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Editor's choice

This is a great pleasure to informing you that we are going to publish "The Beacon Medical Journal" volume-04,number-02 in July, 2021.Next issue will be published in January 2022.The journal has been published 2 issues/year as regular basis. Ten thousands copies have been distributed to graduate doctors throughout the country by our field colleagues . Already we had build a strong advisory & review board to draw the attention of it's authors & readers nationally & internationally.

Editorial of this issue is COVID-19 and Bangladesh:Challenges and How to Address. The end of 2019, coronavirus disease was first identified in china and in March 2020, WHO declared COVID-19 as a pandemic. The virus is contaminated from human to human very rapidly & patients can develop the disease in different forms. Practice of good personal hygiene, washing hand, wearing mask,avoiding mass gathering and vaccination program can prevent Bangladeshi people from COVID-19. Apart from that this issue also contains seven original articles, one review article and one case reports.

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Dr. G.M. Raihanul Islam
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Editorial

Covid-19 and Bangladesh: Challenges and How to Address

The novel human coronavirus disease COVID-19 has become the fifth documented pandemic since the 1918 flu pandemic. COVID-19 was first reported in Wuhan, China, and subsequently spread worldwide. The coronavirus was officially named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses based on phylogenetic analysis. SARS-CoV-2 is believed to be a spillover of an animal coronavirus and later adapted the ability of human-to-human transmission. Because the virus is highly contagious, it rapidly spreads and continuously evolves in the human population. The symptomatology of these patients, including fever, malaise, dry cough, and dyspnea, was diagnosed as viral pneumonia.[1,2] Initially, the disease was called Wuhan pneumonia by the press because of the area and pneumonia symptoms. Whole-genome sequencing results showed that the causative agent is a novel coronavirus. Therefore, this virus is the seventh member of the coronavirus family to infect humans.[3] The World Health Organization (WHO) temporarily termed the new virus 2019 novel coronavirus (2019-nCoV) on 12 January 2020 and then officially named this infectious disease coronavirus disease 2019 (COVID-19) on 12 February 2020. Later, the International Committee on Taxonomy of Viruses (ICTV) officially designated the virus as SARS-CoV-2 based on phylogeny, taxonomy and established practice.[4] Subsequently, human-to-human transmission of COVID-19 occurring within Hong Kong has been shown in clinical data.[5] Since COVID-19 initially emerged in China, the virus has evolved for four months and rapidly spread to other countries worldwide as a global threat. On 11 March 2020, the WHO finally made the assessment that COVID-19 can be characterized as a pandemic, following 1918 Spanish flu (H1N1), 1957 Asian flu (H2N2), 1968 Hong Kong flu (H3N2), and 2009 Pandemic flu (H1N1), which caused an estimated 50 million, 1.5 million, 1 million, and 300,000 human deaths, respectively [6,7,8,9] Recently, it has spread worldwide [8], including Bangladesh, which is one of the most densely populated countries (160 million) in the world[9]

Since its appearance at the end of 2019, coronavirus disease 2019 (COVID-19) has immediately shown a high rate of transmission, forcing the World Health Organization (WHO) to declare in March 2020 that this unknown coronavirus, named severe acute respiratory syndrome coronavirus 2 (SARS CoV-2), can be characterized as a pandemic.[10] In the past twenty years, coronavirus (CoV) infections have raised many concerns for public health. In fact, in 2002, there was the first epidemic due to a coronavirus, originating in China, which was related to a severe acute respiratory syndrome, called SARS-CoV.[11] Subsequently, in 2012, a new viral outbreak with characteristics similar to SARS-CoV was observed in the Middle East (Qatar, Jordan, Saudi Arabia, and the United Arab Emirates), in Europe (UK, France, and Italy), and in Africa, and was called Middle East respiratory syndrome (MERS).[12] The WHO declared the coronavirus disease 2019 (COVID-19) outbreak as a public health emergency of international concern on January 30, 2020, and then a pandemic on March 11, 2020. COVID-19 affected over 200 countries and territories worldwide.[13] Human coronaviruses usually cause mild upper respiratory diseases. However, in the past two decades, two coronaviruses transmitted from animals, SARS-CoV and MERS-CoV, have caused severe pneumonia and death in humans. In addition, since late April 2020, the COVID-19 pandemic has spread globally and consequently resulted in at least 3,149,389 deaths worldwide as of April 28, 2021.[23] The diagnosed cases are 751,659, total deaths 11,228 and total recovered cases are 666,927 in Bangladesh as of April 28,2021. Due to the high sequence homology with a coronavirus isolated from bats, SARS-CoV-2 is considered a zoonotic origin coronavirus. Undoubtedly, SARS-CoV-2 has become the fifth human coronavirus, and it is possible that this virus will continuously circulate in the human population in the future.

COVID-19 patients can develop the disease in different forms: They can be asymptomatic, have mild symptoms, or they can also have severe symptoms that can lead to hospitalization, and in severe cases death.[14] The most serious clinical conditions are characterized by acute respiratory distress syndrome (ARDS), cardiac insufficiency, and septic shock [15,16,17] and this causes tissue damage at the alveolar level, generating pathological tissue alterations, hyperplasia, and infiltration. In addition, the existence of different comorbidities in subjects infected by SARS-CoV-2 may increase the response of the immune system, exacerbating the risk of adverse effects and mortality.[18,19,20] Indeed, the systemic inflammation found in individuals suffering from non-communicable diseases (such as diabetes and arterial hypertension) is strictly related to severe symptoms after the SARS-CoV-2 infection.[21,22] Because specific antiviral treatments and vaccines are still under trial, testing, quarantine, and social distancing are encouraged to prevent virus spread. Nonetheless, since the virus keeps mutating and evolving during the pandemic, studies on viral pathogenicity, treatments and prophylactic vaccines should closely consider the genetic characteristics of the virus.[24]

Evidence suggests that the virus is contaminated from human to human very rapidly.[25] Although complete elimination of COVID-19 outbreak seems impossible, several key measures could reduce the possible transmission of SARS-CoV-2 by avoiding the contact opportunities [26], such as avoiding social mass people gathering, transient closure of school and day care for the peak period of outbreak, traveling and trade restrictions, entry screening of the travelers during outbreak period, isolation of infected cases, and maintaining the physical distance within the workspace. In this backdrop, flexible working schedules/shifts for employees, the opportunity of distance working/teleworking, increased use of email and teleconferences to reduce close contacts, reduced contact between employees and customers, reduced contact between employees, promoting the use of other personal protective countermeasures, and avoiding mass gathering, such as sport events, concerts, religious events, conferences, and so on are advised to maintain in Bangladesh.

According to the WHO, the practice of good personal hygiene is essential.[27] Regularly washing hands with soaps and water and avoid touching the face with the hands are some ways to ensure personal hygiene. Wearing a mask is essential.[28] The infected person should take rest at home or admit to the hospital for complete isolation for 14 days. In case of emergency, the infected person should wear a surgical mask to protect others. Along with several other countries, vaccination against Covid has been rolled out in Bangladesh. The Bangladesh government initiated the public vaccination program which named, the Oxford-AstraZeneca COVID-19 vaccine co-manufactured by Serum Institute of India, on 27 January 2021, with priority for first responders, including physicians, nurses, and government officials, among others. Interested individuals must register through a designated website to receive the vaccination, which is likely to be inconvenient for individuals who do not use the internet, especially older individuals and rural populations.[29]

SARS-CoV-2 is a novel and highly contagious virus, and there is no specific treatment for COVID-19 disease up to now. It must be taken into account that if no effective action is taken and if drugs, vaccines, and patient tracking measures are not widely implemented or effective, intermittent social distancing is likely to continue until 2022. By that time COVID-19 might have affected 90% of the world population and kill over 40 million people.[30, 31] Therefore, it is wise to continue preventive methods and public health measures until an appropriate vaccine and effective drugs are discovered. Combinational therapies with effective drugs or supplements, plus an appropriate immunomodulatory diet, proper mental support and adherence to standards, will eventually be effective against COVID-19.

