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Obstructive Sleep Apnea (OSA): An Underestimated Health Problem

Md. Kamruzzaman

Abstract:

In the last century major death toll was due infections and communicable diseases, but at present major causes of death are non-communicable diseases like cerebrovascular diseases, ischemic heart diseases, chronic respiratory diseases and cancer. Etiology of these listed disorders is multifactorial. Snoring and obstructive sleep apnea was considered as social problem, studies revealed obstructive sleep apnea is important risk factor of life threatening diseases. Morbidity, quality and cost of life depends on good quality sleep which is fragmented by obstructive sleep apnea.

Introduction:

Obstructive sleep apnea (OSA) is the most common sleep-related breathing disorder and is characterized by recurrent episodes of complete or partial obstruction of the upper airway leading to reduced or absent breathing during sleep. These episodes are termed “apneas” with complete or near-complete cessation of breathing, or “hypopnea” when the reduction in breathing is partial. In either case, a fall in blood oxygen saturation, a disruption in sleep, or both, may result. A high frequency of apneas or hypopneas during sleep may interfere with the quality of sleep, which – in combination with disturbances in blood oxygenation – is thought to contribute to negative consequences to health and quality of life.¹ The terms obstructive sleep apnea syndrome (OSAS) or obstructive sleep apnea-hypopnea syndrome (OSAHS) may be used to refer to OSA when it is associated with symptoms during the daytime (e.g. excessive daytime sleepiness, decreased cognitive function).

At present about 85% of adult deaths were due to non-communicable diseases, with ischemic heart disease (21.1%), stroke (22.1%) and chronic respiratory disease (16.4%) comprising about 60% alone among the 65% of community death reporting in Bangladesh¹. Almost all of the causes of death (COD)

due to non-communicable disease are related or very much influenced by obstructive sleep apnea. But unfortunately we are unaware about this problem.

Methods:

PubMed and Google Scholar were searched using the keywords obstructive sleep apnoea without limiting the years of publication. In PubMed 42148 article was found with key word obstructive sleep apnea (OSA). Most recent articles were reviewed in this article.

Results and discussions:

Prevalence of obstructive sleep apnea: Prevalence of obstructive sleep apnea (OSA) ranged from 9% to 38% and it is higher in men. It increased with increasing age and, in some elderly groups, was as high as 90% in men and 78% in women².

Hypertension and OSA: According to a report from American Heart Association prevalence of HTN in the United States adults was 45.6% and OSA is estimated to have a prevalence of 30% to 50% in patients with hypertension³.

OSA causes Stroke: Stroke is directly influenced by OSA. In a study it is determined that 91.2% of the patients had OSA in the acute stage of ischemic stroke, and 70% of the patients had moderate to severe OSA⁴. Apneic and hypoxemic episodes initiate the process of inflammation and there is a cascade of inflammatory markers such as IL-1, IL-6, TNF- α , and interferon- γ . These inflammatory markers damage the endothelial lining of the blood vessels, and there is an increased aggregation of platelets which lead to further oxidative stress and vascular endothelial damage. This repetitive oxidative stress and vascular damage in OSA patients along with fluctuation of blood pressure due to sympathetic activation can cause CVD and stroke.

Type-2 Diabetes and OSA: Sleep fragmentation and intermittent hypoxemia causes sympathetic activation, oxidative stress, inflammation, and neuroendocrine dysregulation which alter glucose homeostasis. Type-2 diabetes has been estimated to be 15% to 30%, with higher prevalence in those with severe OSA⁵.

OSA causes hypogonadism: It is reported an association between sleep disorders and plasma testosterone levels and estrogens and progesterone impact on upper airway stability and respiratory control during the menstrual cycle. Sleep fragmentation, disorganization of sleep cycles and stages, sympathetic activation, intermittent hypoxemia and systemic inflammation has a direct central effect on neurotransmitters, with disturbances in the normal production of hypothalamic pituitary hormones and as well as gonadal functions^{6,7}.

Conclusions:

Obstructive sleep apnea is emerging health problem in developing countries when nutritional deficiency disorders and communicable diseases are near to erased. OSA is important risk factor or predisposing condition of major life threatening non-communicable diseases. To prevent cerebrovascular diseases, hypertension, ischemic heart disease and diabetes OSA management is crucial. Hypo-gonadism, hypo fertility and infertility are also associated with OSA, which is newer problem in our community. So obstructive sleep apnea is not only a social problem and cannot be ignored to achieve healthy life.

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Outcome of Combined Dorsal and Ventral Buccal Mucosal Graft Meatoplasty in Comparison with Dorsal Graft In Meatal Stenosis due to Balanitis Xerotica Obliterans

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Keywords: Balanitis xerotica obliterans (BXO), Buccal Mucosal Graft (BMG), Urethroplasty.

Abstract

Background: Balanitis Xerotica Obliterans (BXO) with meatal stenosis is a very morbid condition. Treatment of meatal stenosis due to balanitis xerotica obliterans is very challenging because of high recurrence rate. Various type of surgical treatment options are practice for BXO with meatal stenosis. Proper treatment is necessary to give a free relief from the sufferings.

Objectives: The purpose of this study was to evaluate the outcome of combined dorsal and ventral buccal mucosal graft meatoplasty with dorsal meatoplasty in the treatment of Balanitis Xerotica Obliterans with meatal stenosis.

Methods: This prospective quasi experimental study was carried out in the department of urology, Dhaka Medical College and Hospital, Dhaka, Bangladesh from July 2013 to June 2015 for a period of twenty four (24) months. All patients presented with Balanitis Xerotica Obliterans with meatal stenosis. Patients were divided into two groups designated as group 1 and group 2 for combined dorsal and ventral buccal mucosal graft meatoplasty and dorsal graft meatoplasty. Post-operative follow up was carried out six months.

Results: Among 60 patients 30 were in group 1 and the rest 30 patients were in group 2. In group 1, the mean $\pm$ SD of operative time was 101.17 ± 16.27 minutes. Six months after in group 1, mean $\pm$ SD of q_{max} was 19.37 ± 4.79 ml/sec and in group 2, mean $\pm$ SD of q_{max} was 16.16 ± 3.69 ml/sec ($p < 0.05$). In group 1, mean $\pm$ SD of voiding time was 29.33 ± 8.16 sec. In Group 2, mean $\pm$ SD of voiding time was 32.73 ± 13.83 ml/sec ($p > 0.05$) in group 1, success was in 25 (83.3%) cases where as in group 2, it was in 19 (63.3%) cases.

Conclusion: However, a prolonged longitudinal follow up is essential for combined dorsal and ventral buccal mucosal graft meatoplasty is better than dorsal graft meatoplasty.

Introduction

Balanitis Xerotica Obliterans (BXO) is a chronic progressive inflammatory dermatological condition of unknown aetiology affecting the male genitalia which can affect the foreskin, frenulum, glans, meatus and urethra. It was first described in 1928 by Stuhmer and is considered as the male genital variant of lichen

sclerosis. The name was derived from the three components of the disease, which are balanitis - chronic inflammation of the glans penis - xerotic - abnormally dry appearance of the lesion and obliterans association of occasional endarteritis¹. The most feared complications of Balanitis Xerotica Obliterans are meatal stenosis and urethral stricture.

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Reported incidence 4%-47% of meatal stenosis and 20%-60% of urethral strictures^{2,3}. Extensive experience shows that in long-standing disease, mucosal involvement and spongiofibrosis can spread proximally as far back as the prostate. Balanitis Xerotica Obliterans has been managed both medically and surgically. Medical treatment can provide useful palliation but is regarded to be limited. The surgical options are more definitive, and include circumcision, dilatation or surgically correction of meatal stenosis and some urethroplasty techniques⁴.

Patient with balanitis xerotica obliterans have significantly higher rate of failure following urethroplasty for distal urethral strictures⁵. Treatment of distal urethral strictures changed in the last decade from dilatation, internal urethrotomy to definitive reconstruction techniques such as penile fasciocutaneous flap urethroplasty and buccal mucosa graft urethroplasty^{6, 7}. Urethral meatal stenosis can be treated by ventral meatotomy or dorsal v-meatoplasty. Meatotomy in balanitis xerotica obliterans is often followed by recurrence. Meatoplasty by buccal mucosal graft produced complete resolution of the disease in their cases⁸. When there is fossa navicularis strictures clinically suspicious for lichen sclerosis, it appears that the use of penile skin for reconstruction increases the likelihood of stricture recurrence. A 100% recurrence rate when penile skin flaps were used with lichen sclerosis compared with only a 6% recurrence rate with oral graft⁵. The use of buccal mucosal graft (BMG) in urethral surgery was first described by humby in 1941, following which it was not reported again until the late 1980s. Since then, it has gained favour as a versatile graft material well suited to repair of the urethra. It is thought to be especially suitable as it is a wet epithelium. It is readily harvested and has been shown to be resistant to recurrence of strictures, especially in the presence of Balanitis Xerotica Obliterans.. Buccal mucosa also has a dense submucosa with a dense capillary network, which facilitates the early imbibition of nutrients from the wound bed as well as early inosculation of neovasculature. Glans penis has a good blood supply providing an efficient graft take⁹.

