MA and NA groups.

Both MA and NA groups had significantly lower Cu, Zn-SOD activity, showing depleted enzymatic antioxidant capacity in both MA and NA groups.

DISCUSSION

D-galactose and its oxidative metabolites have numerous detrimental effects on cell. D-galactose may be oxidized to form reactive aldehydes and hydrogen peroxide (H_2O_2) by galactose oxidase.[14] H_2O_2, mainly through Fenton reactions is known to produce OH- radicals, which are notorious for their direct effects on the oxidation of proteins, lipids and DNA.[15] Another fate of D-galactose is the formation of galactitol by aldose reductase. Galactitol is known to be a cause of osmotic stress, which may lead to increased electrolyte and metabolite imbalances.[16] D-galactose enhances cellular dependence on oxidative phosphorylation.[17] The potential of D-galactose to induce mitochondrial complex I insufficiency is likely to put further stress on the cell.[18] Increased mitochondrial dysfunction and complex I insufficiency are shown to increase superoxide generation.[19] A recent study on the fertility of female mice reported that insufficient neutralisation of free radicals could result in decreased fertility.[20]

As evidenced by the increased levels of protein oxidation biomarkers AOPP and PCO of MA rats, a consistent increase in protein oxidation was documented. Proteins form the structural basis of cells and they are likely to be oxidized due to redox imbalance induced via D-galactose administration.

It has been well known that LHPs are the primary products of early phase of lipid peroxidation.[10] The formation of LHPs is accepted as an important initial event in the progression of lipid peroxidation.[10] A strong relationship between early product of lipid oxidation known as LHPs and their further stable aldehyde derivative MDA has been reported in the current literature.[21] Reactive aldehyde derivatives of membrane lipids are transformed into aldehyde-protein adducts by giving out PCOs through secondary modification reactions. In this study, no significant increase was observed in MA group concerning MDA (p=0.093), which is a late reactive product of lipid peroxidation. It is clearly seen that D-galactose induced an increase in MDA formation when compared to YC. Although this increase was not significant, the tendency of MDA levels to increase in MA group shows that MA group is susceptible to the formation of reactive aldehyde-protein adducts. The increased MDA and LHP levels found in MA rats may be an accelerating factor for protein oxidation rate, as the PCO and AOPP levels in their testicular tissue were found to be elevated. Impaired redox status of testicular proteins may, therefore, be one of the results of the increase in the magnitude of lipid peroxidation and the occurrence of testicular redox homeostasis.

Protein oxidation and lipid peroxidation biomarkers were found to be significantly correlated in testicular tissue, hence this finding was considered as one of the indications of a coupled redox imbalance in mimetically aged testicular tissue.

The results indicate that except the LHP levels, D-galactose induced aging model offers a fast track aging. The difference between MA and NA could be attributed to the lack of consensus on D-galactose administration dosage / the administration period in the current literature.[6] It is also possible that unknown mechanisms that are yet to be discovered may play a role.

Previously reported increased systemic 8-OHdG levels in NA rats may be driven by redox imbalances in aged

tissues.[1] As given in Table I, a significant and similar increase in 8-OHdG levels was also observed in both MA and NA groups. Increased 8-OHdG concentration was comparable with the other oxidative stress biomarkers of testicular tissue. The overall increase in formation of ROS levels and decreased superoxide scavenging capacity may be considered as an aggravating factor of DNA oxidation in aged testicular tissue.

Factors such as D-galactose induced insufficiency of complex I, increased mitochondrial dependency and osmotic stress are shown to induce higher superoxide radical leak through mitochondria, and are removed by Cu, Zn-SOD.[16,17] Antioxidant enzymes such as Cu, Zn-SOD, as well as non-enzymatic antioxidants such as glutathione, work synergistically with mechanisms related to these systems to regulate the levels of oxidatively modified proteins.[22] There were significant changes in Cu, Zn-SOD activities in both MA and NA rats compared to their corresponding YC group. Also, Cu, Zn-SOD levels were found to be similar between NA and MA groups. The reported experimental findings are in conformity with the previous reports on systemic Cu, Zn-SOD activities, also reported by the present authors.[1]

CONCLUSION

Administration of intraperitoneal D-galactose (60 mg/kg daily) for 6 weeks successfully mimics the redox homeostasis biomarkers of natural aging in testicular tissue. Hence, D-galactose administrated MA rats may be considered as an applicable model to investigate aging in testicular tissue.

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ORIGINAL ARTICLE

Effectiveness of Oral Methotrexate Therapy *versus* Systemic Corticosteroid Therapy in Treatment of Generalised Lichen Planus

Rabeeka Bakhtiar, Sahibzada Mahmood Noor and Muhammad Majid Paracha

ABSTRACT

Objective: To compare the effectiveness of oral methotrexate *versus* systemic corticosteroids in treatment of lichen planus.

Study Design: Randomised controlled trial.

Place and Duration of Study: Department of Dermatology, Lady Reading Hospital, Peshawar from September 2013 to February 2014.

Methodology: Patients with generalised lichen planus involving at least 20% of total body area diagnosed clinically and were randomly allocated into two equal groups by lottery method. Patients in group A were subjected to oral methotrexate 10 mg once weekly for eight weeks with standard monitoring of full blood count and liver and renal function tests. Patients in group B were subjected to oral corticosteroids 40 mg for eight weeks taken daily than tapered according to the protocol. The results were assessed at baseline and at the eighth week after starting the treatment. The responses were analysed by Visual Analogue Scale (VAS) and sorted into four categories: 0-3 = poor response, 4-5 = moderate, 6-7 = good, and >7 excellent response. Chi-square test was applied to compare the efficacy in two groups with significance of less than or equal to 0.05.

Results: Group A (methotrexate) had 47 (60%) male patients and 32 (40%) female patients. Group B (oral corticosteroids) had 51 (64%) male patients and 28 (36%) females. Group A 55 (70%) patients had lichen planus in <50% of the body; whereas in group B 53 (67%) patients had lichen planus in <50% of the body. Methotrexate was effective in 63 (80%) patients; whereas, oral corticosteroid was effective in 57 (72%) patients. No remarkable side effects were observed with either agent.

Conclusion: Methotrexate is more efficacious than systemic corticosteroids, but the effect is not statistically significant.

Key Words: *Oral methotrexate. Systemic corticosteroids. Lichen planus.*

INTRODUCTION

Lichen planus is a mucocutaneous inflammatory disorder characterised by shiny, violaceous, and flat-topped polygonal papules and plaques.[1] Methotrexate would be helpful in the treatment of lichen planus through down-regulation of an immunologically mediated mucosal response. Its effectiveness may also be related to its effect on epidermal cell proliferation. An auto-immune pathogenesis is postulated with activated T-cells directed against basal keratinocytes. The existence of rare cases of familial lichen planus and the over representation of certain HLA haplotypes (e.g. HLA-DR1 in cutaneous lichen planus) suggest that genetic factors have a role in susceptibility to this disease. Most reports of lichen planus have come from the South Asian origin.[2,3]

Multiple mechanisms are involved in the suppression of inflammation by corticosteroids; they include reduction of the exudation of leukocytes and plasma constituents, maintenance of cellular membrane integrity, inhibition of lysozyme release from granulocytes, inhibition of phagocytosis, and stabilisation of the membranes of the intracellular lysozymes and also inhibit proliferation of fibroblasts. Other treatment options available are oral metronidazole, oral acitretin, mycophenolate mofetil and sulfasalazine, narrow-band or broadband UV-B therapy, and methotrexate. It is common in females. There is a strong association between lichen planus and hepatitis C infection. Lichen planus has different clinical subtypes based on the morphology of the lesions and the site of involvement. These include papular (classic), hypertrophic, vesiculobullous, actinic, annular, atrophic, linear, follicular, lichen planus pigmentosus, and lichen plnus pigmentosus-inversus.[4-9]

The objective of the study was to compare the effectiveness of oral methotrexate *versus* systemic corticosteroids in treatment of generalised lichen planus.

METHODOLOGY

This was a randomised controlled trial carried out in the Dermatology Department, Lady Reading Hospital, Peshawar, from September 2013 to February 2014. The sample size was 79 patients in each group, using 80%

Department of Dermatology, Lady Reading Hospital, Peshawar.

Correspondence: Dr. Rabeeka Bakhtiar, Trainee Medical Officer, Department of Dermatology, Lady Reading Hospital, Peshawar.
E-mail: rabeekanauman@gmail.com

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effectiveness of corticosteroids, 58% effectiveness of methotrexate, 95% confidence level, and 90% power of test calculated by WHO formula through Goldberg's equation. Sampling technique was non-probability consecutive sampling. Patients with generalised lichen planus diagnosed clinically according to diagnostic criteria "shiny flat topped violaceous papular eruption with skin thickening involving at least 20% of total body area" and who were not taking any treatment for lichen planus. Patients having hepatitis B or C or pregnancy, lactating mothers, with ALT >40 mu/ml and creatinine >1.5 mg/dl were excluded from the study.

The study was conducted after approval from the Hospital Ethical and Research Committee. The purpose and benefits of the study were explained to the patients and a written informed consent was obtained. All patients were subjected to detailed history and clinical examinations and were randomly allocated into two groups by lottery method. Patients in group A were given oral methotrexate 10mg taken once weekly for eight weeks with standard monitoring of full blood count and liver and renal function tests, then stopped after 8 weeks, while patients in group B were given oral corticosteroids 40mg for eight weeks taken daily, then tapered according to protocol. The results were assessed at baseline and at the 8th week after starting the treatment. Treatment results were sorted into four categories according to Visual Analogue Scale (VAS) as follows: 0-3 poor response, 4-5 moderate, 6-7 good, >7 excellent response (Figure 1).

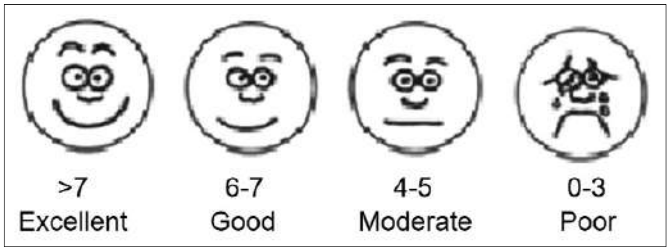

Figure 1: Visual analog score used to evaluate response.

All the observations, including clinical diagnosis and VAS were conducted under supervision of a single expert dermatologist having more than five years experience. All of the information including name, gender were recorded in a pre-designed proforma. Exclusion criteria was followed to control confounders and bias in study results.

Data was analysed in SPSS version 16. Mean value ±SD was calculated for numericals like duration of lichen planus lesions, and total body area involvement. Frequencies and percentages were calculated for categorical variables like gender, response to treatment and effectiveness. Chi-square test was applied to compare the effectiveness in two groups. P-value of less than or equal to 0.05, was considered statistically significant. Results were presented in the form of tables.

RESULTS

Among 79 patients, 63 (80%) patients showed good response to methotrexate. In comparison to that, 57 (72%) patients on oral corticosteroids among 79 patients showed good response of the therapy (p=0.2641).

Methotrexate therapy was effective in 37 (46%) male patients, 36 (45.5%) male patients showed good response to oral corticosteroids therapy (p=0.356). On the other hand, 26 (32.9%) female patients showed good response to methotrexate therapy in group A. In group B, 21 (26.58%) female patients showed good response to treatment (p=0.551). Stratification of effectiveness with respect to total body involvement, showed that in group A, 44 (55.69%) patients with <50% total body involvement showed good response to therapy, and in group B, 38 (48.1%) with <50% total body involvement showed good response to therapy (p=0.313). Among patients with >50% total body involvement, 19 (24.05%) in both groups showed good response to therapy (p=0.614). There were no serious or remarkable side effects with either agent.

Table I: Effectiveness of the methotrexate and oral carticosteroids in various groups.

	Effectiveness	Methotrexate	Oral corticosteroids	p-value
Gender:				
Male	Effective	37 (46%)	36 (45.56%)	0.3560
	Not effective	10 (12.6%)	15 (18.98%)	
Total		47 (59.5)	51 (64.55%)	
Female	Effective	26 (32.9%)	21 (26.58%)	0.5577
	Not effective	6 (7.5%)	7 (8.86%)	
Total		32 (40.5)	28 (35.44%)	
Total Body involvement:				
<50%	Effective	44 (55.69%)	38 (48.10%)	
	Not effective	11 (13.9%)	15 (18.98%)	
Total		55 (69.62%)	53 (67.08%)	
>50%	Effective	19 (24.05%)	19 (24.05%)	
	Not effective	5 (6.32%)	7 (8.86%)	
Total		24 (30.37%)	26 (32.91%)	

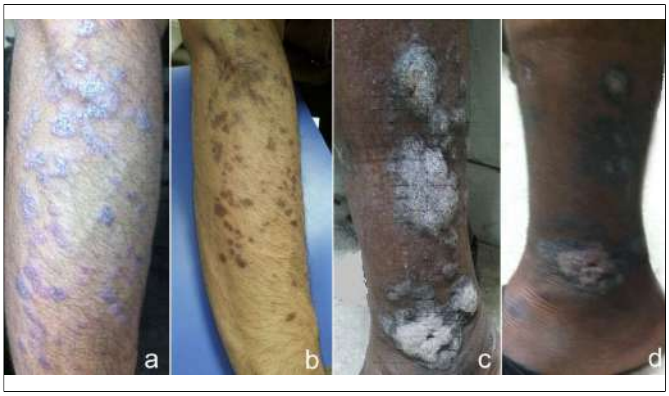

Figure 2 (a-d): Comparative visual response of lesions before and after methotrexate and oral corticosteroids therapy.
(a) Before methotrexate. (b) After methotrexate.
(c) Before corticosteroids. (d) After corticosteroids.

DISCUSSION

To date cortocosteroids are the only treatment modality satisfactory enough for both the patient and the treating physician. Treatment of generalised lichen planus is often disappointing and is associated with relapses; though reports have suggested a beneficial role of various immunosuppressive and immunomodulatory agents.[10,11]

In this study, methotrexate turned out to be a good treatment option that has the benefits of being quick in achieving results, with minimal adverse effects in long term treatment with appropriate monitoring and also with the convenience of single weekly dose. On the other hand, systemic corticosteroids, if used for long time, are associated with multiple side effects. Since much work has not been done on methotrexate in Pakistan, so the aim of this study was to verify the acclaimed effectiveness of methotrexate in the local population. This study gives a clue about the demographic features like gender, possible maximum duration of the disease and then the maximum body area involvement in our local population.

In group A (methotrexate) 60% patients were male and 40% patients were female; while in group B (oral corticosteroids), 64% patients were males and 36% patients were females. A study done by Tag-El-Din Anbar *et al*. at AL-Minya University Hospital in Egypt reflected equal gender distribution of this disease.[12] In this study, there is a male predominance because in this particular setup of K.P.K, male patients tend to seek medical attention more frequently and earlier than females; so the number of male patients can be explained by increased availing of medical facilities by this gender.

Duration of lichen planus was seven to eight months in both groups, respectively. It means that most of the patients presented in the first year of the disease development which is comparable with the study done by Richard *et al*. at University of Texas Health Science Center, San Antonio, Texas.[13] Another study done by Farzam Gorouhi *et al*. conducted in the University of California, USA also showed disease duration from six months to one year, which is also comparable to this study.[14]

Methotrexate was effective in 80% patients and was not effective in 20% patients; whereas, oral corticosteroid was effective in 72% patients and was not effective in 28% patients. In a study done in Iran, 23 out of 46 (50%) patients were treated with systemic corticosteroids and more than 80% of response was observed.[15] Another study by Ilyas *et al*. showed that 52 out of 55 (91%) patients had complete remission of their disease after treatment with methotrexate.[16]

In another study done by Majid *et al*. at Hayatabad Medical complex, Peshawar, 85.3% cases showed good response in patients treated with methotrexate, which is also comparable to the present results.[17]

Methotrexate has proved beneficial in the teatment regarding its good tolerability and minimal side effects with proper monitoring.[18,19] Being an effective, safe, and readily obtainable medicine, methotrexate can be a good option for treatment of lichen planus in developing countries like Pakistan where diabetes, hypertension, and osteoporosis are hazards for prescribing long term steroids.[20]

CONCLUSION

This study concludes methotrexate is not significantly efficacious than systemic corticosteroids in treatment of generalise lichen planus, but it is a good steroid-sparing alternative.

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ORIGINAL ARTICLE

Relationship of Nutritional Status and Functional Capacity in Elderly Patients Visiting Outpatient Clinics of a Tertiary Care Hospital

Sidra Kanwal[1], Waris Qidwai[2] and Kashmira Nanji[2]

ABSTRACT

Objective: To determine the correlation of functional and nutritional status of elderly patients (equal to and more than 60 years of age) visiting family medicine clinics of tertiary care hospital in Karachi.
Study Design: Cross-sectional, descriptive study.
Place and Duration of Study: Family medicine clinics of Aga Khan University Hospital, in Karachi, from August 2014 to February 2015.
Methodology: A total of 200 participants (60 years and above), Family medicine outpatient clinics, were recruited *via* non-probability consecutive sampling. Katz scoring and MNA scale were used for the evaluation of functional and nutritional status, respectively. Spearman's rank correlation coefficient was applied to assess the correlation between nutritional status and functional status of elderly.
Results: Out of 200 participants, 35 % (n=70) were of 60-64 years of age. Most of them (54%, n=109) were males as compared to 46% (n=91) females; 33.5% were at risk of malnutrition and 35.5% were dependent. Spearmen correlation between functional and nutritional status was rho = -0.675, with p-value of p<0.001.
Conclusion: There is a negative correlation between nutritional and functional status. As good nutritional status is essential for older persons to become functionally active; hence, this issue needs to be dealt in a developing country like Pakistan.

Key Words: *Functional status. Nutritional status. Elderly.*

INTRODUCTION

The World Health Organization (WHO) defines malnutrition as "cellular imbalance between supply of nutrients and energy, and body's demand for them to ensure growth, maintenance, and specific functions".[1]

Nutrition plays a significant element in elderly wellbeing. Malnutrition is linked in several ways to diseases like cardiovascular disease, stroke, cancer, which are leading cause of death.[2] Older individuals want to remain healthy and independent so that they would not become burden for others. Malnutrition in the elderly is often overlooked, inadequately recognised and treated, despite being the most common cause of disability in this often neglected population.[3] From primary care to tertiary care centres, malnutrition in elderly is a common problem.

In Pakistan, 6% of the population is over 60 years of age, which number is expected to be doubled by 2025.[4]

[1] *Department of Family Medicine, Indus Health Network, Karachi.*
[2] *Department of Family Medicine, Aga Khan University Hospital, Karachi.*

Correspondence: Dr. Sidra Kanwal, Senior Instructor, Department of Family Medicine, Indus Health Network, Karachi. E-mail: skanwal1986@yahoo.com

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A healthy and balanced diet is favourable for the elderly in several ways; it can help in improving the management of concurrent comorbid diseases. Secondly, it can help in speedy recovery from several illnesses, improves mental, physical and social well-being. It may be difficult for some older individuals to get sufficient food, especially if they are dependent and poor, not capable to drive and wander around.[5]

Likewise, it is an established fact that cognitive impairment, disease burden, low and high BMI index are some risk factors for decline in functional status; and they need to be addressed.[6]

Katz defines functional status as individual ability to complete essential tasks of every day functioning.[7]

In geriatric health assessment, functional capacity is a key component. It affects the quality of life of an older individual as well as his caregiver.[8] A study conducted in UK in 2002 describes a causal relationship between the functional decline and malnutrition represented by spearmen rho (r=0.402).[9]

In Pakistan, the increasing number of elderly population poses a great challenge in terms of the healthcare burden due to various social and biological influences.[10] Due to social and financial factors, the elderly population is at risk of malnutrition and subsequent impairment in their functional activity and affects their quality of life. Some cross-sectional studies have been done inter-

nationally, but no comprehensive assessment has been done in Pakistan regarding this issue. Therefore, the aim of this study was to assess the correlation of nutritional and functional status of elderly people.

METHODOLOGY

This cross-sectional study was conducted from August 2014 to February 2015. A total of 200 participants, 60 years and old, presented to Family medicine clinics at Aga Khan University Hospital, were recruited. The inclusion criteria include all patients with non-urgent general medical problems, who were able to communicate and provided informed consent, were enrolled, *via* non-probability consecutive method of sampling. Exclusion criteria were patients with cancer, bed-bound patients, e.g comatose, paralysis of lower limbs, on total parenteral nutrition (TPN) or peripheral parenteral nutrition (PPN). Sample size was calculated *via* correlation calculator for sample size determination. From the literature review,[9] sample size came out to be based on this value was 48, but the authors recruited 200 study participants.

The study was approved by the Ethical Review Committee of the Aga Khan University Hospital (3014-FM-ERC-14). Informed written consent was obtained from every participant. Sociodemographic factors, like age, gender, education, marital status, current employment status, and comorbid conditions were recorded.

The outcome variables that were the level of functional status were assessed by validated Urdu and English modified version of Katz score which provided information about the individual's ability to perform basic functional tasks. The components of this index were bathing, dressing, toileting, continence over urine and stool, and ability to feed. The response was scored as 0 and 1.[11]

Total was interpreted as >5 indicating full function, 3-4 moderate impairment, and <2 severe functional impairment. Nutritional status was assessed by MNA scale which includes questions regarding any recent weight changes, dietary change, body mass index, recent hospital admission, dementia (self or care-giver reported), and current mobility.[12] Total was interpreted as normal nutritional status = 24 to 30 points, at risk of malnutrition = 17-23.5 points, and less than 17 points indicating malnutrition.

Information was collected *via* face-to-face interviews using a structured, pre-tested questionnaire. The questionnaire was initially prepared in English and then translated into Urdu, for the convenience of the respondents. The questionnaire was also back-translated into English by two non-medical personnel to check for any paraphrasing errors. This provided linguistic validation for the questionnaire. Recall bias was avoided by asking questions related to the current patient's condition.

As medical comorbid condition and family system were the potential confounders, results were stratified on the basis of these confounders. Statistical analysis was done by using SPSS software version 19.0. Baseline information on demographics was analysed using descriptive statistics. Frequencies and proportions were reported for categorical variables such as gender, age, marital status, education, nutritional status of elderly, and functional capacity (dependent, independent). The outcome variables were nutritional status (normal, malnourished) and functional capacity (dependent/ independent) of the elderly. Frequency of nutritonal status and functional capacity was calculated to fulfill the objective. To assess the correlation between nutritional status and functional status of elderly, Spearman's rank correlation coefficient was applied. To identify the relation of demographic variables (age, gender, educational status, living status) with outcome variables stratification was done, and post-stratification spearmen rho correlation was applied. Significance level was taken as p-value of $\leq$0.05. Median IQR, score of nutritional and functional status was calculated.

RESULTS

Out of 200 participants, 109 (54.5%) were males and 91 (45.5%) were females. Two-thirds (64%, n=128) of the individuals were married and approximately one-third (28.5%, n=57) were not formally educated. Table I shows the frequency of sociodemographic variables according to age, education and marital status. Hypertension (67%, n=134) and diabetes 50% were found to be most prevalent diseases. Polypharmacy was seen in 37.5% (n=75) of the study participants.

Table II shows that according to MNA scale 6% (n=12) had severly decreased food intake (more than 75% of baseline) and 5% (n=10) had weight loss of more than 3 kg. There was a 19% (n=38) frequency of dementia. About half of the population i.e. 54% (n=108), had calf circumference more than 31 cm. BMI more than 23 kg/m^2 was seen in 53% (n=106) of the participants.

About one-third of individuals reported difficulty in performing all the six tasks of daily living checklist. About 35.5% (n=71) had difficulty in taking bath, 32.5% (n=65) in getting dressed up and 32% (n=64) participitants needed assitance in getting on and of in toilet and cleaning genital area. Similarly, 33% (n=66) needed assistance in transferring out of bed or chair. Seventy-two (36%) individuals did not have bladder control and 31.5% (n=63) could not eat food without help. Out of 200 indiviuals, 30% (n=60) were found to have severe functional impairement and were at risk of malnutrition.

One hundred and twenty-nine individuals, i.e. 64%, were fully independent, 11 participitants, i.e. 6%, were moderately dependant and 60 elders, i.e 3%, were fully dependant. Furthermore, prevelance of malnutrition

Table I: Socio-demographic variables.

Variable	N=Number / frequency	Percentage %
Age		
60-64 years	70	35
65-69 years	53	26.5
70-74 years	39	19.5
75 and more than 75 years	38	19
Gender		
Male	109	54.5
Female	91	45.5
Education		
Illiterate	57	28.5
Primary education	22	11
Secondary education	48	24
Intermediate	35	17.5
Higher education	38	19
Marital Status		
Married	128	64
Separated	3	1.5
Divorced	9	4.5
Widow / widower / single	60	30
Current employment		
Housewife	72	36
Job / business	25	12.5
Retired	103	51.5
Number of children		
None	14	7
1-2	52	26
3-5	58	29
>5	76	38
Diabetes		
Yes	100	50
No	100	50
Hypertension		
Yes	134	67
No	66	33
Ischemic heart diseases		
Yes	33	16.5
No	167	83.5
Thyroid diseases		
Yes	8	4
No	192	96
Kidney diseases		
Yes	25	12.5
No	175	87.5
Stroke		
Yes	9	4.5%
No	191	95.5
Osteoarthritis		
Yes	42	21%
No	158	79%
Number of drugs		
0-3	125	62.5
More than 4	75	37.5
Family system (live with whom?)		
Alone	13	6.5
With family	183	91.5
Others (friends, nursing home)	4	2

Table II: MNA (mini nutritional assessment).

Variable	N=Frequency	Percentage
Has food intake declined over the past three months?		
Severe decrease in food intake (more than 75% from baseline)	12	6%
Moderate decrease in food intake (decline of 50-75% from baseline)	71	35.5%
No decrease in food Intake	117	58.5%
Have you lost any weight without trying over last 3 months?		
More than 3 kg weight loss	10	5%
Don't know	23	11.5%
1-3 kg weight loss	65	32.5%
No weight loss	102	51%
How would you describe your current mobility?		
Bed- or chair-bound	24	12%
Can get out of bed but not out of home	49	24.5%
Goes out	127	63.5%
Do you have dementia?		
Severe dementia	5	2.5%
Mild dementia	33	16.5%
No psychiatric illness	162	81%
Have you been recently ill? (acute illness)		
Yes	47	23.5%
No	153	76.5%
Calf circumference		
Less than 31 cm	92	46%
CC 31 or greater	108	54%
BMI (body mass index)		
BMI less than 19	15	7.5%
BMI 19 or less than 21	33	16.5%
BMI 21 to less than 23	46	23%
BMI 23 or greater	106	53%

Table III: Activities of daily living (ADL).

	N=frequency	Percentage
Bathing		
Can you take bath yourself completely?		
No	71	35.5%
Yes	129	64.5%
Dressing		
Can you gets clothes from closets and drawers and put on clothes?		
No	65	32.5%
Yes	135	67.5%
Toileting		
Can you go to toilet, get on and off, arranges clothe, cleans genital area without help?		
No	64	32%
Yes	136	68%
Transferring		
Can you move out of bed or chair unassisted?		
No	66	33%
Yes	134	67%
Continence		
Do you have complete self-control over urination and defecation?		
No	72	36%
Yes	128	64%
Feeding		
Can you eat food from plate into mouth without help?		
No	63	31.5%
Yes	137	68.5%
Dialling		
No	101	50.5%
Yes	99	49.5%
Shopping		
No	101	50.5%
Yes	99	49.5%

Table IV: Correlation of functional status and nutritional status.

Nutritional status	Fully functional N (%)	Moderate impairment in functional status N (%)	Severe functional impairment	Spearmen correlation (rho)	p-value <0.001
Malnourished	1 (0.8%)	2 (18.2%)	26 (43.3%)	-0.675	<0.001
At risk of malnutrition	33 (25.6%)	3 (27.3%)	31 (51.7%)		
Normal nutrition status	95 (73.6%)	6 (54.5%)	3 (5.0%)		

were found to be 14.5%, n=29. One hundred and four individuals, i.e. 52%, had normal nutritional status and 67 individuals, i.e. 33.5%, were at risk of malnutriton.

Individuals with higher education were found to be more active in performing activities of daily living. Out of 38 highly educated persons, only six suffered from severely functional impairement (rho=-0.126, p= 0.065). Out of 38 individuals with rising age, i.e. more than 75 years, 20 participitants were severely functional impaired (rho= -0.342 and p = 0.066).

Spearmen correlation between functional and nutritional status was found to be significant with p=<0.001, rho= -0.675 (Table IV). Both were also significantly associated with variables, like age and educational status (rho= 0.347, p<0.001 and rho = -0.139 , p=0.049, respectively).

Median interquarantile range for nutrtional score is 13 (1-14) and functional status score is 6 (0-6).

DISCUSSION

The objective of this study was to assess the relationship of nutritional status and functional capacity in elderly people. It is clear from the results that there is a significant positive correlation between nutritional and functional status, similar to the results in a study conducted in the United Kingdom Spearmen rank correlation of r=-0.402.[9]

The prevalence of malnutrition in the elderly population, according to nutrition check list, was 14.5% (n=29). This is consistent with the study conducted in Hong Kong by Shum *et al*. in which the prevalence of malnutrition was found to be 16.7% in hospitalised elderly.[13] These results of present study differ from another local study, which was conducted in a community dwelling older adults population in Sargodha,[14] which showed the prevalence of malnutrition to be 5.53%. The reason behind this could be that the study was done in community dwelling adults, and the present participants were from Family Medicine clinics. Loss of appetite and changes in taste and smell is often seen with aging, which can lead to more limited food choices and low intake of healthy foods. For many of older adults, it is difficult to shop for food, lift objects and access to food secondary to mobility constraints, so all these factors need to be emphasised in geriatric health assessment.

In this study, 30% had severe functional dependence which is much higher in comparison with a study conducted in Bangladesh in rural area in only 7% reported limitatons in ADL.[15] These findings may be due to selection bias in this study population as patients were recruited from the clinics. As malnutrition is a significant risk factor for functional decline, this makes elderly population more prone to falls, risk of infection and pressure ulcers further leading to nutritional decline. Thus viscous cycle goes on.

In this study, no significant association was found between the living status like living alone and functional status as p-value was found to be 0.288 and Spearmen correlation was 0.076. This is in contrast to study conducted in Brazil which showed significant correlation between family system and functional status.[16] This could be due to the Pakistan family system which is very strong and most of the elderly population depend upon their children for their financial and social support after retirement. Also prevalence of elderly, who are living alone, was found to be low in the present study, i.e. 8.5% (n=17).

It was found that functional status was severely impaired in 33.3% of elderly patients who were more than 75 years of age. This signifies that age is a significant risk factor for functional impairment; similar results were seen in an international study.[16]

Male gender was found to be more malnourished and was functionally dependent too; this could be due to the male predominance in the population sample. Another significant sociodemographic factor was educational status. This study showed that those participants who were illiterate were more functionally dependent and there was positive association found between illiteracy and functional impairment. About 28.5% of respondents found to be illiterate and 64% were married. Almost half of the elderly population was retired from their primary occupation, which is concurrent with another national study, where almost 41% were economically active.[17]

As a secondary outcome, it was noted that a high percentage of elderly had chronic diseases like hypertension (67%), and 50% had diabetes. However, the study did not look at further control of comorbidities.

Polypharmacy has been seen as a risk factor for comorbid condition like falls,[18] and functional decline.[19] In this study, polypharmacy was seen in 37.5%.

There are various tools available internationally for assessment of nutritional and functional status. MNA scale was used for nutrition assessment.[20] For functional assessment, Barthel index was used which was first described in 1965.[21] These scales have excellent reliability and validity. In measuring malnutrition as well as physical disability respectively, it has been validated in an international study.[22]

There are several strengths of this study. Firstly, to the best of the authors' knowledge, it is the first study of its kind to be conducted in the country with specific interest to assess correlation between nutritional and functional status in elderly. Secondly, the survey questionnaire used was Mini Nutritional Scale and Katz index scale which was pretested and was translated in Urdu at patients level of understanding The questionnaire was filled by principal investigator *via* face-to-face interview to prevent interviewer bias. Data was collected from patients presenting to general family medicine clinic due to various reasons, this could ensure recruitment of all patients, with variety of socioeconomic background and various medical conditions.

The limitations are that there is a limited sample size, and samples were drawn from only one hospital site of Karachi, which limits internal validity. Thus, the findings cannot be considered representative of all elderly population in Pakistan. Since the results are based on cross-sectional data, the causal relationship between nutritional and functional status cannot be made. Moreover, certain confounders, like income level, smoking, etc. were not asked; and hence, cannot be commented upon.

CONCLUSION

Older adults presenting to Family Medicine Clinics were at high risk of malnutrition and functional dependence. There is an association between malnutrition and functional status. These interrelationships require further studies to elucidate. Also, it is necessary to pay special attention to functional capacity when planning nutrition care for this vulnerable group. Moreover, age and educational status were statistically significant risk factors for malnutrition and functional decline. An important policy recommendation would be to bring about a change in the whole family's thought perspective. General physicians need to emphasise geriatric care regarding importance of nutritional status through public education. It should also be part of undergraduate and postgraduate curriculum.

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ORIGINAL ARTICLE

Outcome of Endoscopic Management of Post Living Donor Liver Transplant Anastomotic Strictures

Akif Dilshad, Adnan Salim, Muhammad Israr Ul Haq, Johar Amin, Kashif Malik and Altaf Alam

ABSTRACT

Objective: To evaluate the therapeutic efficacy of endoscopic dilatation of anastomotic stricture (AS).

Study Design: An observational study.

Place and Duration of Study: Department of Gastroenterology and Hepatology, Shaikh Zayed Hospital, Lahore, Pakistan from November 2016 to November 2017.

Methodology: Patients presenting with anastomotic biliary stricture following living donor liver transplant (LDLT) underwent endoscopic retrograde cholangio-pancreaticography (ERCP) and treatment of their strictures with dilatation with or without stenting. The patients were then followed up to see adequate resolution of stricture and repeat therapeutic ERCP was performed, if required. The patients were labelled as cured if stricture resolution persisted for a period of up to six months following ERCP.