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Original Article

Association of Subclinical Hypothyroidism with Dyslipidemia in A Tertiary Care Hospital

S Saber [1], MD Hossain [2], MT Alam [3], MM Hossain [4]

ABSTRACT

Background: Hypothyroidism is a common metabolic disorder, results from inadequate production of thyroid hormones. Subclinical hypothyroidism (SH) is a condition usually asymptomatic, in which TSH level is above the reference range and free T3 and T4 levels are within reference range. Thyroid hormone plays a vital role in the regulation of energy homeostasis, in the metabolism of glucose and lipids and regulation of enzymes of lipoprotein transport. Lipid abnormalities are more common in overt hypothyroidism patients and also contribute to the inconsistent increase in cardiovascular risk in those patients.

Objective: This study was designed to explore the associations of lipid profile with subclinical hypothyroid patients.

Method: From January to December 2019, we enrolled 120 consecutive patients diagnosed with subclinical hypothyroidism that visited Bangladesh Medical College hospital, medicine,OPD.Thyroid function was assessed by evaluating serum TSH, FT4 and T3 levels. Fasting lipid profiles were investigated among all the study population

Result: Out of 120 patients, 43 were males and 77 were females diagnosed as subclinical hypothyroidism with majority (39.17%) belonged to the age group 31 – 40 years. Study population mostly belonged from urban areas (60.83%). Data analysis revealed that 15.83% males and 35.83% females had high total serum cholesterol, 20.83% males and 55.83% females had high triglyceride levels and 22.5% males and 52.5% females had high LDL levels with statistical significance ($p<0.001$). In addition, mean HDL-cholesterol levels were found low in 9.17% males and 27.5% in females though it has not proved statistically significant ($p<0.44$) in our study ; 38.33% & 25.83% of study population had family history of thyroid disease and lipid abnormalities respectively though these have not shown any statistical significance here.

Conclusion: It was observed that serum total cholesterol, triglycerides (TG) & low density lipoproteins (LDL) levels were raised in patients with subclinical hypothyroidism. Hence while estimating the lipid profile levels, the thyroid function of the individual should be taken into consideration.

Keywords: Subclinical hypothyroidism, Lipid profile.

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Introduction

Hypothyroidism is a common metabolic disorder with a prevalence range of 4% to 20% in adults,[1] and there is progressive increase in the prevalence with age. Thyroid failure is more common in women. Hypothyroidism results from inadequate production of thyroid hormones. It is classified as overt or subclinical depending on the extent of abnormalities in thyroid hormone levels and degree of clinical severity. Subclinical hypothyroidism (SH) is a hypothyroid condition usually asymptomatic, in which TSH level is above the reference range and free T3 and T4 levels are within reference range,[2] or if a thyrotropin releasing hormone (TRH) test is done, there's a greater than normal rise in TSH response.[3] Thyroid is an important organ involved in the regulation of various cellular processes such as cell proliferation and development, control of resting metabolic rate, thermoregulation, and metabolism of carbohydrates,

proteins, and lipids.[4] Dysfunction of thyroid affects appetite, body weight, muscle mass, as well as brings about changes in the adipose tissue by altering lipolysis, resulting in increased incidences of insulin resistance, type 2 diabetes mellitus (T2DM), and cardiovascular diseases (CVDs)[5]. There are multiple systems on which thyroid hormone acts or contributes to their function but heart and the vessels are the major target organs. Marked changes in these organs occur in patients with thyroid dysfunction.[6] It is also seen that overt hypothyroidism is characterized by hypercholesterolemia and a marked increase in low-density lipoproteins (LDLs) and Apo lipoprotein B. SH is known to be associated with disorders in lipids, characterized by normal or high total cholesterol, raised LDL, serum TG and small dense LDLC (sdLDL-C) levels and lower levels of HDL.[7,8] SH is also related with endothelium dysfunction, aortic atherosclerosis and myocardial infarction.[7] The reported mechanisms for the development of hypercholesterolemia in hypothyroidism include decreased fractional clearance of LDL by a reduced number of LDL receptors in the liver in addition to decreased receptor activity.[9-11] In thyroid disease, dyslipidemia coexists with various metabolic abnormalities and induce insulin resistance and oxidative stress via a vicious cycle. The above associations in combination with the thyroid hormones-induced hemodynamic alterations might explain the increased risk of coronary artery disease (CAD), cerebral ischemia risk, in patients with overt or subclinical hypothyroidism.[12] Therefore the present study was conducted in the Department of Medicine OPD, Bangladesh Medical College Hospital, Dhaka to observe the association of subclinical hypothyroidism with lipid profile.

Method

The present study was hospital based cross – sectional observational in nature conducted in the outpatient department of Bangladesh Medical College Hospital, Dhaka city. It was carried out from January to December 2019.

All the subjects underwent medical history assessment, general clinical examination, before enrollment including examination of thyroid glands. Patients gave informed consent before they participated in the study. Once informed consent was obtained, all participants were asked to complete a questionnaire to collect basic demographic information such as age, gender, family history of thyroid diseases, lipid abnormalities and place of living.

Blood samples 5 ml of venous blood with full aseptic precautions without anticoagulant and allowed it to clot were collected from the antecubital vein between 8 to 10 a.m. in a sitting position after 12 hours of fasting and avoiding of alcohol. Clotted blood was centrifuged and clear serum was collected. Fresh serum samples were taken. Serum was checked for hemolysis and if hemolyzed then that serum was discarded. Serum was analyzed for FT3, T4 and thyroid-stimulating hormone (TSH) for thyroid profile. Serum for analysis was stored at – 20°C. Thawed samples were mixed prior to testing. A total volume of 50 μl of serum was taken to analyze FT3, 25 μl for FT4 and 100 μl for TSH hormone level by the enzyme-linked immunosorbent assay method (Omega diagnostics) at 450 nm filter using micro plate reader model 680 (Bio-Rad). Normal range for T3 was 0.81-1.79 ng/ml, for FT4 was 0.89-1.76 ng/dl and for TSH it was 0.40 – 4.0 uIU/ml.

Statistical Analysis: Data was recorded into semi-structured pre-tested proforma. It was entered into Microsoft Excel and analyzed using SPSS v 16.0. Summarization of data was done according to data types and appropriate statistical tests were done. The various modes of clinical presentation were expressed as the total number of patients presenting with a particular presenting feature and then calculated as a percentage of the total number of patients. p-value of <0.05 was considered to be statistically significant. Informed consent was taken in all the cases and the records were kept confidentially.

Result

Total 120 patients of both sex were included in this study. SH group comprising of 77 females and 43 males.

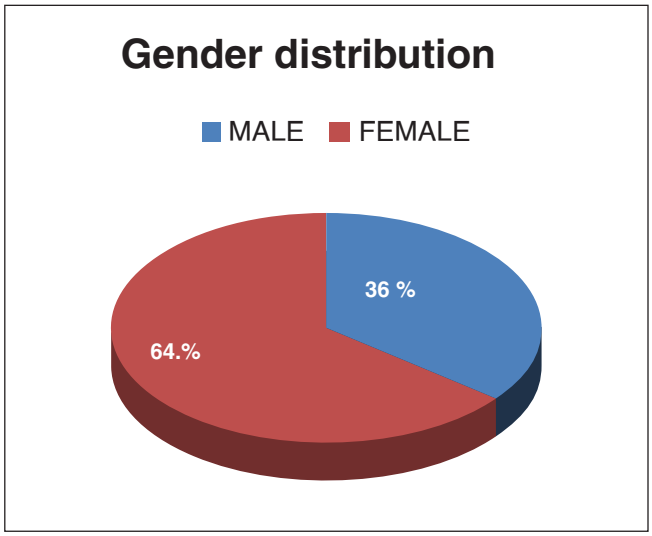

Figure 01: Gender wise distribution of study population

Age Distribution: Among 120 subclinical hypothyroid patients majority (39.17%) belonged to the age group 31– 40 years with female predominance. Least SH patients (9.17%) were observed in the age of above 60 year.

AGE	MALE (n=43)	FEMALE (n=77)	TOTAL (n=120)	Percentage(%) of distribution
18 - 30	8	12	20	16.67%
31 - 40	16	31	47	39.17%
41 - 50	11	12	23	19.17%
51 - 60	5	14	19	15.83%
> 60	3	8	11	9.17%

Table 01: Age wise distribution among the study population

Lipid Profile: The differences in lipid profile are shown in Table 2. Total cholesterol (TC), triglycerides (TG) and LDL were significantly higher in subclinical hypothyroid patients, while high density lipoprotein (HDL) was significantly lower

though it has not shown any statistical significance (p-value<0.44) in this study.