Currently, buccal mucosa graft substitution urethroplasty is the most preferred option for urethral strictures. Whether to place the graft dorsally, ventrally, or laterally is still controversial. Single

ventral graft is more prone to develop fistula formation, sacculation and diverticula formation leading to urinary stasis and ejaculatory dysfunction¹⁰. Excellent long term results have been reported a successful technique for dorsal placement of buccal mucosa graft in long anterior urethral strictures through a ventral sagittal urethrotomy. The procedure is easier to perform and better because the urethra is not mobilized¹¹. The dorsal buccal mucosal graft meatoplasty, the overall success rate were good (87%)¹². Combined placement of double dorsal and ventral buccal mucosal graft creates a neourethra which is sufficiently wide, stable and maintains axial continuity of the urethral lumen. Their technique is founded on the principle of preservation of the integrity of the urethral plate and its vascularity. This surgical technique allows the partial removal of fibrotic urethral tissues without compromising the adequacy of the urethral lumen, thus adding further to the success¹³.

Recently Goel et al. presented their experience with 10 patients with glandular or meatal strictures treated with double buccal mucosa graft technique. They reported a functional and cosmetic outcome in 100% of patients after a mean follow up of 13.5 months¹⁴. The present study is designed to compare the short term outcome of combined dorsal plus ventral buccal mucosa graft and single (dorsal graft) buccal mucosa graft meatoplasty for meatal stenosis due to Balanitis Xerotica Obliterans.

Materials and methods

It was a prospective study (quasi experimental) carried out department of urology, in Dhaka Medical College and Hospital, Dhaka, Bangladesh during the period of July 2013 to June 2015. Total 60 patients of BXO with meatal stenosis were selected as per inclusion and exclusion criteria. Inclusion criteria were Balanitis Xerotica Obliterans with meatal stenosis, stricture length: 2.0 cm or less than 2.0 cm, age of the patient: 20- 50 years and those who agreed to be included in this study.

Sixty patients were counselled about techniques of buccal mucosal graft meatoplasty and possibility of using one of them. Patients were divided in two groups: group 1 and group 2. Patients in group 1 were treated with combined ventral and dorsal buccal musosal graft meatoplasty and group 2 were treated with dorsal buccal mucosal graft meatoplasty. This study was carried out to evaluate the outcome of

meatoplasty by two different surgical procedures. Sampling was done by purposive sampling technique. Selection of patient was done by inclusion and exclusion criteria. All operated patients followed up as per follow up schedule. The patients were followed up after surgery at 1st, 3rd and 6th month for further evaluation. All data processed manually and analyzed with the help of window based microsoft program IBM SPSS (statistical package for social sciences) version 20.0.

Results

Present study intended to compare the outcome between combined (ventral and dorsal) buccal mucosal graft meatoplasty and dorsal graft meatoplasty of 60 patients of BXO with meatal stenosis and were purposively assigned to combined ventral and dorsal graft meatoplasty (group1, n=30) and dorsal buccal mucosal graft meatoplasty (group 2, n=30). The outcome was evaluated in terms of q_{max} , voiding time, urethrocutaneous fistula, recurrence, findings of RGU and MCU between two groups. Mean stricture length was 1.63 ± 0.18 cm and 1.58 ± 0.17 cm in group 1 and group 2 respectively. There was no significant difference in stricture length between these two groups ($p > 0.05$). Mean duration of operation was 101.17 ± 16.27 minutes and 76.77 ± 10.97 minutes in group 1 and group 2 respectively. There was significant difference in duration of operation between these two groups ($p < 0.05$). At the time of 3rd follow up recurrence was seen in 2 (6.7%) patients and in 8 (26.7%) patients in group 1 and group 2 respectively. There was statistical significant difference between these two groups ($p < 0.05$). Finally in this study, in group 1 success was 25 (83.3%) cases where as in group 2 it was 19 (63.3%) cases. Difference was statistically significant ($p < 0.05$).

Table - I: distribution of patients according to the age.

Age	Group		P value
	Group 1 (combined graft)	Group 2 (dorsal graft)	
	N (%)	N (%)	
≤30	6 (20.0)	7 (23.3)	0.619
31 – 40	16 (53.3)	17 (56.7)	
41 – 50	8 (26.7)	6 (20.0)	
Total	30 (100.0)	30 (100.0)	
Mean ± sd	36.27 ± 6.40	35.13 ± 6.05	

T test was done to measure the level of significance.

Table II: Distribution of patients according to length of stricture and duration of operation time.

Variables	Group		P value
	Group 1 (combined graft)	Group 2 (dorsal graft)	
	N (%)	N (%)	
Stricture length (cm)	1.63 ± 0.18	1.58 ± 0.17	0.321
Duration of operation (minutes)	101.17 ± 16.27	76.77 ± 10.97	0.001

Independent t test was done to measure the level of significance.

Table III: Distribution of patients according to voiding time in both groups.

Voiding time (second)	Group		P value
	Group 1 (combined graft)	Group 2 (dorsal graft)	
	N (%)	N (%)	
Pre operative	137.27 ± 7.36	134.33 ± 4.88	0.074*
1 st follow up	25.93 ± 6.40	27.90 ± 7.80	0.290*
2 nd follow up	27.33 ± 9.71	28.86 ± 11.45	0.578*
3 rd follow up	29.33 ± 8.16	32.73 ± 13.83	0.251*
P value (with in groups between pre operative and 3 rd follow up)	<0.001#	<0.001#	

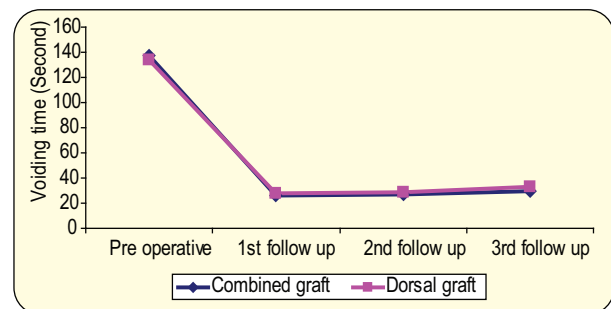


Figure 1: Line diagram showing pre operative and post operative voiding time

Table IV: Distribution of patients according to q_{max} in both groups

Qmax (ml/sec)	Group		P value
	Group 1 (combined graft)	Group 2 (dorsal graft)	
	N (%)	N (%)	
Pre operation	5.26 ± 1.24	5.74 ± 1.10	0.510*
1 st follow up	23.38 ± 5.25	22.26 ± 4.07	0.360*
2 nd follow up	21.51 ± 5.10	19.85 ± 4.19	0.173*
3 rd follow up	19.37 ± 4.79	16.16 ± 3.69	0.005*
P value (with in groups between pre operative and 3 rd follow up)	<0.001#	<0.001#	

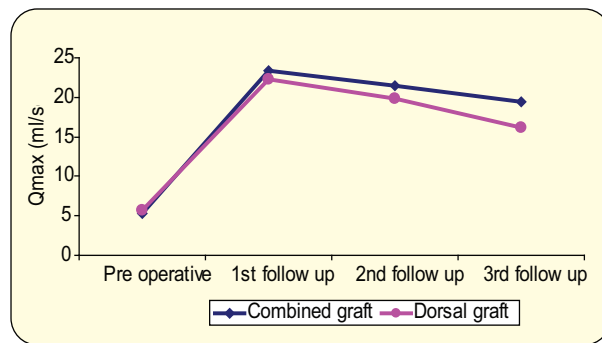


Figure 2: Line diagram showing pre-operative and post-operative $q_{\max}$

Table V: Distribution of patients according to recurrence of meatal stenosis in both groups

Recurrence	Group		P value
	Group 1 (combined graft) N (%)	Group 2 (dorsal graft) N (%)	
1 st follow up	0 (0.0)	2 (6.7)	0.150
2 nd follow up	2 (6.7)	5 (16.7)	0.228
3 rd follow up	2 (6.7)	8 (26.7)	0.035

Chi square test was done to measure the level of significance.

Table VI: distribution of patients according to RGU & MCU findings in both groups

RGU & MCU findings	Group		P value
	Group 1 (combined graft) N (%)	Group 2 (dorsal graft) N (%)	
1 st follow up (narrow)	0 (0.0)	2 (6.7)	0.150
2 nd follow up (narrow)	2 (6.7)	5 (16.7)	0.228
3 rd follow up (narrow)	2 (6.7)	9 (30.0)	0.020

Table VII: Distribution of patients according to final outcome

Final outcome	Group		P value
	Group 1 (combined graft) N (%)	Group 2 (dorsal graft) N (%)	
Success	25 (83.3)	17 (56.7)	
Failure	5 (16.7)	13 (43.3)	
Total	30 (100.0)	30 (100.0)	0.024

Discussion

Balanitis xerotica Obliterans (BXO) with meatal stenosis has been managed by surgically. Meatal stenosis can be treated by ventral meatotomy or dorsal v-meatoplasty or genital flap meatoplasty or non-genital graft meatoplasty. Now the principle of surgical treatment of meatal stenosis in BXO patient is non-genital graft meatoplasty. Among non-genital graft, buccal mucosal graft meatoplasty is most appropriate for meatoplasty in BXO with meatal stenosis. Several techniques are practice such as ventral onlay, dorsal inlay and circumferential graft, combined dorsal and ventral graft meatoplasty. Among reconstruction procedure, ideal surgical techniques for balanitis xerotica obliterans with meatal stenosis is non-genital graft meatoplasty.