Results: Forty-three patients (32 males and 11 females), with post-LDLT AS, who met the inclusion and exclusion criteria were enrolled in the study. Thirty-six (83.7%) patients had a single biliary anastomosis while seven (16.3%) patients had two anastomoses. Ductoplasty was done in 15 (34.9%) of the enrolled patients. Patients with post-LDLT AS required 3.65 $\pm$1.15 sessions of ERCP. Plastic type biliary stent was used in seven (16.3%) patients, balloon dilatation alone was done in five (11.6%) patients and combined balloon dilatation and stent placement was performed in 29 (67.4%) patients, and combined graduated dilator and stent placement was performed in two (4.7%) patients. Five (11.6%) patients required *rendezvous* procedure (whereby a radiologist placed a guidewire percutaneously into the biliary system) as guidewire placement across stricture site was endoscopically unsuccessful. The overall success rate was 88.4%. Mean stent free follow-up was 7.18 $\pm$1.38 months. Recurrence of AS was noted in one (2.3%) patient.

Conclusion: Endoscopic management of post-LDLT AS has an efficacious long-term outcome.

Key Words: *Living donor liver transplant (LDLT). Anastomotic stricture. Endoscopic retrograde cholangio-pancreaticography (ERCP). Stent.*

INTRODUCTION

Liver cirrhosis constitutes one of the commonest causes of death worldwide.[1] Different viral infections, alcohol intake and certain metabolic abnormalities lead to cirrhosis. Once cirrhosis is established. The only curative treatment option is liver transplantation.[2]

Liver transplantation is a life saving procedure in patients with end-stage liver disease (ESLD) and acute hepatic failure. The significant improvement in surgical techniques and medical management of post liver transplant (LT) patients has led to overall one-year survival following liver transplant to over 90% and five-year survival to over 80%.[3] However, biliary complications, rejection and infections are still common causes of morbidity and mortality.

Out of different biliary complications, biliary strictures are more common and troublesome. Post LT biliary strictures can be classified into anastomotic and non-anastomotic strictures. Non-anastomotic strictures are long, multiple and can occur in intra- and extra-hepatic biliary channels. Anastomotic strictures are solitary and mainly related to surgical technique and local ischemia of distal bile duct stump leading to fibrotic scarring at anastomotic site.[4,5]

The reported incidence of anastomotic strictures is 5-15% after cadaveric transplant and 28-32% after LDLT.[6] Anastomotic strictures can present at any time after surgery but major bulk present within one year. Studies have shown that their prevalence is continuously increasing with the time after transplantation.[7] Anastomotic strictures present with characteristic clinical, biochemical and radiological features of biliary obstruction, leading to cholestasis and cholangitis,[8] with related clinical, laboratory and radiological features.

Surgical management was the mainstay of treatment in the past but endoscopic treatment is now the preferred first-line strategy. It is less invasive with fewer complications. Surgical treatment and percutaneous techniques are only employed in case of failure of endoscopic methods. Endoscopic management includes identification of stricture, cannulation by guidewire, dilatation of stricture with dilators and placement of plastic stent, if required.[9]

Department of Gastroenterology and Hepatology, Shaikh Zayed Hospital, Lahore.

Correspondence: Dr. Adnan Salim, Assistant Professor, Department of Gastroenterology and Hepatology, Shaikh Zayed Hospital, Lahore.
E-mail: adnansalim1147@gmail.com

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Usually, multiple sessions of endoscopy are required at six-week to three-month intervals. Strictures are dilated with progressively increasing diameter dilators and, if needed, the number of stents is also increased at each session. Stricture dilatation using balloon only, without stent placement, leads to 40% success. However, stricture dilatation with stent placement leads upto 75% success.[10] Dual or multiple stents provide better outcome. Placement of multiple stents side by side, usually two to three (increasing number of stents at succeeding sessions) will lead to 80 to 90% success rate.[11] The stents are generally replaced every three months to minimize complications of blockage, cholangitis or stone formation.

The aim of this study was to evaluate the outcome of endoscopic management of post liver transplant strictures at Shaikh Zayed Hospital, Lahore.

METHODOLOGY

The study was conducted in the Department of Gastroenterology-Hepatology, Shaikh Zayed Hospital, Lahore, from November 2016 to November 2017. Patients presenting with anastomotic biliary stricture following liver transplantation were included in the study. Patients with non-anastomotic post liver transplant biliary strictures, such as new or recurrence of HCC or cholangiocarcinoma as a cause of bile duct stricture, were excluded.

Anastomotic stricture was defined as a solitary short segment stricture at bile duct anastomotic site with proximal dilatation of biliary channels diagnosed by ultrasound abdomen, CT-scan and/or MRCP in a patient with a history of liver transplant. Successful management was defined in this study as resolution of narrowed anastomotic segment of CBD, as seen on contrast injection under fluoroscopy, after therapeutic dilatation with balloon and/or dilatation catheters or stent placement and which persists for a period of greater than six months following dilatation alone or after removal of biliary stents placed after dilatation. Unsuccessful management was defined as recurrence of or inadequate endoscopic dilatation of anastomotic stricture requiring surgery or unsuccessful wire cannulation of strictured site during endoscopy.

This was a prospective interventional study, carried out after approval of the Institutional Review Board. Patients meeting the inclusion and exclusion criteria were included in the study. Patients presenting with obstructive symptoms like jaundice, itching, clay-color stools or fever due to cholangitis after liver transplant were evaluated for anastomotic biliary stricture by using blood tests (serum transaminase levels, alkaline phosphatase and bilirubin) abdominal ultrasound, CT abdomen and MRCP. In cases where findings were equivocal, a liver biopsy was also done to rule out transplant rejection. ERCP was done for management of stricture. Therapeutic interventions during ERCP included use of stricture dilatation catheters and balloons followed by, if required, placement of plastic biliary stents. The size of balloon used varied from 6mm to 10 mm in diameter. Dilatation catheters were of the graduated variety, and sizes used were 7-8.5 French to 8.5-10 French. Size of the stents used varied from 7 to 10 French in diameter. The length of stents used varied between 10 to 15 cm and depended on the position of stricture. It is standard protocol at the study centre to use dilatation catheters no larger than 8.5 French and/or single stents no larger than 7 French during first ERCP. Beyond first ERCP, larger caliber stents/multiple stents are deployed.

Following ERCP, patients were followed up initially with fortnightly and then monthly with serial LFTs and abdominal ultrasound to check for clinical and biochemical improvement along with monitoring of patency and adequate drainage of any deployed stents. If patients did not undergo stent placement and remained stable for up to six months, they were labelled as having undergone successful management and shifted to routine follow-up at the liver transplant outpatient clinic. If patients had undergone stent placement, they were followed up for up to three months, following which they underwent repeat ERCP with removal of previous stent/stents. If adequate biliary patency with no narrowing is noted on cholangiogram, no further therapeutic intervention was done and the patient was placed on regular monitoring for six months. If narrowing was seen on cholangiogram, repeat dilatation was performed with balloons and/or dilatation catheters and larger caliber stents or more stents were deployed. If during the 3-month follow up following ERCP the patient showed any signs of biliary obstruction (fever, jaundice), then repeat ERCP was performed with an aim for wider dilatation and greater caliber/number of deployed stents. All findings were recorded on a specially designed proforma.

Data was analysed by using the Statistical Package for Social Sciences (SPSS) version 22. Descriptive statistics were reported as frequency and percentages for all qualitative variables like gender. Mean and standard deviation, were calculated for all quantitative variables, such as age.

RESULTS

A total of forty-three patients were inducted who had presented with anastomotic biliary stricture following LDLT. Right lobe of the donor liver was used as graft in all the patients. Mean age of patients enrolled in this study was 46.39 $\pm$9.96 (22-65) years. Out of them, 32 (74.4%) were males and 11 (25.6%) were females. Cause of liver transplant was predominantly hepatitis C related cirrhosis with 32/43 (74.4%) patients affected (Table I).

Thirty-six (83.7%) patients had a single biliary anastomosis while seven (16.3%) patients had two anastomoses. Ductoplasty was done in 15/43 (34.9%) enrolled patients. During surgery, single duct was found in the graft in 22 patients (51.2%) and double duct in 21 (48.8%).

Pruritus was the most frequent presenting symptom, which was noted in 22/43 (51.2%) patients with the remaining presenting with symptoms such as clay-colour stools 5/43 (11.6%) and dark-colour urine 7/43 (16.3%). More than one symptom was present in three (7%) patients. Six (14%) patients had fever secondary to cholangitis. Mean interval between the liver transplant and the first ERCP was 4.55 ±1.70 months.

Biliary balloon dilatation followed by biliary stent placement was combined in the majority, 29/43 (67.4%) patients to treat anastomotic biliary stricture, while stenting or balloon dilatation alone was used in smaller groups (Table II). The total number of ERCP sessions carried out was 3.65 ±1.15. Treatment success was noted in 38 (88.4%) out of 43 enrolled patients (Table II). Mean stent-free follow-up was 7.18 ±1.38 months.

ERCP was unsuccessful in the five remaining patients. One, who had a successful first ERCP session and stent placement, presented after 6 weeks with stent occlusion leading to cholangitis and ultimately died of sepsis and complications. Another patient had a successful resolution of stricture confirmed on cholangiography after two sessions of ERCP, but unfortunately had a recurrence of stricture within six-month follow-up period. The patient presented with cholangitis and underwent surgery. In three patients, endoscopic wire cannulation of bile ducts was unsuccessful. The interventional radiology team passed a guide-wire percutaneously through the liver and ampulla and into the duodenum (*rendezvous* procedure). ERCP was then performed over the guidewire.

Table I: Clinical and demographic profile of patients.

Age (years)	
Mean ±SD	46.39 ±9.96 (22-65)
Gender	
Male	32 (74.4%)
Female	11 (25.6%)
Cause of cirrhosis leading to transplant	
Hepatitis C	32 (74.4%)
Hepatitis B	5 (11.6%)
ALD	2 (4.7%)
Others	4 (9.31%)

Table II: Endoscopic management of stricture.

Number of ERCP sessions	
Mean ±SD	3.65 ±1.15
Therapeutic procedure	
Balloon dilatation followed by stenting	29 (67.4%)
Stenting alone	7 (16.3%)
Balloon dilatation alone	5 (11.6%)
Combination of graduated dilator and stent	2 (4.7%)
Treatment success	
Successful	38 (88.4%)
Unsuccessful	5 (11.6%)
Stent free follow-up in months	
Mean ±SD	7.18 ±1.38

DISCUSSION

LDLT with duct-to-duct anastomosis is mostly performed in Asia and especially in Pakistan, as cadaveric donors are scarce in this part of the world. LDLT with duct-to-duct anastomosis has a high rate of developing stricture at anastomotic site. In some studies, this rate is as high as 30%, and it comprises more than 50% of all complications post-LDLT.[12] Living donor grafts require more complicated surgery, especially reconstruction of the graft biliary channels, which increases the chances of post-surgical biliary complications.[13,14] If left un-managed, it may lead to rapid graft loss.[15]

Management of such strictures is vital to prevent graft loss. Different modalities like surgery, interventional radiological procedures and endoscopic therapies can be offered to patients for this complication. Endoscopy is a convenient, minimally invasive method with minimal complications of all these and is considered first line of therapy.[16,17]

Keeping in view the frequency of biliary complications and their threat to the graft viability, interventions for the treatment of these complications are necessary. In this study, ERCP for management of anastomotic biliary strictures in post-LDLT patients was evaluated. Different studies have shown success rate up to 90% in endoscopic management of such strictures.[18] This study showed a success rate of 88.4% (38 out of a total 43 patients) in managing post-LDLT AS with ERCP.

Performing ERCP in such patients requires a higher skill level than routine ERCP procedures, and a greater in-depth knowledge of the modified biliary anatomy following LDLT. An experienced interventional radiology team is a vital component of the hepatobiliary team that manages patients following liver transplantation. Interventional radiologists can assist greatly by performing percutaneous guidewire cannulation of the common bile duct in cases where endoscopic cannulation is unsuccessful.[19]

Patients can develop biliary strictures very early in post-transplant period. How early an ERCP can be performed after liver transplant is debatable and data is scarce on this topic. The authors usually wait for 4-6 weeks after liver transplant. In these patients, the mean interval between liver transplant and first ERCP was 4.55 ±1.70 months. Chang *et al*. carried out a similar study in which the mean interval between liver transplantation and first ERCP was six months and the mean number of ERCP sessions was 3.2.[14]

Patients require multiple endoscopic sessions for successful stent-free stricture dilatation.[20] In this study, the mean number of ERCP sessions carried out was around 4%. Sphincterotomy was also performed before balloon dilatation and stent placement. This may theoretically predispose to duodenobiliary reflux with resultant development of cholangitis in immuno-compromised patients such as those following liver transplantation.[21] This needs to be evaluated in further studies.

CONCLUSION

Post-LDLT AS is effectively managed by ERCP, with a strictly multidisciplinary team effort. Managing these patients requires active input from the radiology team prior to endoscopic intervention, with interventional radiology staff as backup. In cases where both are unsuccessful, experienced hepatobiliary surgery teams are vital to save the liver graft.

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ORIGINAL ARTICLE

Immune System Activation in Rheumatic Heart Disease

Aqsa Anam[1], Abdul Wajid Khan Faisal[2], Nadeem Afzal[1] and Faheem Shahzad[1]

ABSTRACT

Objective: To assess activation of immune system in rheumatic heart disease (RHD) patients in the form of AECA, ACL and anti GBM antibodies.

Study Design: Descriptive, observational study.

Place and Duration of Study: Department of Immunology, University of Health Sciences (UHS), Lahore, and Outpatient Department, Punjab Institute of Cardiology, from February 2015 to January 2016.

Methodology: Clinically suspected patients of RHD and confirmed by echocardiography were included. AECA, ACL and anti GBM antibodies were investigated in the sera of RHD patients.

Results: Eighty-six RHD patients were included in the study; the mean age of the patients was 30 ±9.3 years. Among these patients, 59 (68.6%) were females and 27 (31.4%) were males. AECA was most commonly detected autoantibody i.e. in 17 (19.8%) patients; whereas, ACL was detected in only 2 (2.3%) subjects. Another 2 (2.3%) patients had both AECA and ACL antibodies. AGBM was not detected in any of the patients. ACL was seen in females with isolated MR. AECA were seen in mixed valvular heart disease patients.

Conclusion: Immune system gets activated in RHD patients leading to formation of different antibodies, and they are also related to the type of lesion. ACL antibodies are present in females with isolated mitral regurgitation, while AECA are present in both the genders with mixed valvular heart disease. Anti GBM antibodies are not seen in RHD patients.

Key Words: *Rheumatic heart disease (RHD). Anti-endothelial cell antibodies. Anti-cardiolipin antibodies. Anti GBM antibodies.*

INTRODUCTION

Rheumatic heart disease (RHD) is a disease of childhood and young adults characterised by damage to heart valves that occurs after group A β-hemolytic *streptococcal* infection.[1] Since early 1900, incidence and prevalence of acute rheumatic fever (ARF) and RHD is declining in developed countries due to better living conditions, better nutrition, and accessibility of antibiotics against group A *streptococcal* infection.[2] All over the world, more than 15 million people are suffering from this deadly disease with 282,000 new cases and 233,000 deaths annually.[3] The situation is even worse in Pakistan where the prevalence of RHD is 22 per 1000 in Lahore and 5.7 per 1000 in rural areas of Pakistan.[4,5]

RHD is a consequence of ARF and most patients present with shortness of breath at 20-50 years of age.[6] RHD results from humoral and cellular immune response that usually develops after 1-3 weeks of group A *streptococcal pharyngitis*. RHD usually results from recurrent episodes of ARF.[7] RHD is an immune mediated disease, the bacterial M protein has structural resemblance to the proteins in heart; and thus the antibodies formed against *streptococci*, damage the heart as well.[8] Disease susceptibility, such as major histocompatibility antigens and tissue specific antigens are under investigation. Auto-antibodies during *streptococcal* infection are also being studied for their role in the pathogenesis of RHD.[9] There are several types of auto-antibodies which are involved in the progression of RHD such as ASO, anti-DNase, anti-mitochondrial, anti-smooth muscle, anti-vimentin,[10] anti-endothelial cell and anti-cardiolipin.[11]

AECA have been detected in many autoimmune and inflammatory/infectious diseases including rheumatoid arthritis, systemic sclerosis, polymyositis, anti-neutrophil cytoplasmic antibody associated vasculitis, Takayasu's arteritis, Behcet disease, leprosy and cytomegalovirus infections.[12] Several studies suggested important role of AECA in RHD, but presence of AECA in RHD is still a matter of debate. Although, different studies have been carried out to determine ACL antibodies in RHD, but their role in RHD, is still unclear, and it should be investigated for better control and management of RHD.[11,13,14] AGBM auto-antibodies are mainly important in Good pasture's syndrome (GPS). AGBM antibodies have also been detected in HIV, SLE, and in healthy persons.[15-17] However, their presence in RHD has still not been studied.

The objective of this study was to assess activation of immune system in rheumatic heart disease (RHD) patients in the form of AECA, ACL and anti GBM antibodies.

[1] *Department of Immunology, University of Health Sciences (UHS), Lahore.*

[2] *Department of Cardiology, Punjab Institute of Cardiology, Lahore.*

Correspondence: Dr. Abdul Wajid Khan Faisal, Associate Professor of Cardiology, Gujranwala Medical College, Gujranwala.
E-mail: drwajidkhan@hotmail.com

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METHODOLOGY

The descriptive study was conducted in the Department of Immunology, University of Health Sciences (UHS), Lahore. Patients were screened from OPD of Punjab Institute of Cardiology (PIC), from February 2015 to January 2016. This study was approved by the Ethical Review Committee of PIC and Advanced Studies and Research Board of UHS Lahore. Clinically suspected patients of RHD confirmed by echocardiography were included in the study. Patients of acute rheumatic fever, endocarditis or congenital valve disease, pregnancy, malignancy, and patients with autoimmune disorders, e.g. RA, SLE, etc. were excluded. In the Department of Immunology, serum was separated by centrifugation at 1800 rpm for 10 minutes and aliquoted in three Eppendorf tubes, which were labelled with the allotted individual sample identification number. It was stored at -80ºC until the study parameters, i.e. anti-endothelial cell, anti-cardiolipin and anti-glomerular basement membrane antibodies were performed by commercially available enzyme linked immunosorbent assay (ELISA) kits.

The sample size was calculated by the formula:

$$n \frac{Z^2 1-\alpha/2 \, P \, (1-P)}{d^2}$$

keeping the confidence level equal to 95% and the margin of error equal to 10% with anticipated population proportion of patients with positive antibodies in RHD patients as 40%.[16]

(Sample size determination in health studies version 2.0.21 WHO calculator).

The data was entered and analysed using IBM SPSS 20.0. Median IQR was calculated for quantitative variables, e.g. age. Qualitative variables, such as gender were expressed as frequencies and percentages. Chi-square test was used to express the association of the qualitative variables with group, while for ≤5 frequency cell fisher exect test was applied. Non-parametric Mann-Whitney test was applied to compare the median of anti-cardiolipin antibodies, anti-endothelial cell antibodies and anti-glomerular basement membrane antibodies with gender distribution. P-value ≤0.05 considered as significant.

RESULTS

A total 86 subjects were recruited for this study, the mean age of the studied subjects was median 29 (IQR: 14). Among these patients, 59 (68.6%) were female and 27 (31.4%) were males.

Among all the four heart valves, mitral valve was the most frequently involved valve in the studied population. The commonest lesion was the mitral regurgitation (MR) present in 63 (73.3%) patients, of which 27 (31.4%) had moderate MR and 27 (31.4%) had severe MR. Mitral stenosis (MS) was the second most common lesion, noted in 61 (70.9%) patients. As far as severity of MS is concerned, 48 (55.8%) patients were suffering from severe MS. Aortic regurgitation (AR) was the third commonest lesion being present in 50 (58.1%) patients. Severity of lesion was almost similar in three subsets of AR patients, i.e. 16 (18.6%) patients had mild, 18 (20.9%) had moderate, and 16 (18.6%) had severe AR. Other lesions were less common, e.g. Aortic stenosis (AS) in 9 (10.5%), trisuspid regurgitation (TR) in 14 (16.3%), only rheumatic TR was considered functional TR was not taken into account, tricuspid stenosis (TS) in 2 (2.3%) and pulmonary regurgitation in 1 (1.2%). None of the patient had pulmonary stenosis (Table I).

AECA was most commonly found autoantibody, present in 19 (22.09%) patients. ACL was found in only 4 (4.65%) patients. Two patients had both AECA and ACL, while AGBM was not detected in any of the patients. Sera of 61 (70.93%) patients were free from any auto-antibody studied (Figure 1).

AECA was found in (19 out of 86 patients) in both genders. 14/59 (23.72%) females and 5/27 (18.51%) males were positive for this auto-antibody. The AECA and ACL with different valve lesions is described in patients (Table II).

AECA was positive in isolated as well as mixed valvular disease; the frequency of mixed valvular lesions was higher than isolated valvular lesions (Table III).

Table I: Baseline demographic data.

Gender			
Female	59 (68.6%)		
Male	27 (31.4%)		
Age (years) Median (IQR)			
Female	32 (12)		
Male	28 (18)		
Type of heart valve disease	Severity	Frequency	Percent
Mitral stenosis	Mild	6	7.0%
N=61 (70.9%)	Moderate	7	8.1%
	Severe	48	55.8%
Mitral regurgitation	Mild	9	10.5%
N=63 (73.3%)	Moderate	27	31.4%
	Severe	27	31.4%
Aortic stenosis	Mild	3	3.5%
N=9 (10.5%)	Moderate	2	2.3%
	Severe	4	4.7%
Aortic regurgitation	Mild	16	18.6%
N=50 (58.1%)	Moderate	18	20.9%
	Severe	16	18.6%
Tricuspid stenosis	Mild	1	1.2%
N=2 (2.3%)	Moderate	1	1.2%
	Severe	0	0
Tricuspid regurgitation	Mild	1	1.2%
(rheumatic) n=14 (16.3%)	Moderate	5	5.8%
	Severe	8	9.3%
Pulmonary regurgitation	Mild	01	1.2%
Pulmonary stenosis	None		

Table II: Echocardiographic picture according to ACL and AECA positivity in patients with RHD.

	AECA positive (n=19)	AECA negative (n=67)	P-value	ACL positive (n=4)	ACL negative (n=82)	P-value
MR						
Present (n=63)	17 (27%)	46 (73%)	0.084	4 (6.3%)	59 (93.7%)	0.570
Absent (n=23)	2 (8.7%)	21 (91.3%)		0	23 (100%)	
MS						
Present (n=61)	13 (21.3%)	48 (78.7%)	0.781	1 (1.6%)	60 (98.4%)	0.072
Absent (n=25)	6 (24%)	19 (76%)		3 (12%)	22 (88.0%)	
AR						
Present (n=50)	9 (18%)	41 (82%)	0.281	1 (2%)	49 (98%)	0.304
Absent (n=36)	10 (27.8%)	26 (72.2%)		3 (8.3%)	33 (91.7%)	
TR						
Present (n=14)	2 (14.3%)	12 (85.7%)	0.726	0	14 (100%)	1.00
Absent (n=72)	17 (23.6%)	55 (76.4%)		4 (5.6%)	68 (94.4%)	
AS						
Present (n=9)	1 (11.1%)	8 (88.9%)	0.677	0	9 (100%)	1.00
Absent (n=77)	18 (23.4%)	59 (76.6%)		4 (5.2%)	73 (94.8%)	
TS						
Present (n=2)	1 (50%)	1 (50%)	0.395	0	2 (100%)	1.00
Absent (n=84)	18 (21.4%)	66 (78.6%)		4 (4.8%)	80 (95.2%)	

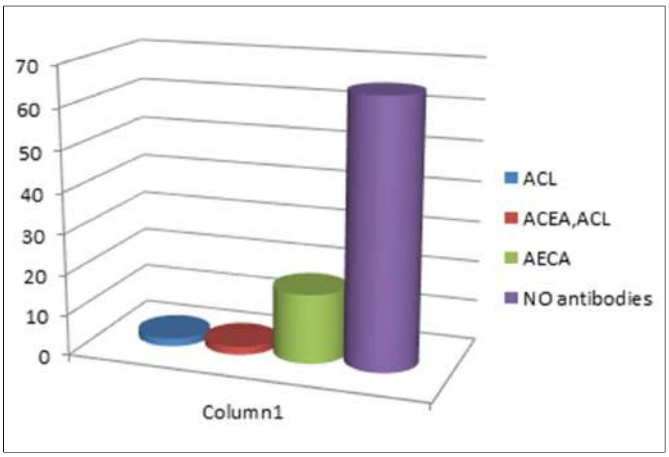

Figure 1: Stratification of auto-antibodies according to frequency distribution.

Table III: Echocardiographic picture and AECA positivity in patients with RHD.

Echocardiographic picture	Number of patients (%) N= 86	AECA positivity (%)
Isolated MS	5 (5.813%)	0
isolated MR	4 (4.651%)	1/4 (25%)
Mitral regurgitation and stenosis	9 (10.465%)	3/9(33.3%)
Mitral and aortic regurgitation	4 (4.651%)	0
Mitral and aortic mixed valve disease	40 (46.511%)	8/40 (20%)
Mitral and tricuspid valve disease	5 (5.813%)	1/5(20%)
Mitral, aortic, and tricuspid valve disease	10 (11.627%)	2/10 (20%)

All patients positive for ACL antibodies had mitral regurgitation. Two patients had both AECA and ACL antibodies positive. One of them had mixed mitral valve disease predominantly having MR, while other had severe MR and mild AR. The remaining two patients, who were positive for ACL antibodies only, had isolated severe MR. All patients positive for ACL antibodies were females (Table IV).

DISCUSSION

The presence of auto-antibodies in RHD is still questionable but quite a few studies i.e. Delunardo *et al*. and Scalzi *et al*. pointed out the importance of these antibodies in RHD.[10,11] In the current study, determination of AECA, ACL and AGBM auto-antibodies was carried out in RHD patients.

In the current study, AECA was detected in 19 (22.09%) RHD patients. AECA plays important roles in the cardiac tissue damage associated with RHD.[11] In the study by Scalzi *et al*., 40% patients were positive for ACEA.[11] These antibodies are related to advancing age and aortic valve disease. The difference in results may be due to the fact that this study included younger patients and aortic valve disease as less frequent. This study had more patients with mitral valve disease. AECA are also positive in many autoimmune and inflammatory conditions, but we excluded these patients in this study. Importantly, AECA in this study was seen in both genders and patients with mixed valvular disease.

Table IV: Antibodies with respect to gender.

Variables	Gender	Frequency	Median	IQR	P-value
Anti-endothelial cell antibodies	Female	14/59	5.9	4.35	0.896
	Male	5/27	5.6	4.38	
Anti-cardiolipin antibodies	Female	4/59	1.43	0.76	0.019
	Male	0/27	1.25	0.60	
Anti-glomerular basement membrane antibodies	Female	0/59	3.0	0.21	0.802
	Male	0/27	3.02	0.26	

Mann-Whitney u test used to compare median (IQR).

In literature, conflicting results are available about the presence of ACL antibodies in RHD patients. Cardiac valve lesions, similar to RF, have been observed in patients with anti-phospholipid syndrome (APS), suggesting that similar pathogenic mechanisms might be involved in both the diseases. In the current study, 4 (4.65%) RHD patient had ACL antibody which is not in accordance with the study of Scalzi *et al*., (2010), who documented ACL antibody in 7.8% of RHD patients.[11] Narin *et al*. documented in his study that ACL is not a marker of disease in rheumatic patient.[14] Here, it was noted that all patients who had ACL antibodies were females having MR. Soeiro, and Camargo *et al*. have also shown female gender associated with ACL.[18,19]

Figueroa *et al*. documented that during active phase of RF, 80% of patients had ACL antibody while during inactive phase only 40% of patients had these antibodies,[13] whereas current study suggested 4.65% RHD patient had ACL antibodies. The difference in results could be due to different study populations as Figueroa *et al*. included acute RF patients along with RHD, while current study included only RHD patients. Ilarraza *et al*. could not detect ACL antibody in the sera of 31 Mexican RHD patients.[20] So the role of ACL in RHD is controversial.

RF is a systemic inflammatory disease, which may cause vasculitis in multiple organs. Gunal *et al*. documented two children with rheumatic mitral valve disease and mitral valve replacement developed myocardial ischemia due to coronary vasculitis.[21] Gross *et al*. detected coronary vasculitis in 33% of RHD patients.[22] There are a number of reports of vasculitis having anti-GBM antibodies but no data is available for the presence of AGBM in RHD patients. Current study is the first study in which detection of AGBM was carried out in RHD patients and none of the study individual had AGBM. Therefore, absence of AGBM in RHD patients with different valve diseases indicates that these antibodies may not have direct involvement in the development of RHD.

This study comprised of a small number of patients of RHD. A study on large sample size is required to evaluate the level of auto-antibodies as the number of patients with ACL was very small. More auto-antibodies should be included in the panel to determine their involvement in the pathogenesis of this disease. No study so far has been done to detect these antibodies in RHD patients in Pakistani population and anti GBM antibodies have never been studied anywhere in the world to the best of the authors' knowledge. Those RHD patients, who are positive for these antibodies, may benefit from immunosuppressive therapy. This treatment may halt the progression of the disease.

CONCLUSION

Immune system gets activated in RHD patients leading to formation of different antibodies, and they are also related to the type of lesion. ACL antibodies are present in females with isolated mitral regurgitation, while AECA are present in both the genders with mixed valvular heart disease. Anti GBM antibodies are not seen in RHD patients.

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ORIGINAL ARTICLE

Gene Expression of Glyoxalase II in Diabetic Retinopathy

Amber Zaidi[1], Palvasha Waheed[1], Amir Rashid[1] and Saleem Ahmed Khan[2]

ABSTRACT

Objective: To study the gene expression of Glyoxalase II among patients of diabetic retinopathy.

Study Design: A cross-sectional comparative study.

Place and Duration of Study: CREAM (Centre for Research in Experimental and Applied Medicine) and the Department of Biochemistry and Molecular Biology, Army Medical College, Rawalpindi in collaboration with Armed Forces Institute of Ophthalmology (AFIO), Rawalpindi, from November 2015 to November 2016.

Methodology: Individuals were enrolled, among whom 30 were cases with diabetic retinopathy and 30 were controls without the disease. Their relevant data were collected and blood samples were drawn. Individual RNA was extracted from respective samples and cDNA was synthesised from each. Expression analysis for Glyoxalase II was done and relative quantification was done using delta delta CT method.

Results: A total of 60 individuals of ages 40-70 years were enrolled in the study, 30 cases and 30 controls. Among these, 34 (56.67%) were males and 26 (43.3%) were females. Mean ages were 60 ±8 years in cases and 59 ±13 years in controls. Down regulation of Glyoxalase II was observed in cases as compared to controls.

Conclusion: Downregulation of Glyoxalase II, seen among patients of diabetic retinopathy, may indicate a failure of detoxifying system leading to accumulation of glycated end products.

Key Words: *Complimentary DNA. Delta CT method. Diabetic retinopathy. RT PCR. Gene expression.*

INTRODUCTION

Glyoxalase system was first discovered by Dakin, Dudely, and Neuberg in 1913.[1] Methylglyoxal is actually a ubiquitous product of cellular metabolism and thus is present in all cells. It is produced via both enzymatic and non-enzymatic routes.[2] The glyoxalase system consists of two enzymes: Glyoxalase I named as lactoylglutathione methylglyoxalase and Glyoxalase II named as hydroxyacylglutathione hydrolase.[3]

Among microvascular complications of diabetes, the most debilitating are cataract and diabetic retinopathy. These may lead to visual impairment, and even blindness. People suffering from diabetes are expected to develop visual impairment about 25 times more than general population.[4] Pakistan ranks eighth in the world regarding diabetes mellitus. Patients with diabetes are expected to rise to 11.6 million by 2025.[5]

Production of methylglyoxal increases in continuous state of hyperglycemia. It is a very potent glycating agent. It reacts with protein, lipids, and DNA to form advanced glycosylated end products (AGEs). These activate specific receptors RAGEs (Receptors for AGEs). RAGEs activate NF-kB, NADPH oxidase, Protein kinase C, MAPK pathway and JNK pathways.

Department of Biochemistry[1] / Pathology[2], Army Medical College, Rawalpindi.

Correspondence: Dr. Amber Zaidi, Senior Lecturer, Department of Biochemistry, Army Medical College, Rawalpindi.
E-mail: amberzaidi11@gmail.com

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Glyoxalase II is the second enzyme of glyoxalase system. Its other name is hydroxyacylglutathione hydrolase (HAGH). It converts S-D lactoylglutathione into D lactate, forming glutathione as a byproduct. It is at locus 16p13.3, with cytosolic and mitochondrial forms. Among these, 9 exons code mitochondrial form while 10 encode its cytosolic form.[6]

Carbonyl stress is relieved by Glyoxalase system.[7] It is actually an enzymic defence against glycation of proteins.[8] Glycation occurs when glucose or its derivatives react with amines of proteins to form AGEs.[9] Chronic hyperglycemia in diabetes leads to development of AGEs.[10] These are thus related to diabetes mellitus and some other age related diseases.[11] These promote oxidative stress and inflammation in human body.[12] Binding of AGEs to their receptors, RAGEs leads to development of long term complications of diabetes.[13] AGEs enhance macrophage differentiation leading to development of inflammation in body.[14] They can be an important element of cascade of reactions of diabetic angiopathy and vascular damage in diabetes.[15]

The objective of this research was to study the expression of Glyoxalase II among diabetic patients and to compare it with normal healthy controls.

METHODOLOGY

Formal approval of the research work was taken from Ethical Review Committee of Army Medical College. Approval for patient enrollment, data, and sample collection was taken from Commandant Armed Forces Institute of Ophthalmology (AFIO). Written informed consent was taken from all patients of diabetic retinopathy

enrolled in the study. A performa was designed and dully filled by all subjects enrolled in the study.