Lipid	Mean (SD)	No. of patients (n=120)		Percentage of distribution (%)		P – value
		Male(n=43)	Female(n=77)	Male	Female	
Total Cholesterol(TC)	240.38	19	43	15.83%	35.83%	<0.001
Triglyceride(TG)	174.40	25	67	20.83%	55.83%	<0.001
High density lipoprotein (HDL)	32.72	11	33	9.17%	27.5%	<0.44
Low density lipoprotein (LDL)	144.13	27	63	22.5%	52.5%	<0.001

Table 02: Comparison of lipid profiles in the SCH group according to gender distribution

Family History of Thyroid Diseases: In this study family history of thyroid diseases found among n = 46 (38.33%) of subclinical hypothyroid patients. However, family history of thyroid diseases was not found statistically significant here (p < 0.695).

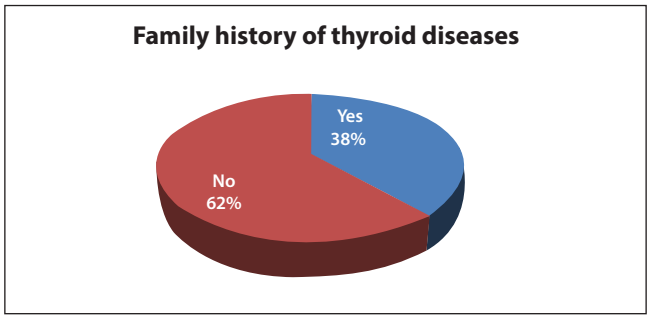

Figure 02: Family history of thyroid diseases among study population

Family history of Lipid Abnormalities: In this study family history of lipid abnormalities found among n = 31 (25.83%) of study population. However, family history of lipid abnormalities was not found statistically significant here (p < 0.495).

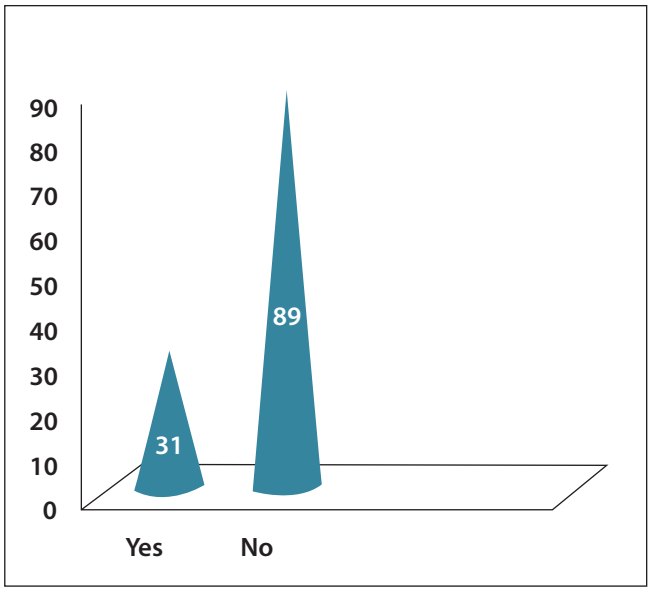

Figure 3: Family history of lipid abnormalities among study population

Area wise distribution: Area wise distribution has shown on the figure 4 where majority of the study population belonged from urban area 60.83% and 39.17% from rural area.

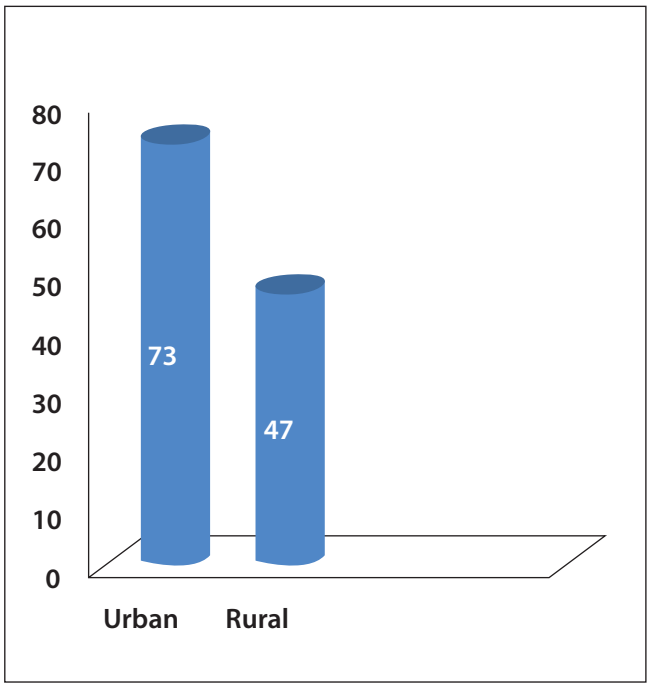

Figure 04: Area wise distribution of study population

Discussion

In 1900, Von Noorden from Vienna, stated that thyroid played a key role in causation of 'fatty disease'.[13] In 1918, scientists ascertained correlation of blood cholesterol to the secretion of adrenals and thyroid. In 1930s the connection of cholesterol with thyroid function and disease was observed.[14] On Christmas day of 1930, a landmark article was published by Mason and colleagues in the New England Journal of Medicine which showed the significance of cholesterol values in hypothyroidism and hyperthyroidism.[15] In a multicenter study of prevalence of hypothyroidism in 752 hyper cholestrolemia patients, primary hypothyroidism occurred in 3.7%.[16]

Thyroid hormones have significant effect on the heart and cardiovascular system.[9] The most common clinical signs are a narrowed pulse pressure, diastolic hypertension, low cardiac output, reduced EF impaired diastolic function and bradycardia.[17] Overt hypothyroidism is associated with accelerated atherosclerosis and CAD due to hypercholesterolemia and diastolic hypertension.[18-21] A prospective study from Japan showed an increase risk of ischemic heart disease in men but not women with subclinical hypothyroidism.[22] A prospective study in the United States, followed up men and women age 65 or older for more than 10 years showed no influence of hypothyroidism (overt or subclinical) on cardiovascular outcome and mortality.[23]

It has been observed that serum cholesterol and triglycerides level were raised in patients with subclinical hypothyroidism. Similar results were observed by Walsh et al in a community based study conducted among Australian participants and

found that serum TSH was positively correlated with total cholesterol, triglycerides and LDL-C whereas no association was observed between serum TSH and HDL- C.[24] Other researchers also observed similar findings.[25,26]

In contrast, Vierhapper et al, in a cross-sectional study done in 7000 thyroid clinic outpatients, observed that total cholesterol and LDL-C were elevated in overt hypothyroid patients, but no significant differences in serum total cholesterol, LDL-C, HDL-C, or triglyceride levels in SH patients and the euthyroid control group.[27] In another study done by Hueston et al, it was found that SH (defined as a serum TSH of 6.7 to 14.99 mIU/liter) was not associated with alterations in total cholesterol, LDL-C, triglycerides, or HDL-C.[28] Thyroid hormones stimulate enzyme, 3-hydroxy-3-methylglutarylcoenzyme A (HMG-CoA) reductase, which is required for the first step in cholesterol biosynthesis. Triiodothyronine (T3) causes upregulation of LDL receptors by controlling the LDL receptor gene activation. T3 also regulates LDL receptor's gene expression by controlling the sterol regulatory element-binding protein-2 (SREBP-2). T3 also protects LDL from oxidation. Thyroid hormones increases cholesteryl ester transfer protein (CETP) activity, which exchanges cholesteryl esters from HDL2 to the very low density lipoproteins (VLDL) and TGs to the opposite direction thereby influencing HDL metabolism. Thyroid hormones stimulate the lipoprotein lipase (LPL), which catabolizes the TG-rich lipoproteins, and the hepatic lipase (HL), which hydrolyzes HDL2 to HDL3 and contributes to the conversion of intermediate-density lipoproteins (IDL) to LDL and in turn LDL to sdLDL.[29] T3 also leads to upregulation of ApoAV which have been associated with decreased levels of TGs. Besides their effect on lipid profile, thyroid hormones can equally affect a number of other metabolic parameters related to CVD risk. Thyroid function can also influence the production of adipokines and adipocyte metabolism.[30]

In the present study, serum total cholesterol (TC) was found to be increased in patients of subclinical hypothyroidism which was highly significant statistically ($p<0.001$). The findings of this study are consistent with results of Petersson and Kjellstrom (2001)[31] who also observed increased TC level in patients of primary hypothyroidism.