The techniques are various and the location of the patch has become a contentious issue with different series reporting buccal mucosal grafts placed either ventrally or dorsally to augment the stricture urethra.^{15,16} Recently palminetri and colleagues have discussed the combined use of both dorsal inlay and ventral onlay of buccal mucosal graft in the management of sever bulbar urethral stricture.

The use of buccal mucosa in urethral surgery was first described by humby in 1941. Since then it has proved to be a versatile graft material well suited to repair the urethra.¹⁷ It is a moist epithelium, which is easily harvested and amenable to surgical manipulation. It has privileged immunity rendering it less prone to infection and is more resistant to stricture recurrence. Buccal mucosa also has dense sub mucosa with a dense capillary network that facilitates the early imbibition of nutrients from the wound bed as well as early inosculation of neovasculature.¹⁸

Over the last decade this graft has become popular for urethral reconstruction and has been associated with excellent outcome.¹⁹

The dorsal graft placement can be performed by Bargbagli method or Asopa technique. Palminetri and colleagues first described the use of a combined ventral and dorsal graft in the bulbar urethra reconstruction. This new approach introduces new concept about the importance of the urethral plate quality and its preservation during bulbar urethroplasty to treat tight and long stricture.

By adopting a combined dorsal and ventral double enlargement of very narrow stricture tracts creating a

neo-urethra sufficiently wide and more stable, reducing the risk of recurrence at distal or proximal graft anastomotic sites.^{13,14}

Usually the dorsal or ventral single graft urethroplasty is performed without resection of any diseased tissues, whereas the double graft enlargement allows the partial removal of the fibrotic urethral tissues without jeopardizing the creation of a wide enough lumen. Furthermore, the dorsal incision aims to release the scarred rings on the urethral plate.

The double patch technique with the inclusion of the residual lateral strips of the urethral plate allows a safer and more stable reconstruction. Avoiding a circumferential anastomosis and preserving the axial continuity of the lumen.¹³

The present work has been carried out to compare the outcome of combined buccal mucosal graft over the only dorsal buccal mucosal graft in the management of BXO with meatal stenosis. A total sixty (60) patients were included, patients underwent combined graft meatoplasty (group=1, n= 30) and patients underwent dorsal buccal mucosal graft meatoplasty (group= 2, n=30). In this study, each sample determined by purposive sampling technique.

In this study, mean ages between two groups were 36.27 ± 6.40 years and 35.13 ± 6.05 years for combined ventral and dorsal buccal mucosal graft meatoplasty, dorsal buccal mucosal graft meatoplasty respectively. In group1 maximum 16 (53.3%) patients and also in group 2, maximum 56.7% patients were in age group 31 – 40 years. There is no significant differences of mean ages between two groups, p value is 0.619 which is >0.05 .

Length of the stricture was determined by retrograde urethrogram (RGU) and micturating cystourethrogram (MCU), all of them were < 2 cm. In combined graft mean stricture length was 1.63 ± 0.18 cm and in dorsal graft was 1.58 ± 0.17 cm. No statistically significant difference was observed between the group i and group ii in terms of length of stricture ($p= 0.321$). The length of the stricture corresponds with the study of Simsek et al; 2014.⁴

Operation time was higher in combined graft meatoplasty due to placement of graft in dorsal and ventral aspect, but in case of dorsal graft meatoplasty only graft placed in dorsal bed. Mean operation time were 101.17 ± 16.27 minutes and 76.77 ± 10.97 minutes respectively group1 and group 2.

In this study, outcome have evaluated on the basis of history and clinical examination, postoperative complication, findings of uroflowmetry ($q_{\max}$, voiding time) and retrograde urethrogram and micturating cystourethrogram.

In terms of preoperative mean voiding time on uroflowmetry in group 1 was 137.27 ± 7.36 seconds and in group 2 was 134.33 ± 4.88 second ($p = 0.074$). But statistically significant difference was present in both groups between preoperative and postoperative $q_{\max}$ and voiding time on follow up at 6th month mean $q_{\max}$ was better in combined graft meatoplasty group (19.37 ± 4.79 ml/sec) than dorsal meatoplasty group (16.16 ± 3.69 ml/sec). Statistically significant difference was present ($p=0.005$). Voiding time was more in group 2 (32.73 ± 13.83 sec) than group1 (29.33 ± 8.16 sec) but there was no statistically significant difference was present ($p=0.251$).

In this study, in terms of RGU and MCU, the difference between these two groups was not present statistically significant in 1st and 2nd follow up but at the time of 3rd follow up narrow urethra was seen in 6.7% cases and in 30.0% cases in combined dorsal plus ventral BMG graft meatoplasty group and dorsal graft meatoplasty group respectively. Finally statistically significant difference was present between these two groups ($p<0.05$).

Final outcome in this study, in group-1 success was 83.3% cases where as in group- 2 it was 63.3% cases. Difference was statistically significant ($p<0.05$). However, the study is prospective, has limitation of having a short follow-up and lacks comparison with other standard simple buccal graft substitution to document its possible advantages.

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Elderly people at the Emergency Department: Study from a District Hospital in Bangladesh

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Abstract

Background: The proportion of elderly population is increasing globally. Very little information is available on the presentation and clinical outcome of elderly patients at the Emergency Department (ED) in Bangladesh. This study was carried out to assess the pattern of elderly patients (65 years and more) who visited the ED of 250 Bedded General Hospital, Pabna (GHP).

Methods: A retrospective observational study was conducted on patients aged 65 years or more at GHP from 2017 through 2021. Patients' demographic information, symptoms, diagnoses and outcome following attendance were studied. Statistical analyses were done using SPSS version 23.

Results: 20.7% (n = 94,905) of all adults (n = 4,57,549) presenting to the ED were aged $\geq$ 65 years. A greater number of elderly patients (58%) required hospitalization than non-elderly adults (37%). The 3 most common symptoms were breathlessness (9.9%), dizziness (9.0%) and abdominal pain (5.3%). The symptoms were mainly acute (< 24 hours, 42%) or less than a week (28.9%). The 3 most common diagnoses were Respiratory tract infections (7.8%), Cerebro-vascular diseases (Stroke/Transient ischaemic attack, 7.6%) and heart failure (7.4%).

Conclusion: Elderly people constituted 20.7% of emergency attendance but 32.5% of admissions in adults. They differ significantly from younger adults in presentation and outcome. A better understanding of this issue will help doctors at the ED provide better management.

Introduction

Elderly population is a growing demographic and an important concern in the healthcare system worldwide. According to the United Nations report, the pace of aging of the world population has increased, and the growth of elderly populations will be faster in Asia than in other regions between 1980 and 2050¹. Elderly patients are more likely to be admitted to the hospital than younger patients². Moreover, these patients are likely to undergo additional diagnostic tests and consultations, and have a longer hospital stay and higher admission rate from the ED^{3,4}. Elderly people account for approximately

12.0-21.0% of all ED visits^{5,6}. In a study from USA, compared to younger patients, the elderly were 4.4 times more likely to use ambulance service, 5.6 times more likely to be admitted to a hospital, and 5.5 times more likely to be admitted to ICUs⁷.

In Bangladesh, improved social conditions and advances in public health during the last half century have contributed to a significant increase in the average lifespan; life expectancy at birth has improved to 72.8 years (74.5 years in women and 71.2 years in men⁸). With one of the highest population densities (1,140/ sq. km) in the world, and with 14 million people aged 60 years and older (8.3% of total

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population), this country needs to assess the health needs of geriatric patients and to formulate an action plan thereafter. In doing so it is vital to have a clear knowledge on their demographic and clinical characteristics. But very little information is available on the prevalence and clinical outcome of elderly patients in the emergency department since little research has been carried out in this area.

The special health care needs of elderly patients utilizing emergency services have been clearly demonstrated in different studies abroad⁹⁻¹⁵. The present ED care models in Bangladesh need to be modified to such an extent that we may be able to cope with the geriatric population who are tend to get sick more often along with multiple co morbidities⁹.

The present study aimed to obtain a critical understanding of the clinical presentation of the elderly people with different features for better planning of emergency care. Four research questions were addressed: (a) What are the most frequent presenting complaints among elderly individuals presenting to the ED? (b) What are the differences in the complaints made by the elderly individuals among the sub-age groups? (c) What are the most common clinical diagnoses among elderly individuals presenting to the ED? (b) What are the differences in diagnoses among the sub-age groups?

Materials and Methods

This retrospective observational study was conducted in the Emergency Department (ED) of 250 Bedded General Hospital, Pabna (GHP), Bangladesh. GHP is a District hospital, having been serving as a Medical College Hospital (tertiary care teaching hospital) with a catchment area exceeding three million inhabitants and an annual ED visit of approximately 90,000 patients and a 37% admission rate. The hospital ED also provides both primary and specialist care 24/7 within the district with a population of 2.6 million.