This was a cross-sectional comparative study conducted at Centre for Research in Experimental and Applied Medicine (CREAM-1) and at the Department of Biochemistry and Molecular Biology, Army Medical College, Rawalpindi in collaboration with Armed Forces Institute of Ophthalmology (AFIO), Rawalpindi from November 2015 to November 2016.

Non-probability purposive sampling was done, in which 30 diagnosed patients of diabetic retinopathy were considered as cases and 30 normal healthy individuals were enrolled as controls. A questionnaire was designed and distributed among the patients.

Inclusion criteria for enrolled patients were diagnosed patients of type 2 diabetes mellitus with already developed retinopathy and having ages 40-70 years. Patients excluded from the study were those having retinopathy due to any other cause and those on any anti-inflammatory therapy. Normal healthy controls enrolled were age- and gender-matched.

Venous blood samples, 5ml, were drawn both from patients and controls. These samples were stored in EDTA tubes and transported on dry ice within half an hour to CREAM, in order to avoid RNA degeneration and to obtain high quality RNA. Then RNA extraction was performed according to the standard kit protocol. From this cDNA was synthesised and stored for expression analysis.

The primers of Glyoxalase II were designed on the basis of previously available sequence of Glyoxalase II in Homosapiens on National Centre for Biotechnology Information (NCBI) Reference Sequence: NC_018927.2. GC content and self complementation was checked at Oligocalc (Oligonucleotide Properties Calculator).

Forward Primer
5' GGCCACGAGTACACCATCAA3'
GC content: 55%
Tm: 60.5°C
Self-complimentary: None

Reverse Primer
5' CCAGGGCCACTCACTCTCA3'
GC content: 63%
Tm: 61.6°C
Self-complimentary: None

For comparison of expression, GAPDH was analysed as a housekeeping gene among both patients and controls. PCR machine (Corbet Inc) was optimised. Respective cDNA were synthesised by standard kit protocol. It was then amplified by RTPCR (Cephid Smartcycler, USA). The dye used was Maxima SYBER Green Mastermix by Thermoscientific USA. Relative quantification was done by using △△CT method.

Data was analysed using SPSS version 22. Numerical data was analysed by mean ± S.D. Categorical data was analysed by frequencies and percentages. For analysis of gene expression,△△CT method was used as proposed by Livak.[16]

RESULTS

Among 60 subjects enrolled mean ages were 60 ±8 years in cases and 59 ±13 years in controls. Mean CT values of Glyoxalase II were 32.36 in patients and 30.12 in controls. Mean CT values of GAPDH were almost same in both.

Table I provides the mean CT values of Glyoxalase II and GAPDH. △△CT has been calculated. As an interpretation, Glyoxalase II expression was found to be downregulated among patients of diabetic retinopathy.

DISCUSSION

The working hypothesis was that downregulation of Glyoxalase II occurs among patients of diabetic retinopathy, which was later proved by these research results.

The proposed underlying mechanism is that in initial stages of diabetes mellitus, a state of hyperglycemia develops in body cells. Thus rate of glycolysis speeds up to get rid of the developed glucose overburden. On the other hand, this leads to accumulation of byproducts of glycolysis like methylglyoxal in the cells.[17] As a response, the detoxifying systems in body become overactive to detoxify the accumulated toxic products. If the detoxifying mechanisms fail to cope with the glycemic stress, there occurs accumulation of glycation products leading to development of diabetic complications both micro- and macro-vascular.[18]

These results are in collaboration with many studies conducted worldwide for expression analysis of Glyoxalase system. John *et al*. in their study, reported that Glyoxalase II is inversely related to methylglyoxal. Expression of Glyoxalase II has been found to be more downregulated than Glyoxalase I.[19]

Another study concluded that in advanced stages of Diabetes, there occurs downregulation of Glyoxalase system leading to accumulation of methylglyoxal resulting in development of cardiovascular complications of diabetes.[20] Skapare *et al*. in their study, reported that

Table I: Interpretation of gene expression by RT PCR by delta delta CT method.

Patient category	Mean CT of Glyoxalase II	Mean CT of GAPDH	△CT Glyoxalase II GAPDH	△△CT= △CT of patients- △CT of controls	$2^{-(\triangle\triangle CT)}$	Interpretation
Patients	32.36	21.68	10.68	3.11	2-(3.11) = 0.116	Down regulation
Controls	30.12	22.55	7.57			

Table II: Results showing CT values of Glyoxalase II.

Site ID	Protocol	Sample ID	Sample Type	Notes	Status	Intcltr Std/Res	Intcltr Ct	empty Std/Res	empty Ct	empty Std/Res	empty Ct	empty Std/Res	empty Ct	Melt Peak1
A1	GLU-1	5Ca	UNKN		Error	POS	31.11	POS	35.56	NEG	0.00	NEG	0.00	73.4
A2	GLU-1	5Cb	UNKN		Error	POS	31.52	POS	35.21	NEG	0.00	NEG	0.00	86.28
A3	GLU-1	6Ca	UNKN		Error	POS	29.60	POS	33.24	NEG	0.00	NEG	0.00	75.93
A4	GLU-1	6Cb	UNKN		Error	POS	21.52	POS	25.40	NEG	0.00	NEG	0.00	76.03
A5	GLU-1	7Ca	UNKN		Error	POS	31.96	NEG	0.00	NEG	0.00	NEG	0.00	89.28
A6	GLU-1	7Cb	UNKN		Error	POS	31.66	NEG	0.00	NEG	0.00	NEG	0.00	88.91
A7	GLU-1	8Ca	UNKN		Error	POS	28.41	POS	31.80	NEG	0.00	NEG	0.00	88.12
A8	GLU-1	8Cb	UNKN		Error	POS	28.66	POS	32.92	NEG	0.00	NEG	0.00	87.56
A9	GLU_2	5Ca	UNKN		Error	NEG	0.00	NEG	0.00	NEG	0.00	NEG	0.00	
A10	GLU_2	5Cb	UNKN		Error	NEG	0.00	NEG	0.00	NEG	0.00	NEG	0.00	
A11	GLU_2	6Ca	UNKN		Error	NEG	0.00	NEG	0.00	NEG	0.00	NEG	0.00	
A12	GLU_2	6Cb	UNKN		Error	POS	35.15	POS	39.41	NEG	0.00	NEG	0.00	85.1
A13	GLU_2	7Ca	UNKN		Error	POS	37.74	NEG	0.00	NEG	0.00	NEG	0.00	
A14	GLU_2	7Cb	UNKN		Error	NEG	0.00	NEG	0.00	NEG	0.00	NEG	0.00	
A15	GLU_2	8Ca	UNKN		Error	POS	28.11	POS	32.40	NEG	0.00	NEG	0.00	86.57
A16	GLU_2	8Cb	UNKN		Error	POS	28.25	POS	33.00	NEG	0.00	NEG	0.00	86.54

Ch #	Dye Name	Usage	Bkgnd Sub	Bkgnd Min Cycle	Bkgnd Max Cycle	Curve Analysis	Thresh Setting	Manual Thresh Fluor Units	Auto Thresh #SD's	Auto Min Cycle	Auto Max Cycle	Valid Min Cycle	Valid Max Cycle	Bo
1	Intcltr	Assay	ON	5	40	Primary Curve	Manual	9.9	NA	5	10	3	60	0
2	empty	Assay	ON	5	40	Primary Curve	Manual	30.0	NA	5	10	3	60	0
3	empty	Assay	ON	5	40	Primary Curve	Manual	30.0	NA	5	10	3	60	0
4	empty	Assay	ON	5	40	Primary Curve	Manual	30.0	NA	5	10	3	60	0

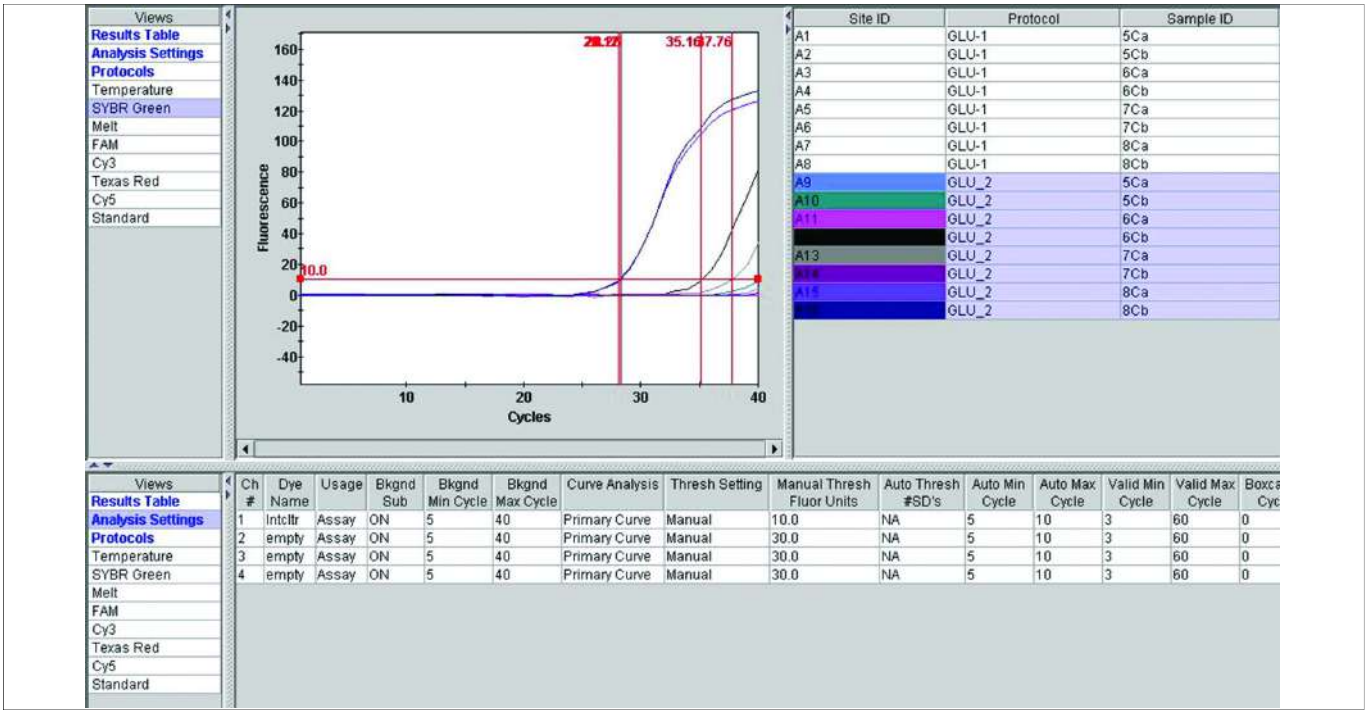

Figure 1: Curves showing cut off CT values of Glyoxalase II in enrolled patients. Graph showing CT values of Glyoxalase II.

there occurs downregulation of enzymes of glyoxalase system with already developed microvascular complications like nephropathy.[21]

The few limitations in current study were time restriction, insufficient financial resources, and small sample size. Moreover, patients were enrolled from only a specific geographical area instead of from all over Pakistan to consider ethnic variability too, as an influencing factor.

Derivatives of methylglyoxal are under study as a metabolic marker for early diagnosis of diabetic complications. This study will contribute in the research work being done in this prospect. Moreover, this research

work will also add into the pool of current work being done on inducer agents of Glyoxalase system, which are under study for prevention of macrovascular and microvascular complications of diabetes.

CONCLUSION

Expression of Glyoxalase II is downregulated among patients of diabetes mellitus with already developed complications like retinopathy. This indicates that the detoxifying system is failing leading to accumulation of glycated end products, contributing in further progression of diabetic complications.

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ORIGINAL ARTICLE

Expression of Epidermal Growth Factor Receptor in Colorectal Adenocarcinoma and its Correlation with Clinicopathological Factors

Dalal M. Nemanqani[1], Kanwal Aftab[1], Samia H. Al-Malki[2] and Walaa M. Al-Sufyani[2]

ABSTRACT

Objective: To identify the expression of epidermal growth factor receptor (EGFR) in colorectal cancer (CRC) and its relationship with clinicopathologic factors.

Study Design: Descriptive study.

Place and Duration of Study: Department of Laboratory and Blood Bank, King Abdul Aziz Specialist Hospital, Taif, Saudia Arabia, from January 2008 to June 2011.

Methodology: Diagnosed cases of colorectal carcinoma reports and slides were reviewed and cilnicopathological features were recorded. EGFR immunohistochemical staining was performed. All slides were assessed by light microscopy and scored after assessing the percentage of cells staining (grade) and intensity of the staining. Colectomy specimens of colorectal carcinomas with complete clinical information and good fixation were included. Biopsies specimens diagnosed as colorectal adenocarcinomas were excluded. The studied characteristics included age, gender, clinical presentation, tumor site, tumor size, degree of histological differentiation (well, moderate, poor), vascular and perineural invasion. Statistical analysis was done by SPSS version14 and Chi-square test was used for comparing the histological factors with EGFR expression.

Results: Thirty-five colectomy specimens showed mean age of 61.5 ±12.36 years and male to female ratio 1:2 (35% and 65%, respectively). Expression of EGFR was detected in 74% of the studied specimens. There was strong expression in most of cases. EGFR expression was found in mostly grade II (85%) and stage T3 tumors (69%).

Conclusion: Patients presented mostly with late stages of CRC and EGFR was expressed on tumor cells in the majority.

Key Words: *Colorectal cancer. Immunohistochemical expression. Epidermal growth factor receptor. Carcinoembryonic antigen. Adenocarcinoma. Prognostic factors.*

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer and fourth most common cause of death due to cancers worldwide.[1] Kingdom of Saudi Arabia is considered a low incidence area for colorectal cancer. However, according to cancer incidence report by National Cancer Registry, Ministry of Health, Saudi Arabia, CRC is the second common malignancy after the breast cancer and ranks first and third among the male and female population, respectively.[2] College of American Pathologists (CAP) consensus statement 1999 updated the current state of knowledge regarding pathologic prognostic factors (factors linked to outcome) and predictive factors (factors predicting response to therapy) in colorectal cancers. Histologic features extensively studied as prognostic factors in the literature and proven to be of prognostic value (category I & II A). However, the molecular markers, transforming growth factor (TGF), epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF) have not been studied sufficiently to determine their prognostic value (category III).[3] Literature showed few studies regarding these molecular markers, e.g. EGFR, proliferating cell nuclear antigen and mdr gene, most of these studies showed that expression of these markers could be helpful in making decision for treatment protocols.[4,5] Epidermal growth factor receptor (EGFR), also known as Her 1 or c-erb1, is a member of the c-erb family of transmembrane receptor tyrosine kinases. Deregulation of EGFR signalling is a hallmark of many cancers, including colorectal cancers (CRC).[6] It has been implicated in colorectal tumorigenesis, tumor progression, and metastasis.[7] After the development of EGFR inhibitors for anticancer treatment, some investigators also studied the possible role of EGFR inhibitors in colorectal tumors.[6,8,9]

Most of the investigated CRC cases in Saudi Arabia showed the burden of the disease and clinicopathological features,[2,10] while the expression of molecular markers have not been sufficiently studied. With this background,

[1] *Department of Pathology, King Abdul Aziz Specialist Hospital, Taif, Kingdom of Saudi Arabia.*

[2] *Medical Student, College of Medicine, Taif University, Taif, Kingdom of Saudi Arabia.*

Correspondence: Dr. Kanwal Aftab, Specialist Histopathology, Department of Pathology, King Abdul Aziz Specialist Hospital, Taif, Kingdom of Saudi Arabia.
E-mail: kanwalaftab18@yahoo.com

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the present study aimed to evaluate the expression of EGFR in CRCs and to analyse its relationship with clinicopathologic factors.

METHODOLOGY

The study was conducted from January 2008 to June 2011. Data of colorectal resection specimens of diagnosed cases of colorectal adenocarcinomas were retrieved from the files of Histopathology Section, Laboratory Department of King Abdul Aziz Specialist Hospital, Taif, Saudi Arabia. Reports, slides and blocks were retrieved from the files. Reports and slides reviewed by histopathologist. The studied characteristics included age, sex, clinical presentation, tumor site, tumor size, degree of histological differentiation (well, moderate, poor), vascular and perineural invasion.

Blocks were selected for the performance of EGFR immunohistochemical staining.

All cases diagnosed as adenocarcinoma and staged according to International Union for Cancer Control (UICC) and American Joint Committee on Cancer (AJCC), the TNM System,[11] and tumor stage (T), nodal status (N) and metastasis (M) were recorded.

Carcinoembryonic antigen (CEA) levels were also retrieved from the files which were preformed preoperatively for all cases. CEA levels were measured by sandwich chemiluminescence immunoassay using ADVIA Centaur analyzer (Siemens, USA). According to CAP consensus statement recommendations for prognostic factors in colorectal cancer, CEA levels of $\geq$5 ng/ml are considered elevated or high and <5 ng/ml considered not elevated or low.[3]

Immunohistochemistry was performed using the bond automated system utilising the BondTH Polymer Refine Detection kit. Bond Polymer Refine Detection is a biotin-free, polymeric horseradish peroxidase (HRP)-linked antibody conjugate system for the detection of tissue-bound mouse and rabbit IgG and some mouse IgM primary antibodies. Three µm-thick sections were cut from formalin-fixed paraffin embedded tissue. The tissue sections were processed using the bond system.

First, deparaffinisation and hydration was done then antigen retrieval was done using Citrate pH 6.0 (ER1) for 30 minutes. Incubation with 3.0% Hydrogen peroxide was done to quench endogenous peroxidase activity. After that, primary mouse monoclonal antibody EGFR diluted 1:100 was applied and incubated for 30 minutes (NCL-L-EGFR-384 Novocastra Laboratories Ltd.) then incubated with post-primary antibody solution which enhances penetration of the subsequent polymer reagent, and finally with poly-HRP anti-mouse/rabbit IgG reagent, which localises the primary antibody. Then the substrate chromogen 3'3-diaminobenzidine (DAB) was applied, which visualised the complex via a brown precipitate. Finally, the sections were counterstained with Hematoxylin. The slides were dehydrated with alcohol and cleared with xylene and mounted using DPX. For each run, negative and positive control tissues were included. Brain tissue diagnosed as glioblastoma multiforme and known to express EGFR was used as a positive control.

All slides were assessed by light microscopy and scored according to Goldstein guidelines of scoring,[12] the histopathologist after assessing the percentage of cells staining (grade) and intensity of the staining. The percentage of the positive cells were graded as follows: grade 0, no positive cells; grade 1=1-25% positive tumor cells; grade 2=25-50% positive tumor cells; grade 3 >50% positive tumor cells. Intensity of the staining seen in the cytoplasm and cell membrane scored as 0 for negative, 1 for weak, 2 for moderate, and 3 for strong. A composite score was obtained by multiplying the grade by intensity, ranging from 0-9. Two groups were made according to staining into strong expression (score >6) and weak expression (score <6).

Statistical analysis was done by SPSS version 14. Chi-square test was used for comparing the histological factors with EGFR expression. Level of significance ($p \leq 0.05$), relevant descriptive statistics frequency with percentages were calculated to report categorical variables and mean ±SD for continuous variables.

RESULTS

Thirty-five colectomy specimens were retrieved from histopathology section files. Demographic data showed age ranging from 32-80 years with mean age of 61.5 ±12.36 years. There were 23 (65.71%) females and 12 (34.29%) males. Majority of patients were presented with bleeding per rectum (25=71.4%) followed by intestinal obstruction in 10 cases (28.6%). Left-hemi colon (descending) was the site of primary tumor in 17 cases (48.57%) and right-hemi colon (ascending) in 16 cases (45.7%). In only two cases, primary tumor was in anorectum. The average size of the tumor was 4.8 ±1.77 cm ranging from 2-10 cm.

Histopathological examination (Table I) showed that majority of adenocarcinomas was moderately differentiated (28 cases, 80%). According to the TNM staging, most of the tumor was invading through the muscle into pericolonic fat (T3) in 26 cases (74%). Nodal examination showed positive nodes in 21 cases (60%) and up to three nodes were positive (N1) in 13 cases (37%). Vascular invasion was found in 14 cases (40%) and majority of these cases were moderately differentiated (grade II, 11 cases), T3 (12 cases) and with positive lymph nodes in 11 cases (N1=5 cases, N2=6 cases). Perineural invasion was present in only 3 cases (8.6%) and all of them were grade II, T3 and N2 (four or more nodes involved). Metastasis was present in

6 cases (17%) and the commonest site of metastasis was the small bowel (3 cases) followed by liver (2 cases) and ovary was involved in one case.

Preoperative assessment of CEA level showed that the level was low in 22 cases (63%) and in 37% (13 cases) the level was high. Comparing the CEA levels with histopathological variables (Table I), higher levels were mostly found among grade II (10 cases), stage T3 (9 cases) and with nodal metastasis (7 cases).Vascular invasion was present in 5 cases and perineural invasion in only one case.

Expression of EGFR was detected in 26 cases (74%), 21/26 showed a strong expression (Figure 1) and weak in 5/26 cases (Figure 2). Considering the histological variables, EGFR expression was found in mostly grade II (22 cases, 85%) and stage T3 tumors (18 cases, 69%). Fourteen cases of positive vascular invasion (54%) showed EGFR expression and all the 3 cases with perineural invasion showed EGFR expression. Regarding the 21 cases with positive lymph nodes, 15 cases (71%) showed EGFR expression (N1=9 cases, N2=6 cases). Using the univariate analysis in comparing the expression of EGFR with different histological features (Table II), it showed no significant association (p>0.05).

Table I: Histopathological characteristics and high CEA levels in colorectal adenocarcinomas.

Tumor differentiation	*Number of cases (percentage)	**High CEA levels
Well	6 (17%)	3
Moderate	28 (80%)	10
Poor	1 (2.8%)	-
Tumor stage (T)	Number of cases (percentage)	High CEA levels
T1	-	-
T2	3 (8.6%)	1
T3	26 (74%)	9
T4	6 (17%)	3
Nodal status (N)	Number of cases (percentage)	High CEA levels
N0	14 (40%)	6
N1	13 (37%)	2
N2	8 (22.8%)	5
Metastasis (M)	Number of cases (percentage)	High CEA levels
M0	29 (83%)	-
M1	6 (17%)	-
Vascular invasion	Number of cases (percentage)	High CEA levels
Present	14 (40%)	5
Absent	21 (60%)	8
Perineural invasion	Number of cases (percentage)	High CEA levels
Present	3 (8.6%)	1
Absent	32 (91.4%)	12

**Total number of cases of colorectal adenocarcinomas was 35.*
*** High levels of CEA found in 13 cases.*

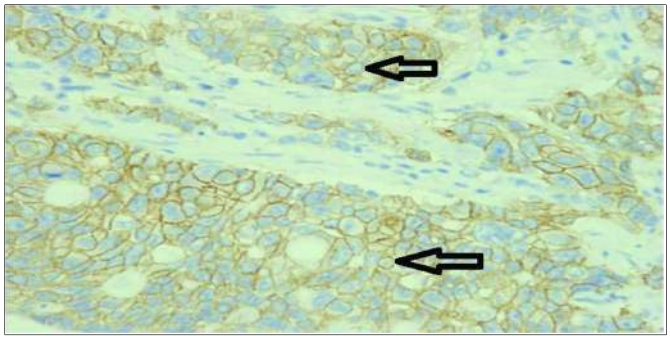

Figure 1: Colonic adenocarcinoma with strong expression of EGFR, EGFR antibody. (NCL-L-EGFR-384 Novocastra Laboratories Ltd, Newcastle, UK, 400 x.).

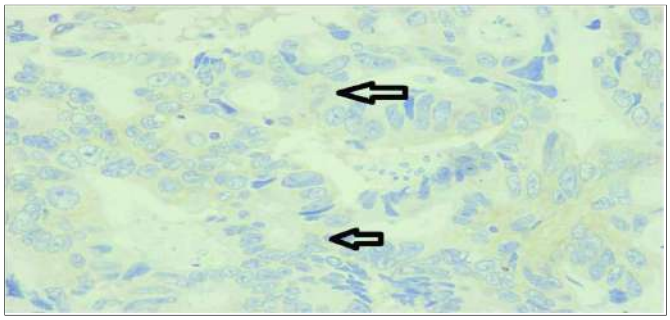

Figure 2: Colonic adenocarcinoma showing weak expression of EGFR, EGFR antibody. (NCL-L-EGFR-384 Novocastra Laboratories Ltd, Newcastle, UK, 400 x.).

Table II: Expression of EGFR in 35 colorectal cancer cases, distributed by their histological features.

Histological features	EGFR expression			Total	P-value of difference
	Strong positive No. (%)	Weak positive No. (%)	Negative No. (%)	No. (%)	
Tumor grade					
Well differentiated	4 (19)	0 (0)	2 (22)	6 (17)	P = 0.3 NS
Moderate differentiated	17 (81)	5 (100)	6 (67)	28 (80)	
Poor differentiated	0 (0)	0 (0)	1 (11)	1 (3)	
Vascular invasion					
Absent	12 (57)	4 (80)	5 (56)	21 (60)	P = 0.6 NS
Present	9 (43)	1 (20)	4 (44)	14 (40)	
Perineural invasion					
Absent	18 (86)	5 (100)	9 (100)	32 (91)	P = 0.3 NS
Present	3 (14)	0 (0)	0 (0)	3 (9)	
Tumor stage					
T2	2 (9)	1 (20)	0 (0)	3 (9)	P = 0.5 NS
T3	14 (67)	4 (80)	8 (89)	26 (89)	
T4	5 (24)	0 (0)	1 (11)	6 (17)	

NS = Not significant

DISCUSSION

Seventy-four percent of the CRC cases showed over-expression of EGFR. Literature showed overexpression in 25% - 82% of CRC.[5] Most of the studies have used the immunohistochemical method; but this variation in the result may be due to different factors including fixation time, detection kits, etc. In earlier studies, investigators found that EGFR expression is not uniform throughout different regions of colorectal tumors and higher reactivity seen in the deepest regions beyond the muscularis propria.[5,13] The present results are in agreement with these studies as a strong expression was found in stage T3 tumors. In univariate analysis, comparison of the expression of EGFR with histological factors including grade, vascular invasion, perineural invasion, tumor stage (T) revealed absence of significant correlations. This could be explained by the small sample size, as the hospital covers a small population residing Taif city in Kingdom of Saudi Arabia. Few patients, after the diagnosis of carcinoma on endoscopic biopsy, were referred directly to the oncology centres in the region. The surgically treated patients, who had colectomy after the diagnosis of CRC on endoscopic biopsy, were referred to other oncology centres in the region for follow-up. Due to these reasons collectively, only 35 cases could be recruited along the study duration and follow-up was not available.

Considering clinical characteristics, mean age of the patients at the diagnosis was 61.5 years and this came in accordance with the cancer incidence reports of KSA.[14] Concerning gender incidence, CRC was more in females than males (65% & 35%, respectively). However, one local study showed that CRC is more common in males.[10] Regarding the site of primary tumor in the present study, there was a very slight increase in tumor on left side of colon (48%) compared to right side (45%) and the majority of tumors were moderately differentiated (80%); both of these findings paralleled what was reported by Al-Ahwal and AL-Ghamdi.[10] A study about the prognostic factors in CRC showed that around 90% of colon and rectal cancer patients presented with T3-T4 disease,[15] that came in agreement with our findings where 94% of the patients presented with disease at T3 and T4. Considering the histopathological variables predicting poor prognosis like vascular invasion and lymph node metastasis, it was found 71% of tumors with these features expressed EGFR. Studies have also correlated the expression of EGFR with more advanced and aggressive disease,[16] and preclinical and clinical trials have demonstrated the efficacy of EGFR inhibitors in advanced colorectal carcinomas.[9,17] Owing to continuous research investigators now find resistance to EGFR-targeted therapies in some cases and some biomarkers also have been studied to predict the efficacy of anti-EGFR therapy and are still under research.[18,19]

Over-expression of EGFR is associated with poor prognosis in the majority of studies.[20,21] Unfortunately, owing to the unavailability of follow-up for the actual patients in the present study, the laboratory findings could not be correlated with prognosis. As disease presentation in advance stage is one of the poor prognostic factors and based on finding advance stage at time of presentation and presence of relatively higher proportion of left sided disease, local investigators earlier suggested the need for awareness, education and screening for early detection and cure.[10] We would also like to highlight and recommend the role of screening for early diagnosis and better control.

CONCLUSION

Patients presented mostly with late stages of CRC and EGFR were expressed on tumor cells in the majority of cases. A statistically significant correlation was not found in the expression of EGFR and histological factors.

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ORIGINAL ARTICLE

Epidemiology, Clinical Features and Consequences of Spinal Cord Injury in Children

Haider Darain[1], Aatik Arsh[2], Amir Zeb[2], Syed Muhammad Ilyas[2], Dildar Muhammad[3] and Muhammad Naseem Khan[4]

ABSTRACT

Objective: To describe epidemiology, clinical features and clinical consequences of Spinal Cord Injury (SCI) in children.
Study Design: Case series.
Place and Duration of Study: Paraplegic Centre, Hayatabad, Peshawar, from July 2011 to March 2017.
Methodology: SCI patients having age up to 15 years, admitted to Paraplegic Centre, were inducted in 2017. Exclusion criteria was foreign-national SCI patients, and/or SCI patients re-admitted to paraplegic centre. List of all SCI patients admitted to the centre was retrieved and 102 patients were identified. Data of these patients was evaluated for demographic information, physiological intactness (complete SCI/incomplete SCI), neurological level and complications.
Results: A total of 102 patients (66 males and 36 females) with mean age 10.9 ±3.7 years were included in this study. Firearm injury was the most common cause (n=39, 38.2%) of SCI in these patients, followed by fall from height (n=23, 22.5%), road traffic accidents (n=14, 13.7%), and weight fallen over (n=14, 13.7%). Bomb blast injury (n=7, 6.9%), diving accident (n=3, 2.9%), and sports related injuries (n=2, 2.0%). Majority of the patients (n=82, 80.4%) had complete SCI (ASIA A); the commonest SCI level was thoracic region (n=59, 57.8%) and the least reported region was (n=14, 13.7%) cervical. Out of the total, 50 (49.0%) patients had pressure ulcer in which 15 (30.0%) patients were having grade IV pressure ulcer, 9 (18.0%), 15 (30.0%) and 11 (22.0%) patients were had grade I, grade II and grade III pressure ulcer, respectively.
Conclusion: Majority of causes of SCI in children are similar to those reported in adult population. However, the commonest causes of SCI in children in Pakistan were firearm injury and bomb blast, which are rarely reported in other countries. Like adult population, these children with SCI are prone to developing pressure ulcer.

Key Words: *Children. Epidemiology. Pakistan. Paraplegic. Spinal cord injury.*

INTRODUCTION

Spinal Cord Injury (SCI) in children is uncommon yet associated with developing extreme physical and psychological problems to the children and their family members.[1] Assessment and care of children with SCI is difficult as most of the time children are unable to precisely localise their symptoms.[2] Some reports suggest that neurological recovery in children is better compared to adults.[1,3] Although, children with SCI have been reported with low community participation, nevertheless they live a good quality of life compared to adult population who sustained SCI.[2] It has been reported that SCI in children ranged from 1 to 10%.[4,5] It is noteworthy that anatomical and biomechanical differences exist between the spine of children and adults; and therefore, injury to child spine results in distinctive injury pattern.[4,6] Moreover, medical, physical, psychological and social needs of children with SCI are different compared to that of adult population.[2] In comparison with normal children, children with SCI have different developmental needs due to the challenges faced by these children.[7] The latter challenges and their consequences on the development of children with SCI have been reported in the literature.[1,2,8]

Pediatric injuries are more common in low and middle income countries compared to high income countries.[9,10] However, data about the children with SCI in these countries are often not available. Pakistan is one such country where data regarding pediatric injuries is scarce. A limited number of published studies about the pediatric injuries in the country can be found in the literature.[10-12] To the authors' knowledge, there is not a single study conducted in Pakistan which reports SCI in pediatric population. Although traumatic SCI is common in young age, yet previously conducted research studies in Pakistan have not focused on this different young age group.[13] Epidemiological characteristics and mechanism of injuries in children with SCI were different from those reported in adult population.[1] The latter fact suggests a dire need to conduct this study to report the epidemiology, clinical features and complications of SCI children in Pakistan. Presentation of epidemiological data, clinical features, associated injuries and complications of children with SCI in Pakistan will not only help in understanding the distinctive features of

[1] *IPMR, Khyber Medical University, Peshawar.*
[2] *Paraplegic Centre, Peshawar.*
[3] *INS, Khyber Medical University, Peshawar.*
[4] *IPH and SS, Khyber Medical University, Peshawar.*

Correspondence: Dr. Haider Darain, Assistant Professor, Khyber Medical University, Peshawar.
E-mail: haider.kmu@hotmail.com

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these SCI sufferers, but would provide guidance to prevention strategies for children.

METHODOLOGY

This study was conducted at Paraplegic Centre Peshawar. Paraplegic Centre Peshawar (PCP), is an autonomous body working under Department of Health, Govt. of Khyber Pakhtunkhwa, providing free-of-cost, comprehensive physical rehabilitation services to patients. SCI patients aged less than 15 years admitted to PCP from July 2011 to March 2017 were included in this retrospective study. Exclusion criteria was foreign-national SCI patients, and/or SCI patients re-admitted to paraplegic centre. Patients were categorised into three age groups in order to identify differences in demographics and clinical characteristics. These groups were 0-5 years, 6-10 years, and 11-15 years. Data of these 102 patients was accessed and information regarding demographics, physiological intactness of SCI (complete SCI/incomplete SCI), neurological level, and complications were recorded. Data was analysed using SPSS version 20. Descriptive statistics were used for analysis.