In the present study, serum LDL levels were found to be increased in patients of subclinical hypothyroidism which was highly significant statistically ($p<0.001$). The findings of this study are in favour of results of Huesca et al (2002)[32] who also observed increased LDL levels in patients of primary hypothyroidism.

In the present study, serum Triacylglycerol (TAG) levels were found to be increased in the study population which was also found statistically significant ($p<0.001$). The findings of this study are consistent with the results of Petersson and Kjellstrom (2001)[31] who also observed higher Triacylglycerol level in patients of primary hypothyroidism.

In India, a population based study done in Cochin[33] on 971 adult subjects estimated the prevalence of hypothyroidism to be 3.9% and that of subclinical hypothyroidism to be 9.4%. In women, the prevalence was higher (11.4%), whereas it was 6.2% in men. The prevalence of subclinical hypothyroidism increased with age. The present study found a female preponderance among the cases, with a M: F ratio of around 1:2 for subclinical hypothyroid cases. Takashi et al.[34] reported a M:F ratio of 1:6 for hypothyroidism, which is higher than the present study, whereas John et al.[35] reported the ratio to be 1:4, which is in comparison to the present study. Deshmukh et al.[36] reported a M:F ratio of 1:3.7 for subclinical hypothyroidism, which is also in comparison to the present study.

In our study the prevalence of hypothyroidism were maximum at the age group of 31 – 40 years(39.17%). Minimum prevalence was noted in the age group of >60 years (9.17%). Multivariate logistic regression analysis proved that female and increasing age were independent risk factors of hypothyroidism. Degenerative changes occurring in the thyroid of old people and combined effect of oestrogen [37] and progesterone in female may account for it. Unnikrishnan et al. [38] reported that the prevalence of overt hypothyroidism was highest in the age group of 46–54 years and lowest in the age group of 18–24 years whereas subclinical hypothyroidism was most prevalent in the age group of >55 years and least prevalent in the age group of 18–24 years.

Conclusion

Hypothyroidism is associated with significant increased level of atherogenic lipids.

Recommendation

Abmormalities in the thyroid function can have an inpact on lipid profile. While diagnosing or treating patients with dyslipidemia, biochemical screening for thyroid dysfunction should be taken into consideration. Further research should be done to evaluate the role of subclinical hypothyroidism on dyslipidemia and whether the thyroid dysfunction influences the morbidity and mortality of cardiovascular disease among patients.

Study Limitations

Limitation of the current study was that it was a cross – sectional type of observational study, no follow – up of the study participants was done and it is not possible to evaluate whether the associations are causal. Therefore a controlled study would be more appropriate to confirm the diagnosis, association of hypothyroidism with dyslipidemia and its complications.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Pattern of Epilepsy in Children with Cerebral Palsy and Their Prognosis

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ABSTRACT

Background: About a quarter of chronic childhood problem are neurological in origin. Cerebral palsy is a common neurological condition in Bangladesh. The condition posses considerable diagnostic and therapeutic challenges to the physician with degree of involvement ranging from mild to severe disability, associated with several comorbid condition. Cerebral Palsy management is a long time process so it is important to create awareness and receive proper step to reduce the risk of Cerebral Palsy.

Objective: To describe the characteristics and prognosis of epilepsy in a population of patients with cerebral palsy.

Method: This observational cross-sectional study was performed in the Department of Pediatrics, Combined Military Hospital, Dhaka, during the period of 6 months .After meeting the inclusion and exclusion criteria a purposive sampling technique was applied for selection of 55 patients. Findings were explored in tables and graphs. Data were analyzed through standard statistical methods by using SPSS software, version 22.0.

Result: Among the children with cerebral palsy, 18.1% were spastic diplegic, 27.2% were spastic quadriplegic, 16.3% were spastic hemiplegic, 18.1% were extrapyramidal, 14.5% were ataxic and 5.4% mixed variety. Classification of epilepsies and epileptic syndromes showed 29.1% symptomatic generalized, idiopathic localization 16.4%, symptomatic localization related 7.3%. Associated problems of the epileptic children with cerebral palsy were intellectual deficiency in 32.7% children, 18.2% had behavioral disturbances, 5.4% had visual impairment, 16.4% had inability to walk, 3.6% children had hearing impairment. Associated prenatal causes of the epileptic children with cerebral palsy, 3.6% patients had maternal illness (HTN), 9.1% patients had maternal history of preeclmapsia. Associated perinatal causes of the epileptic children with cerebral palsy, delayed cry was observed in 18.2% patients, 12.7% patients had birth trauma, 5.5% children were preterm, 9.1% children had neonatal seizure, 7.3% had severe neonatal jaundice. Focal epileptiform activity was the common EEG findings observed in 29.1%. Generalized atrophy was observed in 36.4%, periventricular leucomalacia in 14.5%. 27.3% patients responded to treatment with monotherapy and 72.7% patients responded to treatment with polytherapy. Maximum patients took sodium valproate 40%. 74.5% patients were continuing anti-epileptic Drugs, no withdrawal of anti-epileptic Drugs was possible because none of them was seizure free for at least 2 years which is prerequisite for discontinuation of anti-epileptic Drugs. Among relapsed cases, seizure relapsed in 7.3% patients within 7-12 months of anti-epileptic Drugs withdrawal and in 12.7% within 1-6 months of anti-epileptic Drugs withdrawal.

Conclusion: Symptomatic generalized epilepsies were more common in the children with epilepsy and CP. Perinatal asphyxia is the most common perinatal cause among the children with epilepsy and CP. Abnormal neuroimaging was predominant in cases and needed more use of polytherapy. Refractory to treatment and relapse rates of epilepsies were high in the children with epilepsy and CP.

Recommendation: These factors need to be considered when planning for intervention services are going to be made for the children with epilepsy and cerebral palsy.

Keywords: Epilepsy, Cerebral Palsy, Prognosis.

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Introduction

Cerebral palsy is the most common cause of physical disability in early childhood. Epilepsy is known to have a high association with cerebral palsy. All types of epileptic seizures can be seen in patients with cerebral palsy. Complex partial and secondary generalized ones are the most frequent seizure types.[1]

Cerebral Palsy is a diagnostic term used to describe a group of permanent disorders of movement and posture causing activity limitation that are attributed to nonprogressive disturbances in the developing fetal and infant brain. The

motor disorders are often accompanied by disturbances of sensation, perception, cognition, communication and behavior as well as by epilepsy and secondary musculoskeletal problem.[2]

Cerebral palsy is one of the common childhood neurological problems which occurs due to defect or lesion in immature brain. Cerebral palsy is not a single disease rather it is a neurodevelopmental condition of children which is not curable and condition that persist for life long. Around 15,000 to 20,000 children are with CP in Canada and 1,50,000 in the United States, that the massive majority of whom are cared for at home by their parents and families.[3] A study in UK showed that prevalence rates differs from 1.5/1000 live births to 3/1000 live births.[4]

Cerebral palsy (CP) is one of the major causes of childhood disability with an estimated global incidence between 2 and 3 per 1000 live births. Although it is estimated that CP is 5 to 10 times more common in underprivileged parts of the world .An estimated prevalence of CP up to 3.7/1000 children in Bangladesh (95 % CI 3.5–3.9) . According to this conservative estimate, there are 260,000 children with CP in Bangladesh.[5]