The initial data included ED visits by 96,803 individuals aged e" 65 years during a five-year study period (January 2017 to December 2021). Cases with missing information on age, sex and/ or presenting symptoms (n=1,898, 1.96%) were excluded, and the final data included 94,905 ED visits by the elderly. Both manual and electronic record systems to extract data on demographic and clinical characteristics of patients were used. Information on age, sex, time of

arrival (work shift), presenting complaints (only the three most significant symptoms), duration of symptoms, level of consciousness, vital signs, and disposition from the ED were collected and recorded.

Patients were classified as dead on arrival (DOA) if they arrived in the ED with cardiac arrest and did not recover despite resuscitative attempts as per BLS/ ACLS guidelines. Those transferred to another (higher) facility due to non-availability of high-dependency beds, financial constrains or on their will, were termed "Referred". Data available on 94,905 patients aged 65 years and more were processed and prepared for analysis. The study population was categorized into three age groups: young-old group (65 to 74 years), middle-old group (75 to 84 years), and old-old group (85 years and above); and the data were compared among the groups.

Statistical analysis was done with Statistical Package for Social Sciences (SPSS) version 23.0. Descriptive statistics were used for the demographic variables and the characteristics of the ED visits. The 10 most common CCs on ED visits and 10 most common diagnoses were analyzed separately based on age groups.

The study was reviewed and approved by the Ethical Review Committee of 250 Bedded General Hospital, Pabna, Bangladesh.

Results

A total of 457,549 ED visits by patients aged e" 18 years were documented during the study period, among which 94,905 (20.7%) were by those e" 65 years. An increasing trend in the number of ED visits by the elderly was observed over time (Figure 1).

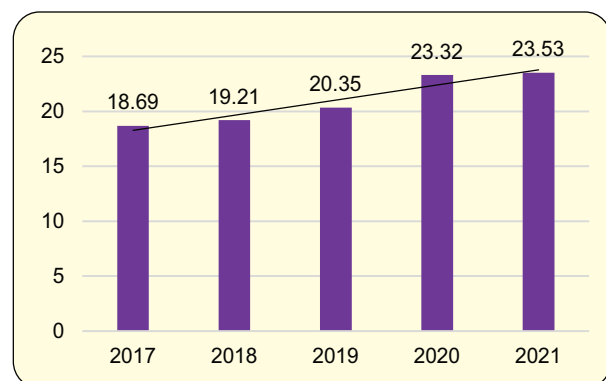


Figure 1: Trends of visit of Elderly people at ED

Table 1. Basic demographic characteristics of patients

	18-64 years (n=362,644)	≥ 65 years (n=94,905)
Gender		
Male	51.3%	45.6%
Female	48.7%	54.4%
Disposition		
Sent home	56.2%	24.8%
Admitted	31.5%	58.0%

The number of elderly female patients (54.4%) was greater than the number of male ones (45.6%), and the female: male ratio was found to be highest (1.7: 1) in the old-old group. More than half (55.6%) of the ED attendees were from the young-old group. 90.7% of the sample were alert at the time of ED visit, but this number was greatly reduced in the old-old group (79.3%).

Table II: Basic demographic characteristics of elderly patients attending ED

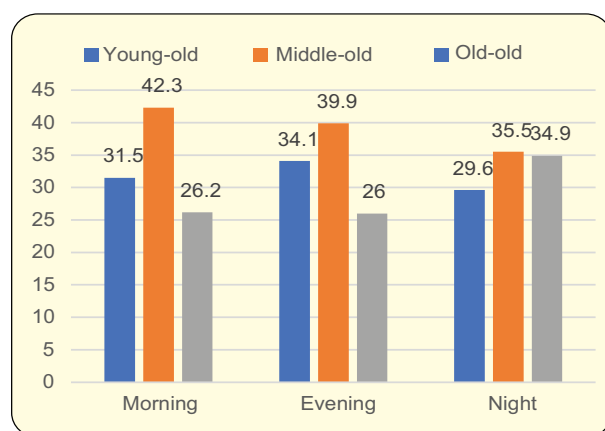
	Young-old (n=52,814)	Middle-old (n=36,8471)	Old-old (n=5,220)	Total (n=94,905)
Male	46.9%	44.8%	37.8%	45.6%
Female	53.1%	55.2%	62.2%	54.4%
Total	55.6%	38.9%	5.5%	100%

Table III: Level of consciousness of elderly patients attending ED

	Young-old(%)	Middle-old(%)	Old-old(%)	Total(%)
Alert	93.0	88.9	79.3	90.7
RTV	3.1	4.1	6.8	3.7
RTP	2.4	3.0	5.9	2.8
NR	1.5	4.0	8.0	2.8

Note: RTV- Response to voice, RTP- Response to pain, NR- No response

Most of the ED visits took place in the morning and evening shifts among the young-old and middle-old groups while the largest number of the old-old group of patients (34.9%) used to visit ED during the night shift.

**Figure 2.** Shifts of ED visits by the elderly

Most of the patients (42%) presented with acute symptoms lasting for less than 24 hours.

Table IV : Duration of symptoms

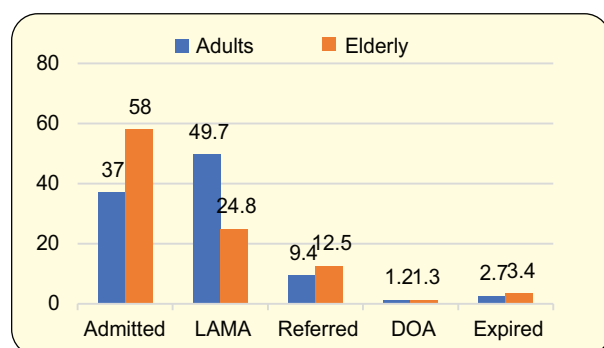
	Young-old (n=52,814)	Middle-old (n=36,8471)	Old-old (n=5,220)	Total (n=94,905)
<24 hours	42.5	41.6	39.8	42.0
1-7 days	29.1	28.5	30.3	28.9
1-4 weeks	16.9	15.5	13.5	16.1
>1 month	7.9	6.4	6.6	7.3
Other	3.7	8.0	9.8	5.7

The 10 most common presenting symptoms (chief complaints, CCs) were analyzed separately for each age group. While dizziness was the most predominant symptom (11.1%) in the young-old group, dyspnoea topped (9.9%) the overall list, followed by dizziness, abdominal pain, fever, chest pain, dysuria, cough, headache, vomiting, and syncope. The presentation of dyspnoea as a CC was noticed to be increasing along with an increase in age. Fall and disorientation were common CCs amongst the old-old age-group. The 10 commonest CCs combined 47.8% of the presenting complaints of ED visits.

Table V: Most common symptoms in admitted patients aged ≥ 65 years

Young old (29,951)			Middle old (21,536)			Old old (3,558)			Total (55,045)	
1	Dizziness	11.1	Dyspnoea	12.5	Dyspnoea	13.8	Dyspnoea	9.9		
2	Dyspnoea	7.6	Fever	8.3	Dizziness	8.7	Dizziness	9.0		
3	Abd pain	5.8	Dizziness	6.2	Abd pain	7.8	Abd pain	5.3		
4	Fever	5.5	Abd pain	4.1	Fever	5.5	Fever	4.9		
5	Chest pain	5.3	Cough	3.9	Dysuria	3.2	Chest pain	4.5		
6	Headache	3.6	Chest pain	3.8	Syncope	2.3	Dysuria	3.4		
7	Dysuria	3.3	Dysuria	3.5	Headache	2.0	Cough	3.2		
8	Cough	2.9	Vomiting	3.3	Cough	1.9	Headache	2.9		
9	Vomiting	2.2	Syncope	2.7	Fall	1.8	Vomiting	2.6		
10	Arthritis	2.0	Asthenia	2.6	Disorientation	1.8	Syncope	2.1		
Sum		49.3		50.9		48.8		47.8		

58% of the ED visits by the elderly resulted in the patients being admitted to an inpatient department. The proportion of admission in the elderly is more than 1.5-fold higher than that in the total adult population (37%) and almost twice the number of the patients in the 18 to 64-year age group (31.5%). Almost a quarter (24.8%) of the elderly individuals were sent home with advice and 12.5% of the attendees referred to other (higher) facilities for better management (Figure 2).

**Figure 3.** Disposal from ED

Of the 94,905 patients, 55,045 (58%) were admitted to hospital. Of those admitted, 53.4% were females and 46.6% males. Female patients (64.5%) greatly outnumbered their male counterparts (35.5%) in the old-old group. Majority (54.4%) of the patients admitted in ED were from the young-old group. While 86.6% of the individuals were alert on admission, this proportion was much less in the old-old group (79.3%), amongst whom 1 in 10 had no response to voice or pain.