RESULTS

A total of 102 SCI patients having age 0-15 years were admitted to Paraplegic Centre, Peshawar from July 2011 to March 2017. The mean age of the participants was 10.9 ±3.7 years. A total of 66 (64.7%) patients were boys while the rest 36 (35.3%) were girls. There were 11 children in age group 0-5 years, out of whom 5 (45.5%) were boys and 6 (54.5%) were girls. There were 32 children in age group 6-15 years, out of whom 23 (71.9%) were boys and 9 (28.1%) were girls; while there were 59 children in age group 11-15 years out of whom 38 (64.4%) were boys and 21 (35.6%) were girls. Only one (1.0%) girl, aged 15 years, was married while all others (n=101, 99.0%) were singles. Most of the patients 82 (80.4%) were from Khyber Pakhtunkhwa, while the remaining 20 (19%) were from either other provinces of the country or the tribal areas of Pakistan. By profession, 30 (29.4%) patients were students at primary level, 17 (16.7%) patients were students at middle level, 2 (2.0%) patients were students at matric level, while remaining 53 (52.0%) patients were uneducated or were below the schooling age.

Firearm injury (FI) was reported to be the most common cause (38.2%, n=39) of SCI in children followed by fall from height (FFH, n=23, 22.5%), road traffic accidents (RTA, 13.7%, n=14) and weight fallen over (13.7%, n=14). Other causes of SCI are given in Table I with age group-wise distribution.

Majority of the patients 82 (80.4%) had complete SCI (ASIA A) while the remaining 20 (19.6%) patients had incomplete SCI (ASIA B, C, D and E). More than half of the patients (57.8%, n=59) had complete thoracic paraplegia (Table II).

Table I: Table showing causes of SCI in different age groups.

Cause of injury	0-5 years	6-10 years	11-15 years	Total
FAI	4 (10.3%)	18 (46.2%)	17 (43.6%)	39
FFH	2 (8.7%)	4 (17.4%)	17 (73.9%)	23
RTA	2 (14.3%)	6 (42.9%)	6 (42.9%)	14
Weight fallen over	3 (21.4%)	2 (14.3%)	9 (64.3%)	14
BBI	0 (0.0%)	1 (14.3%)	6 (85.7%)	7
Diving accident	0 (0.0%)	0 (0.0%)	3 (100.0%)	3
Sports injuries	0 (0.0%)	1 (50.0%)	1 (50.0%)	2

FAI=Fire-arm injury; FFH=Fall from height; RTA=Road traffic accident; BBI=Bomb blast inury.

Table II: Table showing different levels of SCI in children with different age groups.

Cause of injury	0-5 years	6-10 years	11-15 years	Total
Complete cervical tetraplegia	0 (0.0%)	1 (12.5%)	7 (87.5%)	8
Incomplete cervical tetraplegia	0 (0.0%)	1 (16.7%)	5 (83.3%)	6
Complete thoracic paraplegia	7 (11.9%)	23 (39.0%)	29 (49.1%)	59
Incomplete thoracic paraplegia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0
Complete lumbar paraplegia	4 (26.7%)	5 (33.3%)	6 (40.0%)	15
Incomplete lumbar paraplegia	0 (0.0%)	12 (85.7%)	2 (14.3%)	14

Out of these 102 patients, 50 (49.0%) patients were having pressure ulcer (PU) at the time of admission to the rehabilitation centre, while the skins of the remaining 52 (51.0%) patients were intact. Out of the former 50 patients, PU in 23 (46.0%) patients was located at sacrum-coccyx region, followed by trochanter (22.0%, n=11), gluteal (20%, n=10), ischial (10%, n=5) and elbow (2%, n=1) regions. In these patients with PU, 15 (30.0%) patients had grade IV PU while 9 (18.0%), 15 (30.0%), and 11 (22.0%) patients had grade I, II and III PU, respectively.

DISCUSSION

During the last decade, the number of studies conducted in Pakistan regarding traumatic SCI has increased suggesting the significance of the problem.[13-15] However, limited data regarding children with SCI in the country has been reported in the literature. Children with SCI have distinct epidemiological features compared to those adults who sustained SCI,[16] that is one of the reasons that this study was conducted to determine epidemiology, clinical characteristics, and complications of children with SCI. This was the first study conducted in Pakistan, which reported information regarding children with SCI. SCI patients having age between 0-15 years were included in the current study. There was a risk that inclusion of SCI patients aged 16 and above would inflate the results, therefore, SCI patients aged 16 and above were excluded from the study.Similar approach was adopted in previous studies conducted on children with SCI in other countries and SCI patients having age above 16 years were not included.[2,17]

In this study, we reported the outcome of epidemiological features of more than 100 children with SCI who were admitted to rehabilitation centre during the last six years. The number of boys with SCI was high in all age groups compared to their counterparts (girls) except age group 0-5 years. This is in accordance to other studies carried out on SCI in adult population in the country.[13-15] The number of boys who sustained SCI in this study was less (45.5%) compared to girls (54.5%) in the age group 0-5 years. American spinal injury association (ASIA) reported that in all age groups of SCI patients, males dominated in numbers compared to females, except in the age group 0-5, in which females outnumbered males.[5]

Although early age marriages are common in Pakistan, especially in Pashtun society,[18] yet only one girl aged 15 years was married and the rest of the boys and girls were unmarried.

In comparison to other studies conducted in Pakistan regarding SCI where FFH was reported the most common cause of SCI, followed by RTA and FAI,[13-15] results of the current study showed that the most common cause of traumatic SCI among children (38.2%) was FAI.These results are contrary to the results of previous studies carried out on SCI in children in other countries where RTA, FFH and sport injuries remained the main contributors to SCI in children.[2,5] Though some previous studies reported that gunshot was a cause of SCI for considerable percentage of children, yet literature search revealed that current study was the first which reported that FAI was the major cause of SCI in children. This can be explained by the fact that majority of patients in the current study were from Khyber Pakhtunkhwa, where guns are kept and used as a cultural sign. Ariel firing is common in this region, practised at marriage ceremony celebrations, festivals and other occasions of happiness.

Besides FAI, results of the current study showed FFH and RTA as the major causes of SCI in children. These results are in accordance with the previous studies conducted in Pakistan on adult SCI patients.[13-15,19,20] FFH has remained the commonest cause of SCI in both children and adults who belong to hilly areas of Khyber Pakhtunkhwa province. Kite-flying at roof of houses is quite common in both children and adults in some parts of the province and that might be one of the reasons that FFH remained the commonest cause of SCI in children. Apart from FFH, another commonly cited cause of SCI in children has been RTA.[2,5,16] As children have not reached complete developmental, behavioural, and physical abilities, they have difficulties in evaluating speed and distances in complex situations making them vulnerable to RTA.[2] In this study, a unique cause like BBI was reported to be one of the causes of SCI in the included children. Very few studies throughout the world reported BBI as a cause of SCI in general population, and limited data might be seen related to children of the age group included in this study.[21-23] Pakistan is continuously struggling against the war on terrorism and extremism, and the number of bomb blast attacks in the country has increased manifolds in the last two decades. Therefore, the number of causalities due to these attacks has increased. Apart from injuries to innocent adults in these attacks, a large number of injuries to children have been reported. This might be one of the reasons that BBI is one of the contributing factors to SCI in children in the country.

Majority of the patients (80.4%) in current study were having complete SCI while a small (19.6%) proportion of the patients were having incomplete SCI. ASIA reported that children with SCIs are more liable to complete injuries than incomplete SCI.[5] In accordance with the results of previous studies, current study reported that majority of patients (57.8%) were having thoracic paraplegia,[13-15] and cervical injuries were the least encountered injury in these patients. Brown *et al*. also reported that cervical spine injuries in children are rarely found, and children with SCI have injuries to other parts of their spines. Moreover, injuries to cervical region of specific age group, less than five years, may not be found in the literature.[2,16] Analysis of data of this study showed similar results and no one in the included population was found having SCI in age group 0-5 during the last 5 years. This might be explained as children in the latter age group at a high risk of mortality rates and most of the children in the age group might have not survived.

Results of the current study revealed that almost half of the children with SCI were having PU at the initial presentation to the rehabilitation centre. Development of PU is common both in children and adults having SCI. Previous studies conducted in Pakistan reported high prevalence of PU in adult SCI patients.[14,15,19,20,24] However, children have been reported more vulnerable to develop PU due to their thinner and resilient skin.[5] Similarly, refusal to take care for themselves is another common issue in children with SCI.[2,5] In addition, children with SCI are more prone to complications because of their dependency on other family members.[7] It is, therefore, necessary to provide continuous counselling to children to prevent complications in children with SCI.[2] Majority of children with SCI in current study had PU at sacrum-coccyx region, followed by trochanter, gluteal, ischial and elbow regions. Similar pattern was also reported by other studies conducted in Pakistan, which reported PU in adult SCI patients.[14,15,19]

Currently, there are no specific guidelines available in Pakistan for the prevention of SCI in children. Similarly, no specific documented protocols for the rehabilitation and community re-integration of these children are followed in our country. Though, in recent years, SCI rehabilitation centers in Pakistan have focused on evidence-based practice for the rehabilitation of adult SCI patients, yet children with SCI received less attention. Due to physical and psychosocial development, SCI in

children presents distinctive features which need to be addressed.[13-15] SCI is lifelong disability and, therefore, effective rehabilitation programme is necessary for children who are suffering from SCI in the country. One of the primary steps for this might be developing proper guidelines for the rehabilitation of children with SCI in the country. This might help these children to combat the adverse environment where they are living. For this purpose, all centres working on rehabilitation of these children may pay special attention to this issue and may develop rehabilitation guidelines that enable these children to live an independent or nearly-independent life.

Despite the fact that current study is the first study, which reported information regarding children with SCI in Pakistan, it was conducted in a rehabilitation centre, thus has several limitations. First of all, the current study included only those children who were referred and admitted to rehabilitation centre. Secondly, a number of children with SCI may not survive after SCI, especially those with cervical injuries. So their characteristics are out of the scope of current study. Thirdly, information provided in the current study was limited to condition of children with SCI at the time of initial presentation at the rehabilitation centre. These patients may improve or worsen with time; but as their follow up was not reported, so no comments can be made regarding it.

CONCLUSION

Majority of causes of SCI in children are similar to those reported in adult population. However, the commonest cause of SCI in children in Pakistan are firearm injury which has not been reported in other countries. Moreover, a large number of these children sustained SCI due to bomb blasts, which is rarely reported in other countries. Like adult population, children with SCI are prone to developing pressure ulcer.

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ORIGINAL ARTICLE

Assessment of Frequency and Transience Rate for Ventilator-Associated Pneumonia (VAP) in Geriatric Patients in Tertiary Care Settings of Karachi, Pakistan

Saba Zubair[1], Huma Ali[3], Syed Faheem Raza[4], Jawaid A. Warind[2], Anwer Ejaz Beg[1] and Rabia Bushra[5]

ABSTRACT

Objective: To assess the risk factors, frequency and transience rate for ventilator-associated pneumonia in geriatric patients.

Study Design: Cross-sectional, descriptive study.

Place and Duration of Study: Various campuses of Ziauddin University Hospital and Civil Hospital, Karachi, from April 2016 to May 2017.

Methodology: Critically ill geriatric patients (aged 60 years and above) in intensive care units, were selected who had received mechanical ventilation. Various risk factors, microbial fate, and related clinical outcomes were measured in the selected cohort of 350 patients.

Results: It was found that 72% (n=252) of study population was elderly who received ventilation for more than 48 hours with a higher mortality rate of 59.5%. Frequency of VAP was found to be 18% (n=63). A high rate of VAP was observed in geriatric cohort, i.e. n=47 association of age in VAP (p=0.611) in non-significant while mortality values and admission status were significantly associated with VAP (p<0.001).

Conclusion: The factual challenge nowadays is to present the real estimate of the clinical consequences of VAP in geriatric cohort. Such studies will help in formulating an optimal institutional policy and rational approach to decrease rates of mortality.

Key Words: *Ventilator-associated pneumonia. Geriatric. Risk factors. Frequency. Mortality.*

INTRODUCTION

Ventilator-associated pneumonia (VAP) is basically a type of nosocomial pneumonia (NP) happening in patients being on mechanical ventilation (MV) for successive 48 to 72 hours or further on airway intubation.[1] Since this mechanical ventilation is entirely different from the physiological ventilation, hence causing mechanical ventilation-related lung injury and problems.[2] It has been documented that about 8-28% of patients on intubation have developed VAP that consequently prolong the hospitalisation period with high treatment expenses and mortality rate.[3,4] The incidence of NP leading to VAP is identified to be 3 to 10-fold higher in patients of Intensive Care Unit (ICU) with MV rather other hospital wards without MV. VAP is also listed to be the second common reason for nosocomial infection of hospital ICU. Nevertheless, the old age patients are found to be admitted frequently into ICU due to multiple complications in their health status and are thus more prone to have VAP subjected to MV.[3,5] Co-morbidities in geriatric cohort would also alter the baseline immune reactions resulting inadvertent dynamic changes of microbiological flora in contrast to their younger counterparts. Therefore, the recognition of contributory organisms is also found to be the crucial in the management of VAP to optimise the remedy.[5,6] Furthermore, tube thoracostomy, bronchoscopy, elevated acute physiological and chronic health assessment scores, and enteral feeding have been elucidated to be high risks of VAP.[7-9] Higher death rates were estimated in patients of VAP ranged between 24 - 50% in early time periods.[3] However; in past few years the rate of mortality has been reduced to 9-13% through various preventive measurements.[4]

The present study was aimed to recognise different risk factors connected with the development and progression of VAP in elderly patients admitted to ICUs in tertiary care settings of Pakistan, Karachi. The influence of VAP on patient's outcomes including mortality, inpatient resource utilisation and management of disease complications were also determined.

METHODOLOGY

This descriptive study was performed in the Intensive Care Units of various campuses of Ziauddin University

[1] *Faculty of Pharmacy / Pulmonology[2], Ziauddin University, Karachi.*
[3] *Department of Pharmaceutics, IPS, Jinnah Sindh Medical University, Karachi.*
[4] *Critical Care Medicine, Civil Hospital, Karachi.*
[5] *Department of Pharmaceutics, Dow University of Health Sciences, Karachi.*

Correspondence: Dr. Rabia Bushra, Associate Professor, Department of Pharmaceutics, Dow University of Health Sciences, Karachi.
E-mail: rabia_pharmacist@hotmail.com

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Hospital and Civil Hospital of Karachi, Pakistan to evaluate the risk factors, various significant medical parameters and clinical outcome of ventilator-associated pneumonia (VAP) in elderly patients. This study was designed and performed in the light of National guidelines (Infectious disease society of Pakistan), Institutional guidelines and International recommendations (Ammi Canada Guidelines).[10]

Study was performed during the period of one year from April 2016 to May 2017. Medical records were reviewed in order to obtain the relevant data. Ethical approval was obtained from independent Ethical Review Committee of Ziauddin University (Ref: 0251115SZPHARM). Confidentiality of patients' records was maintained thoroughly during the research period. Hospitals' permissions were also obtained before study.

Medical records were examined for acquiring data. All patients admitted to ICU for any clinical, medical and surgical reason and satisfied the criteria for VAP were prospectively enrolled in this study during the mentioned period. A retrospective investigation of medical records was also made concurrently to determine the overall patients admitted to the respective ICU for mechanical ventilation. Patients were also grouped according to age, i.e. below and above 60 years. Amongst these patients, all those who were above 60 years were specifically determined for risk factors, rate of mortality, and frequency of VAP. The patients were selected in the study were intubated ICU patients with VAP. Controls were group of mechanically ventilated subjects who had stayed in the ICU for >48 hours and had not developed VAP. Patients admitted with pneumonia in ICU and COPD were excluded.

Data was collected from the daily reviews of patients' profile, lab recordings and their medication charts in each of the participating intensive care units. The relevant information was collected on a pre-designed data collecting form. Data including age, gender, admittance and date of discharge, main diagnosis, and comorbid conditions at the time of admission were recorded. The other data consisting of the length of intubation and ventilation, if there were re-intubation and tracheotomies and usage of antibiotics was extracted from patient's follow-up chart. Frequency of VAP cases was calculated. Microbiological sources of ventilator-associated pneumonia were also evaluated using patient laboratory record for frequency and isolation of organism. In case of any query during the collection and analysis of any information, respective department/ physician was taken on board. For calculation of clinical pulmonary infection score, temperature (°C),[11] leukocytes count, tracheal secretions status, oxygenation level, pulmonary radiography and tracheal aspirate cultures were taken into account and candidates with score above 6 were considered potential candidates of VAP.

The actual sample size was calculated to be 302 cases, using the standard formula of Cochran's sample size for categorical data. The value of prevalence was taken 27%.[12-14] The bound of error was considered 5% with 95% confidence interval. The sample size was inflated to 350 to exclude non-response and poorly filled records. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) Version 20. The descriptive approach, i.e. frequency with percentages was taken in consideration to interpret the results and study outcomes. Furthermore, relative risk scores and Chi-square test of association was also applied with 95% level of significance.

RESULTS

Out of 350 mechanically ventilated patients, 63 developed VAP. The median (interquartile range) value of age was 71 (24) years. The median (interquartile range) value of age in VAP group was 70 (25) years while in non-VAP group was 71 (70) years and the incidence of MV was 72% (n=252). Amongst 63 patients, 39 (61.90%) were males, and 24 (38.09%) were females. The frequency of VAP in total cohort was found to be 18% (n=63) with non-significant association with age groups (74.60% of 18%, n=47 out of 63 in total, p=0.611, Table I). Regarding admission details in VAP groups 9.52% were admitted with surgical, 84.12% with medical and 6.34% with trauma conditions which also showed significant associated of admission with VAP (p <0.001). Furthermore, neurological, cardiovascular and liver disorders were observed as the most prime causes for mechanical ventilation pursued by renal abnormalities, diabetes mellitus and spinal trauma (Table II). Risk factors were assessed with respect to host-associated, device-associated like orogastric or nasogastric tubes and personal related manner which are identified from literatures. Host-related factors were further classified as modifiable and non-modifiable factor like age, gender, medical status, intubation (number and frequency), body position of patient, consciousness scale, and use of medications. Related to microbial and culture details of 63 samples, 36 (57.14%) illustrated mono-microbial and 27 (42.85%) demonstrated the growth in poly-microbial manner. *Acinetobacter, Pseudomonas aeroginosa* and *Staphylococcus aureus* were the most frequently isolated species in order of 21 (44.68%), 18 (38.29%), and 11 (23.40%), respectively. *Escherichia coli, Klebsiella, Enterobacterand Candida species* were also isolated in variable ratios (range 3-9% (Table II). Mortality was found to be in 57 patients (16.2%) out of the 350 patients. Percentage mortality was calculated to be comparatively low in non-VAP group (14.14%; n=29 out of 205) in contrast to VAP group (59.57%; n=28 out of 47).

The median length of hospital stay was 14 days (interquartile range: 20 days) in VAP patients. The

median length of hospital stay was 8 days (interquartile range: 7 days) in non-VAP patients. Chi-square test showed insignificant association of age (p=0.611) and gender (p=0.945) with VAP while significant association of admission status (p <0.001) and mortality with VAP (p <0.001, Table I). The logic and computational details of the Chi-square for age and other factors are described in Table I. Table III showed a detailed description of ventilator-associated pneumonia related with age, gender, admission and mortality status was given with respect to relative risk and odd ratio.

Table I: Patients' demographic and clinical characteristics with and without VAP.

Characteristics	Patients without VAP N=287 (%)	Patients with VAP N=63 (%)	p-value
Age (years)			
Below 60	82 (28.60)	16 (25.40)	0.611
Above 60	205 (71.42)	47 (74.60)	
Gender			
Male	179 (62.40)	39 (61.90)	0.945
Female	108 (37.60)	24 (38.10)	
Type of admission			
Surgical	85 (29.60)	6 (9.50)	<0.001
Medical	140 (48.80)	53 (84.10)	
Trauma	62 (21.60)	4 (6.30)	
Mortality status			
Yes	29 (10.10)	28 (44.40)	<0.001
No	258 (89.90)	35 (55.60)	

Table II: Frequency of primary diagnosis and distribution of causative organismsin elderly group on mechanical vantilation.

Primary diagnosis	**Number (N=252)**	**Frequency (%)**
Diabetes mellitus	25	9.92
Renal failure	38	15.07
Cardiovascular disorders	61	24.20
Liver failure/cirrhosis	55	21.82
Neurological disorders	64	25.39
Spinal trauma	9	3.57
Microbial Isolates	**Outcome (N=47)**	**Frequency (%)**
Pseudomonas aeroginosa	18	38.29
Acinetobacterbaumanni	21	44.68
Escherichia coli	9	19.14
Klebsiellapneumoniae	5	10.63
Staphylococcus aureus	11	23.40
Enterobacter	3	6.38
Candidaalbicans	4	8.51

Table III: Relative risk estimates of ventilator associated pneumonia (VAP).

Characteristics	Crude Odd Ratio (95% CI)	p-value
Age		
≤60 years	1	
>60 years	1.175 (0.631-2.190)	0.612
	Relative risk 1.143 (0.681-1.915)	
Gender		
Male	1	
Female	1.020 (0.582-1.789)	0.945
Admission status		
Surgical	1	
Medical	0.914 (0.247-3.377)	0.893
Trauma	0.170 (0.059-0.492)	<0.01*
Mortality Status		
Yes	1	
No	0.141 (0.075-0.263)	< 0.001*

DISCUSSION

A substantial rise (72%) in ICU admission of elderly population is documented in literature.[12,13,18] In particular, geriatric patients' management is different from other adult or pediatric groups of patients. Age alone should not be used to triage ICU patients. Elderly ICU patients are at a particularly high risk of developing significant morbidities. Severity of illness and age are the important factors in determining the ICU survival.[15] In Pakistan, elderly population is defined as aged above 60 years. Pakistan is having increasing geriatric population.[18,19] Owing to the fact of critical illness, recurrent comorbidity, absence of economical and social sustainability, drug interactions and changes in mental function make geriatric population more intricate to deal. Ventilator-associated pneumonia is the major impediment connected with MV and reported to be 9-27%.[12,14] The prevalence of VAP ranged from 15.87%-37% per 1,000 ventilator days in Asian and Western countries.[19-21]

Elderly population has been investigated rarely for the incidence of VAP in context to Pakistan. In this study, 63 subjects of VAP were matched to 287 subjects of non-VAP (an approximate of 4.5 subjects as control were corresponded for individual case of VAP). In this case (VAP)-control (non-VAP) study more subjects are male i.e., 62.36% vs. 61.90% (Table I). There was a statistically noteworthy disparity in mortality between patients groups with and without VAP (14.14% vs. 59.57%, p=0.001). The subjects with VAP were classified in accordance to the time of VAP onset from both perspectives, i.e. admission to hospitals and initiation of mechanical ventilation (MV). Twenty-three episodes of VAP (36.5%) cropped up between the first three days of admissions, contrasted to 28 episodes (44.44%) noted during 4 to 6 days, and 12 episodes (19.04%) identified after sixth day of hospitalisation. Correspondingly, nine cases (14.28%), 21 (33.34%) and 16 (23.80%) of VAP diagnosed within 48 hours, 96 hours and after 96 hours of mechanical ventilation; while actual time of onset for 17 cases could not be concluded. Table I describes the ventilator associated pneumonia is significantly associated with admission (p <0.001) and mortality status (p <0.001), while no significant association was noted with age group (p=0.611) and gender (p=-0.945) in VAP patients.

In the present study, a significant ratio of mortality associated with VAP and older age group has been found. Moreover, subjects with VAP had shown a statistically significant outcome: an average addition of

8.2, 7.3 and 13.5 days of mechanical ventilation, in the ICU and in the hospital, respectively. In present investigation, major identified risk factors were age, gender, comorbid conditions, and a poly-microbial load. Table 3 describes the ventilator-associated pneumonia associated with age, gender, admission and mortality status. Women above 60 years of age were more likely to develop ventilator-associated pneumonia compared to patient below 60 years of age (OR=1.175, 95% CI=0.631-2.190). Female were more likely to VAP compared to male (OR=1.020, 95% CI=0.582-1.789). In admission status, medical admission was less likely to develop VAP compared to surgical admission (OR=0.914, 95% CI=0.247-3.377) and trauma admission was less likely and significantly associated to develop VAP (OR=0.170, 95% CI=0.059-0.492) as compared to surgical admission. No significant association was noted when age, gender, and admission status in VAP patients. Mortality was significant associated with VAP (OR=0.141, 95% CI=0.075-0.263). Preceding investigations have endorsed this study finding in well tolerated way. Numerous studies have elucidated age, male gender, and admission in traumatic condition, severity of illness, and transitional risks of predicted mortality as sovereign risk factors coupled with VAP.[22]

In present investigation mono- and poly-microbial growth of microorganisms were observed with highest proportion of *Acinetobacter, Pseudomonas aeroginosa* and *Staphylococcus aureus*. Researcher in Egypt elucidated the distribution of various respiratory contagions in the elderly people. The Egyptian study comprised of 60 patients with 71.4% males and rest of females group with mean age of 74 ±8 years. Microbial fates were discovered in order of 25% *K. pneumonia*, 23.3% *Acinetobacter*, 21.6% *P. aeruginosa*, 8.3% MRSA, *Candida* and *Escherichia coli, Staphylococcus* 6.6%, and 3.3% Proteus.[23] While in another study, researchers concluded that *S. aureus* was the most frequent organism (44%) while rest of the microbes were *Acinetobacter, P. aeruginosa, Stenotrophomonas* and *K. pneumonia*. Mean age of studied population was found to be 69 years with a range of 56-77 years.[24]

In the current study, major identified risk factors were age, gender, comorbid conditions and a poly-microbial load. Logistic regression analysis ingrained the importance of older age in the progress of the risk of VAP and mortality; and relative risk (RR) value further supports the evidence (RR=1.143). Development of VAP is less likely to be dependent on the severity of illness. On the other hand, numerous studies have documented high mortality with VAP. Such increase may be associated with the bacterial infection of antibiotic resistant origin, medical complications as compare to surgical problems and improper preliminary antibiotic treatment.[25]

CONCLUSION

Recent epidemiological transition geriatric population is expected to offer unsullied challenges to healthcare providers in near future. These groups of patients are vulnerable to various disabilities, nutritional challenges and loss of independent functioning and depression as a consequence of complications arising from chronic diseases. This in turn enhances the need for the availability of robust systems to maintain and improve function and better quality of life among these dependent individuals. A detailed study needs to be initiated with the inclusion of national multi-facet record along with the chronological information in order to estimate the related clinical and economic outcomes of VAP.

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ORIGINAL ARTICLE

Influence of Obesity on Gleason Score Inconsistencies between Biopsy and Radical Prostatectomy Specimens

Aytac Sahin[1], Ahmet Urkmez[2], Ozgur Haki Yuksel[1] and Ayhan Verit[1]

ABSTRACT

Objective: To evaluate the association of obesity with Gleason scores determined in biopsy and radical prostatectomy specimens.

Study Design: Cohort study.

Place and Duration of Study: Urology Department, Fatih Sultan Mehmet Research Hospital, Istanbul, Turkey from 2007 to 2015.

Methodology: A total of 111 patients, younger than 65 years who underwent radical prostatectomy (RP) with the diagnosis of prostate cancer, were included in the study. Histopathology reports of the surgical, and TRUS-guided prostate biopsy specimens were analysed. Body mass index (BMI) and prostate specific antigen (PSA) levels were also evaluated.

Results: Mean age of the patients was 59.06 ±4.10 (range = 47-64 years) years. Mean BMI of the patients was 25.59 ±3.24 kg/m^2 (range = 19-35 kg/m^2). In patients whose BMI measurements were equal or above 25 kg/m^2; a significant difference was found between Gleason scores of the needle biopsy and RP specimens (p=0.001).

Conclusion: BMI and PSA, which are known to be the most important parameters effecting Gleason score, were evaluated in combination. Regarding non-concordance with Gleason scores, it has been observed that as a predisposing factor, obesity can explain these incompatibilities similarly to PSA.

Key Words: *Obesity. Body mass index. Prostate cancer. Nomograms. Gleason score inconsistency. Prognosis.*

INTRODUCTION

Prostate cancer (PCa) is the most frequently encountered solid tissue cancer in men. Gleason score (GS) of the prostate cancer is the most important parameter, which provides the most important data about biological behaviour of the cancer and effects the selection of the treatment and its outcomes. Therefore, accuracy of GS, based on histopathological analysis of the biopsy material, has a critical importance. In recent publications, inconsistencies between GSs estimated for biopsy and radical prostatectomy specimens have been reported. It has been reported that histopathology of the transrectal ultrasound guided (TRUS) biopsy materials obtained from 30-40% of the patients who had undergone radical prostatectomy were erroneously reported.[1] GS 2-4 grade cannot be determined solely based on histopathologic examination of biopsy material, and GS 9-10 grade is rarely observed. As a consequence, only Gleason grade scores of 9 and 10 can be identified, and pathologists' histopathological assessments of extremely small biopsy specimens differ widely.

Obesity is a serious health problem worldwide. The relationship between obesity and cancer has attracted much less attention relative to its association with its cardiovascular effects. However, in many investigations, the relationship of obesity with esophagus, colon, kidney, thyroid, liver and PCa in men, and endometrial, esophagus, ovarian, postmenopausal breast, pancreas, and thyroid cancer in women has been detected.[2] Obesity can contribute to development and progression of a tumor by creating a suitable carcinogenic, endocrinological and biochemical microenvironment for tumors. In obese individuals, the secretion of insulin and insulin-like growth factor-1 increases, which especially enhances the risk of PCa. In obese individuals, a persistent chronic inflammatory state is present which increases oxidative stress facilitating induction of cancerogenesis. Cytokines secreted from the adipose tissue increase risk of cancer.

Many nomograms have been constructed with an attempt to predict histopathological stage of RP specimens and also to explain the prognosis of the patients with established diagnosis of PCa. In both pathological and prognostic nomograms, clinical or histopathological stage, prostate specific antigen (PSA) and GS can be observed as common parameters. In consideration of the difficulties in performing open surgery, previously used in obese patients together with currently evolving surgical techniques (laparoscopy and robot-assisted laparoscopy), it can be said that

[1] *Department of Urology, University of Health Science, Fatih Sultan Mehmet Research and Training Hospital, Istanbul, Turkey.*

[2] *Department of Urology, University of Health Science, Haydarpasa Numune Research and Training Hospital, Istanbul, Turkey.*

Correspondence: Dr. Ahmet Urkmez, MD, Department of Urology, University of Health Science, Haydarpasa Numune Research and Training Hospital, Istanbul, Turkey.
E-mail: ahmeturkmez@hotmail.com

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treatment parameters are also developing favourably on behalf of the obese patient.

In this study, the authors aimed to evaluate obesity as a parameter, which can explain the inconsistencies between GSs determined in biopsy and RP specimens. It is, therefore, also intended to assess the contribution of obesity to the treatment modality to be selected. During this evaluation process, statistical parameters were used in comparison with PSA.

The objective of this study was to evaluate the association of obesity with Gleason scores determined in biopsy and radical prostatectomy specimens.

METHODOLOGY

Patients younger than 65 years whose prostate volumes were <80 grams, and who underwent RP with the diagnosis of PCa based on TRUS biopsy at Urology Department, Fatih Sultan Mehmet Research Hospital, Istanbul, Turkey from 2007 to 2015, were included in this study. Patients with suspected malignancy as detected with digital rectal examination (DRE) were excluded. Patients who received radiotherapy or androgen ablation treatment before RP, were also excluded from the study.

Histopathology reports of the surgical, and TRUS-guided prostate biopsy specimens were analysed retrospectively. PSA values and DRE findings were obtained, and recorded before TRUS-guided biopsies. TRUS-guided biopsy materials, and RP specimens were evaluated by the same uro-pathologist. After routine screening examination under light microscope, suspected areas were subjected to immunohistochemical examinations (mainly p63, HMWCK and AMACR).

For statistical analysis IBM, SPSS Statistics 22 program was used. The parameters with normal distribution were evaluated using Shapiro-Wilks test, and fitness of data to normality was determined. For evaluation of quantitative data, and intergroup comparisons of parameters in addition to descriptive statistical methods (mean, standard deviation, and frequency), McNemar test was used. Kappa coefficient was used to evaluate the fit between the parameters. Statistical significance was considered at a level of $p<0.05$.

RESULTS

A total of 111 patients were included in the study. The mean age of the patients was 59.06 ±4.10 (range = 47-64) years. Mean BMI of the patients was 25.59 ±3.24 kg/m^2 (range = 19-35 kg/m^2).

In patients whose BMI measurements were less than 25 kg/m^2, there was a significant difference between Gleason scores of the needle biopsy and RP specimens ($p=0.004$; $p<0.01$). While the cases of Gleason scores of the needle biopsy were classified >7 pts in 12.2, it was classified 34.1% in cases of RP specimen Gleason scores. A statistically significant positive concordance was detected between scores at a level of 42.3% (Kappa: 0.423, p:0.001; $p<0.01$).

In patients whose BMI measurements were equal or above 25 kg/m^2, there was a significant difference between Gleason scores of the needle biopsy and RP specimens ($p:0.001$; $p<0.01$). While the cases of Gleason scores of the needle biopsy were classified >7 in 20, it was classified 42.9% in cases of RP specimen Gleason scores. A statistically significant positive concordance was detected between scores at a level of 31.3% (Kappa: 0.313, p:0.003; $p<0.01$).

In patients whose PSA levels were below 10 ng/ml, there was a significant difference between Gleason scores of the needle biopsy and RP specimens ($p:0.001$; $p<0.01$). While the cases of Gleason scores of the needle biopsy were classified >7 in 12.8, it was classified 30.7% in cases of RP specimen Gleason scores. A statistically significant positive concordance was detected between scores at a level of 35.4% (Kappa:0.355, p:0.001; $p<0.01$).

In patients whose PSA levels were equal or over 10 ng/ml, there was a significant difference between Gleason scores of the needle biopsy and RP specimens ($p:0.003$; $p<0.01$). While the cases of Gleason scores of the needle biopsy were classified >7 in 27.3%, it was classified as 60.6% in cases of RP specimen Gleason scores. A statistically significant positive concordance was detected between scores at a level of 28.1% (Kappa:0.281, p:0.042; $p<0.05$, Table I).