There are 2 types of classification of cerebral palsy- Physiological and Topograhical. Physiological type include- spastic, dyskinetic, hypotonic, athetoid and mixed. Topogrphical type include- quadriplegia, hemiplegia, diplegia, monoplegia, triplegia.[6] A Scandinavian study reported that 33% of the CP population was hemiplegic, 44% diplegic and 6% quadriplegic.[7] A study in United states in 2002 showed Cerebral Palsy occurred at a rate of 3.6 cases per 1,000 children. Spastic Cerebral Palsy was the most common form, accounting for 76.9 percent of all cases.[8]

The brain abnormality may occur prenatally, perinatally or postnatally.[9] CP is known to be associated with a host of proven etiologic factors–severe perinatal asphyxia, birth trauma, kernicterus, hypoglycaemia, CNS infection like meningitis, encephalitis. The established risk factors- Prematurity, infection, ischaemia, metabolic disorder, thromboembolic disorder, periventricular haemorrhagic infarction etc.[2]

Patients with upper limb dominant hemiperesis tends to have large lesions involving the cerebral cortex and subcortical white matter (e.g. major arterial territory infarcts, porencephaly, polymicrogyria, cortical and subcortical atrophy). Conversely children with leg dominant hemiperesis tend to have smaller lesions involving central and periventricular white matter (e.g. periventricular leucomalcia, small post- haemorrhagic porencephalies.[10]

CP can manifest itself in several ways, mainly spastic, athetoid and ataxic palsies; moreover, it is one of the most common causes of motor disability in children and frequently is associated with other problems, such as mental retardation, sensory defects and epilepsy.[11,12,13]

Epilepsy is a common problem in children with cerebral palsy. In general population only 7.3 per thousand children suffer from epilepsy while 20%-50% patients of cerebral palsy have epilepsy.[14] Epilepsy is considered to be present when 2 or more unprovoked seizure occur in a time frame of longer than 24 hr.[2]

It has been observed that epilepsies associated with cerebral palsy tend to have an earlier onset, necessitating the use of more than 1 antiepileptic drug (AED) with the high risk of seizure relapse after AED discontinuation.[13,14]

The present study aimed to describe the characteristics and prognosis of epilepsy in a population of patients with cerebral palsy.

Method

This observational cross-sectional study was performed in the Department of Pediatrics, Combined Military Hospital, Dhaka, during the period of 6 months .After meeting the inclusion and exclusion criteria a purposive sampling technique was applied for selection of 55 patients. Findings were explored in tables and graphs. Data were analyzed through standard statistical methods by using SPSS software, version 22.0.

Result

This present hospital based cross-sectional observational study in 55 epileptic children with cerebral palsy who had completed at least three years follow up after onset of treatment with antiepileptic drug both male and female in the Department of Paediatrics neurology unit, Combined Military Hospital, Dhaka in a period of six month, different observations are shown as below –

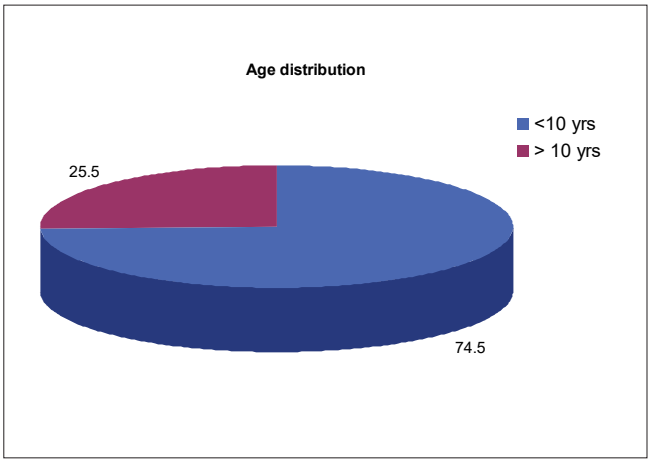

Fig. 3.1: Pie diagram showing age distribution of the study samples . Among the children 74.5% were aged below 10 years and 25.5% were aged above 10 years.

Table-3.1: Distribution of the children by sex (n=55)

Sex	Frequency	Percent
Male	29	52.7
Female	26	47.3
Total	55	100.0

Table-3.1 showed the sex distribution of the study respondents. Among the children 52.7% were male and 47.3% were female. Male : Female ratio 1.1:1

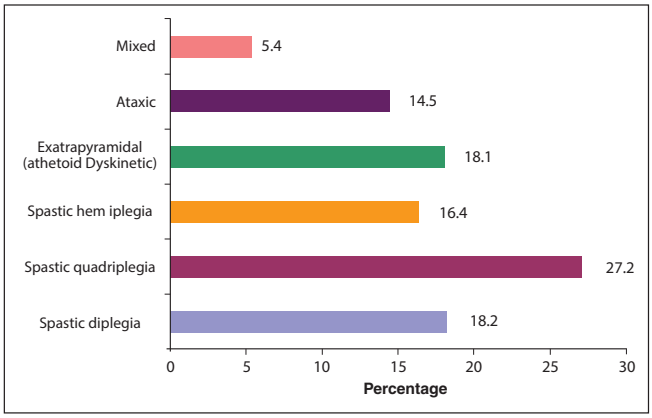

Fig. 3.2: Bar diagram showing the clinical type of CP.18.2% were spastic diplegic, 27.2% were spastic quadriplegic, 16.4% were spastic hemiplegic, 18.1% were extrapyramidal, 14.5% were ataxic and 5.4% mixed variety.

Table 3.3: Distribution of the study patients by epileptic seizure (n=55)

Types of epileptic seizure	Frequency	Percentage
Simple partial	8	14.5
Complex partial	8	14.5
Focal myoclonic	4	7.3
Partial seizure with secondary generalization	2	3.6
Generalized tonic-clonic	12	21.8
Generalized tonic	7	12.7
Generalized myoclonic	2	3.6
Atonic	4	7.3
Absence	3	5.4
Infantile spasm	3	5.4
Mixed	2	3.6
Total	55	100.0

Table-3.3 showed the types of epileptic seizure of the study patients. Among them atonic seizure were observed 7.3%, simple partial 14.5%, complex partial 14.5%, generalized tonic 12.7%, generalized tonic-clonic 21.8%, focal myoclonic 7.3%, absence 5.4%.

Table-3.4: Classification of epilepsies and epileptic syndromes of the studied children (according to ILAE, 1989)

Classification of epilepsies and epileptic syndromes	Frequency	Percentage
Idiopathic localization-related	9	16.4
Symptomatic localization-related	10	18.2
Probable symptomatic localization-related	4	7.3
Idiopathic generalized	9	16.4
Symptomatic generalized	16	29.1
Probably symptomatic generalized	2	3.6
West syndrome	2	3.6
Juvenile myocloclonic	1	1.8
Absence seizure	2	3.6
Total	55	100.0

Table-3.4 showed classification of epilepsies and epileptic syndromes, among patients symptomatic generalized 29.1%, idiopathic localization 16.4%, symptomatic localization related 18.2%, idiopathic generalized 16.4%, probable symptomatic localization related 7.3%.

Table-3.5: Distribution of the study patients by associated problems/disabilities (n=55)

Associated problems	Frequency	Percentage
Intellectual deficiency	18	32.7
Speech delay	8	14.5
Visual impairment	3	5.4
Hearing impairment	2	3.6
Behavioral disturbances	10	18.2
Inability to walk	9	16.4
No problem	5	9.1
Total	55	100.0

Table-3.5 showed the associated problems of the epileptic children with cerebral palsy, 32.7% children had intellectual deficiency, 18.2% had behavioral disturbances, 14.5% had speech delay, 16.4% had inability to walk, 3.6% children had hearing impairment, 5.4% had visual impairment, 9.1% children had no associated problem.

Table-3.6: Distribution of the study patients by associated prenatal causes /risk factors (n=55)

Prenatal causes/ risk factors	Frequency	Percentage
Maternal illness (Hypertension)	2	3.6
Pre-eclmapsia	5	9.1
Convulsion	3	5.5
Fever	4	7.3
Rash	3	5.5
Profuse bleeding due to incomplete abortion	1	1.8
No problem	37	67.3
Total	55	100.0

Table-3.6 showed the associated prenatal causes of the epileptic children with cerebral palsy, 3.6% patients had maternal illness (Hypertension), 9.1% patients had maternal history of preeclmapsia, 5.5% patients had convulsion and 7.3% patients had history of maternal fever. 67.3% patients had no prenatal causes.