Table VI: Basic demographic characteristics of elderly patients admitted from ED

	Young-old (n=29,951)	Middle-old (n=21,536)	Old-old (n=3,558)	Total (n=55,045)
Male	48.8%	45.4%	35.5%	46.6%
Female	51.2%	54.6%	64.5%	53.4%
Total	54.4%	39.1%	6.5%	100%

Table VII: Level of consciousness of elderly patients admitted from ED

	Young-old(%)	Middle-old(%)	Old-old(%)	Total(%)
Alert	89.5	84.6	73.8	86.6
RTV	4.6	4.9	8.2	4.9
RTP	3.6	4.4	7.5	4.2
NR	2.3	6.1	10.5	4.3

Note: RTV- Response to voice, RTP- Response to pain, NR- No response

Table VI: Basic demographic characteristics of elderly patients admitted from ED

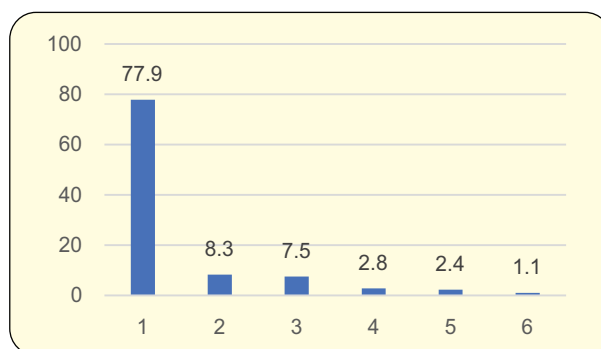
	Young-old (n=29,951)	Middle-old (n=21,536)	Old-old (n=3,558)	Total (n=55,045)
Male	48.8%	45.4%	35.5%	46.6%
Female	51.2%	54.6%	64.5%	53.4%
Total	54.4%	39.1%	6.5%	100%

Table VII: Level of consciousness of elderly patients admitted from ED

	Young-old (%)	Middle-old (%)	Old-old (%)	Total (%)
Alert	89.5	84.6	73.8	86.6
RTV	4.6	4.9	8.2	4.9
RTP	3.6	4.4	7.5	4.2
NR	2.3	6.1	10.5	4.3

Note: RTV- Response to voice, RTP- Response to pain, NR- No response

As there was neither an Intensive Care Unit (ICU), nor a Department of Geriatric Medicine in the hospital, more than three fourths (77.9%) of the patients were admitted to Medicine Department (1), followed by 8.3% in General Surgery (2), 7.5% in Cardiology (3), 2.8% in Gynaecology (4), 2.4% in Orthopaedic Surgery (5), and 1.1% in other Departments (6).

**Figure 4.** Distribution of patients in Departments

Among the admitted patients, the 10 most common clinical diagnoses were analyzed separately for each age group. Respiratory tract infections (7.8%), cerebrovascular diseases (7.6%), and heart failure (7.4%) were the table-toppers, followed by obstructive airway diseases (COPD/ bronchial asthma), acute gastroenteritis, acute coronary syndrome (ACS), urinary tract infections, sepsis, diabetic complications, and pyrexia of unknown origin (PUO). The occurrence of RTI and HF were frequently observed in middle-old and old-old age groups. Sepsis was a diagnosis more commonly found amongst the old-old age group. The 10 commonest diagnoses represented 55% of the total disease profile.

Table VIII: Most common diagnoses in admitted patients aged ≥65 years

	Young old (29,951)		Middle old (21,536)		Old old (3,558)		Total (55,045)	
1	Stroke/TIA	8.2	RTI	9.9	HF	9.4	RTI	7.8
2	COPD/BA	7.4	HF	8.1	Stroke/TIA	8.9	Stroke/TIA	7.6
3	HF	6.7	Stroke/TIA	6.9	RTI	8.8	HF	7.4
4	RTI	6.2	AGE	5.9	Sepsis	7.7	COPD/BA	6.6
5	ACS	6.0	COPD/BA	5.8	ACS	6.5	AGE	5.8
6	AGE	5.9	ACS	5.3	AGE	4.8	ACS	5.7
7	UTI	4.4	UTI	4.7	COPD/BA	4.7	UTI	4.5
8	Sepsis	3.9	DM comp	3.6	UTI	4.4	Sepsis	3.6
9	PUO	3.2	Sepsis	2.6	Cellulitis	2.8	DM comp	3.2
10	DM plus	3.0	Malignancy	2.5	Malignancy	2.4	PUO	2.8
Sum		54.9		55.3		60.4		55.0

Discussion

Our study depicts the patterns of ED visits by elderly individuals compared to young adults of a tertiary care teaching hospital in Bangladesh. The study compared the variability of presentation among the three age-groups of the senior citizens. The ED is a major portal of entry of the elderly into the hospital and is often their first contact with the medical services¹⁶. 20.7% of the adult patients visiting the ED were ≥ 65 years old while these older individuals constitute only 8.3% of the general population. (HB 2020) Similar results were shown in the studies from Pakistan and Taiwan¹⁷⁻¹⁹. (B, B 11, B 21) Such disproportionate usage of the health system by the elderly is supported by some studies in western countries as well^{7,10,19-21}.

Though the elderly constituted only 20.7% of the ED attendance in adults, they contributed to 32.5% of the total admission. This picture is consistent with the scenario reported in South Asian, Far East, and the Western literature^{10,11,17,22}. An increasing trend in the elderly patients' ED visits over the years was found which is similar to the findings in a study in Pakistan¹⁷.

The number of elderly females (54.4%) was greater than that of the males (45.6%), and the female: male ratio was found to be highest (1.7: 1) in the old-old group. Majority (55.6%) of the ED attendees were from the young-old group. More than 90% of the sample were alert while visiting ED, but this number was greatly reduced to $< 80\%$ in the old-old group. All these findings are consistent with that reported in a South Korean literature²³.

Vast majority of the older individuals visited in the morning and evening shifts while the old-old group of patients used to visit ED during the night shift. Similar results were observed in the studies from Pakistan and South Korea^{17,23}.

More than two thirds of the patients presented with acute symptoms lasting for less than 24 hours, which contradicts with the finding in a Korean study showing $> 90\%$ acute symptoms²³. This may be explained with the fact that ours is a lower-middle income country with most of the people have low level of education and little health awareness resulting in delayed arrival to hospital.

The most common presenting symptoms at the ED was difficulty in breathing or shortness of breath. It is a common symptom found in respiratory tract

infections, heart failure, ischaemic heart disease and obstructive airway disease. The presentation of dyspnoea as a CC was found to be increasing with increasing age. Fall and disorientation were more commonly encountered amongst the old-old patients. Identical findings were observed in reports from Singapore, South Korea and Australia²²⁻²⁴. Falls are often the symptom of underlying silent and underdiagnosed conditions, therefore should not be taken lightly without proper assessment²².

The elderly individuals aged ≥ 65 years attending ED were 1.8 times more likely to be admitted compared to the non-elderly adults (58% versus 31.5%). Fayyaz et al. had the similar finding but Lim et al. had reported differently (57.3% vs 15.5%)^{17,22}.

The most common diagnoses were related to cardio-respiratory disorders and infections. Schwartz et al and Ettinger et al also noticed that elderly patients have a higher proportion of cardiac and pulmonary diseases^{11,25}.

Only 1.2% of the elderly were dead on arrival, and a further 3.4% breathed their last in the ED. This is a rather interesting observation in the context of our resource-poor setting. This may be explained by the fact that a large number of patients (12.5%) were transferred (referred) to higher centres due to non-availability of HDU and ICU in the hospital.

Elderly individuals are at greater risk of medical complications and functional decline after an ED visit. Evidence shows that the current disease-oriented and episodic models of emergency care do not adequately address the complex care needs of elders who visit the ED²⁶. Emergency care in elderly people should consider the unique factors that may differ them from younger people, including the complex and atypical presentations of symptoms, cognitive impairment, comorbid conditions, screening for polypharmacy, need for tailored diagnostic tests, decreased functional reserve, need for psychosocial/community support, and baseline functional status²⁷.

With an increase in the need for ED care among elderly individuals, it is vital for ED staff to receive geriatric emergency training and administer appropriate and tailored care. Evidence shows that EDs staffed with geriatric professionals may be effective in preventing the unnecessary admission of elderly visitors²⁸.

Limitation

The present study represents a small fraction of the total scenario. We obtained information from the registry data (bed-head tickets of the patients) where complete clinical records were not available, and which may include multiple visits by the same person. Information on comorbidities, investigation reports, medications and multiple diagnoses could not be ascertained in this study design. The clinical features and diagnoses were not analyzed separately based on disease- or injury-related presentation and gender. Further research in different levels of health care facilities is, therefore, needed to have a clear understanding of the issues in managing geriatric population.

Conclusion:

The health care needs of the elderly population significantly differ from those of the younger adults. The elderly individuals often have multiple and complex pathologies and atypical presentations leading to disproportionately higher admission rates and more resource utilization. A better understanding of the common presenting symptoms and diagnoses would help our health care professionals to provide proper service through a dedicated geriatric care unit in ED.

Conflict of interest:

The authors declare no potential conflict of interest.

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Endoscopic Management of Biliary Ascariasis

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Abstract

Background: *Ascaris lumbricoides* is common intestinal parasite and biliary ascariasis is the commonest extra intestinal manifestation of round worm. This study was aimed to review the predisposing factors, presentation and the role of endoscopic management of biliary ascariasis.

Method: We performed retrospective analysis of 182 patients diagnosed and admitted as biliary ascariasis in the department of General Surgery, Bangabandhu Sheikh Mujib Medical University, Dhaka from April 2016 and April 2021. Ultrasonographic findings of abdomen were the mainstay of diagnosis.

Results: Biliary ascariasis was more common in female (78%). The most common presentation was pain (100%). ERCP was done successfully in 90.7%. All patients were given anthelmintic. There was no complication.