In patients whose BMI measurements were <25 kg/m^2, and PSA levels <10 ng/ml, there was no statistically significant difference found between Gleason scores of the needle biopsy, and RP specimens ($p>0.05$). While the cases of Gleason scores of the needle biopsy were classified >7 in 10.7 it was classified 21.4% in cases of RP specimen Gleason scores. A statistically significant positive concordance was detected between scores at a level of 61.1% (Kappa: 0.611, p:0.001; $p<0.01$).

In patients whose BMI measurements were <25 kg/m^2, and PSA levels <10 ng/ml, a statistically significant difference was found between Gleason scores of the needle biopsy and RP specimens ($p:0.031$; $p<0.05$). Gleason scores of the needle biopsy, and RP specimens were >7 in 15.4% and 61.5 % of the cases, respectively. A statistically significant concordance was not found between scores (Kappa:0.204; p:0.224; $p>0.05$).

In patients whose BMI measurements were >25 kg/m^2, and PSA levels <10 ng/ml, a statistically significant difference was found between Gleason scores of the needle biopsy, and RP specimens ($p:0.007$; $p<0.01$). Gleason scores of the needle biopsy, and RP specimens were >7 in 14% and 36.7% of the cases, respectively. A statistically significant concordance was found between scores at a level of 24.5% (Kappa: 0.248, p:0.035; $p<0.05$).

Table I: Concordance between Gleason scores of the needle biopsy, and RP specimens in BMI, and PSA groups.

		Gleason score		p value
		<7 n (%)	≥7 n (%)	
BMI				
<25 kg/m² (n=41)	Gleason score of the needle biopsy specimen	36 (87.8)	5 (12.2)	0.004**
	Gleason score of the RP specimen	27 (65.9)	14 (34.1)	
≥25 kg/m² (n=70)	Gleason score of the needle biopsy specimen	56 (80)	14 (20)	0.001**
	Gleason score of the RP specimen	40 (57.1)	30 (42.9)	
PSA				
<10 ng/ml (n=78)	Gleason score of the needle biopsy specimen	68 (87.2)	10 (12.8)	0.001**
	Gleason score of the RP specimen	54 (69.2)	24 (30.8)	
≥10 ng/ml (n=33)	Gleason score of the needle biopsy specimen	24 (72.7)	9 (27.3)	0.003**
	Gleason score of the RP specimen	13 (39.4)	20 (60.6)	

*McNemar test; **p<0.01*

Table II: Concordance between Gleason scores of the needle biopsy, and RP specimens in BMI, and PSA groups.

		Gleason score		p value
		<7 n (%)	≥7 n (%)	
<25 kg/m², and <10 ng/ml (n=28)	Gleason score of the needle biopsy specimen	25 (89.3)	3 (10.7)	0.250
	Gleason score of the RP specimen	22 (78.6)	6 (21.4)	
<25 kg/m², and ≥10 ng/ml (n=13)	Gleason score of the needle biopsy specimen	11 (84.6)	2 (15.4)	0.031*
	Gleason score of the RP specimen	5 (38.5)	8 (61.5)	
≥25 kg/m², and <10 ng/ml (n=50)	Gleason score of the needle biopsy specimen	43 (86)	7 (14)	0.007**
	Gleason score of the RP specimen	32 (64)	18 (36)	
≥25 kg/m², and ≥10 ng/ml (n=20)	Gleason score of the needle biopsy specimen	13 (65)	7 (35)	0.125
	Gleason score of the RP specimen	8 (40)	12 (60)	

*McNemar test; * p<0.05; **p<0.01*

Table III: Concordance between Gleason scores of the needle biopsy, and RP specimens in all patients.

	Gleason score		p value
	<7 n (%)	≥7 n (%)	
Gleason score of the needle biopsy specimen	92 (82.9)	19 (17.1)	0.001**
Prostat Gleason score of the prostate specimen	67 (60.4)	44 (39.6)	

*McNemar test; **p<0.01*

In patients whose BMI measurements were >25 kg/m², and PSA levels >10 ng/ml, a statistically significant difference was not found between Gleason scores of the needle biopsy, and RP specimens (p>0.05). Gleason scores of the needle biopsy, and RP specimens were >7 in 35.1% and 60% of the cases, respectively. A statistically significant concordance was not found between scores (Kappa:0.340; p:0.085; p>0.05, Table II).

In all patients a statistically significant difference was found between Gleason scores of the needle biopsy, and RP specimens (p:0.001; p<0.01). Gleason scores of the needle biopsy RP specimens were >7 in 14.4% of, and 39.6% of the cases, respectively. A statistically significant positive concordance was found at a level of 35.3% (Kappa:0.353, p:0.001; p<0.01, Table III).

DISCUSSION

Prostate cancer is an androgen-dependent malignancy affecting the aged male population. Overweight and obesity are described as the excessive accumulation of adipose tissue, and classification in these categories is often made based on an individual's BMI. BMIs between the ranges of 18.5 and 24.9 kg/m² are considered as having normal weight. Individuals with a BMI of 25-29.9 kg/m² or >30 kg/m² are considered overweight, and obese, respectively.

Obesity is a major risk factor for many diseases, including cancer (especially endocrine cancers), and this caused approximately one-third of the cancerrelated deaths in 2012.[3] Obesity causes increase of incidence and progression of many cancers including, endometrium, intestinal, prostate cancer, and postmenopausal breast cancer.[4] Three mechanisms have been suggested to explain the relationship between obesity and aggressive prostate cancer including insulin/insulin-like growth factor-1 axis, the action of sex hormones and adipokine signaling.[5] Adipose tissue is a complex organ consisting multiple cell types including adipocytes, adipocyte progenitor cells, mesenchymal stem cells, endothelial cells and various resident and infiltrating immune cells. It is unlikely that adipose tissue expansion per se is responsible for the growing of obesity-related complications; but rather, however, complications become evident when adipocyte hypertrophy occurs in the absence of appropriate neovascularisation. Some propose that this process leads to an inadequate supply of nutrients, growth factors and oxygen that in turn

initiates a sequelae of events including localised hypoxia, cellular death, inflammation, extracellular matrix remodeling and fibrosis and other stress responses. This process of aberrant adipose tissue expansion is thought to cause the metabolic and endocrine dysregulation related with obesity. In this regard, numerous metabolic, endocrine and inflammatory changes that occur with obesity might cause progression of prostate cancer.[6]

In a meta-analysis of 16 studies, a positive correlation was found between obesity and the incidence of PCa. However, when these studies were evaluated individually, in one study a significant correlation could not be found between obesity, and PCa[7]; while in two studies, obesity was determined as a risk factor for the development of PCa.[8,9] In the remaining 13 studies, the protective role of obesity on the development of PCa was demonstrated.[10,11] In the first study, the authors examined the connection between obesity and the 10-year postoperative prostate cancer nomogram, and their findings suggest an independent inverse connection between obesity and the probability of remaining progression-free; and finally it was concluded that obese RP patients have an improved risk of experiencing prostate cancer progression.[12] In a meta-analysis of 17 cohort studies, a statistically significant correlation could not be found between obesity, and incidence of PCa. However, the parameters were examined in detail, and the authors found that obese men had received diagnosis of more aggressive, higher grade, and clinical stage prostate cancer.[13-15]

In parallel with these considerations, obese men are less probably diagnosed with low-risk, and localised prostate cancer. Still in a meta-analysis encompassing many prospective studies, obesity has been shown to have no impact on localised PCa or exert marginal protective effect. In fact, obesity has been connected with an increased coincidence of advanced-stage PCa.[16] In addition, the presence of high BMI in a cancer-free population has significantly correlation of higher risk of future PCa-associated mortalities. Moreover, most of the large-scale observational series showed that obesity is a risk factor for adverse pathological features, advancedstage disease, and biochemical recurrence after RP and PCa-related mortality.[17,18]

Although, there has been progress toward identifying the best candidates for active surveillance (AS) in recent years, risk factors for reclassification and progression are not adequately characterised. Emerging data showed that demographic factors, such as race or BMI, may help identify better candidates for surveillance.[19] Lower testosterone level and hemo-dilution resulting from the increased plasma volume in obese men may be responsible for decreasing of serum PSA levels, causes delay of diagnosis.[20] Increased BMI is connected with shorter time to PSA treatment failure after RP and androgen suppression therapy or radiation therapy for clinically localised PCa.[21] On the basis of this, a key question is whether obesity is a risk factor of PCa progression in men having PCa who are on active surveillance (AS)? Previous nomograms have not analysed possibly important clinical predictors of upgrading, such as volume of prostate, smoking, obesity, and history of family PC. In the recent study, authors evaluated the association of BMI and progression in patients with low-risk PCa who met the inclusion criteria for the AS protocol. They concluded that obese men are at higher risk of upgraded and upstaged disease.[22] In another study, authors evaluated large number of pathological and clinical versions, many of which have not been previously studied. They found that obesity, prostate size, and PSA density were clinical variables, predicted Gleason score upgrading (GSU) in itself.[23]

The current strategy for the histological assessment of PCa is mainly based on the GS. However, 30-40% of patients who underwent RP were misclassified at histopathological evaluation of biopsy specimens. In the recent study, authors developed a nomogram for the prediction of GSU in patients who were subject to radical prostatectomy after TRUS biopsy. And they found that BMI or obesity may have a significant relaton with GSU, as patients with a higher BMI show higher likelihood of Gleason score upgrading in Chinese population.[24] The result of this study is similar to a study performed in a western population.[25]

In this study, BMI and PSA, which are known to be the most important parameters effecting Gleason score, were evaluated in combination. Regarding non-concordance with Gleason scores, it was observed that as a predisposing factor, obesity can explain these incompatibilities similarly to PSA. Limitations of the present study include one-time measure of BMI. In addition, other measures of body composition, such as waist-to-hip-ratio, were not available for examining their potential effects for central adiposity. The study population consisted of men undergoing prostatectomy, thus may not represent the full range of BMI that might be seen in the general population. Scarce number of patients, and inability to follow-up operated patients in the long term as for their prognosis, are other limitations of this study.

CONCLUSION

Despite potentially higher complications of surgical treatment in obese patients, they require more aggressive therapeutic interventions compared to non-obese patients. Determination of both histopathological stage and prognosis, BMI may be included in the nomograms as a basic parameter.

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CLINICAL PRACTICE ARTICLE

Diagnostic Accuracy of Initial Chest X-Rays in Thorax Trauma

Ozlem Tataroglu[1], Secil Telli Erdogan[2], Mehmet Ozgur Erdogan[3], Ismail Tayfur[3], Mustafa Ahmet Afacan[3], Burcu Genc Yavuz[1] and Sahin Colak[3]

ABSTRACT

Objective: To evaluate the efficacy, sensitivity and specificity of chest x-ray as a diagnostic imaging tool in management of thorax traumas.

Study Design: Descriptive study.

Place and Duration of Study: Haydarpasa Numune Training and Research Hospital, Istanbul, Turkey, between December 2014 and December 2015.

Methodology: Case records of patients admitted to the emergency department with thoracic trauma were retrospectively analysed through the hospital database. Plain postero-anterior chest X-rays and thorax computerised tomography (CT) scans were evaluated seperately by same radiologist. Accurcy of signs of thoracic trama was determined using CT scan as gold standard.

Results: Nine of 23 pneumothorax patients were diagnosed by chest X-ray. Sensitivity and specificity of PA chest X-ray in the diagnosis of pneumothorax was 39.1% and 100%, respectively. Positive predictive values of chest X-ray for diagnosis of pneumothorax was 100% and negative predictive value was 97.1%. Twenty-four patients had pleural effusions on CT scans, while only 15 could be diagnosed in chest X-rays. Chest X-rays were 62.5% sensitive and 100% specific with positive and negative predictive values of 100% and 98.1%, respectively. Twenty of 41 rib fractures were diagnosed with X-rays. Chest x rays had a 48.8% sensitivity and 100% specificity, and positive and negative predictive values were 100% and 95.6%, respectively.

Conclusion: Chest X-ray should not be used as a sole diagnostic imaging tool for exclusion of pneumothorax, hemothorax, and lung contusion. Due to high predictive values of chest X-rays, they can be used for follow-up.

Key Words: *Thorax trauma. Chest X-ray. Thorax CT.*

INTRODUCTION

Trauma is the leading cause of death in the population under 40 years of age. Thoracic traumas constitute about 20-25% of the deadly traumas.[1] It is the third common cause of trauma-related mortality. Post-traumatic mortality rate is highest in Eastern Europe, while mortality rate is lowest in North America, Western Europe, China, Japan and Australia. Ninety percent of traumatic deaths occur in low-middle income countries.[2] Mortality related with thorax trauma increases with the presence of accompanying extra-thoracic injuries. Thorax trauma should be managed according to clinical and radiological findings. Plain X-ray is an easy and rapid method of imaging, in the evaluation of thorax injuries. However, this tool might not be always useful for diagnosis of pneumothorax, pleural effusion, and mediastinal enlargement. The diagnostic value of computerised tomography in thorax traumas is increasing day by day. There are a few studies on the ultrasound imaging techniques used for pneumothorax daignosis, too.[3] Today, conventional radiographs have been replaced by multislice computed tomography (CT) in many organ systems for rapid and effective evaluation of trauma patients in emergency departments.[4]

Several prospective studies of traumatic patients have found ultrasound to be significantly more sensitive than supine chest radiographs for diagnosing pneumothorax.[5] CT scan is taken as gold standard for diagnosing pneumothorax.[6]

In this study, the aim was to calculate the sensitivity and specificity of chest X-ray in thorax trauma, considering thoracic CT as the gold standard.

METHODOLOGY

A retrospective analysis of the thorax trauma patients, who were treated in Haydarpasa Numune Training and Research Hospital, Turkey, between December 2014 and December 2015, was carried out. The hospital was the first place of admittance for all the patients included in this study. Their work-up was carried out according to the recent trauma guidelines.

Hospital database was used to reach the records of these patients. Their plain postero-anterior (PA) chest

[1] *Department of Emergency Medicine, University of Health Sciences Haseki Training and Research Centre, Istanbul, Turkey.*

[2] *Department of Radiology, Istanbul Medipol Mega University Hospital, Turkey.*

[3] *Department of Emergency Medicine, University of Health Sciences, Haydarpasa Numune Training and Research Center, Istanbul, Turkey.*

Correspondence: Dr. Sahin Colak, Associate Professor, Department of Emergency Medicine, Haydarpasa Numune Training and Research Center, Istanbul, Turkey.
E-mail: dr.sahincolak@gmail.com

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X-rays and thorax computerised tomography (CT) scans were evaluated seperately by the same radiologist, and recorded. Age, gender, and trauma type were also recorded. Pneumothorax, traumatic pleural effusion, contusion, rib fracture, subcutaneous emphysema, scapula fracture, sternum fracture, diaphragmatic hernia, and para-aortic haematoma were the possible outcomes of trauma that we investigated. Patients who had missing or inaccessible files, died before being examined in the ED, and were referred to an external centre were excluded.

Data was analysed with Statistical Package for Social Sciences version 16.0. Normality of the continuous variables was evaluated with the Kolmogorov-Smirnov test. Descriptive statistics of the non-normally distributed variables were expressed as median (25%-75%). Sensitivity, specificity, false positive and false negative values were analysed with diagnostic tests and given as percentages.

RESULTS

Between December 2014 and December 2015, 499 patients [330 (66.1%) males, 169 (33.9%) females] were admitted to the Emergency Department with thoracic trauma. Mean age of males was 35.0 (25.0-51.0) years while of females 57.0 (39.0-75.5) years.

Nine of the 23 pneumothorax patients were diagnosed by the chest X-ray. Sensitivity and specificity of PA chest X-ray in the diagnosis of pneumothorax were 39.1% and 100%, respectively. False positive value was 0.0% and false negative value was 60.9%. Positive predictive value of chest X-ray on diagnosis of pneumothorax was 100%, and negative predictive value was 97.1%.

Twenty-four patients had pleural effusions in CT scans, while only 15 were diagnosed in chest X-rays. Chest x-rays were 62.5% sensitive and 100% specific. False positive value was 0.0% and false negative value was 37.5%. Positive and negative predictive values for chest X-ray's pleural effusion diagnosis were 100% and 98.1%, respectively.

Twenty of the 41 rib fractures were diagnosed with x rays. Chest X-rays had 48.8% sensitivity and 100% specificity values. False positive value was 0.0% and false negative value was 51.2% Positive and negative predictive values for chest X-ray's rib fracture diagnosis were 100% and 95.6%, respectively.

Its sensitivity in the diagnosis of 24 lung contusion cases was only 8.7%, while the specificity was 99.8%. False positive value was 0.2% and false negative value was 91.3%. Positive and negative predictive values for chest X-ray's lung contusion diagnosis were 66.7% and 95.8%, respectively.

All injuries are shown at Table I. Sensitivity and specificity values of PA chest X-ray for different traumatic conditions are shown in Table II.

Table I: Frequency of all injuries of the study group.

	Chest X-ray (PA view)	Thorax CT
Pneumothorax	9	23
Pleural effusion	15	24
Rib fracture	20	41
Lung contusion	2	23
Clavicle fracture	2	2
Scapula fracture	0	5
Sternum fracture	0	1
Aorta hematoma	0	1

Table II: Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of PA chest x-ray in different trauma related conditions.

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Pneumothorax	39,1	100	100	97,1
Pleural effusion	62.5	100	100	98,1
Rib fracture	48,8	100	100	95,6
Lung contusion	8,7	99,8	66,7	95,8
Clavicle fracture	100	100	100	100

DISCUSSION

The diagnostic use of computerised tomography (CT) is increasing in the thoracic traumas. It helps diagnose pathologies that cannot be seen in chest x-rays. Still, the routine use of CT is limited. With the use of CT scan, rib fractures, sternum fractures, sternoclavicular dislocations, retrosternal hematomas, anteromedial and subpulmonary pneumothoraxes and fluid collections can easily be diagnosed. Diagnosis of injuries like pneumomediastinum, in which plain chest X-rays are not very sensitive, can easily be achieved by the CT scans. The cardiac silhouette enlargement, which is seen in pericardial effusion and hemopericardium cases, can be diagnosed earlier.

In this study, thorax CT was considered as the gold standard diagnostic tool for trauma patients and calculated the plain chest X-ray's sensitivity and specificity. It was aimed to find out whether chest X-ray is enough to evaluate the thoracic trauma or thorax CT should be a routine study in trauma patients suspected to have thoracic injury.

Chardoli *et al*. found that 5.5% of pneumothorax cases cannot be seen in the chest X-rays.[7] In this study, the sensitivity of an initial chest X-ray, obtained in emergency department for pneumothorax, was only 39.1%. The specificity, however, was 100%. It is obvious that most of the pneumothorax cases are missed with plain chest X-rays. The lack of pneumothorax signs in chest X-ray, definitely, does not exlude pneumothorax; so in any case suspected to have pneumothorax, CT scan is necessary.

In the same study, Chardoli *et al*. claimed that 4% of all hemothorax cases are missed in chest X-rays.[7] In this study, the sensitivity and specificity of the PA chest X-ray for traumatic pleural effusion is 62.5% and 100%, respectively. Hemothorax is a life-threatening complication of thoracic traumas. Thorax CT is the modality of choice if there is suspicion of hemothorax. However, due to high

sensitivity and specificity, it can be used in the management.

Rib fractures are the most common results of blunt thoracic traumas. Chest X-rays miss a significant number of rib fractures. Also, especially in the lower rib fractures, the evaluation of organs such as the kidneys, spleen and liver is essential.[8-11] In this study, chest X-rays could detect the rib fractures with a sensitivity of 48.8% and specificity of 100%. Low sensitivity of the chest X-ray shows us that the lack of fracture findings in the X-ray does not exclude the possibilty of fractures; so if the clinical suspicion persists, CT should be the modality of choice.

Esme *et al*. evaluated the diagnostic capability of the chest X-rays in lung contusions and came out with the result that it has a low sensitivity.[12] Other studies indicate that when compared with the thorax CT scans, 60% of the pulmonary contusions are missed in the chest x-rays. Some recent studies indicate that the size of contusion areas seen in chest X-rays are one-third of the areas seen on CT images.[13,14] Chest X-ray is a tool with low sensitivity in the diagnosis of pulmonary contusions. In one study, 11 CT images confirmed lung contusion cases showing no sign of injury in chest X-rays.[15] If lung contusion is suspected, the work-up should never be limited to chest X-ray and thorax CT should be the modality of choice. Especially in pediatric cases, lung contusions can be seen without rib fractures. Alongwith the low sensitivity, this makes X-ray infavourable modality in children.

Chest X-rays showed excellent sensitivity (100%) in clavicle fractures. Subcutaneous emphysema was seen in 50% of the CT confirmed cases. Scapula and sternum fractures, aorta hematoma, and diaphragmatic rupture could only be diagnosed with CT; and chest X-rays revealed no signs of injury. Thus, chest X-ray has no diagnostic value in these cases.

CONCLUSION

Chest X-ray is an important part of initial management of a trauma patient with high negative and positive values for the diagnosis of thorax injuries. However, chest X-ray should not be used as a sole diagnostic imaging tool for exclusion of the diagnosis of pneumothorax, hemothorax, and lung contusion. Due to high predictive values of chest X-rays, they can be used for follow-up in previously confirmed injuries.

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CLINICAL PRACTICE ARTICLE

The Relationship between Burnout, Self-Esteem and Professional Life Quality of Nurses

Unal Erkorkmaz[1], Ozlem Dogu[2] and Nursan Cinar[3]

ABSTRACT

Objective: To evaluate the correlation between burnout, self-esteem and quality of life among nurses.
Study Design: Analytical, cross-sectional study.
Place and Duration of Study: Sakarya Training and Research Hospital, Turkey, in 2013.
Methodology: The sample was made-up of 131 volunteering nurses after obtainnig informed written consent from the participants, ethical committee, and corresponding institutions. Data were collected by personal information form (21 questions), Maslach Burnout Inventory (MBI-22 items), Rosenberg Self-Esteem Scale (RSES-10 items), Professional Quality Of Life Scale (ProQOL-30 items).
Results: The scales were analysed in terms of internal consistency. Cronbach Alpha coefficients were determined as reliable for our sample. MBI 3 subscale total scores of the participant nurses were low for emotional exhaustion and depersonalization, high for personal accomplishment. Total score from RSES was 15.32 ±3.70. Total scores from 3 subscales of ProQOL were 29.78 ±9.02 for compassion satisfaction, 24.65 ±5.75 for burnout, and 15.12 ±6.54 for compassion fatigue.
Conclusion: In this study, it was detected that burnout in nurses affected compassion satisfaction and individual success negatively.

Key Words: *Nurses. Burnout. Self-esteem. Quality of life. Relationship.*

INTRODUCTION

Professional quality of life for those providing care has been an issue of growing interest over the past 25 years.[1] Prolonged fatigue, emotional exhaustion and personal accomplishment caused by work can cause symptoms which can influence negatively over professional work quality and nurse's mental life. Quality of life comprises the individual's physical functions, psychological state, social relations within the family or in the community, how much she/he is influenced by the environment, and how much this situation affects the individual's functionality. Health, overlapping with the definition of quality of life that is well-being, suggests that life quality scale can also be used in healthcare.[2,3]

Burnout syndrome includes negative personal reactions towards the difficulties faced in career.[4] Burnout is accepted as an occupational hazard exposure, which people working in face to face jobs such as education or healthcare services.[5,6] Burnout among nurses who are effective members of healthcare may hinder their duties of caregiving.[7]

Department of Biostatistics[1] / Fundamentals[2] / Pediatrics[3], Sakarya University, Sakarya, Turkey.

Correspondence: Prof. Nursan Cinar, Department of Pediatrics, Faculty of Health Sciences, Division of Nursing, Sakarya University, Sakarya, Turkey.
E-mail: ndede@sakarya.edu.tr

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Low self-esteem is an underlying cause of submissive behavior. Necessary communication skills and behaviors for work are particularly come into prominence in occupations based on interaction such as nursing.[2-6] Nurses, as a member of healthcare staff, should have good communication with both their team mates and the patient. They should provide a holistic and desirable nursing care, incorporate the patient and his/her family into the caring process, have skills of protecting the patient, and leading the process.[8]

The aim of this study was to examine the correlation between burnout, self-esteem and quality of life among the nursing staff of Training and Research Hospital, Sakarya, Turkey.

METHODOLOGY

It was an analytical and cross-sectional study. The population of the study was consisted of the whole nursing staff of Training and Research Hospital, Sakarya Metropol Western City, Turkey in 2013. Nurse who patrticipated voluntarily completed the forms used for the research. Hospital authorities were called and an appointment was made. Units were visited on the designated day and time, giving information about the aim of the study. Nurses were visited in the units, they were informed about the study and their questions were answered.

The data were collected via a Personal Information Form (21 items), Maslach Burnout Inventory (MBI-22 items), Rosenberg Self-Esteem Scale (RSES-10 items) and

Professional Quality Of Life Scale (ProQOL-30 items). Forms related to the study were distributed to nurses in a closed envelope by visiting their units and collected in envelope again two weeks later.

Personal Information Form, including 21 questions, were prepared by the researchers themselves. Personal Information Form includes items like, age, experience, years in department, marital status, educational status, and if they have any children.

Maslach Burnout Inventory (MBI) was developed by Maslach and Jason. Its reliability and validity in Turkish was performed by Cam (1992) and Ergin (1992). Being a 5-items Likert scale (0: Never; 1: Rarely; 2: Sometimes; 3: Often; 4: Always), it includes 22 questions with three dimensions: Emotional Exhaustion (EE, 9 items: 1,2,3,6,8,13,14,16,20), Depersonalization (D, 5 items: 5,10,11,15,22), and Personal Accomplishment (PA, 8 items: 4,7,9,12,17,18,19,21).

Rosenberg Self-Esteem Scale (RSES) was used for the evaluation of self-esteem in our study. This scale was developed by Morris Rosenberg in 1965. Its Turkish validity and reliability was performed by Cuhadaroglu (1986), and its validity coefficient (Cronbach Alpha) was found to be 0.71.

Professional Quality Of Life Scale (ProQOL), it is a self-report assessment tool consisting of thirty items and three subscales. "Compassion satisfaction" is the first subscale and it is about the feeling of satisfaction and pleasure that a staff gets when he helps another person in need of assistance in a field related to her/his profession or business. The high score from this scale shows the level of satisfaction or pleasure of the helper.

The sample consisted of nurses who participated voluntarily and completed the forms used for the research. Ethical permission was obtained from the Ethical Committee, Sakarya University (71522473\ 050.01.04), and written consents from relevant institutions. Participants gave verbal consent for the use of their data for this study.

Scales used in the study were assessed by reliability analysis in terms of internal consistency and Cronbach Alpha coefficients were calculated. Kolmogorov-Smirnov test was used to evaluate whether the distribution of scales were normal. Two independent sample t-test or Mann-Whitney U test were used to compare the scales between two groups. One Way Analysis of Variance ANOVA or Kruskal Wallis Analysis of Variance were used for comparing the scales among groups. Spearman correlation coefficients were performed for relation among ProQOL, MBI and RBSO. Multiple linear regression analysis was used to determine the effect of MBI subscales and RBSO on ProQOL subscales. The scales were presented as the mean ± standard deviation or median [IQR]. A p-value <0.05 was considered significant. Analyses were performed using IBM SPSS Statistics, Version 23.0.

RESULTS

The scales used in this study were analysed in terms of internal consistency. Cronbach Alpha coefficients were calculated as 0.846, 0.526 and 0.717, respectively for the subscales of compassion satisfaction (CS), burnout and compassion fatigue (CF) of ProQOL; 0.836, 0.637 and 0.820 for emotional exaustion (EE), depersonalization and personal accomplishment (PA) subscales of MBI respectively, and 0.617 for RSES. According to these results, all three scales were determined as reliable for the sample (Table I).

Table I: Internal consistency coefficients (Cronbach Alpha), according to subscales.

Scales	Sub-scales	Cronbach Alpha (α)
ProQOL	Compassion Satisfaction (CS)	0.846
	Burnout	0.526
	Compassion Fatigue (CF)	0.717
MBI	Emotional Exhaustion (EE)	0.836
	Depersonalization	0.637
	Personal Accomplishment (PA)	0.820
RSES	Total	0.617

Demographical features of the nurses in the study were assessed; 87.0% of them (n=114) were females, 69.5 % were (n=91) younger than 25 years old, 57.3% were (n=75) married and 52.7 % of them (n=69) had children, 38.2% (n=50) had been working for 1-5 years, 69.5% (n=91) were graduates of university, 59.5% (n=78) worked more than 40 hours a week and 39.7% (n=52) stated that they had sleep quality with moderate sleep complaints.

Median [IQR] values of MBI's three subscales were 16.00 for EE [10.00] (min=2, max=34, low), 6.00 for depersonalization [6.00] (min=0, max=17, low) and 19.00 for PA [8.00] (min=1, max=28, high). Total score of RSES was 16.00 (3.00, min=5, max=30). ProQOL's three subscales were 30.00 for CS (11.00, min=9, max=50), 24.00 for burnout (7.00, min=13, max=48) and 15.00 for CF (10.00, min=1, max=37, Table II).

According to the comparisons made in terms of subscale total scores of demographical features; there was a significant difference between 25 years and younger, and 25 years and older in EE and depersonalization subscales of MBI (p=0.026 and 0.022, respectively) and burnout subscale of ProQOL (p=0.010). There was also significant difference between females and males in terms of PA subscale of MBI (p=0.046, Table II).

There was a significant correlation between EE which is a subscale of MBI and CF (r=-0.217, p=0.013), burnout (r=0.468, p<0.001) and CF (r=0.334, p=0.001) which are subscales of quality of life. The correlation between depersonalization and burnout (r=0.280, p<0.001), CF

(r=0.300, p<0.001) which is a subscale of quality of life was significant. The correlation between PA and CS (r=0.565, p<0.001) and burnout (r=0.385, p<0.001) which are subscales of ProQOL was significant, too (Table III).

Table II: The comparison between the scales and sociodemographic features.

Features	MBI			ProQOL			RSES
	Emotional exhaustion	Depersonalization	Personal accomplishment	Compassion satisfaction	Burnout	Compassion fatigue	
Overall	16 [10]	6 [6]	19 [8]	30 [11]	24 [7]	15 [10]	16 [3]
Age							
<25 (n=91)	17,04±6,7	6 [6]	19 [7]	30.77±9.03	25.51±5.78	15.16±6.5	16 [4]
≥25 (n=40)	14,2±6,5	4 [4]	18 [13]	27.55±8.72	22.72±5.28	15.02±6.72	16 [3.5]
p	0.026	0.022**	0.075**	0.060	0.010	0.911	0.860**
Educational status							
College (n=31)	15,94±7,22	6 [6]	18 [7]	30.1±8.41	25 [8]	13.32±6.92	15 [3]
High school grad.(n=91)	16,46±6,76	6 [6]	19 [8]	29.18±9.37	24 [7]	15.81±6.27	16 [4]
MSc or PhD (n=9)	14,11±4,86	9 [5]	21 [4]	34.89±5.97	26 [5]	14.33±7.47	17 [5]
p	0.596	0.478*	0.544*	0.190	0.791*	0.175	0.838*
Gender							
Female (n=114)	16.49±7.07	6 [6]	19 [7]	29.75±9.02	24.9±5.83	14.99±6.64	15 [4]
Male (n=17)	14.06±3.38	6 [7]	14 [9]	30±9.32	23±5.1	16±5.94	16 [4]
p	0.166	0.479**	0.046**	0.917	0.205	0.555	0.155**
Marital status							
Married (n=75)	15.96±6.27	5 [6]	19 [9]	29.51±8.86	24.49±5.1	15.69±6.22	15 [3]
Single (n=56)	16.46±7.38	7 [5]	18.5 [8.5]	30.16±9.3	24.87±6.57	14.36±6.94	16 [4.5]
p	0.674	0.096**	0.880**	0.683	0.709	0.249	0.264**
Working status							
Fixed shift (n=58)	15.41±6.72	5 [6]	19 [9]	31.33±9.44	24.93±6.06	15.52±6.88	16 [3]
Variable shift (n=73)	16.78±6.75	6 [6]	19 [8]	28.56±8.55	24.44±5.53	14.81±6.29	15 [4]
p	0.251	0.269**	0.258**	0.081	0.628	0.540	0.639**

*Descriptive statistics were shown as mean ±standard deviation and median [IQR]; *Nonparametric Kruskal Wallis test results. **Nonparametric Mann-Whitney-U test results.*

Table III: The correlations between ProQOL scores and RSES and MBI scores.

	ProQOL					
	Compassion Satisfaction		Burnout		Compassion Fatigue	
	r	p	r	p	r	p
RSES	0.098	0.264	0.044	0.617	0.150	0.088
MBI						
Emotional exhaustion	-0.217	**0.013**	0.468	**<0.001**	0.334	**<0.001**
Depersonalization	-0.071	0.421	0.280	**0.001**	0.300	**<0.001**
Personal accomplishment	0.565	**<0.001**	0.385	**<0.001**	0.190	0.030

r: Spearman's correaltion coefficient; p-values of the statistically significant correlation coefficients were shown as bold.

Table IV: Multiple linear regression models for ProQOL sub-scales.

Dependent variable	Independent variables	β coefficient	SE of β	95% CI of β		p
				Lower	Upper	
ProQOL - Compassion satisfaction	Constant	18.829	3.739	11.428	26.229	<0.001
	MBI Emotional exhaustion	-0.473	0.116	-0.701	-0.244	<0.001
	MBI Depersonalization	0.226	0.219	-0.207	0.660	0.304
	MBI Personal accomplishment	0.833	0.112	0.612	1.055	<0.001
	RBSO	0.138	0.174	-0.206	0.482	0.428
ProQOL – Burnout	Constant	12.699	2.400	7.950	17.448	<0.001
	MBI Emotional exhaustion	0.361	0.074	0.214	0.508	<0.001
	MBI Depersonalization	0.099	0.141	-0.179	0.377	0.483
	MBI Personal accomplishment	0.348	0.072	0.206	0.490	<0.001
	RBSO	-0.052	0.111	-0.272	0.169	0.644
ProQOL – Compassion Fatigue	Constant	3.193	3.095	-2.931	9.318	0.304
	MBI Emotional exhaustion	0.209	0.096	0.020	0.398	0.031
	MBI Depersonalization	0.329	0.181	-0.029	0.688	0.072
	MBI Personal accomplishment	0.171	0.093	-0.012	0.355	0.067
	RBSO	0.223	0.144	-0.061	0.508	0.123

The relationship between the subscales of ProQOL and MBI was determined using multiple linear regression model and ProQOL significantly affected CS subscale, MBI on the subscales of EE and PA, and ProQOL on burnout subscale ($p<0.001$). The EE subscale of MBI had effected on medium level ProQOL compassion fatigue subscale ($p<0.001$, Table IV).