Table-3.7: Distribution of the study patients by associated perinatal causes /risk factors (n=55)

Perinatal causes/ risk factors	Frequency	Percentage
Antepartum haemorrhage	2	3.6
Instrumental delivery	2	3.6
Preterm	3	5.5
Delayed cry	10	18.2
Birth trauma	7	12.7
Severe neonatal jaundice	4	7.3
Exchange transfusion needed	2	3.6
Neonatal seizure	5	9.1

Perinatal causes/ risk factors	Frequency	Percentage
Neonatal sepsis	2	3.6
No perinatal cause	18	32.7
Total	55	100.0

Table-3.7 showed the associated perinatal causes of the epileptic children with cerebral palsy, delayed cry were observed in 18.2% patients, 5.5% children were preterm, 12.7% had birth trauma, 9.1% children had neonatal seizure, 7.3% had severe neonatal jaundice. 32.7% patients had no history of perinatal problem.

Table-3.8: Distribution of the study patients by postnatal or early childhood causes or risk factors (n=55)

Postnatal causes/ risk factors	Frequency	Percentage
Meningoencephalitis	3	5.5
Head injury	1	1.8
None	51	92.7
Total	55	100.0

Table-3.8 showed the associated postnatal causes of the epileptic children with cerebral palsy, 5.5% children had meningoencephalitis and 1.8% had head injury.

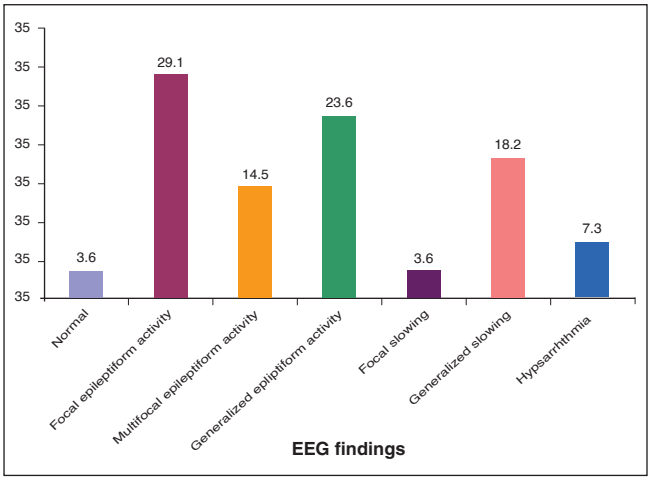

Fig. 3.3: Bar diagram showing the EEG findings of CP patients. Regarding EEG findings of the epileptic children, focal epileptiform activity was the common EEG findings observed in 29.1%, multifocal epileptiform activity in 14.5%, generalized slowing in 18.2% and Generalized epliptiform activity in 23.6%.

Table-3.9: Distribution of the study children by neuroimaging findings (n=55)

Neuroimaging findings	Frequency	Percentage
Normal	7	12.7
Bilateral central atrophy	6	10.9
Bilateral cortical atrophy	7	12.7
Generalized atrophy	20	36.4
Hemiatrophy	5	9.1
Periventricular leukomalacia	8	14.5
Subdural haematoma	1	1.8
Cerebellar atrophy	1	1.8
Total	55	100.0

Regarding neuroimaging findings of the epileptic children, Bilateral central atrophy were observed in 10.9%, Bilateral cortical atrophy in 12.7%, Generalized atrophy in 36.4%, Hemiatrophy in 9.1% and Periventricular leukomalacia in 14.5%.

Table-3.10: Distribution of the study children by conventional antiepileptic drug (AED) (n=55)

Conventional antiepileptic drug	Frequency	Percentage
Carbamazepine	4	7.3
Sodium valproate	22	40.0
Phenobarbitone	9	16.4
Clonazepam	6	10.9
ACTH	1	1.8
Nitrazepam	2	3.6
No antiepileptic drug	11	20.0
Total	55	100.0

Table-3.10 showed the conventional antiepileptic drugs uses, maximum patients take sodium valproate 40.0%, phenobarbitone 16.4%, clonazepam 10.9%, carbamazepine 7.3%.

Table-3.11: Distribution of the study children by new antiepileptic drug (AED) (n=55)

New antiepileptic drug	Frequency	Percentage
Cloabazam	5	9.09
Oxcarbamazepine	10	18.2
Levetiracetum	7	12.7
Topiramite	3	5.4
Gabapentine	2	3.6

Table-3.11 showed the new antiepileptic drugs uses, maximum patients take oxcarbamazepine 18.2%, levetiracetum 12.7%, clobazam 9.09%.

Table-3.12: Distribution of the study children by response to treatment (n=55)

Treatment	Frequency	Percentage
Response to monotherapy	15	27.3
Response to polytherapy	40	72.7

Table-3.12 showed that 27.3% patients responded with treatment with monotherapy, 72.7% patients were responded with treatment with polytherapy.

Table-3.13: Relapse rate after discontinuation of AED in studied children (n=55)

Relapse rate	Frequency	Percentage
No withdrawal of AED	41	74.5
Relapse within 1-6 month AED withdrawal	7	12.7

Relapse rate	Frequency	Percentage
Relapse within 7-12 month of AED withdrawal	4	7.3
No relapse within 1 year of AED withdrawal	3	5.5
Total	55	100.0

Table-3.13 showed that 74.5% patients were continuing AED, no withdrawal of AED was possible due to absence of seizure free period for at least 2 years which was prerequisite for discontinuation of AED. In 12.7% patients seizure relapsed within 1-6 months of AED withdrawal. Among relapsed cases, seizure relapsed in 7.3% patients within 7-12 months of AED withdrawal and no relapse was found within 1 year of AED withdrawal in 5.5% patients.

Discussion

The study was a cross-sectional study based on 55 children having clinical evidence of cerebral palsy after meeting inclusion and exclusion criteria, in the Department of Peadiatrics, neurology unit, Combined Military Hospital, Dhaka and got follow up for at least 3 years.

In current study age group distribution of the children, 74.5% were age group below 10 years and 25.5% were age group above 10 years. Minimum age 2 years and maximum 15 years. Mean age of the children was 7.09±3.05 years. Among the study subjects, 52.7% were male and 47.3% were female. Male : Female ratio 1.1:1. The first 10 years of life has been reported as the period with the highest incidence. Individuals suffering epileptic attacks in childhood and adolescence may therefore typically be exposed to severe educational complications.[74]

Epilepsy has been reported in some studies as slightly more common in males than in females. For example, Wong determined a M/F ratio of 1.22:1, while Karabiber determined a ratio of 1.42:1 in a study of children aged 1-12 in Malatya, Turkey.75,76 In contrast, Sidenvall reported M/F ratio of 0.91, similar to that in our study.[77]

The most common types are the spastic types worldwide. Similarly, most of our patients (61.8%) were spastic CP. Among the children with cerebral palsy, 18.2% were spastic diplegic, 27.2% were spastic quadriplegic, 16.4% were spastic hemiplegic, 18.1% were extrapyramidal, 14.5% were ataxic and 5.4% mixed variety. However, the distribution of the clinical subtypes of spastic CP in our study differed from the results of western countries. Das et al reported spastic Cerebral Palsy (80%) was the largest group followed by mixed CP(8%), atonic CP were seen in 7.0% cases and athetosis constituted 5.0% of the total cases.85 Gowda et al had reported1 6% cases of spastic diplegia and 71.6% cases of spastic quadriplegia.86 In European countries, studies reported 18% -20.8% cases of spastic quadriplegia and 40.9% - 54.9% cases of spastic diplegia which is in contrast to our studies. The probable explanations of this finding may be the decreased perinatal mortality of premature babies as a result of more available and equipped newborn intensive care units in western countries. [87,88]

In current study, among the children with cerebral palsy, 18.2% were spastic diplegic, 27.2% were spastic quadriplegic, 16.3% were spastic hemiplegic, 18.1% were extrapyramidal, 14.5% were ataxic and 5.4% mixed variety. In various study the incidence of spastic type of CP varied from 40-89% which is similar to our study.[70,71]

In this present study intellectual deficiency was 32.7% in epilepsy with CP patients. Anil Kaushik reported intellectual deficiency 85% in epilepsy with CP patients.[78] In the present study speech delay was 14.5% in the patients with epilepsy. Rahman M M found speech delay in 58% patients with epilepsy.[79] These differences are may be due to early diagnosis and early intervention in our study group which decreased comorbidities.