Conclusion: Ultrasound is a reliable screening test for diagnosis and ERC provides confirmation. Once diagnosed, endoscopic extraction of the worm is often successful and provides prompt relief to the patient. Anthelmintics should be administered for eradication of worms from the intestine and to prevent their reentry into the biliary tree.

Introduction

Ascaris lumbricoides is the largest common nematode causing human ascariasis¹ and 33% of the world population are estimated to be infested with it.² It is possibly the first recorded parasitic worm disorder affecting human being and referred to old Greco-Roman and Chinese books. Linnaeus presented the first precise interpretation of the genus *Ascaris*, Epstein and Grassi revealed that the contamination occurs by ingestion of eggs.³

Ascaris is common in tropical countries with low standards of hygiene, malnutrition, heavy rainfall and where untreated sewage is discharged into rivers, lakes and agricultural land or is used as fertilizer. It affects the lungs, intestine, appendix, liver, bile duct and pancreas. It shows no clinical manifestation in maximum infected patients.^{4,5}

Different types of severe disease may develop from those affected by ascariasis the number of which is roughly calculated to be 60 million. Disease manifest

clinically when the burden of is substantial (13- 40) and around 10,000-20,000 deaths occurs annually globally due to severe disease.^{6,7,8} Epidemics of ascariasis can occur.⁹ The adult round worm normally lives in the small intestine. Because they have 'wanderlust' and tend to explore ducts and cavities they often invade bile or pancreatic duct. Most of the patient in our study presented with upper abdominal colicky pain.¹⁰

It infects about 25% of the world's population; around 20 thousand deaths occur per year from an adverse clinical course of the disease. Although an endemic disease of tropical and subtropical countries, increasing population migration facilitated by fast improving communication facilities demands that clinicians everywhere be familiar with the clinical profile and management of biliary ascariasis.

Methods

A total of 182 patients with diagnosis of biliary ascariasis were analyzed retrospectively those who got admitted

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in the department of General Surgery, Bangabandhu Sheikh Mujib Medical University, Dhaka from April 2016 and April 2021. Ultrasonographic findings of abdomen were the mainstay of diagnosis. Before being admitted to our hospital all the patients were managed conservatively with intravenous fluids, antibiotics and antispasmodic. All patients got a single dose of albendazole. Endoscopic intervention was carried out only after the conservative management failed. If a part of the round worm was found outside of the ampulla of Vater, it was pulled out by holding in a Dormia basket. When the worm had migrated fully inside the common bile duct we performed sphincterotomy and removed worm or worms. The clinical features, imaging findings treatment and follow-up of patients were recorded. The principal tool for diagnosis was sonographic findings.

Results

A total of 182 patients were included in this study. Biliary ascariis was found to be higher incidence in female (78%) (Table I). In our study biliary ascariis was more common in middle class (76.4) (Table II). All the patients had pain (100%) (Table III).

Table I: Socioeconomic status

Socio-economic status	Frequency	Percent
Lower	34	18.7
Middle	139	76.4
Upper	9	4.9
Total	182	100.0

Table II: Clinical presentation

	Frequency	Percent
Pain	182	100.0
Jaundice	8	4.4
Fever	9	4.9
Vomiting	3	1.6
History of sphincterotomy	5	2.7

Table III: Contents of CBD

	Frequency	Percent
Nothing	5	2.7
Linear echogenic structure with anechoic core	162	89.0
Linear structure	1	.5
Stone	14	7.7
Total	182	100.0

Table IV: Worm extraction findings

	Frequency	Percent
No worm	26	11.5
Worm	113	53.3
Worm & Stone	26	8.2
Stone	16	2.7
Total	138	75.8
	182	100.0

Table V: Worm number

	Frequency	Percent
No	23	12.6
One	117	64.3
Two	20	11.0
Three	17	9.3
>3	5	2.7
Total	182	100.0

Table VI: Worm clearance

	Frequency	Percent
Failed	17	9.3
Complete	165	90.7
Total	182	100.0

Table VII: Advice after ERCP

	Frequency	Percent
Repeat ERCP	6	3.3
Regular Dewarming	176	96.7
Total	182	100

Table VIII: Immediate pain relieve

	Frequency	Percent
No	6	3.3
Yes	176	96.7
Total	182	100

Table IX: Results

	Frequency	Percent
Recurrence	1	.5
No recurrence	181	99.5
Total	182	100.0

Discussion

In the present study higher prevalence of biliary ascariasis was found in the female sex which was consistent with other reports.^{1,4,8} This has been attributed to progesterone induced sphincter of Oddi relaxation encourages relocation of worm in bile duct.⁴ In other study previous sphincterotomy has been accredited as the prime reason for biliary ascariasis.⁵ In our study five patients had earlier endoscopic sphincterotomy and choledochoduodenostomy for biliary bypass in a single case. Thus, pain, jaundice fever, vomiting history of sphincterotomy as the most important cause of the worms into the biliary tree.

Pain is the commonest mode of presentation in biliary ascariasis and has been reported in 60-90% patients across various series.^{1,2,3,4,8} Though described as biliary colic in these reports, the round worm produced agony in our study was classic and deserve advanced modification. All but one patient presented with acute onset pain abdomen that mimicked pancreatic pain i.e. acute upper abdominal pain radiating to the back, except that it was waxing and waning in nature with minimal abdominal signs. The serum amylase was normal in these patients thus excluding pancreatitis as the cause of pain.

Biliary ascariasis may present with the features of surgical jaundice, cholangitis, cholecystitis, pancreatitis and suppuration in the liver.^{1,2,3,4,8} Acute cholecystitis was observed in a single case in our study.

When the patient has had prior sphincterotomy they show no clinical or biochemical evidence of biliary obstruction as it does not allow complete obstruction. In addition the movement of a live worm in and out of the CBD resulting in an intermittent obstruction is a well known phenomenon.

Dependable screening test for the diagnosis of biliary ascariasis is trans-abdominal ultrasound examination.^{7,9} This study confirms worms in 114 patients and worm with stone in 26 patients while performed ERCP. During the procedure of ERCP worm protruding out of ampulla was observed in several cases that confirmed the diagnosis. On ERC linear or curvilinear filling defects in the biliary tree confirm ultrasound findings and the diagnosis of biliary ascariasis. As they have tendency to walk backwards and forwards in the common bile duct absence of filling defect in the cholangiogram but

positive results in USG may be interpreted by their existence near the papilla

Conservative treatment and oral antihelminthics have been found to be successful in more than 80% of patients with biliary ascariasis.^{2,4,6} Some authors, however, recommend early intervention to ward off complications.^{1,3,8} Surgical intervention can be undertaken in the form of cholecystectomy and/or CBD exploration with complete removal of the worms.^{2,3} Synchronous enterotomy and worm extraction has also been performed to ward off re-infection. When facilities are available endoscopic extraction of the worms appear to be a better alternative and gives prompt relief.^{1,4,5,8,9} Endoscopic extraction was successful in all our patients and provided a prompt relief to the agonizing pain they were suffering from. Re-infection was noted in one of our patients. This is similar to the experience reported by other authors.² To minimize the problem of recurrence, they recommend endoscopic balloon sphincteroplasty instead of conventional sphincterotomy prior to worm extraction from CBD. Though we concur with the authors on this issue, we did not have the opportunity to employ this in our patients.

Conclusion

Biliary ascariasis, though uncommon in non-endemic area, should be considered in the diagnosis of acute abdomen. This is particularly true in patients who have undergone prior biliary sphincter ablation/bypass procedures like sphincterotomy or choledochoduodenostomy. Pain could be the only presenting feature and is often out of proportion to the abdominal signs. Ultrasound is a reliable screening test for diagnosis and ERC provides confirmation. Once diagnosed, endoscopic extraction of the worm is often successful and provides prompt relief to the patient. Antihelminthics should be administered for eradication of worms from the intestine and to prevent their reentry into the biliary tree.

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Cell Biology of Aging - A Review

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Introduction:

Human aging has been a mystery from the dawn of civilization because of its biological complexity -genetic composition, inheritance, epigenetics – along with a constantly changing living environment. Age is different from aging. Age can be identified as a unit of time, such as years (e.g., chronological age). Aging is multifaceted. For example, lifespan/lifecycle is viewed as the duration between the biological conception (gestation) of an individual to the termination of life or death. However, individual genetic inheritance, generational changes, and living environment in different age cohorts (and their bio-psycho-social characteristics) complicate the understanding of aging. Nevertheless, the aging process demonstrates a constant change in molecular composition in human cells with or without external environmental stimuli.

There is a significant amount of research identifying several hallmarks of the aging process. There are twelve hallmarks identified in relation to aging. All of them are specific changes at the molecular level. Genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, disabled macro autophagy, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, chronic inflammation, and dysbiosis are the twelve hallmarks of aging^{1,2}

Genomic instability describes the change in a gene's function due to an internal or external cause. Internal mechanisms such as oxidation and hydrolysis, external components such as chemicals, physical, biological agents disrupt the stability and integrity of genomic components³. Genomic instability is identified when one or more molecular structures such as nuclear deoxyribose nucleic acid (DNA), mitochondrial DNA and nuclear architecture are disrupted, altered, or damaged^{1,2,3}. Several molecular mechanisms are identified in disruption, alteration, and genomic damage. Point mutation in a specific location of the DNA, deletion of a DNA sequence, translocation, telomere shortening, one or both DNA strand breakdown, chromosomal rearrangement, and abnormality in the nuclear structure, along with infection by virus and other pathogens, are responsible for breach of integrity and genomic instability^{1,2,3,4}

Heritability is measured as a proportion of genetic inheritance and the sum of genetic inheritance and exposure to environmental factors⁵. Famous twin studies claim that genetic inheritance contributes 20% to 30%, and a study of families with one or more centenarians showed that heritability contributes 48% in male and 33% in female longevity.