DISCUSSION

In this study, nurses' EE (16.00) and depersonalization (6.00) median scores were found low, which was a good result in terms of burnout syndrome. Emotional exhaustion is the most significant determinant of burnout which measures a person's level of feeling her/his self-estranged to work and indifference to others. Depersonalization is the insensitive attitude and behaviour that a person shows towards the people she/he gives care as if they were objects. The fact PA scores (19.00) were high meant that nurses had problems in PA. In other studies, there were similar results supporting these. Personal accomplishment describes the feelings of success and sufficiency at work, tendency to evaluate oneself as insufficient when there is a decrease in the success, and due loss of motivation and occupational accomplishment. In other studies, there were similar results supporting this. The data by Sahin *et al*. and Ayraer *et al*. were parallel to this study.[9,10]

It was found that high occupational stress was related with an increase in EE and a decrease in PA. Nurses, who have a crucial role in healthcare services, face severe strain and get stressed due to factors like excess workload, the necessity to give the patients and their relatives the support they need, low wages, administrative difficulties, professional image and lack of self-esteem. Altay *et al*. and Sayil *et al*. found that DT and D averages were at medium level, which was contrary to the results of this study, while they found scale averages to be higher, which was parallel to our study.[11,12] As seen in these studies, DT and D subscale scores were satisfactory while the score from personal accomplishment showed that nurses in general had a moderate level of burnout. The results obtained so far support the results of other studies conducted on this topic. It was seen that the results obtained from the studies conducted in different regions and samples were similar to the results of other studies carried out in Türkiye.[10-15] The results obtained so far support the results of other studies conducted on this topic.[13]

CS, one of the subscales of ProQOL, expresses the feeling of pleasure and satisfaction because of the help one gives to another person in need of assistance in a field related to her/his profession or job was found in the medium level with an average score of 30.00. Burnout, which is a feeling of despair due to difficulties in coping with problems of work, had an average score of 24.00 at medium level. CF, which measured the symptoms when faced with a stressful event, was found out to be at a low level with an average score of 15.00. According to these results, healthcare staff has a medium level of life quality in general. The low level of compassion fatigue average scores shows that they do not need any help or support. In a study by Yildirim and Hacihasanoglu, which was carried out among the healthcare staff, it was also detected that they had a medium level of life quality.[6]

It was observed that MBI subscales EE, Depersonalization and PA had a significant correlation with age while they had no significant correlation with other socio-demographic data. The majority of the participants (69,5%) were below 25 years of age (Table II). The younger the age was, the higher the EE, D and PA sub-scores was, which is similar to the literature. The reason why burnout is seen less among the older people is that they respond in a more mature way to the events and they have less expectation. The conclusion that experience in advanced age affects one's outlook on life is stated in many studies.[6,16-19]

In other studies, it was detected that gender had a distinctive effect on burnout.[3,5,10] The average scores of nurses for PA varied according to age and gender was found to be high, as shown in Table II. In the comparative analyses, it was seen that they had significant correlation while their average scores were close to each other. Armutcu *et al*., Helvaci and Turhan and Kaya found similar results in their studies. They stated that advanced age and being female was a positive factor increasing the level of personal success.[2,19-21] The present study has similarity with these data (Table II).

While there was a significant correlation between MBI subscale EE and PA, quality of life subscale compassion satisfaction, EE, D, PA between quality of life subscale burnout and MBI subscale EE, D between quality of life subscale CF, no correlation was found with RSES and ProQOL. It was determined that personal accomplishment highly influenced the quality of life. It is frequently seen that psychiatric comorbidities affect the quality of life negatively. The facts that nurses have hard working conditions, they may experience burnout due to the feature of their job, and this would negatively affect their life quality put forward the necessity of improving current working conditions of nurses (Table III).[16,19]

The limitation of this study is that it was carried out among nurses at only one hospital, hence the results of this study cannot be generalised for all nurses who may experience different working conditions. The authors recommend that since this study included only one hospital, the study can be replicated using a larger sample size from multiple hospitals so that the reliability of the data may increase and the findings may become more generalised.

CONCLUSION

Burnout is considered as an occupational hazard exposure for those working face-to-face with people, as in education and health services. In this study, burnout among nurses affected compassion satisfaction and personal accomplishment in a negative way.

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Postoperative Complications of Endoscopic Versus Microscopic Transsphenoidal Pituitary Surgery: A Meta-Analysis

Jincheng Fang[1], Shan Xie[2], Nan Li[2] and Zhiquan Jiang[2]

ABSTRACT

Transsphenoidal microscopic pituitary surgery is an effective way of treating pituitary tumors. However, minimal invasive approach endoscopic transsphenoidal pituitary surgery has become much more prevalent these days. Endoscopic surgery resects the maximum tumour with less complications. As endoscopic surgery is much safer and less invasive as compared to the microscopic transsphenoidal surgery, selection of technology for the treatment of pituitary adenoma is becoming increasingly equivocal. The main aim of this systematic review was to assess the safety of endoscopic and microscopic transsphenoidal pituitary surgery in terms of postoperative complications. Relevant studies between January 1992 and January 2017 were searched in the Cochrane Library electronic databases, EMBASE and MEDLINE, through a systematic literature search. A total of 1,463 patients reviewed (microscopic group=684, endoscopic group=779), the proportion of diabetes insipidus, septal perforation and other complications related to surgery (include lip anesthesia, nasal anesthesia, deviated septum, saddle nose, sinusitis, synechiae, anosmia) in those patients who had endoscopic surgery were significantly lower ($p<0.05$). No significant difference emerged between the two approaches in the incidence rates of cerebrospinal fluid leak, meningitis, epistaxis or hypopituitarism ($p>0.05$). These results support the safety of endoscopic transsphenoidal pituitary adenoma surgery.

Key Words: *Pituitary surgery. Endoscopic surgery. Microscopic transsphenoidal surgery. Complication.*

INTRODUCTION

After the 19th century, since Horsley completed the first resection of a pituitary adenoma through subfrontal approach,[1] the area of pituitary surgery has evolved and developed constantly. In 1907, Schoffer first reported transsphenoidal approach in a sella tumor.[2] Until 1960, Hardy perfected approach with the application of the operative microscope.[3] Because of the low complication and mortality, transsphenoidal approach gradually replaced subfrontal approach, and has been considered as the standard approach since then. With the development of neural endoscopic technology, Jankowski put forward neural endoscopic treatment of pituitary adenoma for the first time in 1992.[4] Nowadays, this minimal invasive approach, endoscopic transsphenoidal pituitary surgery, has become more popular than the microscopic transsphenoidal pituitary surgery. However, the endoscope lacks the three-dimensional view that can be obtained through a microscope. Thus, which kind of technology for the treatment of pituitary adenoma is better has increasingly equivocal. Our main purpose of this study is to assess the safety of endoscopic and microscopic transsphenoidal pituitary surgery by the postoperative complications.

[1] *Department of Neurosurgery, the First Affiliated Hospital of Wannan Medical College, Wuhu, Anhui, China*

[2] *Department of Neurosurgery, the First Affiliated Hospital of Bengbu Medical College, Bengbu, Anhui, China.*

Correspondence: Prof. Zhiquan Jiang, Department of Neurosurgery, the First Affiliated Hospital, Bengbu Medical College, Bengbu, Anhui, China.
E-mail: bbjiangzhq@163.com

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METHODOLOGY

The relevant studies between January 1992 and January 2017 were searched in the Cochrane Library electronic databases, EMBASE and MEDLINE. The search terms used were 'transsphenoidal', 'transnasal', 'endonasal', 'endoscopic/endoscopy', 'microscopic/ microsurgery', combined with 'pituitary/hypophysoma' and limited to 'human'. In addition, for possible inclusion, references to all relevant studies were reviewed. Besides, the results were located to the English language.

All the inclusion criteria before retrieval have been completed, studies were suitable for literature search, if they met the selection criteria. The study was direct comparison between sublabial or transeptal microscopic and endoscopic for pituitary adenoma without significant differences in tumor types or revelant bony density. The study should ensure each group included at least 10 or more adult patients and all of those patients had been operated in the same centre without techinical mistakes. The studies' observation indices should be complete, include total complication rate, CSF leak rate, post-operative diabetes insipidus rate, and the rates about incidence of other intracranial and nasal complications. Newcastle-Ottawa scale was applied to quality evaluation of the retrospective comparative studies.[5] Besides, the Cochrane Non-Randomized Studies Methods Working Group also recommended a scale. Score was $\geq$6, it was defined as grade 'I'; and grade 'II', if the score was $\leq$5.

The Review Manager Software, version 5.3 (The Cochrane Collaboration; Oxford, UK) was used to combine the results for meta-analysis. All outcomes were defined as

dichotomous; for this reason, proportions with their corresponding 95% confidence interval (CI) were determined and odds ratio (OR) was used for the summary statistics. For each analysis, Chi-square and a value of I2 was used to test heterogeneity. A fixed-effect model for heterogeneity ($p>0.05$, I2=0%) or minimal heterogeneity existed ($p>0.05$, I2 <25%), and a significant heterogeneity stochastic-effect model ($p<0.05$, I2>50%). Besides, on the summary, both of Harbord-Egger bias indicator and Begg-Mazumdar bias indicator had been used to assess the effect of publication and selection bias. We considered it statistically significant, if the two-tailed $p<0.05$.

The outcomes were the rate of patients who had intraoperative or postoperative cerebrospinal fluid leak (CSF); postoperative diabetes insipidus (DI); meningitis attributable to the surgical approach; postoperative epistaxis; postoperative hypopituitarism; and septal perforation attributable to the surgical approach. Other complications (lip anesthesia, nasal anesthesia, deviated septum, saddle nose, sinusitis etc.) were also considered, if it could be attributed to the surgical method.

RESULTS

Through the above search strategy, 3,035 publications were preliminarily identified in the study. Later, the manuscripts were examined to exclude unrelated studies, leading to 40 potential qualified articles. Then, a thorough study of those studies was carried out, and 20 articles were ruled out because they did not qualify for the inclusion criteria. Eventually, 20 articles comparing microscopic versus endoscopic surgery in the surgery postoperative complications of pituitary adenomas were approved. Table I summarises the characteristics of the study.[6-25] Through counting, 1,463 patients were reviewed in the aggregate (684 in microscopic group, and 779 in endoscopic group). Table II summarises the characteristics of the complications included in the study. All studies were defined as retrospective case series. According to the selected method, 15 studies were identified as grade I and five as grade II. In order to determine the potential source of the observed heterogeneity and the stability of the test results, it was necessary to remove the grade 'II' studies to carry out further sensitivity analysis.

By examining the characteristics of the surgical procedures, 18 studies reported cerebrospinal fluid leakage. On the basis of the results of these studies, the fixed-effect model was used because there was no obvious heterogeneity evidence (X2=15.79, p=0.54, I2=0%). There was no significant difference in the occurrence rate of CSF leak between microscopic and endoscopic groups [OR: 1.33, (95% CI: 0.80-1.59); p=0.54; 11.7% versus 10.5% in endoscopic group and microscopic group, respectively Figure 1).

Fifteen studies reported on diabetes insipidus.[6,7,9-12,15-18,20-23,25] What was the difference between the endoscopic and the microscopic groups was statistically remarkable [OR=0.93, (95% CI: 0.68-1.28); $p<0.001$; 16.2% versus 18.4% in endoscopic and microscopic groups, respectively, Figure 2). The proportion of diabetes insipidus was relatively lower for those who had endoscopic surgery. Due to the relatively high heterogeneity (X2=51.73, $p<0.05$, I2=73%), a sensitivity analysis was performed, and three articles had been removed.[7,9,25] After that the results showed that the differences between the endoscopic and microscopic showed no obvious differences, which was in line with

Table I: Characteristics of included studies.

Study	Publication year	Type of study	Quality grade	Number of endoscopic cases	Number of microscopic cases
Sheehan *et al.*[6]	1999	Retrospective	I	26	44
Cappabianca *et al.*[7]	1999	Retrospective	II	10	20
Koren *et al.*[8]	1999	Retrospective	II	20	20
Shah *et al.*[9]	2001	Retrospective	I	26	55
White *et al.*[10]	2004	Retrospective	I	50	50
Casler *et al.*[11]	2005	Retrospective	I	15	15
Neal *et al.*[12]	2007	Retrospective	II	14	15
Jain *et al.*[13]	2007	Randomized	II	15	13
Duz *et al.*[14]	2008	Retrospective	II	28	40
Atkinson *et al.*[15]	2008	Retrospective	I	21	21
Choe *et al.*[16]	2008	Retrospective	I	12	11
O'Maley *et al.*[17]	2008	Retrospective	I	25	25
Higgins *et al.*[18]	2008	Retrospective	I	16	25
D'Haens *et al.*[19]	2009	Retrospective	I	60	60
Graham *et al.*[20]	2009	Retrospective	I	58	118
Messerer *et al.*[21]	2011	Retrospective	I	82	82
Cheng *et al.*[22]	2011	Retrospective	I	68	59
Razak *et al.*[23]	2013	Retrospective	I	40	40
Dallapiazza R.[24]	2014	Retrospective	I	56	43
Fathalla H.[25]	2015	Retrospective	I	42	23

Table II: Characteristics of the cases of complications for included studies.

Study	Cerebrospinal fluid leak		Diabetes insipidus		Epistaxis		Meningitis		Hypopituitarism		Septal perforation	
	E	M	E	M	E	M	E	M	E	M	E	M
Sheehan *et al.*[6]	3	7	1	0	0	0	NA	NA	NA	NA	0	2
Cappabianca *et al.*[7]	0	0	4	2	0	0	NA	NA	NA	NA	NA	NA
Koren *et al.*[8]	4	5	NA	NA	0	2	NA	NA	NA	NA	2	6
Shah *et al.*[9]	NA	NA	20	4	NA	NA	NA	NA	NA	NA	NA	NA
White *et al.*[10]	6	7	11	11	1	8	1	0	NA	NA	0	1
Casler *et al.*[11]	4	3	3	2	0	1	NA	NA	NA	NA	0	3
Neal *et al.*[12]	4	8	1	5	0	0	NA	NA	NA	NA	NA	NA
Jain *et al.*[13]	2	5	NA	NA	NA	NA	NA	NA	0	5	NA	NA
Duz *et al.*[14]	8	10	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Atkinson *et al.*[15]	3	2	3	3	0	0	NA	NA	NA	NA	NA	NA
Choe *et al.*[16]	2	2	1	1	0	0	0	1	1	3	NA	NA
O'Maley *et al.*[17]	3	1	1	4	0	0	0	1	0	1	NA	NA
Higgins *et al.*[18]	1	1	5	7	0	0	NA	NA	1	2	1	4
D'Haens *et al.*[19]	6	1	NA	NA	1	1	1	0	1	0	NA	NA
Graham *et al.*[20]	7	3	10	38	NA	NA	NA	NA	NA	NA	NA	NA
Messerer *et al.*[21]	10	7	7	8	4	1	3	4	5	9	NA	NA
Cheng *et al.*[22]	3	2	2	3	1	1	0	1	0	1	1	2
Razak *et al.*[23]	4	6	4	11	NA	NA	1	0	NA	NA	NA	NA
Dallapiazza R.[24]	5	4	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Fathalla H.[25]	2	2	9	12	1	1	NA	NA	5	1	NA	NA

NA = Not available.

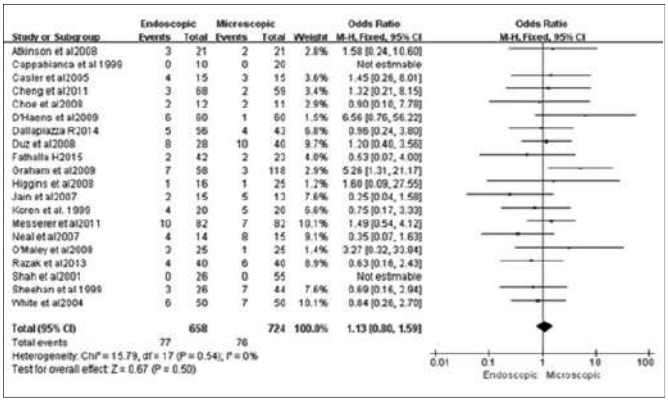

Figure 1: It shows the odds ratio of incidence of CSF leak in postoperative period to evaluate the statistical distinction between endoscopic and microscopic group in terms of endoscopy (P>0.05). In this figure, squares present the results of each study. Diamonds present the results of the meta-analysis. A vertical line is plotted as well, presenting no effect. CI: confidence interval; M-H: Mantel/Haenszel model.

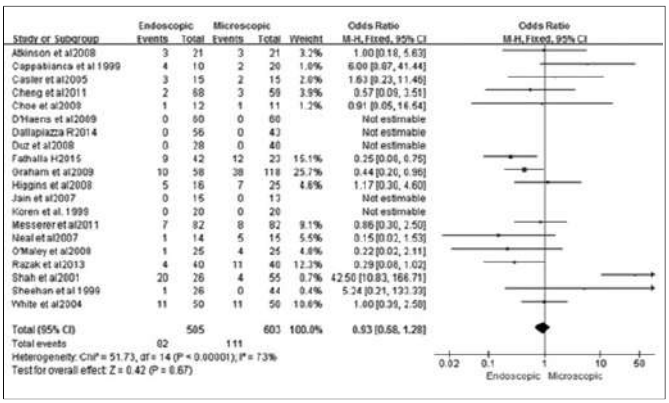

Figure 2: It shows the odds ratio of incidence of diabetes insipidus in postoperative period to evaluate the statistical distinction between endoscopic and microscopic group in terms of endoscopy (P<0.05). In this figure, squares present the results of each study. Diamonds present the results of the meta-analysis. A vertical line is plotted as well, presenting no effect. CI: confidence interval; M-H: Mantel/Haenszel model.

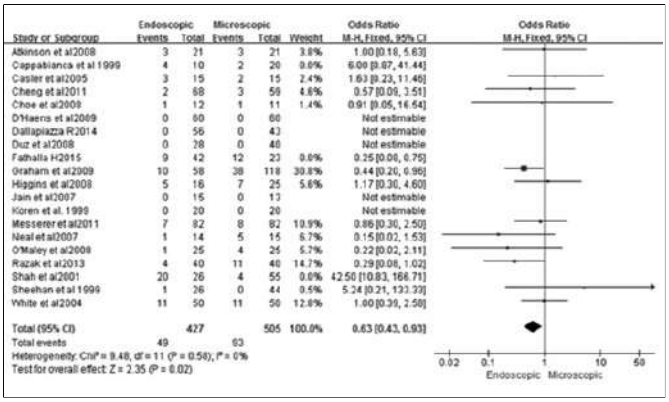

Figure 3: It shows the odds ratio of incidence of diabetes insipidus in post-operative period after sensitivity analysis to evaluate the statistical distinction between endoscopic and microscopic group in terms of endoscopy (P>0.05). In this figure, squares present the results of each study. Diamonds present the results of the meta-analysis. A vertical line is plotted as well, presenting no effect. CI: confidence interval; M-H: Mantel/Haenszel model.

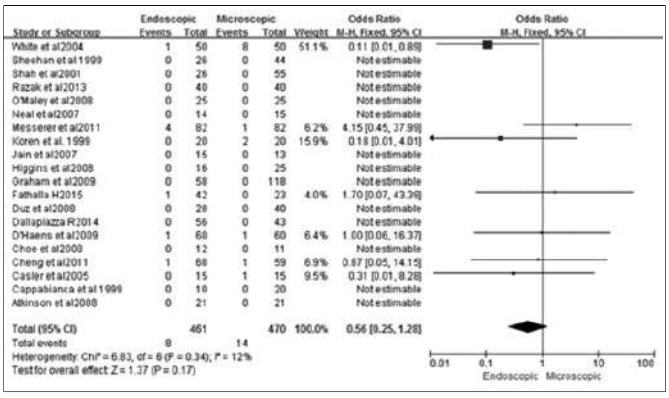

Figure 4: It shows the odds ratio of incidence of epistaxis in postoperative period to evaluate the statistical distinction between endoscopic and microscopic group in terms of endoscopy (P>0.05). In this figure, squares present the results of each study. Diamonds present the results of the meta-analysis. A vertical line is plotted as well, presenting no effect. CI: confidence interval; M-H: Mantel/Haenszel model.

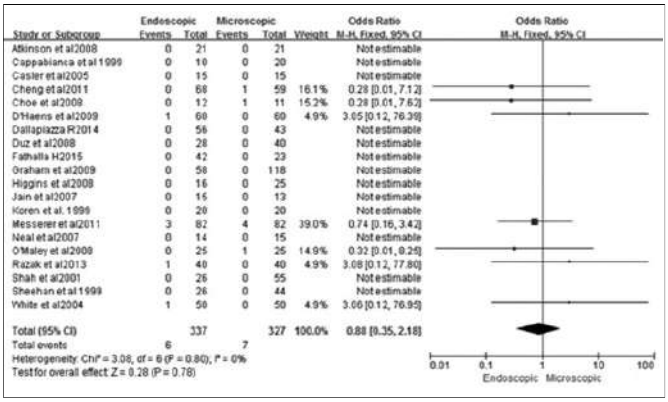

Figure 5: It shows the odds ratio of incidence of meningitis in postoperative period to evaluate the statistical distinction between endoscopic and microscopic group in terms of endoscopy (P>0.05). In this figure, squares present the results of each study. Diamonds present the results of the meta-analysis. A vertical line is plotted as well, presenting no effect. CI: confidence interval; M-H: Mantel/Haenszel model

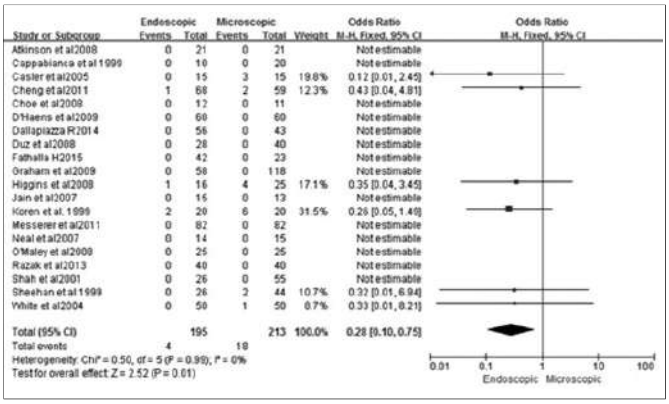

Figure 7: It shows the odds ratio of incidence of septal perforation in postoperative period to evaluate the statistical distinction between endoscopic and microscopic group in terms of endoscopy (P<0.05). In this figure, squares present the results of each study. Diamonds present the results of the meta-analysis. A vertical line is plotted as well, presenting no effect. CI: confidence interval; M-H: Mantel/Haenszel model.

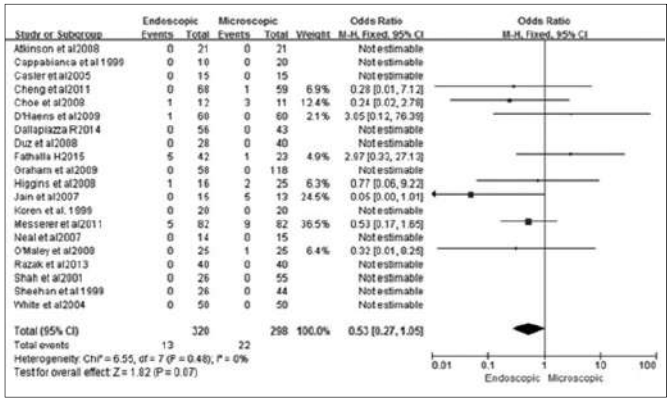

Figure 6: It shows the odds ratio of incidence of hypopituitarism in postoperative period to evaluate the statistical distinction between endoscopic and microscopic group in terms of endoscopy (P>0.05). In this figure, squares present the results of each study. Diamonds present the results of the meta-analysis. A vertical line is plotted as well, presenting no effect. CI: confidence interval; M-H: Mantel/Haenszel model.

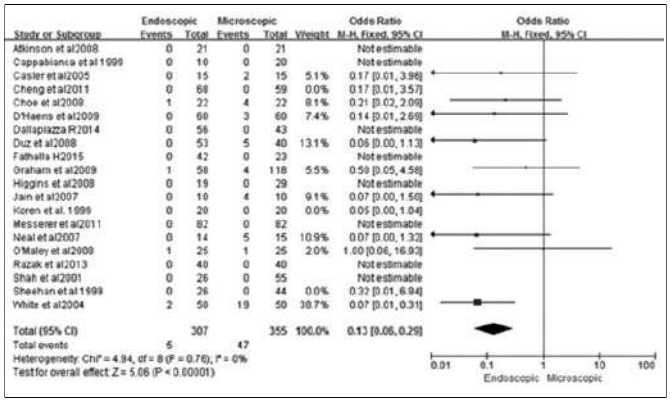

Figure 8: It shows the odds ratio of incidence of other complications which have relation to surgery in postoperative period to evaluate the statistical distinction between endoscopic and microscopic group in terms of endoscopy (P<0.05). In this figure, squares present the results of each study. Diamonds present the results of the meta-analysis. A vertical line is plotted as well, presenting no effect.CI: confidence interval; M-H: Mantel/Haenszel model.

the previous results [OR=0.63, (95% CI: 0.43-0.93); p=0.58; 11.5% versus 18.4% in endoscopic group and microscopic group, respectively, Figure 3).

Fourteen studies reported on epistaxis, but only seven articles reported the available data.[8,10,11,19,21,22,25] Fixed-effect model was used because there was no obvious heterogeneity evidence (X2=6.83, p=0.34, I2=12%), and the incidence of epistaxis could attribute to the choice of surgical procedure and there was little obvious statistical differences between microscopic and endoscopic groups. [OR: 0.56, (95% CI: 0.25-1.28); p=0.17; 1.7% versus 3.0% in endoscopic group and microscopic group, respectively, Figure 4).

Seven studies reported on meningitis.[10,16,17,19,21-23] Fixed-effect model was used because there was no obvious heterogeneity evidence (X2=3.08, p=0.8, I2=0%). The incidence of meningitis could be ascribed to the choice of surgical procedure with no difference between microscopic and endoscopic groups [OR: 0.88, (95% CI: 0.35-2.18); p=0.78; 1.8% versus 2.1% in endoscopic and microscopic group, respectively, Figure 5).

Eight studies reported on hypopituitarism.[13,16-19,21,22,25] Fixed-effect model was used because there was no obvious heterogeneity evidence (X2=6.55, P=0.48, I2=0%), and there was insignificant difference between microscopy and endoscopy in the incidence of meningitis caused by surgical procedure selection [OR: 0.53, (95% CI: 0.27-1.05); p=0.07; 4.1% versus 7.4% in endoscopic group and microscopic group, respectively, Figure 6).

Six studies reported on septal perforation.[6,8,10,11,18,22] According to the results of these studies, the fixed-effect model was used on account of there being no obvious heterogeneity evidence (X2=0.50, p=0.99, I2=0%). However, the incidence of meningitis was distinctly different between microscopic and endoscopic groups due to the choice of surgical procedure. [OR: 0.28, (95% CI: 0.10-0.75); p=0.01; 2.1% versus 8.5% in endoscopic and microscopic group, respectively, Figure 7). Patients with septum perforation were significantly lower in number in the microscope under endoscope.

Considering the other complications related to surgery rate being low and the number of cases reported being less, analysis of these complications was integrated, like lip anesthesia, nasal anesthesia, deviated septum, saddle nose, sinusitis, synechiae, anosmia. Again the fixed-effect model was used because there was no obvious heterogeneity evidence (X2=4.94, p=0.76, I2=0%), the total incidence in microscopic was higher [OR: 0.13, (95% CI: 0.06-0.29); p<0.001; 1.6% versus 13.2% in endoscopic group and microscopic group, respectively, Figure 8).

DISCUSSION

In the treatment of pituitary tumors, transsphenoidal microscopic pituitary surgery is an effective way as confirmed by time, and it depends on three-dimensional visualisation and the ability to operate in three-dimensional space. Since the late 1990s, based on the visualisation of panoramic improvements, more and more scholars advocated endoscopic pituitary surgery to the surgical treatment of pituitary adenomas.[26] As a result, it could be readily to build the ability to visualise structures, such as the structure of optico-carotid recesses. In microscopic pituitary surgery, it is extremely difficult to directly catch sight of the suprasellar areas, even if in the hands of more experienced surgeons.[26,27] However, endoscopic pituitary surgery is bi-dimensional and thus lacks the depth perception, even if there are suggestions for exercises to reduce this shortcoming.[28]

No matter what kind of operation procedure, to be successful pituitary procedure, an essential goal is to avoid the complications. As opposed to the bi-dimensional space provided by most endoscopic platforms, the microscope provides three-dimensional space. Advocates of the microscopic transsphenoidal pituitary surgery procedure suggest that visuospatial awareness is necessary to avoid iatrogenic injury to critical parasellar neurovascular structures.[29] The results of this meta-analysis show that endoscopic surgery is superior to microscopical methods in postoperative complications. The endoscopic approach showed a significantly decreased rate of postoperative diabetes insipidus, septal perforation and other complications related to surgery (lip anesthesia, nasal anesthesia, deviated septum, saddle nose, sinusitis, synechiae, anosmia). Nevertheless, there was no significant difference between the two types of surgery for CSF leak, epistaxis, meningitis and hypopituitarism. The incidence of CSF leakage in the surgical procedure is the only index that was higher in endoscopic group than microscopic groups; 11.7% versus 10.5% in endoscopic group and microscopic group, respectively. Even so, the meta-analysis shows no significantly difference between microscopic and endoscopic groups [OR: 1.33, (95% CI: 0.80-1.59); p=0.54]. The main complication of most patients undergoing pituitary surgery is diabetes insipidus.[30] In this analysis, the results manifested that an evident difference existed between the endoscopic and microscopic groups, and the proportion of diabetes insipidus was relatively lower for those who had endoscopic surgery. [OR=0.63, (95% CI: 0.43-0.93); p=0.54; 11.5% versus 18.4% in endoscopic group and microscopic group, respectively]. The results remained unchanged after sensitivity analysis.

The results of this study have some potential limitations. First, the study consisted mainly of retrospective studies, with very few published long-term studies tracking the patients postoperatively; their sample size is small, the follow-up time is short, not enough to detect the clinical difference. In addition, all studies included in this reserach were English-language articles; therefore, potential selection bias cannot be excluded, as some relevant researches in other languages may have been neglected. For these reasons, the results of this meta-analysis should be carefully applied.

CONCLUSION

This meta-analysis found that the proportion of diabetes insipidus, septal perforation and other complications related to surgery were significantly lower in patients with endoscopic surgery; while the proportion of cerebrospinal fluid leak, meningitis showed no statistical significant difference between endocopic surgery and microscopic surgery. For other complications, like lip anesthesia, nasal anesthesia, deviated septum, saddle nose, sinusitis, synechiae, and anosmia, the incidence in microscopic was higher than in endoscopic group. In a way, the results support the safety of endoscopic transsphenoidal pituitary adenoma surgery.

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Cost-effectiveness of Screening and Confirmatory Tests for Multiple Myeloma in Pakistani Population: An Audit Report

Safia Fatima[1], Aamir Ijaz[1], Dilshad Ahmed Khan[1], Fozia Fatima[2], Naveed Asif[1], Ayesha Hafeez[1] and Muhammad Mukarram[1]

Abstract

Objective: To find out the use of screening and confirmatory tests for diagnosis of multiple myeloma as ordered by clinicians.

Study Design: An Audit.

Place and Duration of Study: Department of Chemical Pathology and Endocrinology, Armed Forces Institute of Pathology, Rawalpindi, from January 2012 to January 2017.

Methodology: Data retrieved from Laboratory Information Management system (LIMs) by selecting serum protein electrophoresis (SPE) as screening test and immunoelectophoresis (IE) and immunofixation (IF) as confirmatory tests.

Results: There were 3,108 tests of serum protein electrophoesis and 1,329 tests of immunoelectophoresis had been performed in last five year. Cost-effective clinical audit of SPE tests showed that only 17.1% tests of SPE were either used for proper diagnosis of multiple myeloma (totally justified tests 13%) or useful for diagnosis of other important diseases whose early diagnosis were helpful for patients management (partially justified tests 4.1%). The cost related to these tests were justified while 82.8% tests of SPE were either normal (total unjustified tests 24.4%), or diagnosed irrevalent and nonspecific diseases (partially unjustified 58.4%). IE and IF audit revealed that only 26.6% tests were properly utilised for diagnosis and differentiation of multiple myeloma and its subtypes and cost attributable to these tests were justified while 73.4% of these confirmatory tests were normal and cost related to them was not justified.

Conclusion: Overutilisation of laboratory tests for diagnosis of multiple myeloma can be minimised by proper clinical scrutiny of request forms.