In the present study as far as risk factors of epilepsy with CP, 67.3% was perinatal, 32.7% prenatal and 7.3% postnatal. Bruck I found that among risk factors of CP, 37% were perinatal, 41% prenatal, 10% postnatal and in 12% cases no risk factors was determined.[80]

In the present study history of delayed cry considered here as perinatal asphyxia was more common 18.2% patients with CP, 12.7% had birth trauma, 5.5% children was preterm, 9.1% children had neonatal seizure, 32.7% patients had no history of perinatal problem. A study showed that among the cerebral palsy children there were seizure in 31.8%, vision defect in 19.8%, speech defect in 29.5%, hearing defect in 6.7% and learning disability in 25.4% children. Spastic CP is the most common type of CP and involvement of four limbs is rapid. Children with CP have delay on independent sitting, standing, crawling and walking or can never achieve these abilities in their life span.81 Presence of neonatal seizure was the predominant risk factor for subsequent epilepsy in CP (48.4%) patients of the study of Bruck I.[80]

This similarity in some figure and dissimilarity in other figure were probably related to sample size because Bruck et al. studied in 100 children of epilepsy with CP. But sample size of epilepsy with CP for the present study was only 55. It may be explained by another way which is in developing countries like Bangladesh perinatal asphyxia is more common due to poor newborn care in rural areas.

The present study showed the associated postnatal causes of the epileptic children with cerebral palsy, 5.5% children had meningoencephalitis and 1.8% had head injury. In a study of Tabib SSB stated only 2.8% of the cases had history of head injury and 2.7% cases with meningitis contributing to cerebral palsy.[28]

Birth trauma, head trauma, infection, central nervous system (CNS) infection and febrile convulsions head the list of the preventable causes of epilepsy and increase the incidence of epilepsy in developing countries.[82] Olaffson E determined a history of head trauma in 4% of epileptic patients and Çalışır in 7.6%. Calisir observed epileptic attacks in 12.5% of people with head trauma.[83,84] There was a history of head trauma in 1.8% of our cases.

In the present study among CP children, types of epilepsies are symptomatic generalized 29.1%, idiopathic localization 16.4%, symptomatic localization related 18.2%, idiopathic generalized 16.4%, probable symptomatic localization

related 7.3%. Zafeiriou DI found symptomatic localization-related epilepsies more common (85.4%) followed by symptomatic generalized (14.6%) in the patients with epilepsy and CP than those with epilepsy without CP where symptomatic localization-related epilepsies were 30% and symptomatic generalized epilepsies were 4.7%.[72]

In this present study regarding neuroimaging findings of the epileptic children, bilateral central atrophy were observed in 10.9%, Bilateral cortical atrophy 12.7%, Generalized atrophy 36.4%, Hemiatrophy 9.1% and PVL 14.5%. According to Gururaj et al in children of epilepsy with CP abnormal CT/MRI findings were found in 80.4% cases. Gururaj et al also found brain atrophy significantly more common in children with epilepsy and CP.[73]

The current study in children with CP, 45.5% patients were treated with monotherapy, 54.5% patients were treated with polytherapy. 60% patients responded to treatment with monotherapy, 83.3% patients were responded to treatment with polytherapy.

According to Aksu in children of epilepsy with CP 72.6% patients needed monotherapy, 70.0% needed polytherapy of the children with CP. which also almost correlated with the figure of the present study.[53]

In the present study, 74.5% patients were continuing AED, no withdrawal of AED was possible due to absence of seizure free period for at least 2 years which was prerequisite for discontinuation of AED. Among relapsed cases, 12.7% patients developed relapse of seizure within 1-6 months AED withdrawal, seizure relapsed in 7.3% patients within 7-12 months of AED withdrawal and no relapse was found within 1 year of AED withdrawal in 5.5% patients. In the study of Aksu 86% patients with epilepsy there was no withdrawal of AED and among the patients of drug withdrawal seizure relapsed in 62.5% patients.[53] This slight variation of figure with that of the present study would be probably due to variation of sample size.

Conclusion

Symptomatic generalized epilepsies were significantly more common in the children with epilepsy and CP. There is a higher association of perinatal asphyxia with the children with epilepsy and CP. Abnormal neuroimaging was predominant in cases with epilepsy and needed more use of polytherapy. Refractory to treatment and relapse rate of epilepsies were high in the children with epilepsy and CP.

Recommendation

A multidisciplinary team is needed for the comprehensive care of children with CP with epilepsy specially when all of them are severe. Managing epilepsy in children with CP should follow general principles of treating epilepsy with special attention on possible side effects of antiepileptic drugs (AEDs) or others drugs used for relieving symptoms or comorbidities. Further studies looking in to possible genetic and early prenatal factors may lead to better understanding of the cause of epilepsy in CP.

Limitations

This is a cross-sectional observational study in a short duration of period and small sample size which may not represent the real scenario of epilepsy with CP patient

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Original Article

Knowledge, Skills and Attitude of Mothers Attending the Lactation Management Center (LMC)

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ABSTRACT

Introduction: Proper infant feeding is crucial for child nutrition, survival and development. Breast milk is the gold standard for infant feeding. There are three determinants of good health, nutrition and child survival. These are food security, care and disease control. Breast feeding is an excellent example of all these three things in one.

Objective: To assess knowledge, skills and attitude of mothers attending the lactation management center.

Method: A semi-structured data sheet was used to collect data from mothers attending the lactation Management Centre (LMC) of IMCH. 100 lactating mother were included in this study over period of 6 (six) months from 1st June 2009 to 1st December 2009. Data from the respondents was collected by the researcher herself by physical examination and face to face interview using a semi-structured data sheet.

Result: Thirty two percentages of respondents belonged to `20 years' age group and 50% of them were primipara. The average age of the babies was about 5.4 months and their weight ranged from 890 grams to 13.75 kg. 27% of the respondents were literate; 93.0% of the female were house wives and 61.0% of the cases belonged to `poor' socio-economic status. 24.0% cases delivered their last baby at hospital and 87.0% respondents had vaginal delivery. All the mother`s (75), who were not exclusively breast feeding, gave extra food to their baby. About one-fifth of the respondents were suffering from various complications (PET 5, Eclampsia 5, GDM 8 and other diseases 5) during last pregnancy. 63% of the respondents learned their knowledge on breast feeding from their mother. All the women (63%), who took medications during last pregnancy, used to take both Iron and Calcium. Most of the cases correctly kept the baby`s `body, close to mother' (86.0%) and facing breast, nose opposite the nipple (84.0%). But negative remarks were for `straight head and body' (84.0%) and `the whole body fully supported' (85.0%); `Lower lip turned outward' (14.0%) and `More areola above than below the mouth' (15.0%). 88.0% of the respondents did not know how to effectively express the breast with `C position'. Emotional satisfaction' was the most (26.0%) expressed attitude. Only 20.0% respondents had some sort of infection involved in the breast. Most of the respondents did not have adequate `knowledge' (9.0%). All the respondents received advice on breast feeding. Only the patients (20) with infection received antibiotics for their treatment, remaining was treated symptomatically.

Conclusion: In general women of Bangladesh are used to breast feed their babies. Education of the pregnant women during ANC about barest feeding improve their knowledge and skill.

Keywords: Attitude, Lactation management center.