However, in a recent genealogy study of several million families, heritability contributed only 10% to 16% to longevity, and previous findings were identified as overstated. It is important to cite that genetic inheritance accounts for 45-69% in cardiovascular disease and heritability contributes 61% in Alzheimer's disease and 78% in diabetes⁵. It is believed that gene expression is regulated by the integrity and stability of the genome, which subsequently contributes to longevity or long lifespan². A better understanding of integrity, stability

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and genomic regulation are critical for a healthy lifespan and aging process^{3,4,6}

Telomere Attrition: In 1961, Leonard Hayflick and Paul Moorhead discovered that cell division has a limit, which is widely known as the Hayflick limit, or cellular senescence⁵ Telomeres are DNA sequences that are located at the end of each DNA sequence of a chromosome. Elizabeth H. Blackburn, Carol W. Greider and Jack W. Szostak jointly won the Nobel prize in 2009 for discovering the telomerase enzyme. Telomerase enzymes protect telomeres and are responsible for important functions such as DNA transcription and translation⁷. Greider and Blackburn¹⁴ found that the telomerase enzyme is required for telomeric DNA repeat synthesis, such as transcription and translation of a DNA sequence, e.g., TTGGGG to AACCCC, where adenine pairs with thymine and cytosine pairs with guanine. The adenine-thymine and cytosine-guanine base pair is designed in a way that they are complementary and antiparallel in DNA structure. Adenine, thymine, cytosine, and guanine are the fundamental structural elements of DNA. There are 2.91-billion base pairs of protein found in the human genome⁸. Each daughter cell divides in the cell cycle; this process is known cell division. Approximately 50-200 base pairs of telomeric DNA are deleted in each cell division⁹. Deletion of DNA base pairs can produce abnormal and/or ineffective protein, which could prevent required intracellular or extracellular functions and trigger disease. The progressive deletion of DNA base pairs of telomere ends is a significant characteristic feature in the aging process and mortality risk^{1,5,6}.

Understanding telomere length regulation is by far the most important mechanism in the aging process. Shortening of telomeres leads to gradual shortening of the lifespan. It could be either normal shortening (due to age or year of life) or disease related shortening (through internal or external stimuli). Telomerase enzymes play a vital role regulating and maintaining the telomeres' length. Therefore, telomerase enzymes are the target of major research/intervention to understand their exact function, regulation, and contribution to longevity. Future collaborative research may involve cell molecular biology along with psycho-social and environmental risk factors that are responsible for telomere length shortening and its cumulative impact on the aging process, longevity, and disease trajectory.

Epigenetic Alterations describes the change in genes due to living environment and behavior. Epigenetic alterations are reversible. Epigenetic alteration involves methylation or acetylation to the DNA, post-translational histones modification, transcriptional alterations, chromatin remodeling and changes in gene expression^{1,9}. Methylation and/or Acetylation is a biochemical process of adding or removing biochemical structures such as methyl and/or acetyl groups to a specific DNA. Histones are known as a supporting protein structure to DNA. Histone modification (mainly through acetylation) can be beneficial or detrimental depending on the binding site and structural modification of DNA (López et al., 2023). Cellular homeostasis, age-associated metabolic decline, and over expression of DNA protein are major examples because of histone modification¹ A better understanding of the epigenetic alteration in the aging process can improve our understanding of serious disease (e.g., cancer), and it can also be an important target for anti-aging treatment¹⁰.

Antagonistic pleiotropy (AP) is a well-accepted evolutionary theory of aging proposed in 1957 by George Williams. However, it is not proven yet whether AP represents the same features in epigenetic alteration. AP explains when a single gene controls more than one trait or characteristic features. These characteristics (or traits) are specific and special features of a gene that can be transferred from parent to child, which represent specific physical appearance or behavioral expressions. This is known as phenotypic expression. The theory of AP claims that with the same gene, one trait is beneficial in early life and the other trait is harmful to later life due to the natural selection process¹¹

Testosterone could be a good example of this. Testosterone is hormone beneficial in early life, as it is related to growth maturation, but excess testosterone could produce prostatic hyperplasia in later life¹¹. Another good example is insulin-like growth factor-1 (IGF-1). Abdellatif et al. (2023) claim that cardiac IGF-1 is essential in early age but harmful for older adults. Their study showed that overexpression of the IGF-1 receptor is beneficial at early age because it accelerates cardiac activities, but it is detrimental in old age because overproduction of IGF-1 results in premature heart failure¹².

Loss of Proteostasis: The human cell maintains coordinated activities during new protein production, such as RNA translation, folding, synthesis, repair, and degradation^{1,13}. These activities are known as proteostasis or protein homeostasis. Proteostasis demonstrates the regulatory mechanism of protein production that protects protein integrity and prevents damages. Intracellular components such as proteasome and lysosome are involved in such activities and regulation. The loss of protein regulation is characterized by the failure of protein production due to misfolding, oxidation, glycation, and ubiquitination. Misfolding, oxidation, glycation, and ubiquitination are different bio-chemical or structural processes inside the cell, but the end results are the same, such as producing dysfunctional or ineffective proteins¹¹. There are several age-related diseases, e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease, and cataracts, which occur due to loss of protein regulation¹.

Disable Autophagy: Phagocytosis is an important mechanism that removes waste material from the cell. For example, phospholipid phosphatidylserine is one of the mechanisms that protect cell death, maintain cellular homeostasis, and prevent infection¹³. Change in phospholipid phosphatidyl serine mediated phagocytosis is considered an important therapeutic target for atherosclerosis, neurodegenerative disease, and cancer. There are several active intracellular mechanisms which are responsible for digestion, reuse, recycling, and elimination of damaged intracellular elements. Lysosomes execute such digestion and elimination functions¹⁴. López et al. claim that there are several autophagy genes that decrease with age, such as ATG5, ATG7, and BECN1. Several phagocytosis mechanisms are observed inside the cell such as micro-autophagy, macro-autophagy, and chaperone-mediated autophagy¹. Phagocytosis mechanisms decrease with the advanced age, while phagocytosis executes important cellular functions such as digestion, homeostasis, metabolism, and elimination and prevents intracellular damage^{1,14}.

Deregulated Nutrient-Sensing: Each cell has its own cellular metabolic activities and regulator for nutrients. Deregulated nutrient-sensing is characterized by an inability to regulate anabolism and storage of intracellular nutrients due to lack of nutrient regulators^{1,15}. Deregulation of nutrient sensing pathways are commonly found in metabolic

diseases. Glucose, amino acids, and lipids are basic cellular components that synthesize and break down to produce adenosine triphosphate (ATP), which is the energy unit of our body¹⁶. ATP is required for growth, development, reproduction, and survival. Limitation in nutrient intake, or caloric restriction, is an important theory of aging. Intracellular and extracellular glucose, amino acid, and lipid sensing mechanisms and signaling events are deregulated in several important diseases¹⁵. For example, IGF regulates growth, development, and tissue homeostasis through neuronal signals and neuronal circuits. The United Kingdom biobank study shows that higher production of IGF-1 is associated with dementia, diabetes, vascular disease, and osteoporosis in older adults^{1,2,16}.

Mitochondrial Dysfunction: Mitochondria are known as a powerhouse; they are a major intracellular component, responsible for energy production. ATP is a unit of energy in our body. Our entire body function is dependent on the total amount and rate of energy generation by mitochondrial internal machines, known as the electron transport chain (ETC)¹⁷. In 1988, Anita Harding and Doug Wallace discovered that a large deletion and a point mutation in mitochondrial DNA produce several diseases, and they are linked to maternal inheritance¹⁹. Mitochondrial dysfunction primarily results from the mutation of mitochondrial DNA¹. However, accumulation of increased amounts of reactive oxygen species (ROS) is an important mechanism of mitochondrial dysfunction where oxygen molecules are unable to enter the mitochondrial ETC where ATP is produced¹⁷. Reactive oxygen species, also known as free radicals, are characterized by the unpaired oxygen which enhances oxidative stress and cellular degeneration¹⁷. With age, the number of increased free radicals decreases energy production and restricts the functional capacity of a cell.

Cellular Senescence is described as irreversible change in the cell or complete loss of function resulting in cell death¹⁸. The mechanism of cell death is known as senescence-associated secretory phenotype^{1,6}. There are several mechanisms that characterize cellular senescence or cell death, such as telomere shortening, genomic mutation, epigenic alteration, dysregulation of autophagy, drugs/chemicals, radiation, and oncogenic and metabolic insults^{1,6}. Huang et al²⁰ have reported that senescent cells

demonstrate cell cycle arrests or morphological alterations of cells. Several biomarkers of cellular senescence have been identified, including SA- β gal, p16 and p21²⁰. However, senescence-associated secretory phenotype (e.g., irreversible cell-cycle and pro-inflammatory characteristics) due to mitochondrial dysfunction is considered the most important driver of cellular senescence and the aging process^{18,21}.