Key Words: *Serum protein electrophoresis (SPE). Immunoelectrophoresis (IE). Immunofixation (IF). Multiple myeloma. Screening. Cost-effective analysis.*

INTRODUCTION

Serum protein electrophoresis (SPE) is a screening method which is used to identify patients with multiple myeloma and others diseases.[1] Further confirmation of protein subtypes of myeloma is achieved by immuno-electrophoresis (IE) and immunofixation (IF).[2] The most common indication of serum protein electrophoresis were suspected multiple myeloma and other monoclonal gammopathy.[3] Multiple myeloma (MM) is a monoclonal gammopathy, that can be detected by the presence of monoclonal band in serum. It accounts for 10% of the haematological malignancies worldwide, typically occurs in elderly patients, and prevalence of this disease is low, about 1% of all the cancers.[4] SPE is an easy-to-perform laboratory test which can be used for detection and quantification of monoclonal gammopathy as preliminary test for suspected cases of multiple myeloma, and confirmation is done by IE and IF.[5-10]

[1] *Department of Chemical Pathology and Endocrinology, AFIP, National University of Medical Sciences, Rawalpindi.*

[2] *Faculty of Social Sciences, National University of Modern Languages (NUML), Islamabad.*

Correspondence: Dr. Safia Fatima, Department of Chemical Pathology and Endocrinology, AFIP, Rawalpindi.
E-mail: sofy_asim@hotmail.com

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As the study was receiving a large number of advices of this test with limited clinical notes, it was planned to carry out an audit retrospectively in order to find out the actual diagnostic performance of these tests. Adoption of this strategy will increase the diagnostic utility of SPE, IE and IF in multiple myeloma and overall improvement in the healthcare.

The aim of this study was to find out the financial impact of justified and unjustified costs of SPE, IE and IF that were used for screening and confirmation of multiple myeloma.

METHODOLOGY

After approval by the Ethical Review Board of the institute, a retrospective cross-sectional descriptive study design was planned. Patients were identified through the electronic database that had SPE, IE and IF records from January 2012 to January 2017. An inclusion criterion was used for all patients who underwent for SPE and immunoelectrophoresis with and without clinical notes. Data retrieved from LIMs by selecting SPE as a test, which was done on Sebia (Automatic), and IE and IF done on conventional cellulose acetate membrane.

Audit report was measured manually by considering international audit guidance, which was divided into four groups such as: totally justified cost for number of tests

which were clinically and biochemically correlated and benefited for patients; totally unjustified cost for number of tests that were clinically and biochemically not correlated and benefited for patients; partially unjustified cost for number of cases with byproduct diseases indentified whom treatment will not be beneficial and partially justified cost for number of cases with by-product diseases indentified whom if treated get patient benefited. As each test cost at the department was 1500 PKR, different types of costs were calculated by standard formulae used for financial audit manually.

Data were analysed by statistical package for social science version 21 (SPSS Inc, Chicago, IL, USA). Descriptive statistics in the form of median with interquartile range (IQR) values used to present non-parametric data. Frequency with percentage values were used for nominal data. Median differences were measured through Mann-Whitney U-test in the case of gender differences with level of significance at $p \leq 0.05$.

RESULTS

A total of 3,108 subjects with mean age 56 ±15.6 years had underwent serum protein electrophoresis; among them, there were males 1,858 (59.8%) and females 1,250 (40.2%). Age (years) of the test participants were divided into different groups such as group-1 (9-29), group-2 (30-50), group-3 (51-71), group-4 (72-92) and group-5 (93-113). Frequencies and percentages of these five age groups were 326 (10.5%), 680 (21.9%), 1,655 (53.2%), 415 (13.4%) and 32 (1.0%), respectively. The distribution of different diagnoses on SPE were normal (n=759, 24.4%), chronic inflammation (n=1659, 53.4%), monoclonal band (n=404, 13.0%), beta gamma-bridging (n=31, 1.0%), nephrotic syndrome with raised α2 band only (n=128, 4.1%), protein losing enteropathy (n=48, 1.6%), chronic active hepatitis including chronic inflammation and b-gamma bridging (n=22, 0.7%), sample unfit for analysis (n=51, 1.6%), haemolyzed (n=06, 0.2%). Gender differences are given in Table I.

Table I shows mean, median, IQR and level of significance (p-value) for variables such as serum total protein (60-80 g/l); serum albumin (33-50 g/l); serum gamma (5-15 g/l); serum α 2-globulin; serum beta 1-globulin; serum α1-globulin and serum beta 2-globulin.

For IE and IF, 1,329 subjects with mean age 64 ±16.2 years were recruited; and among these males were 864 (65%) and females were 465 (35%). Different varieties of diseases identified on immunoelectrophoresis and immunofixation were; normal (n=972, 73%), monoclonal Ig G kappa (n=204, 15.3%), monoclonal Ig G lambda (n=75, 6.0%), monoclonal Ig A Lambda (n=16, 1.2%), monoclonal Ig M kappa (n=14, 1.0%), monoclonal Ig A kappa (n=12, 0.9%), free Lambda light chains (n=12, 0.9%), monoclonal Ig M Lambda (n=10, 0.7%), free Kappa light chains (n=8, 0.6%), b-gamma bridging (n=4, 0.3%), and Ig G Bichrome gammopathy (n=2, 0.1%).

Audit was carried out on the last five years data of SPE for diagnosis of multiple myeloma. It revealed: totally justified cost=No. of tests positive for multiple myeloma x cost/test=404 x 1500 PKR, = (606000 PKR). On SPE 404 tests, i.e. (12.9% of total 3,108 tests) were identified as multiple myeloma and cost expenditure in relation to these tests were totally justified; totally unjustified cost was calculated as no. of tests with normal findings in which no disease identified x cost/test =759 x 1500PKR = (1138500 PKR). On SPE, 759 tests, i.e. (24.4% of total 3,108 tests) had normal finding. Hence, cost expenditure in relation to these tests were totally unjustified; partially

Table I: Gender difference (N=3108).

Variables	N	Mean	Mann-Whitney U-test	Median (1QR, p-value)
Serum total protein (60-80 g/l)		74.04	1007551.000	75 (12, p<0.001)
Male	1858	1471.78		
Female	1250	1677.46		
Serum albumin (33-50 g/l)		35.39	1130270.500	37 (11, p=0.206)
Male	1858	1571.17		
Female	1250	1529.72		
Serum gamma (5-15 g/l)		16.70	1061564.500	17 (08, p<0.001)
Male	1858	1500.85		
Female	1250	1634.25		
Serum alpha 2-globulin		6.688	1135395.500	07 (01, p=0.283)
Male	1858	1568.42		
Female	1250	1533.82		
Serum beta 1-globulin		3.762	1140189.000	04 (01, p=0.371)
Male	1858	1565.84		
Female	1250	1537.65		
Serum alpha 1-globulin		3.314	1152402.500	03 (01, p=0.703)
Male	1858	1549.74		
Female	1250	1561.58		
Serum beta 2-globulin		4.015		04 (01, p=0.800)
Male	1858	1551.28	1155263.000	
Female	1250	1559.29		

unjustified cost was the number of tests in which irrelevant diseases identified whom treatment is not beneficial x cost/test = (1,659 of chronic inflammation +31 of beta gamma bridging +48 of protein losing enteropathy +22 of chronic active hepatitis +51 sample unfit for analysis +06 hemolyzed sample) x 1500PKR= (2725500 PKR).

SPE also identified above irrelevant disease; collectively these number of tests were 1,817 tests, i.e. (58.4% of total 3,108 tests) whom diagnosis did not give any additional benefits to patients. Hence, cost expenditure in relation to these tests were partially unjustified.

Partially justified cost was for the number of tests that diagnosed byproduct disease, which if treated would lead additional health benefit x cost/test = nephrotic syndrome identified on 128 tests x 1500 PKR =192000 PKR). On SPE, 128 tests i.e. (4.1% of total 3,108 tests) had nephrotic syndrome which if treated earlier leads to many health benefit to patients. Hence, cost expenditure in relation to these tests were partially justified. The audit of IE and IF were divided into two categories. Totally unjustified cost was for the number of tests with normal finding (negative cases) x cost /test = (972 of normal +4 of beta gamma bridging) x 1500 PKR = (1464000 PKR). Nine hundred and seventy-six tests i.e. (73.4% of total 1,329 tests) had normal finding. Hence, cost expenditure in relation to these tests were totally unjustified. Totally justified cost for the number of positive cases x cost/ test = (353 cases of different type of monoclonal gammopathy) x 1500 PKR = 529500 PKR. Three hundred and fifty-three tests i.e. (26.6% of total 1,329 tests) were identified collectively as different type of monoclonal gammopathies (multiple myeloma). Hence, cost expenditure in relation to these tests were totally justified.

Overall, 82.8% SPE tests were overutilised so the costs attributed to these tests were either totally or partially unjustified. Overall, 73.4% IE and IF tests were also overutilised so the costs attributed to these tests were also unjustified.

DISCUSSION

In the clinical practice, serum protein electrophoresis is used as a screening test in the initial evaluation of multiple myeloma and other numerous clinical conditions. This study showed that only 13% cases of multiple myeloma on screening with SPE and 26.6% different types of monoclonal gammopathy, which were confirmed on IE and IF and among which monoclonal Ig kappa was most common (15.3%), similar to other studies.[7,8] In this study, a slight male predominance was also found which was similar to Nayak *et al*.[9] The disease manifested in the middle ages, similar to other studies.

Audit revealed some important facts. First, it showed that positive cases of multiple myeloma were very few in comparison to normal and inflammatory disease cases, which did not require SPE as a preliminary test as their other more specific and sensitive tests are available; so this screening test was overutilised. Secondly, immunoelectrophoresis and immunofixation when used in strongly suspected cases of multiple myeloma as a confirmatory tests also revealed 73.4% normal cases and only 26.6% true positive cases identified, which corroborates the findings of previous studies.[10] Thirdly, the audit showed that both of these tests were irrationally advised and not properly accompanied with clinical history and general physical examination, which if used, can minimise the workload and save manpower and economy. To the best of the authors' knowledge, no supplementary evidence demonstrates such type of audit in Pakistan governmental sector; where due to free laboratory services, most of the laboratory services were overutilised without considering average loss to the government and lesser or no benefit to the patients.

The main limitation of this study is that it is a retrospective audit. This is problematic because it is dependent upon accurate data entry at the time of patient presentation.

Further studies addressing these limitations will provide more authenticity for these findings, and may guide clinical practice towards rational use of these tests in the future.

CONCLUSION

This study concluded that SPE, IE and IF tests were overutilised for diagnosis of multiple myeloma. Taking proper history, clinical examination, and awareness among physicians are required for minimising of the workload and proper utilisation of these tests.

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CASE REPORT

Solitary Fibrous Tumor of Kidney

Ameet Kumar Lalwani, Syed Muhammad Faiq and Jogindar Ahuja

ABSTRACT

Solitary fibrous tumor of kidney is an unusual condition. It is spindle cell tumor with mesenchymal in origin so most commonly reported cases are in pleura, and extra-pleural sites are very rare. It is mostly benign in nature but malignant variant are also reported. Treatment is *en bloc* resection as in other sites whether pleural or extra-pleural. Prognosis is excellent. This tumor is difficult to diagnose only on imaging features; so for diagnosis, histopathology is needed mostly with immunohistochemical markers like CD34, CD99, Bcl2 proteins. A middle-aged male presented initially with clinical and radiological features, suspected of renal cell carcinoma. Surgery was performed, which proved solitary fibrous tumor on histopathology; and patient on follow-up remained tumor-free till the last follow-up.

Key Words: *Solitary fibrous tumor. Spindle cell. Mesenchymal. Pleura. Renal cell carcinoma.*

INTRODUCTION

Solitary fibrous tumor (SFT) of the kidney is a rare entity with less than 50 cases described in literature.[1-3] The first case was described by Gelb *et al*. in 1996.[4]

SFT usually arises from pleura; however, unusual extra-pleural locations have been reported involving urogenital system like kidney, urinary bladder and prostate. It is difficult to diagnose on imaging, so definite diagnosis depends on histopathology. On histopathology, it is a spindle cell tumor having vascular, fibrous, adipose, or other mesenchymal tissue differentiation. On the basis of the histological features and clinicobiologic behaviour, adult renal mesenchymal tumors may be further classified into benign and malignant tumors.[4,5]

This report describes this rare condition involving the kidney.

CASE REPORT

A 35-year adult presented with right flank pain and swelling for two months without haematuria. Clinical examination showed a mobile non-tender mass in right lumbar region; rest were unremarkable. Gray scale and Doppler sonography of abdomen revealed a well defined heterogeneous predominantly hypoechoic right exophytic renal mass with internal vascular flow in it.

MDCT tripashic contrast study showed large well circumscribed exophytic heterogeneous density mass lesion diffusely involving right kidney. On arterial phase peripheral puddling, progressive filling on venous phase and becoming isodense on delayed phase (Figures 1 and 2). It measured 19.8x16.3x13.7 cm. Superiorly, it was abutting inferior surface of liver, posterolaterally it was reaching up to respective abdominal wall with indistinct fat planes, and medially it was abutting right psoas muscle and also displacing adjacent bowel loops and pancreas without evidence of frank infiltration. The rest of right kidney showed normal enhancement and excretion. There was no evidence of loco-regional lymphadenopathy or renal vein thrombosis. Left kidney and other viscera were unremarkable.

After all above clinical and radiological workups, differential diagnosis of hemangioma versus renal cell carcinoma was made, surgery was planned, and right tumor nephrectomy was done by urologist.

On gross examination, specimen was a huge, exophytic, well circumscribed, grey white, lobulated tumor mass involving almost two-thirds of the kidney parenchyma with spared portion of native kidney. It is also showing few scattered areas of hemorrhage and necrosis.

On microscopic examination, specimen showed neoplastic lesion composed of spindle-shaped cells containing eosinophilic cytoplasm and blunt ended oval nuclei in the background of myxoid stroma. At places, large bizarre-shaped multinucleated cells and geographic areas of necrosis were also appreciated. Few foci of atypical mitosis were also seen. There was no lymphatic/vascular invasion. Immunohistochemistry showed diffuse positivity for vimentin, CD 34 and p53 (Figure 3).

DISCUSSION

SFT of kidney is a rare benign spindle cell neoplasm and difficult to differentiate from hemangiopericytomas with presence of CD 34 positivity. It is characterised by the presence of a mass that is composed of predominantly fibrous lesions containing large collagenised areas and hyalinised vessels.[1,4-5] Malignant SFT of the kidney is particularly rare.[6]

Department of Radiology, Sindh Institute of Urology and Transplantation (SIUT), Karachi.

Correspondence: Dr. Ameet Kumar Lalwani, Senior Lecturer, Department of Radiology, Sindh Institute of Urology and Transplantation (SIUT), Karachi.
E-mail: dramitsl@gmail.com

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Histopathologic characteristics of SFTs were first described by Klemperer and Rabin in 1931 as pleura-localised fibrous mesotheliomas.[7,8] Reports suggest that SFTs also originate from extra-pleural sites such as the pelvis, abdomen, retroperitoneum, buccal space, maxillary sinus, liver, pancreas, suprarenal region, and kidneys.[8]

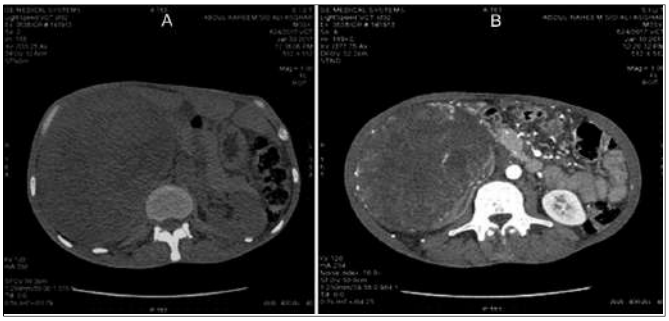

Figure 1: (A) Plain phase: Large well circumscribed exophytic heterogeneous density mass lesion diffusely involving right kidney. **(B)** Arterial phase: Peripheral puddling of contrast enhancement in right renal mass.

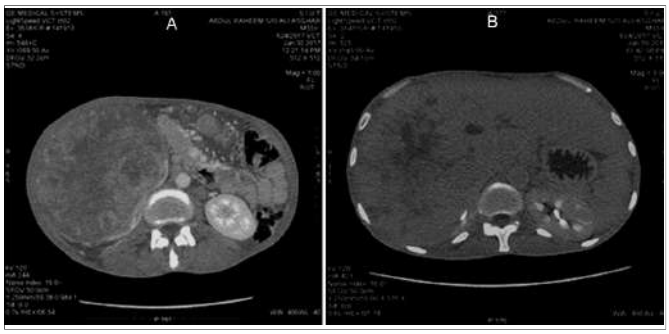

Figure 2: (A) Venous phase: Progressive filling of contrast in right renal mass on venous phase. **(B)** Delayed phase: Becoming isodense with central necrotic component on delayed phase.

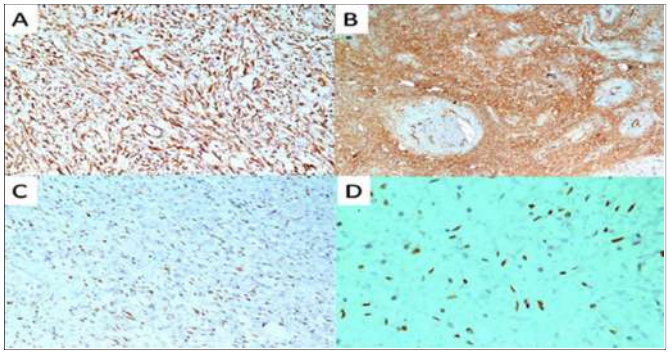

Figure 3: Immunohistochemical (IHC) features of the lesion. **(A)** Low-power photomicrograph showing diffuse positivity of tumor cells for vimentin. (anti-vimentin IHC, ×40). **(B)** Low-power view showing positivity of tumor cells and endothelial cells of blood vessels for CD34. (anti-CD34 IHC, ×40). **(C)** Low-power view showing nuclear positivity of tumor cells for p53. (anti-p53 IHC, ×40). **(D)** High-power view showing nuclear positivity of tumor cells for p53. (anti-p53 IHC, ×200).

The findings of SFTs on CT and MRI are generally non-specific for a pathognomonic diagnosis. Differential diagnosis of STF includes mesotheliomas in the pleura, dural-based meningiomas or hemangiopericytomas in the brain, angiomyolipomas in the kidney, and so on.

Mostly behaviour of this tumor is benign; but in few cases, malignant characteristics can be detected on histopathological features including increased mitosis (>4 mitosis/10 high power field), pleomorphism, cellularity, hemorrhage and necrosis. Treatment is complete resection with favourable prognosis. Recurrence after surgery has never been documented.[9]

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Tuberculous Paraspinal Abscess Invading Esophagus: A Rare Cause of Dysphagia

Shazia Shad, Ayesha Aslam Rai, Ghous Bux Soomro and Nasir Hassan Luck

ABSTRACT

Esophageal involvement by *mycobacterium tuberculosis* is a rare entity even in the endemic regions. The common presenting complaint in esophageal tuberculosis are deglutition disorders in which patients primarily present with difficulty in swallowing. The most common site of esophageal involvement is the middle-third at the level of carina. Herein, the case of an adolescent boy is presented who had complains of dysphagia, abdominal pain along with weight loss for a month. On evaluation, he was found to have esophageal narrowing resulting in dysphagia. CT scan revealed a fistulous communication of tuberculous paraspinal abscess with the esophagus, which had resulted in dysphagia. The diagnosis of tuberculosis was made by using gold standard method of Polymerase Chain Reaction (PCR) of *mycobacterium tuberculosis*. He had marked symptomatic improvement within a month of starting anti tuberculous therapy (ATT) and was successfully treated with ATT for 9 months.

Key Words: *Tuberculosis. Deglutition disorders. Paraspinal abscess. Esophageal fistula. Dysphagia.*

INTRODUCTION

Tuberculosis of gastrointestinal (GI) tract is the sixth most frequent extra-pulmonary site after lymphatic, genitourinary, skeletal, miliary, and meningeal tuberculosis.[1] *Mycobacterium tuberculosis* involvement of esophagus is rarely reported in both immunocompetent and immuno-compromised patients even in countries with high incidence rates like India and Pakistan.[2] Esophageal tuberculosis constitutes about 0.3% of GI tuberculosis cases in countries with high incidence of tuberculosis.[3] It is considered to be one of the rarely involved organs, usually secondarily infected from adjacent viscera, as seen in this case.

Here, the authors are reporting a case in which tuberculous paraspinal abscess had invaded esophagus and caused dysphagia in an adolescent.

CASE REPORT

A 13-year boy presented with history of progressive dysphagia for solid food along with undocumented weight loss for the last one month. He had no associated history of cough, nasal regurgitation, choking with meal ingestion, odynophagia or fever. He had no history of tuberculosis contact. General physical and systemic examinations were unremarkable.

His baseline investigations including complete blood picture, renal function test and electrolytes were within normal range. Chest X-ray revealed right sided pleural effusion which could not be aspirated with radiology assistance (ultrasound) because of thick septations. Erythrocyte sedimentation rate (ESR) was raised up to 75 mm after 1st hour, however, purified protein derivative (PPD) revealed no induration (0 mm). Barium swallow was performed, which revealed a stricture in distal part of esophagus (Figure 1a).

Esophagogastroduodenoscopy (EGD) was performed later on, which revealed a bulge with overlying edematous and erythematous mucosa in the distal esophagus located at 30-cm from incisors teeth. A non-discharging fistulous communication was also noted in the centre of the bulge and it was occluding almost half of the lumen, multiple biopsies was taken from this site in distal esophagus. Histopathological examination of the esophageal biopsy showed features of chronic non-caseating granulomatous inflammation, while there was no evidence of malignancy.

Computerised tomography scan (CT scan) chest revealed soft tissue density mass in posterior mediastinal region at sub-carinal level with air lucencies in it. These findings were suggestive of fistulous communication with esophagus. The mass was also causing esophageal narrowing with proximal dilatation, extending down to paravertebral region up to the level of D7, measuring approximately 3 x 4 cm in cranio-caudal dimension (Figure 1b). Findings were highly suggestive of abscess. CT scan guided needle aspiration of paravertebral abscess was performed, and obtained fluid was sent for gram stain culture and sensitivity, acid fast *bacilli* (AFB) polymerase chain reaction (PCR), and cytology. Cytology, gram stain, culture and sensitivity of sampled fluid was negative for malignant cell and bacteria, while AFB PCR was positive.

The patient was started on first line anti-tuberculous (ATT) regimen (Isoniazid, ethambutol, pyrazinamide and rifampicin). On follow-up after a month, he had marked improvement in symptoms and also have gained weight.

Department of Hepatogastroenterology, Sindh Institute of Urology and Transplantation (SIUT), Karachi.

Correspondence: Dr. Ayesha Aslam Rai, Postgraduate Trainee, Department of Hepatogastroenterology, Sindh Institute of Urology and Transplantation (SIUT), Karachi.
E-mail: daar@hotmail.com

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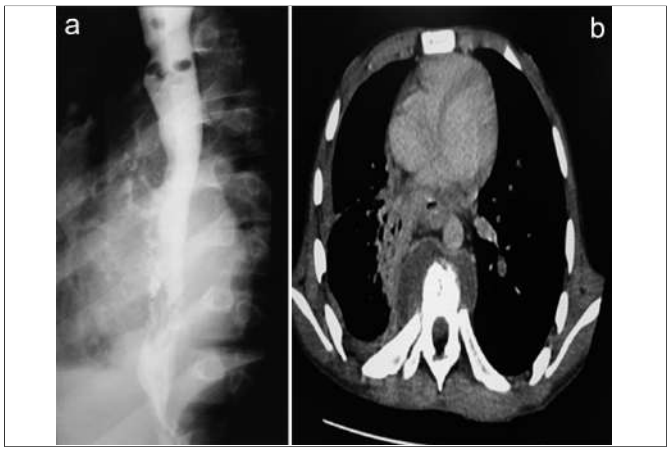

Figure 1: (a) Barium swallow showing distal esophageal narrowing. **(b)** CT scan image showing paraspinal abscess.

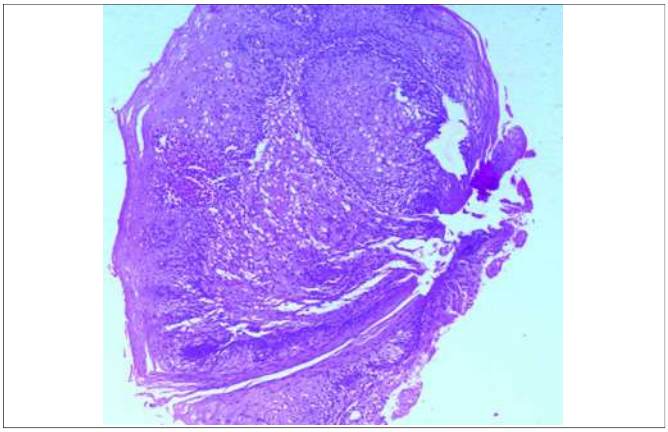

Figure 2: Non-caseating granuloma in esophageal biopsy. Arrow pointing towards multinucleated giant cell in granuloma.

DISCUSSION

Esophageal tuberculosis is a rare entity, which constitutes around 0.3% of the cases in highly endemic areas.[3,4] Involvement of gastrointestinal tract occurs through ingestion of infected sputum or hematogenous spread from primary pulmonary TB. In most instances, cases of esophageal tuberculosis are secondary to direct extension from adjacent structures; primary esophageal tuberculosis is even rarer. Esophageal involvement by tuberculosis usually affects the middle third of esophagus at the level of carina,[5] as seen in this patient. Most common symptoms are dysphagia or retrosternal pain with or without weight loss.[6] Diagnosis is usually made by upper gastrointestinal endoscopic examination and tissue is obtained for histology, as in this case, esophageal biopsy showed granulomatous inflammation. It can also present as dysphagia, if there is esophageal strictures secondary to external compression of the viscera in the mediastinum, cervical lymph nodes or as a result of mediastinal fibrosis induced by tuberculosis.[6,7] This patient also presented with history of dysphagia, which was secondary to external esophageal compression by paraspinal abscess. Further complications such as stricture, bleeding, perforation, fistula formation or aspiration pneumonia were also reported in literature.[2,8] In this case fistulous communication of paraspinal abscess with esophagus was observed.

The differential diagnosis of esophageal tuberculosis includes esophageal carcinoma, Crohn's disease, actinomycosis and syphilis, which were excluded in this patient by microscopic and histological examination. Esophageal TB is managed with anti-tuberculous therapy; surgery being reserved for complications including a non-healing trachea-esophageal or broncho-esophageal fistula, stricture, or bleeding from an aorto-esophageal fistula.[2,8,10] A six-to-twelve months course of ATT chemotherapy is sufficient for immunocompetent patients treated with a regimen. This patient was managed according to the standard protocol which consisted of four first-line drugs, namely isoniazid, rifampicin, ethambutol, and pyrazinamide for the initial 2 months, then continuing with isoniazid and rifampicin for another 4-7 months.[8,10]

Dysphagia in an adolescent is very unusual problem. However, esophageal tuberculosis is one of the rarest cause of this symptom at this age in an immunocompetent individual; but it must be kept in mind in endemic regions.

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CASE REPORT

Enteroenteric Fistulae in Acute Bowel Ischemia

Muhammad Salman Khan[1], Inamullah Khan[2], Amir Humza[2], Y. Bashir Hadi[2] and Zeeshan Haider[1]

ABSTRACT

Gastrointestinal fistulae are classified as enteroenteric or enterocutaneous. Most gastrointestinal fistulae are formed after surgical procedures for inflammatory bowel disease or malignancy. For spontaneous enteroenteric fistulae, ischemia has been reported as a possible etiology. We report two cases of spontaneous enteroenteric fistulae arising after bowel ischemia; a 38-year male with a 10-day history of severe abdominal pain with fever and vomiting, and a 22-year female with a one-week history of abdominal pain and diarrhea. Arterial and venous thrombi in association with enteroenteric fistulae were identified on computed tomography. These cases point towards acute mesenteric ischemia as a rare cause of spontaneous enteroenteric fistulae. Surgical management of these fistulae can be effective in resolving this complication.

Key Words: *Infarction. Intestinal fistula. Mesenteric ischemia. Acute abdomen. Enteroenteric fistula. Abdominal radiography. Computed tomography.*

INTRODUCTION

Fistulae are abnormal connections between two organs. Enteric fistulae are classified as internal or external, the former draining to an abnormal site in the gastro-intestinal lumen or any other internal organ; and the latter draining to a perforation in the skin.[1] Abdominal surgery is the most commonly reported cause of such fistulae, followed by Crohn's disease which accounts for about 20-30% of them.[2] Ischemia has been hypothesised as a possible etiology for spontaneous enteroenteric fistulae,[3,4] but as yet no cases of enteroenteric fistulae definitively arising from mesenteric ischemia have been reported. Given the rarity of enteroenteric fistulae secondary to mesenteric ischemia, there is no guideline regarding their ideal course of management.

We report two cases of spontaneous enteroenteric fistula formation in association with mesenteric ischemia resulting from arterial or venous thrombi that were surgically managed and resulted in complete resolution of symptoms.

CASE REPORT

Case 1: A 38-year male presented to the emergency room with a 10-day history of severe abdominal pain associated with fever and vomiting. Past medical and surgical history was unremarkable as was drug history. Family history was positive for hypertension in the patient's father. He was an alcoholic with a 10-year history of alcohol consumption. Review of systems was unremarkable. Physical examination revealed a vitally stable patient with generalised abdominal tenderness and no other positive findings.

Computed tomography (CT) scan of the abdomen showed an eccentric plaque-like partial thrombus at the origin of superior mesenteric artery (SMA). Based on clinical presentation and CT scan findings, a diagnosis of bowel ischemia secondary to SMA thrombosis was made. He was kept on *nil per oral* (NPO) regimen and a nasogastric tube was passed. Conservative management with total parenteral nutrition, intravenous (IV) antibiotics and warfarin infusion was started. Subsequently, his condition improved and he was discharged. A follow-up visit after one week was planned.

The patient presented again 28 days later with complaints of abdominal pain and vomiting. On examination, the only positive finding was tachycardia, with a heart rate of 123 beats per minute. CT scan of the abdomen revealed progression of mesenteric ischemia with an increase in SMA thrombus size, dilated thick-walled jejunal, and ileal loops and developing pneumatosis intestinalis (Figure 1). Again, he was conservatively managed and discharged on the fifth day of admission upon resolution of symptoms.

Four months later, he presented with abdominal pain and 23 kgs weight loss. Physical examination did not yield any positive findings. CT scan of the abdomen showed ischemic strictures in jejunal loops with multiple loops coalescing to form an enteroenteric fistula. These findings were confirmed on CT scan and barium follow through (Figures 2a and 2b). Based on these findings, a diagnosis of chronic SMA thrombosis with ischemic jejunal stricture and enteroenteric fistula was made.

The patient underwent small bowel resection anastomosis with stricturoplasty. Intraoperatively, the small bowel was found to be dilated with loops adherent to omentum and

[1] *Department of Radiology, The Aga Khan University Hospital, Karachi.*
[2] *Researcher, The Aga Khan University Hospital, Karachi.*

Correspondence: Dr. Inamullah Khan, Research Associate, The Aga Khan University Hospital,Stadium Road, Karachi. E-mail: inamullah.aku.co15@gmail.com

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colon, forming a closed loop obstructed region. The presence of the enteroenteric fistula was confirmed intraoperatively. Three to four matted loops with multiple strictures were also noted. Postoperative recovery was unremarkable. At a one year follow-up period, the patient did not report any symptoms.

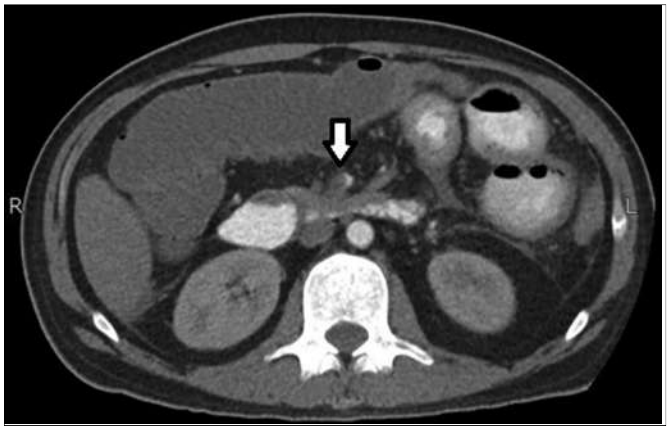

Figure 1: Axial post-contrast arterial phase CT image shows dilated thick-walled small bowel loops in left mid abdomen showing fat stranding in the adjacent mesentery, suggestive of ischemic loops. Note the partial thrombus in SMA (arrow).

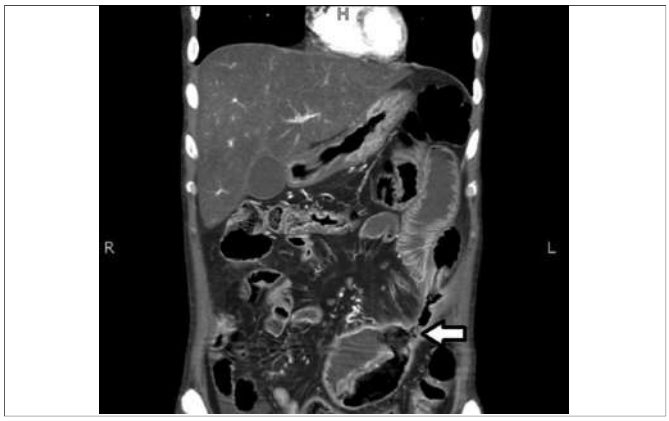

Figure 2a: Same patient 5 months later coronal post-contrast CT scan demonstrating development of ischemic strictures in left-sided jejunal loops with multiple loops coalescing and forming enteroenteric fistula (arrow). There is resolution of bowel thickening and enhancement of bowel walls with dilated lumen proximal to stricture. Note development of fatty infiltration of liver.

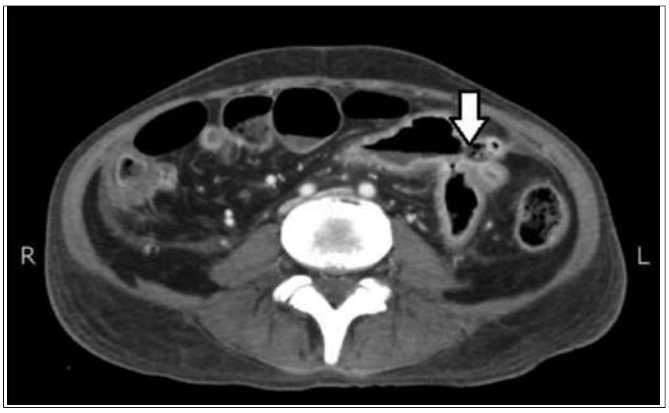

Figure 2b: Axial post-contrast CT image of the same patient after 5 months of initial ischemic ictus, demonstrating coalescing small bowel loops showing enteroenteric fistula formation in left abdomen with stricture and enhancement.

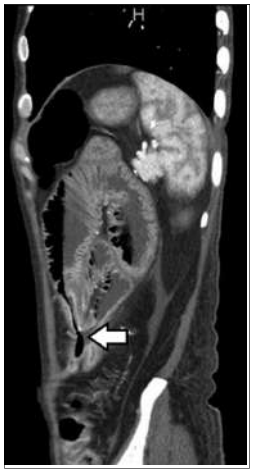

Figure 3a: Sagittal-post contrast CT image of the same patient after 5 months of initial ischemic ictus, demonstrating coalescing small bowel loops showing enteroenteric fistula formation in left abdomen with stricture and enhancement. Note after coalescing, there is tiny outpouching simulating a diverticulum (arrow).

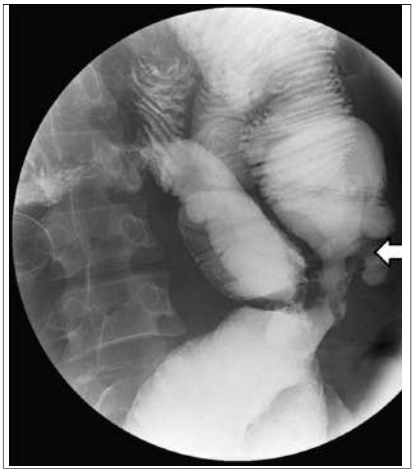

Figure 3b: Same patient after the CT, barium follow through. Image after 5 months of initial ischemic ictus, demonstrating clustered and strictured small bowel loops showing enteroenteric fistula with superimposed strictured and a few dilated small bowel loops in left abdomen showing tiny outpouching simulating a diverticulum (arrow).

Case 2: A 22-year female presented to the general surgery service with a one week history of abdominal pain and diarrhoea. The pain was sudden in onset and was aggravated by oral intake. The patient also complained of bilious vomiting and nausea. She had no significant comorbid condition and the review of systems was unremarkable. On examination, she was vitally stable. Abdominal exam revealed generalised tenderness, while a ballooned rectum with smooth walls was found on digital rectal examination. Other systemic examinations were unremarkable.

Abdominal CT scan showed thrombosis in the mesenteric and portal veins with ischemia of the duodenum and proximal jejunal loops. She was kept on NPO regimen and a nasogastric tube was passed. Conservative management was planned and the patient was started on IV fluids, antibiotics and anticoagulants, which resulted in clinical improvement and complete resolution of symptoms by the fifth day of admission. The nasogastric tube was removed on the seventh day of admission and the patient was discharged two days later with the plan for a follow-up visit after one week.

The patient presented to the emergency room five days later with complaints of abdominal pain and vomiting for the past two days. Physical examination revealed a vitally stable patient with a mildly tender abdomen that was dull to percussion. A CT scan was performed which showed a stricture at the duodenojejunal junction with marked gastric and duodenal dilatation proximal to the stricture. An enteroenteric fistula was found between the proximal jejunal loops (Figures 3a and 3b). Exploratory laparotomy and gastrojejunostomy was performed. She was discharged on the 14th day of admission after an uneventful recovery. The patient was stable and symptom-free at a nine-month follow-up period.

DISCUSSION

Gastrointestinal fistulae are uncommonly encountered in surgical practice. The etiological categories of gastrointestinal fistulae include postoperative fistulae, spontaneous fistulae, and trauma-induced fistulae. About 75-85% of gastrointestinal fistulae form following surgical procedures for Inflammatory Bowel Disease (IBD), pancreatitis or malignancy, while 15-25% form spontaneously, without any preceding surgical intervention.[4]

The most common cause of spontaneous fistula formation is Crohn's disease with around half of all patients with Crohn's disease developing a fistula during the disease course.[5] Abscess formation, appendicitis, diverticulitis, perforation and obstruction of bowel loops resulting from inflammatory conditions, such as pancreatitis and IBD, can also cause spontaneous fistula formation.[4-6] Pancreatic and gynaecologic malignancies and radiotherapy for malignancies are other causes of spontaneous fistula formation.[4]

The patients presented in this report developed spontaneous fistulae in the absence of the above-mentioned conditions. Both developed spontaneous enteroenteric fistulae against a backdrop of ischemic bowel documented on radiological imaging. The first patient had SMA thrombosis, while the second had mesenteric vein and portal venous thrombosis. In both patients, there was an obvious progression from bowel ischemia to enteroenteric fistulae in the ischemic region, as documented on radiology (Figures 2a and 3a). Although bowel ischemia has been mentioned as a possible cause of spontaneous enteroenteric fistula formation in literature,[4,9] an extensive literature review failed to yield any case report or other record of spontaneous enteroenteric fistula formation as a result of ischemic bowel disease. Thus, this is the first report of spontaneous enteroenteric fistulae resulting from bowel ischemia. Notably, although post-contrast CT scan was effective in diagnosing enteroenteric fistulae in the reported cases, the sensitivity of this modality, or the most sensitive modality, for diagnosis of this complication remains undetermined.

Mesenteric ischemia can be categorised into three categories based upon the underlying pathophysiology: acute mesenteric arterial embolism, acute mesenteric arterial thrombosis and acute venous thrombosis.[7] In contrast to embolic vascular occlusion which causes a sudden onset of abdominal pain, thrombotic insults usually result in a relatively insidious onset of abdominal pain and progressive weight loss.[7]

A recent meta-analysis concluded that acute abdominal pain (sensitivity range 60-100%), nausea and vomiting (sensitivity range 39-93%) and pain out of proportion to physical examination findings (sensitivity range 45-54%) were the most common presenting complaints in patients with acute mesenteric ischemia (AMI) while diffuse abdominal tenderness and peritoneal signs (sensitivity ranges 54-90% and 13-65%, respectively) were the most common physical examination findings.[8] The World Society of Emergency Surgery (WSES) 2017 guidelines recommend that severe abdominal pain out of proportion to physical examination findings should be assumed to be AMI until disproven.[7]

Laboratory results can help in diagnosis of AMI; around 90% of patients with AMI have an abnormally elevated leukocyte count while 88% have metabolic acidosis with elevated lactate level.[7] WSES recommends an early CT angiogram in patients with lactic acidosis in combination with abdominal pain that do not otherwise appear clinically ill.[7] The multi-detector CT (MDCT) angiogram - which has a sensitivity of 93% and a specificity of 100% - has replaced formal angiography as the diagnostic study of choice for AMI.[7] MDCT findings in AMI can include intestinal dilatation and thickness, portal venous gas, reduced or absent visceral enhancement, pneumatosis intestinalis and pneumoperitoneum.[7] Mesenteric ischemia can lead to mucosal ulceration, gangrene and bowel perforation resulting in peritonitis, stricture formation or haemorrhage.[9] Both the patients presented here developed ischemic strictures after AMI (Figures 2a, 2b and 3a). It is noteworthy that, based on this report, enteroenteric fistula formation is a new addition to the list of possible complications of mesenteric ischemia.

In conclusion, this article serves to highlight enteroenteric fistulae as a rare complication of AMI, which can significantly alter the disease course and choice of treatment. A high level of suspicion and appropriate radiological investigations (e.g. CT scan, as in this case) can help in diagnosis of this condition. There is no definite guideline for the management of enteroenteric fistulae secondary to bowel ischemia. In our experience, surgical management of these fistulae can be effective in completely resolving this complication and its associated symptoms.

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CASE REPORT

Cranially Migrated Ventriculoperitoneal Shunt in Patient with Bilateral Subdural Empyema

Mirza Faisal Ahmed Rafiq

ABSTRACT

A right-sided ventriculoperitoneal (VP) shunt was placed in patient with congenital hydrocephalous in the first month of life. Three-month review visit showed no improvement and after evaluation and computerised tomogram (CT) scan brain, another VP shunt was placed on the left side without handling the previous right sided VP shunt. Patient did not improve and again presented with fever and fits. CT scan brain with and without contrast was repeated, which showed bilateral subdural empyema and right-sided cranially migrated VP shunt. Cerebrospinal fluid (CSF) analysis demonstrated infection. Bilateral burr hole drainage of subdural empyema with subsequent removal of right-sided migrated VP shunt was done. Cranial end of left-sided VP shunt was converted into external ventricular drain (EVD) and its abdominal end removed. Patient was placed on intravenous as well as intraventricular antibiotics through the EVD. Later, right-sided VP shunt was placed after clearance of infection. Regular follow-up showed that the patient is doing well.

Key Words: *Ventriculoperitoneal shunt migration. Subdural empyema. Infection. Congenital hydrocephalus.*

INTRODUCTION

Placement of ventriculoperitoneal (VP) shunt is the most common mode of treatment in patients with hydrocephalous.[1] It is a surgically implanted hardware having infection rate ranging from 5 to 15%.[2] More than 50% of shunt infection is caused by *staphylococcus* species. However, gram-negative bacteria are also responsible for rest of 40%. Certain other factors like age and time since insertion also play a role. Younger the age, higher is the chance of infection (68%) and most of infections (79%) occurred within the first two months of procedure.[3] This infection can lead to both intra-axial and extra-axial complications like ventriculitis, subdural empyema and epidural abscess.[2] The most common encountered symptoms are fever and seizures, and signs of raised intra-cranial pressure. Ventricular CSF analysis and culture, ultrasonography of the head, CT scan of brain with contrast, and magnetic resonance imaging (MRI) brain with contrast are the common investigations that are usually done to confirm diagnosis and to know cause.[3] Among other recognisable complications are distal tube migration and detachments into the abdomen.[1] Treatment of infection is with antibiotics after culture and sensitivity,[3] drainage of empyema and evacuation of its source.[4] All these infective complications can ultimately lead to revision of VP shunt surgery, and have considerable morbidity and mortality.[3]

Department of Neurosurgery, Valley Medical Complex, Abbottabad.

Correspondence: Dr. Mirza Faisal Ahmed Rafiq, Consultant Neurosurgeon, Valley Medical Complex, Abbottabad. E-mail: faisalmar9229@gmail.com

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CASE REPORT

A seven-month male infant presented in paeds surgery ward, KRL General Hospital, Islamabad, with chief complaints of fits and high grade fever. This patient had congenital hydrocephalous and underwent right side VP shunt placement in the first month of life. Symptoms like enlarging head did not resolve till three months after surgery, and patient was again reviewed by a paeds surgeon. Patient underwent CT scan of brain (Figure 1a) and VP shunt was found non-functional. Paeds surgeon put another VP shunt on left side of patient and did not do anything with right-sided VP shunt, and sent him home. After about two months, patient again came with chief complaints of fits and fever. CT scan of brain with and without contrast (Figure 1b) showed wholly migrated right-sided VP shunt into cranial cavity along with bilateral subdural empyema. Left-sided VP shunt was in place; but by CSF examination, it was found infected with raised proteins and leucocyte counts.

Patient was put on intravenous antibiotics; and after preparation, bilateral burr hole drainage of subdural empyema was done and greenish-yellow 30 ml of pus (18 ml right side; 12 ml left) was drained and sent for culture and sensitivity, which was found to have no growth. Right-sided VP shunt was removed (Figure 2) through Frazier's burr hole; and abdominal end of left-sided VP shunt was also removed and its ventricular catheter was converted to EVD. Intraventricular Amikacin (25 mg / day) was started in EVD converted ventricular catheter. Intravenous antibiotics (Vancomycin 15mg/kg, Amikacin 8mg/kg) and intra-ventricular Amikacin was continued till six weeks. Repeated complete blood picture, CSF analysis; and meanwhile, serum creatinine was done. Right-sided VP shunt was placed after normalisation of blood total leucocyte count

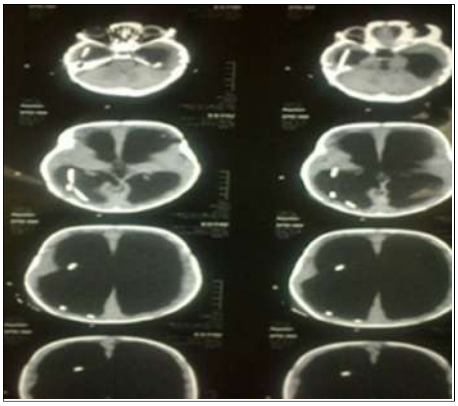

Figure 1(a): CT scan brain axial slices showing hydrocephalous and right side VP shunt in initial stages.

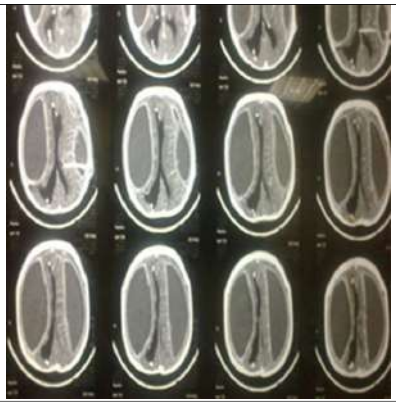

Figure 1(b): CT scan brain with contrast showing both VP shunts and bilateral subdural empyema.

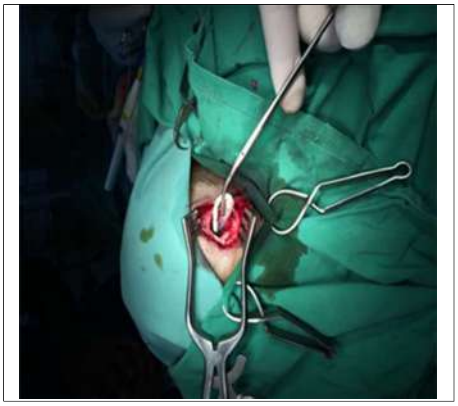

Figure 2: Burr hole removal of right side VP shunt.

(TLC), and when biochemical report of three alternate CSF analysis was found normal with TLC count less than five and normal protein content.

Patient was regularly followed monthly for one year and till last follow-up he was doing well with functional VP shunt.

DISCUSSION

Various studies have listed VP shunt complications.[4-6] To the best of author's knowledge, not a single reported case has this rare combination of subdural empyema with infected one of VP shunt and total migration of other VP shunt inside the cranial cavity. Shunt disconnections are also reported.[4,7] Either cranial ventricular catheter[6] or distal abdominal tubing,[1] was found disconnected in respected cranial or abdominal cavity. In one case, Codman-Hakim programmable valve was used and proximal tube including pre-chamber migrated into the cranial cavity.[8] However, all these reports have either the infective complications or the disconnection and none had this combination.

Migration of proximal tubing inside the cranial cavity is rare complication.[6] However, migration of whole of VP shunt is one of its kinds. In this case, it was the Chhabra VP shunt that was migrated, while it was said to have greatest of frictional force and least of stiffness, rendering perforation of abdominal viscera more common happening,[6] rather than migration into cranial cavity.

Management in such cases is tricky as every case is individualised and different clinical judgements and treatment strategies are required in every case.[9] The recommendations for treatment of subdural empyema are timely surgery and use of antibiotics and both of these said to render favourable outcome. Same strategy was adopted in this case. Bilateral burr hole evacuation was done and right-sided cranially migrated Chhabra VP shunt was removed, which was constant source of infections; it was in accordance with Eom *et al*.[4]

Right-sided VP shunt (Medtronic medium pressure) was placed after CSF was clear of infection (three alternate samples through EVD). This was in accordance with protocol of Tamber *et al*.[8] and patient was followed for up to a year. As in the case reported by Romero-Pizarro *et al*.,[6] culture and sensitivity of the content of subdural empyema drained from bilateral burr holes yielded no growth.

The other main aspect of treatment was the use of antibiotics. This patient was prescribed antibiotics (Vancomycin and Amikacin) for prolong period (twelve weeks of intra-venous antibiotics) as recommended by Goeser *et al*.[5] However, intra-ventricular antibiotics (Amikacin) were also used in addition to it, and EVD was portal used for it.

All these measures stabilised the patient who was doing well till the last follow-up.

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Aspirin in Primary Prevention of Myocardial Infarction/Angina and Stroke in Hypertensive Patients

Sir,

Hypertension is the leading attributable risk factor for mortality in the global burden of cardiovascular diseases (CVD).[1] Role of aspirin has been under debate in the past decade. In contrast, in a recent systematic review published in 2015 on 103,787 patients, reported risk of major gastrointestinal bleeding was increased and risk of hemorrhagic stroke or other intracranial bleeding tended to be increased in primary prevention trials in patients on aspirin.[2]

In many large trials which were conducted, the use of aspirin and cardiovascular outcomes on South-Asian population was not represented although they are relatively at higher risk of CVD.[3] Hence, aspirin use for prevention of CVD may have different results (both beneficial and adverse outcomes). So, the objective of this study is to determine the impact of aspirin use on cardiovascular disease including myocardial infarction (MI/angina and stroke) in hypertensive patients.

We did a cross-sectional study conducted in the Department of Medicine, The Aga Khan University Hospital, Karachi, Pakistan over a 3-year period from 2010 to 2012. Ethical clearance was taken from the Ethics Review Committee of The Aga Khan University (2827-Med-ERC-13). All participants aged greater than 40 years with history of hypertension, admitted through emergency room with MI/angina or stroke, were recruited. History of using aspirin was recorded. Hypertension was defined as SBP >140 mm Hg and DBP >90 mm Hg.[4] Use of aspirin defined as using a minimum dose of 75-81 mg of aspirin for minimum 4 weeks prior to ER visit was recorded.

A total of 575 patients were included in the study. Mean age was 63.96 +11.67 years, of which 372 (64.7%) were males and 203 (35%) were females. Aspirin use was present in 330 (57.4%) patients. Out of the 343 (59.7%) who had MI/angina, 208/343 (60.6%) were on aspirin for upto one month prior to the ER visit. Out of the 193 (33.6%) stroke patients, 99/193 (51.3%) were on aspirin. Upper gastrointestinal bleeding occurred in 49 (8%) patients and 26 (4.5%) were on aspirin. The OR of use of aspirin with myocardial infarction/angina and stroke is reported in Table I.

Use of aspirin did not show a clear benefit in primary prevention for ischemic heart diseases (IHD) and stroke in this hypertensive patient population. This concept has remained a topic of debate in the last decade. As use of aspirin in secondary prevention of IHD and stroke is well established in the high-risk prevalent atherosclerotic cardiovascular diseases including IHD and stroke, aspirin decreases acute CVD event (approximately 20% reduction in coronary events and total stroke).[5] This study demonstrated that there is no clear role of aspirin in primary prevention of IHD or stroke in hypertensive patients. Hence, we conclude that aspirin has no clear role in primary prevention of IHD or stroke in hypertensive patients; and this effect is irrespective of age and gender. However, more studies are required to further confirm this conclusion as this study has limited external validity.

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Aysha Almas[1], Muhammad Salman Ghazni[2], Shahrukh Hashmani[3] and Zain Mushtaq[1]

[1] Department of Internal Medicine, The Aga Khan University Hospital, Karachi.
[2] Department of Adult Cardiology, Tabba Heart Institute, Karachi.
[3] Department of Adult Cardiology, The Aga Khan University Hospital, Karachi.

Correspondence: Dr. Aysha Almas, Associate Professor, Department of Internal Medicine, The Aga Khan University Hospital, Stadium Road, Karachi.
E-mail: aysha.almas@aku.edu

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Table I: Association of aspirin use with ischemic heart disease and stroke adjusted for covariates.

Aspirin used N (%)	Crude OR 95% CI	p-value	Adjusted model * OR 95% CI	p-value	Adjusted Model** OR 95% CI	p-value
208 (60.6)			**Ischemic heart disease (N=343)**			
	0.76 (0.5,1.0)	0.06	0.72 (0.5,1.0)	0.06	0.8 (0.51,1.2)	0.3
99 (51.3)			**Stroke (N=193)**			
	0.69 (0.49,0.9)	0.04	0.7 (0.49,1.0)	0.7	0.7 (0.5,1.1)	0.2

**Adjusted for age and gender **Adjusted for prior history of myocardial infarction, stroke, diabetes , dyslipidemia and chronic kidney disease.*

Peripheral Ameloblastic Fibroma of Anterior Maxillary Gingiva Simulating Pyogenic Granuloma

Sir,

Peripheral odontogenic tumors (POTs) are rare in comparison to their central counterparts.[1] POTs show the histopathological features similar to their central counterparts. On clinical appearance, they often imitate other different soft tissue tumors.[2] Ameloblastic fibroma is a relatively uncommon neoplasm of odontogenic origin characterised by proliferation of both epithelial and mesenchymal components without formation of dental hard tissue.[3] Peripheral Ameloblastic Fibroma (PAF) is exceedingly rare; and as per our best knowledge, only seven cases have been reported in the literature so far.[3]

A 51-year male of a poor socioeconomic status, presented to the Department of Oral Medicine and Radiology of our Institution with the chief complaint of a swelling on upper front region of the jaw for two years. The swelling was initially small, and gradually it reached the current size. The past medical history and family history was non-contributory to the presented lesion. Personal history revealed the habit of tobacco chewing 5-6 pouches every day for the last 30 years. Intraoral examination revealed a solitary reddish swelling extending from #14 to #23, measuring about 3 × 2 cm (Figure 1a). On palpation, the swelling was soft to firm in consistency. No signs of discharge and ulceration were found. Intraoral periapical radiograph revealed that the lesion was not attached to the underlying bone. A provisional diagnosis of pyogenic granuloma was given with the differential diagnoses of irritational fibroma and peripheral ossifying fibroma. Hematological tests were normal. Excisional biopsy was performed under local anesthesia (Figure 1b) and the tissue was sent to the Department of Oral and Maxillofacial Pathology for the histopathological evaluation (Figure 1c).

Histopathological examination of soft tissue section revealed numerous finger-like strands of cuboidal cells resembling primitive odontogenic epithelium. The connective tissue stroma revealed numerous intervening fibrils of collagen interspersed by fibroblasts resembling dental papilla (Figure 1d). The vascular component was less and no mitotic figures were found. Based on histo-pathological examination, a final diagnosis of PAF was given. The follow-up period for one year was uneventful.

PAF is an uncommon tumor of soft tissue, histopatho-logically characterised by simultaneous growth of epithelial and mesenchymal components without production of enamel and/or dentine-like material.[1,3] PAFs are usually asymptomatic and often imitate the clinical course of different soft tissue tumors, i.e. pyogenic granuloma, peripheral ossifying fibroma, iritational fibroma, peripheral giant cell granuloma etc. Histopathologically, PAF needs to be differentiated from peripheral odontogenic fibroma (POF), which is more frequent. Histopathologically, POF comprises of fibrocellular connective tissue stroma with active or inactive islands of odontogenic epithelium; formation of dental hard tissue may or may not be present.[4] Conservative surgical excision is the treatment of choice and lesions do not recur as seen in this case.

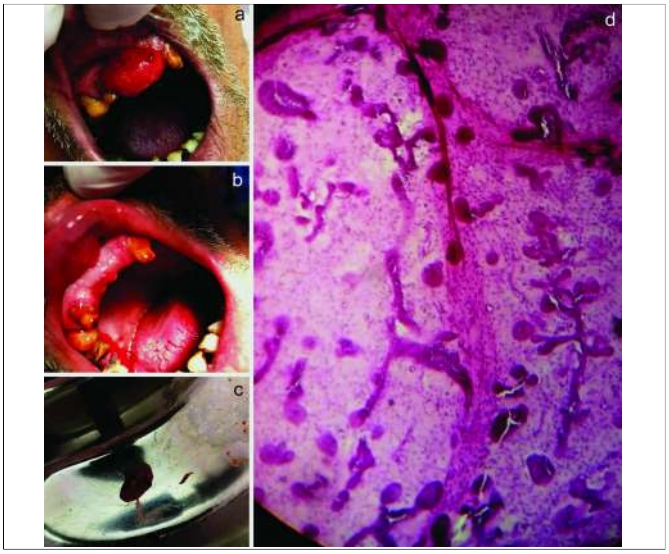

Figure 1: (a) Clinical picture of the lesion. **(b)** Site in oral cavity after removal of the lesion. **(c)** Excised specimen. **(d)** Strands and nests of primitive odontogenic epithelium with stroma resembling dental papilla (Hematoxylin and Eosin staining X20).

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Manas Bajpai[1], Nilesh Pardhe[1] and Pradkshana Vijay[2]

[1] Department of Oral and Maxillofacial Pathology, NIMS Dental College, Jaipur, India.

[2] Department of Oral and Maxillofacial Pathology, King George's Medical University (KGMU), Lucknow, Uttar Pradesh, India.

Correspondence: Dr. Manas Bajpai, Associate Professor, Department of Oral and Maxillofacial Pathology, NIMS Dental College, Jaipur, India.
E-mail: dr.manasbajpai@gmail.com

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Cancer Rehabilitation: Emerging Role of Physiatrists in a Multi-Disciplinary Cancer Care Team

Sir,

Cancer is a debilitating condition associated with significant mortality and long-term morbidity. This can be due to the disease itself or because of metastasis to various organs and the adverse effects of the treatment (including chemotherapy and radiation). This results in impairments causing pain, disability, reduced mobility, and overall a poor quality of life. Globally, the management of a cancer patient is primarily under the care of an oncologist. Oncology rehabilitation has developed in the West in the last decade where a rehabilitation physician, along with members of a multidisciplinary team led by a rehabilitation medicine physician (physiatrist), diagnoses, evaluates and manages the impairments and disability related to cancer and its treatment. Unfortunately, this is conspicuously missing in cancer care in Pakistan; and currently, no cancer hospital in Pakistan has a physiatrist leading a multidisciplinary cancer rehabilitation programme for the cancer survivors. We will highlight the important role of a multidisciplinary rehabilitation team to improve the quality of life (QOL) of cancer survivors.

The editorial "Evolving and Expanding Role of Pathologists in Multidisciplinary Team Cancer Care" was very informative, where they explained the role of the pathologist in cancer care as a member of a multi-disciplinary team.[1] This encouraged us to highlight the emerging role of a rehabilitation medicine physician (physiatrist) in multidisciplinary cancer care team.

Cancer and its treatment adversely affect different body systems of the patient, which may result in debilitating impairments involving musculoskeletal and nervous systems.

Depending on the site, cancer can result in various impairments; many are caused by adverse effects of treatment. These include cancer-related fatigue (CRF), pain, lymphedema, neuropathies, balance problems, mobility issues, bladder and bowel problems, dysphonia, communication difficulties, dysphagia, cardiopulmonary dysfunction, sexual disorder, and cognitive and psychosocial problems.[2] These impairments can lead to functional deficits, reduced mobility, and a poor quality of life.[3,4] Many of these conditions can be diagnosed and managed by a multi-disciplinary rehabilitation team (Table I).[3]

Table I: Conditions requiring rehabilitation evaluations and interventions.

Systemic
Deconditioning
Cachexia and muscles wasting
Cancer-related fatigue
Neurologic
Brain Injury from brain mass
Todd paralysis
Radiation necrosis
Spinal cord injury due to spinal mass and/or compression from vertebral fracture
Leptomeningeal disease with/without intrathecal chemotherapy
Central nervous system radiation necrosis
Radiculopathy due to tumor invasion
Brachial and lumbosacral plexopathy due to radiation or tumor invasion
Chemotherapy-induced peripheral neuropathy
Neurogenic bowel
Neurogenic bladder
Spasticity
Cognitive deficits, including "chemo brain"
Autonomic dysfunction including orthostatic hypotension
Dysphagia
Dysphonia
Musculoskeletal
Peripheral edema due to other conditions (e.g., bone marrow transplant inflammation, hypoalbuminemia)
Pathologic bone pain
Amputation and prosthetic rehabilitation
Chemotherapy-induced myopathy

Since the functional impairments from metastasis and side effects of anti-neoplastic medicines vary in severity, the cancer continuum of care offered to a cancer patient including recommendations for regular exercise and management plan is individually tailored according to patient's need. This goal can be achieved successfully under the care of a physiatrist being part of the multidisciplinary cancer care team, with expertise in prescribing cancer-specific exercises and cancer care plans as per medical condition and symptomatology that need to be addressed in addition to drug therapy and surgical interventions.

The primary aim of a cancer rehabilitation multidisciplinary team of rehabilitation professionals is directed towards maintaining or restoring function, reducing symptom burden, maximising independence, and improving quality of life.[5] Although advance cancer management adds years to cancer patient's life;[4] to these years, rehabilitation adds life.[6]

Cancer rehabilitation interventions include physiatrist-directed diagnostic imaging, injections, and pharmacologic symptom management, along with physical, occupational or speech therapy, therapeutic exercise, and psycho-social and cognitive interventions. A physiatrist can offer apposite advice to the surgical team planning for limb amputation due to cancer. This may include advice

regarding the level of amputation, pre-surgical evaluation and post-surgical preparation of the residual limb and appropriate prosthesis prescription. Majority of physiatrists are formally trained in pain management and diagnostic blocks which can alleviate the pain and suffering of the patients. These cancer rehabilitation interventions improve functioning and quality of life of cancer survivors.[3] Cancer rehabilitation enables cancer survivors to gain control over different aspects of his life and remain independent as much as possible.[3] Cancer rehabilitation not only improves functions but is also cost-effective in the long-run leading to the concept of 'prehabilitation' in rehabilitation oncology practice.[7]

There are estimated 150,000 new cancer cases in Pakistan each year.[8] Cancer care has substantially improved in Pakistan over the last two decades. There are currently two cancer registries and cancer care facilities in 21 dedicated cancer hospitals and 50 general hospitals around the country.[8]

The multidisciplinary cancer teams in Pakistan currently lack physiatrists and none of the dedicated cancer care hospitals have a physiatrist as the team member. The only rehabilitation service available in some centres is the physical therapy which is provided as an optional service rather than as a continuum of care. This implies that an important aspect of the cancer patient care is not being addressed, adequately. There is a need for all health professionals involved in cancer care in Pakistan to integrate rehabilitation services as a part of the comprehensive cancer care in order to effectively rehabilitate the cancer survivors. Physiatrists should be part of a comprehensive cancer care team to offer advice regarding pain management, surgical planning for amputations, mobility training, and to counter the effects of immobility syndrome.

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Sami Ullah[1], Farooq Azam Rathore[2] and Dilshad Hunain Al Arabia[3]

[1] *Department of Rehabilitation Medicine, Rehabilitation Hospital, King Fahad Medical City, Riyadh, Saudi Arabia.*
[2] *Department of Rehabilitation Medicine, PNS Shifa Hospital, Karachi.*
[3] *Department of Rehabilitation Medicine, Institute of Physical Medicine & Rehabilitation (IPMR), DUHS, Karachi.*

Correspondence: Dr. Sami Ullah, Assistant Consultant, Department of Rehabilitation Medicine, Rehabilitation Hospital, King Fahad Medical City, Riyadh, Saudi Arabia.
E-mail: drsamipmr@gmail.com

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Religion/Spirituality: A Tool to Better Help Psychiatric Patients

Sir,

Mental health continues to be a severely neglected subject in Pakistan despite efforts to highlight it. It is estimated that in a population of over 180 million, 10-16% people suffer with mental illnesses, with only 400 psychiatrists and 5 psychiatric hospitals in the country.[1]

Two of the six leading chronic causes of disability due to psychiatric disorders include depression and schizophrenia. In Pakistan, there has not yet been a national survey but estimates point to a high prevalence of both these disorders, based on findings from other developing countries in the region.[2,3]

As an Islamic republic, Pakistan hosts a population which largely identifies itself as followers of religion, 98% of which are Muslims.[4]

The link between religion and psychiatric disorders (mainly depression and schizophrenia) is well established. It has been shown that spiritual or religious beliefs and practices equip patients, suffering from depression, to tackle their disorder significantly better; with spiritual/ religious patients having about one-fourth the risk of having a relapse of their depression over a 10-year prospective period compared with others.[5] On the other hand, this firm belief in religion or spiritual/supernatural phenomena can be a vital source for the precipitation of symptoms of schizophrenia; between a fifth and two-thirds of all delusions in these patients are reflections of religious beliefs/practices.[6]

With such an impact of religion and spirituality in the causality and prognosis of mental illnesses, it is important and necessary that we consider it as a helping tool when dealing with our patients. Ho et al. in their study investigated how integrating religion/spirituality in a clinical setting can further help psychiatric patients, if used correctly. Patients were more open and responsive about their issues and more at ease with their mental healthcare professionals, if they identified and connected about each other's spiritual beliefs. The study highlighted how important the mental healthcare professionals' (psychiatrists, psychologists etc.) own views were affecting their relationship with their clients.[7]

In our society, it is unfortunate that stigmata have been attached to both, the mental healthcare professionals (by the highly 'conservative') and the religious scholars and preachers (by the more 'liberal'). It is time that we grow beyond these stigmata and work together to foster better communication and understanding where the religious scholars and mental healthcare professionals can interact; and together take their clients towards attaining better mental health.

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Manzar Shahid[1] and Syed Shahid Raza[2]

[1] Department of Medical Services, Karwan-e-Hayat, Psychiatric Care and Rehabilitation Centre, Karachi.

[2] Department of ENT, Buraidah Central Hospital, Buraidah, Saudi Arabia.

Correspondence: Dr. Manzar Shahid, RMO, Department of Medical Services, Karwan-e-Hayat, Psychiatric Care and Rehabilitation Centre, Karachi.
E-mail: manzar.shahid@hotmail.com

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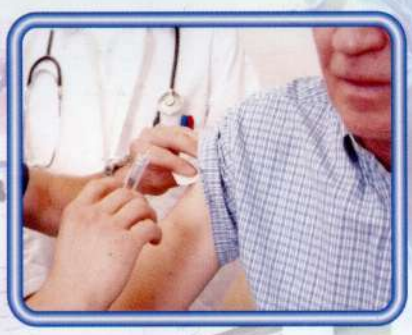

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