Stem Cell Exhaustion: Stem cells are characterized by reproducing either the same type of cell or different types of cells, and their ability to tissue-specific differentiation is critical for survival and regeneration²². Stem cell exhaustion describes the loss of renewal capacity that is required for repair of tissue injury; however, it is not clear whether aging causes a reduced number of stem cells or decreases the number of stem cells is associated with aging. However, accumulation of toxic metabolites such as reactive oxygen species, epigenetic alteration of DNA damage, accumulation of damaged protein, and mitochondrial dysfunction can reduce the number of stem cells^{1,2,22}

Altered Intercellular Communication describes the change or loss of communication between cells. For example, neuro-hormonal systems, renin-angiotensin systems, and insulin-IGF-1 systems are responsible for producing specific signals for specific intracellular or intercellular functions¹. The loss of internal signal-response capacity or maintaining homeostasis to execute normal functions is characterized as altered intercellular communication^{1,2}. For example, Wang et al.¹⁰ have reported that intercellular communication in hepatic tumors involves tumor proliferation, invasion, apoptosis, angiogenesis, metastasis, inflammatory response, gene mutation, immune escape, metabolic reprogramming, and therapeutic resistance.

Chronic inflammation describes an increased level of inflammatory cytokines and biomarkers, such as CRP (C-reactive protein), TNF- α , and IL-6, which prevents growth and repair, increases intracellular damage, and destabilizes cellular homeostasis^{1,2}.

Dysbiosis is described as a rate of change in the number of gastrointestinal microorganisms which regulate the distribution, absorption, metabolism, and elimination of nutrients^{1,2}.

Conclusion

Intracellular mechanisms and hallmarks of aging demonstrate either a change in function, or a loss of

function. Regardless of the change or loss of functions, the ultimate result presented either as disease, or systemic abnormality or death. The consequence of aging is better supported as gradual decline in cellular digestion, decreased elimination, maldistribution, and the inability to reproduce and maintain homeostasis. Nevertheless, cell molecular biology alone does not explain aging. Bio-psycho-social collaboration is essential for a better understanding of aging.

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Case Report

The Girl with Protruded Left Eye: A Case Report

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Abstract

Unilateral proptosis means forward protrusion of one eyeball caused by various pathology. An abnormal protrusion of the eyeball, beyond the boundaries of the bony orbit, is termed 'proptosis'. A similar appearance, seen in endocrine dysfunction, especially thyroid disorders, is called 'exophthalmos'. Protrusion of eyeball is commonly seen in Graves' ophthalmopathy, also known as thyroid eye disease which is mostly bilateral. Unilateral proptosis is rare in this condition. Graves' Ophthalmopathy is an immune mediated inflammation in orbital and retroorbital tissues, occurs mainly with Thyrotoxicosis, more frequently in female. Natural history of unilateral Graves' Ophthalmopathy is unknown and the diagnosis remains challenging. In this article, a 19-year-old female presented to the outpatient department of Pabna Medical College with the complaints of protrusion of left eye and palpitation for 2 months.

Introduction

The most common extrathyroidal manifestation of Graves' disease is Thyroid Eye disease observed in 25- 50% of the Graves' patients. A total of 75% of the patients with thyrotoxicosis develop Graves' Ophthalmopathy within a year of diagnosis¹. In majority of patients, both eyes are equally affected. Unlike bilateral proptosis, which is mostly seen in thyroid disease, unilateral proptosis has a great variety of differentials including orbital pseudotumor, orbital cellulitis, cavernous sinus thrombosis, intra-orbital neoplasms, vascular lesions which may delay the appropriate diagnosis and management². Unilateral Ophthalmopathy mostly progresses to bilateral disease, while only 5- 11% of cases are pure unilateral³. This case report details an instance of unilateral Graves' Ophthalmopathy in a 19- year- old female presenting with unilateral proptosis and occasional palpitation for 2 months highlighting the clinical features, diagnostic approaches, treatment strategies. The rarity of the unilateral presentation emphasizes the importance of considering Graves'

Ophthalmopathy in the differential diagnosis of unilateral orbital processes, in patients with no history of thyroid dysfunction⁴.

Case Description

A 19-year-old female presented to the outpatient department with the complaints of protrusion of left eye and palpitation for 2 months. Bulging of her left eye was insidious in onset and was increasing gradually without visual impairment. Palpitation was occasional without any aggravating factor. She had no history of weight loss, fever, night sweat, chest pain, cough, breathlessness, menstrual irregularities. No remarkable prior medical history, family history or drug history. She was normotensive, nonsmoker, non-diabetic, non- alcoholic.

On examination, she was anxious, co-operative with body weight 54 kgs, blood pressure 110/70 mmHg, Pulse 120 b/m, respiratory rate 16 breaths/min, axillary temperature 97p F. Thyroid gland was not palpable. On ocular examination, eye movements were normal, there was retraction of left upper eyelid,

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visual acuity was 6/6 in both eyes. There was no color change of surrounding skin, lid swelling, conjunctival congestion, watering or tenderness.



Figure 1: *Protrusion of left eyeball*



Figure 2: *No thyroid gland enlargement*

Laboratory investigation revealed a hemoglobin level of 12.8 g/dL and a white blood cell count of 8600 /mm³ with 55% neutrophil. The free T3 level was 9.86 pmol/ml (reference 3.50-8.56 pmol/ml), free T4 level was 26.70 pg/ml (reference 8.9- 17.20 pg/ml), TSH was 0.005 μ IU/ml (reference 0.35-4.50 μ IU/ml), TSH receptor antibody was 7.39 IU/L (reference 0.82-40 IU/L), anti- thyroglobulin level was 1087.53 IU/ml (reference < 75 IU/ml), anti- thyroid peroxidase level was 552 IU/ml (reference < 30 IU/ml), blood glucose, liver and renal function tests were within normal limit, Sinus tachycardia on Electrocardiogram. Thyroid scan revealed normal position of the gland with diffusely increased uptake. CT scan of both eyeballs was normal. She was diagnosed as Graves' Disease with Graves' Ophthalmopathy and started Carbimazole and Beta blocker. She has been advised for regular follow up also.

Discussion

The patient presented with unilateral proptosis, palpitations without visual disturbance. This is a rare presentation of Graves' Disease.

Graves' Disease is an autoimmune disorder that is more frequent between 20 and 50 years of age and occurs in 2% of women¹. The annual incidence of Graves' Ophthalmopathy is 16 per 100,000 women. The symptoms of GO include a dry, gritty feeling in the eyes, photophobia, excessive tearing, double vision, and pressure feeling behind the eyes, as reported by nearly half of the patients of Graves' hyperthyroidism^{1,5}. The most typical symptoms of GO are proptosis, ophthalmoplegia, orbital congestion, eyelid edema, eyelid erythema, conjunctival chemosis, difficulty moving eyes, eyelid retraction, and less frequently, compression of the optic nerve. Proptosis can cause corneal exposure and injury in severe cases^{2,6}.

The most widely accepted cause of Graves' orbitopathy is the formation of autoantibodies against thyrotropin receptors located in both the thyroid gland and the orbit¹. This activates T cells, resulting in the release of inflammatory mediators. Inflammatory cells and hyaluronans infiltrate the muscle, causing enlargement of the EOMs, an increase in the orbital fat volume, and ultimately, collagen deposition leading to fibrosis. The disease often progresses via two distinct phases: an active, inflammatory phase followed by a static, non-inflammatory phase with fibrosis^{3,4,7}.

The risk factors for Thyroid eye disease as smoking, older age, extreme physical or psychological stress, prior treatment with radioactive iodine, and increased titers of antithyroid-stimulating hormone receptor antibodies are well described in published literature. However, unilateral proptosis can be attributed to several factors, such as an asymmetrical distribution of antigens, anatomical variations in blood flow or lymphatic drainage, the elasticity of orbital septa, or other localized conditions. Infections or differences in the ability to generate adipose tissue can be a potential trigger for unilateral proptosis^{4,5,8}.

This patient had positive anti thyroglobulin and anti-thyroid peroxidase antibody with a rise in free T3, T4, undetectable TSH with a negative TRAB and normal orbital CT scan, diffusely increased uptake on thyroid scan. Different studies have shown that unilateral Graves' may be present in hyperthyroid, euthyroid, TRAB negative patients^{8,9}.

Treatment strategy varies with patient's symptoms. Management of Hyperthyroidism by Carbimazole or Methimazole or Propylthiouracil, treatment of eye symptoms with pulse methylprednisolone, artificial tear supplements are primarily started. Radiotherapy, Surgery, Immune therapy are different treatment modalities according to different patient's overall condition. This patient started anti thyroid drugs only as she didn't have ocular symptoms or visual disturbance and was advised for regular follow up

Conclusion

This clinical case is a diagnostic challenge because the true unilateral disease is rare, and bilateral asymmetric eye involvement is seen in GO. Besides, patient did not have adequate symptoms. Numerous differential diagnoses should be considered and studied before diagnosing this uncommon entity. Prompt treatment, patient's education, regular follow up, ultimately a tailored approach is crucial for this.

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