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Introduction

The human species is the only one among mammals in which breast feeding in not governed only by instinct. Therefore, breastfeeding have to be learned. Currently, especially in modern societies, women have few opportunities to learn something about breastfeeding because their traditional sources of learning from more experienced women in the family-were lost as extended families were replaced by nuclear families. Consequently, inexperienced women become mothers with little or no knowledge about the proper technique to breastfeed, which makes them more vulnerable to difficulties faced during the process. Breast feeding is convenient, safe, economical and emotionally satisfying to most women. Breast feeding has advantages not only for baby but also for the mother and society. A mother`s milk is especially suited for her own baby. The composition of all breast milk is no alike. Colostrum, preterm milk and mature milk changes from month to month, day to day and feed to

feed to meet each particulars baby`s needs. So breast feeding should start as soon as possible. Exclusive breast feeding for six months and babies should continue to breast feed for up to two years or beyond with increase of complimentary food and cup feed liquids. Breast milk provides not only nutrients for physical growth but also both immune and nonimmune elements for protection against disease and an opportunity for interaction between new born and mother which may, at least in higher species of mammals, initiate the learning process necessary to the transition to independent living. One hundred million infants are born in the developing countries each year, ten million of which die before their first birthday, five million of this succumbs to diarrhea and dehydration, and one million of the infant deaths have been attributed directly to contaminated infant formula.

Common problems related to breastfeeding including breast enlargement, painful nipple, nipple infection, mastitis, breast abscess, poor milk production. Incorrect techniques, infrequent breastfeeding and breastfeeding on scheduled times, pacifiers and extra food from outside are important risk factors that can predispose to lactation problems. The adequate management of these conditions are fundamental, and if not treated lead to early weaning. To encourage the exclusive breast feeding and to yield maximum breast milk during these period health professionals can play important role to overcoming such difficulties, but for that they need specific knowledge, attitude and skills.

Method

This observational study was carried out in the COVID-19 dedicated hospital of Faridpur (situated in Faridpur Medical College Hospital, Faridpur) from April 2020 to September 2020 for a period of 06 month. All clinically suspected patients confirmed by RT PCR were included as cases and those who were not confirmed, excluded from this study. Cases were selected irrespective of age and sex on a random basis. Patients admitted in corona ward were selected for symptom analysis, comorbidities and hospital outcome whereas patients admitted in ICU were excluded from symptom analysis. Data were collected by detailed history from patients or their relatives followed by thorough physical examination as well as diagnostic evaluation; then those were checked, verified for consistency and edited for result. After editing and coding, the coded data were analyzed by using the SPSS software package.

Result

A total of 627 patients were included in the study of which 552 were treated in Covid ward and 75 patients were treated in ICU. Among Covid ward admitted (552) patients 354 (64.13%) were male and 198 (35.86%) were female with a male to female ratio of 1:0.56;young adult patients (19 to 50 years) were more affected and admitted (62.86%) and people living in urban area were more affected (52.71%) than rural area (47.28%) (Table I).

Table I: Distribution of patients according to age, sex and residence (n= 552)

Demographics		Frequency (%)
Age group	<19 years	24 (4.3)
	19-50 years	347 (62.86)
	>50 years	181 (32.78)
Sex	Male	354 (64.13)
	Female	198 (35.86)
Residence	Urban	291 (52.71)
	Rural	261 (47.28)

Fever, cough and shortness of breath (63.04%, 45.47% and 42.39% respectively) were predominant symptoms followed by asymptomatic and other symptoms like sore throat, headache , generalized body ache and other non -respiratory problems. (Table II)

Table II: Distribution of patients according to presentation (n=552)

Symptoms	Frequency (%)
Fever	348 (63.04)
Cough	251 (45.47)
SOB	234 (42.39)
Sore throat	24 (4.34)
Headache	16 (2.8)
Generalized bodyache	13 (2.3)
Asymptomatic	46 (8.33)
Others	14 (2.3)

Regarding comorbidities, 44.20% patients have one or more comorbidities whereas 55.79% patients have no comorbidity. Hypertension (17.57%) was the predominant comorbid condition followed by diabetes (15.94%), ischemic heart disease (05.61%), COAD (05.61%), CKD (2.3%), Stroke (1.44%), Heart failure (0.54%) and Cancer (0.36%) (Table III).

Table III: Distribution of patients according to comorbidities (n=552)

Comorbidities	Frequency (%)
Hypertension (HTN)	97 (17.57)
Diabetes Mellitus (DM)	88 (15.94)
Ischemic Heart Disease(IHD)	31 (5.61)
Heart failure (HF)	03 (0.54)
Chronic Obstructive Airway Diseases (COAD)	31 (5.61)
Chronic kidney disease (CKD)	13 (2.3)
Cerebrovascular disease (CVD)	08 (1.44)
Cancer	02 (0.36)

Regarding hospital outcome, 96.8% covid ward patients and 45.34% of ICU admitted patients discharged uneventfully whereas 03.26% covid ward patients and 54.66%of ICU

admitted patients expired. Deaths were more in elderly patients (n=43; 72.88%). Common comorbidities found among the patients who expired were Hypertension, Diabetes and Ischemic heart diseases (42.37%, 37.28% and 16.94% respectively). A total of 75 patients needed ICU support that was 11.96% of total cases; most of them were elderly patients (64 out of 75 i.e. 85.33%). Out of total mortality, death rate was much more higher in ICU than in COVID ward (69.49% vs 30.50%).The male to female ratio of ICU death was 3.2:1.The mortality rate in ICU was higher in those with one or more comorbid conditions; the predominant comorbidities were hypertension (42.37%) and diabetes (37.28%) followed by IHD, COAD, CKD and CVD. No comorbidity was found in 27.11% of ICU death (Table IV, V, V I).

Table IV: Distribution of Patients according to ICU Treatment and Outcome

Age Group of ICU Treated Patients (n=75, 11.96%)		<51 year	11 (14.66%)
		>51 year	64 (85.33%)
Outcome (n=627)	Recovery (n=568)	Covid Ward	534 (96.74%)
		ICU	34 (45.34 %)
	Death in Total cases (n=627)	Covid Ward	18 (3.26%)
		ICU	41 (54.66%)
	Comparison of death (n=59)	Covid Ward	18 (30.50%)
		ICU	41(69.49%)

Table V: Distribution of mortality according to age, sex and comorbidities (n=59)

		Frequency (%)
Age group	<19 years	02 (3.38)
	19-50 years	14 (23.72)
	>50 years	43 (72.88)
Sex	Male	45 (76.27)
	Female	14 (23.72)
Comorbidities	Comorbidity present	43 (72.88)
	Comorbidity absent	16 (27.12)

Table VI: Distribution of mortality according to pattern of comorbidities (n=59)

Co morbidity in dead patients	Comorbidities	Frequency (%)
Present (n=43)	HTN	25 (42.37)
	DM	22 (37.28)
	IHD	10 (16.94)
	COAD	07 (11.86)
	CKD	04 (6.77)
	CVD	04 (6.77)
	Others	04 (6.77)
Absent (n=16)		16 (27.11)

Discussion

In this study a total of 627 patients were included (552 from Covid ward and 75 from ICU) and demographic, clinical presentation as well as pertinent data regarding impact of comorbidities on COVID-19 disease outcome were collected.

In our study, adult patients especially the economically productive age group i.e.19-50 were mostly affected (62.86%) followed by elderly population (32.78%). The percentage of under 19 with confirmed COVID-19 cases is far lower (4.3%) than the standard population percentage. These findings were closely related to a review done by Dominic Cortis, where three studies were included. Two studies were from China by Zhang and Guan et al. and another one from South Korea by Korea Centers for Disease Control and Prevention. Those studies showed that the percentage of youths with confirmed COVID-19 cases is far lower than the standard population percentage. The proportion of COVID-19 confirmed cases for youths (age group 0-14 year:) is lower in China (1.55%, 0.89%) than South Korea (4.04%).The predominant population affected in all three studies were 15-64year groups (76.93%, 83.98% in China and 78.60% in S.Korea) followed by elderly population (21.53%,15.13% in China and 17.36% in S.Korea).10 A study conducted in China showed the age distribution for all patients where 61.5% were aged <60 years and the other cases were aged ≥60 years; this is consistent with our studies (67.16% in below 50 group vs 32.78% in above 50 group).[11] A study conducted in India showed that 21–50 age group, contributes to the maximum proportion (60%) of the total cases followed by those below 20 years of age constituting nearly 13% of the cases.[12] There is a deviation of this study to ours as well as to China and South Korean studies in respect of younger peoples' Covid-19 positivity.

Regarding sex distribution, in a study that included a total of 5700 patients admitted into 12 different hospitals of USA found 39.7% female and 60.3% male as Covid 19 positive.[13] In another study conducted in India males contribute to 66% of the total positive cases.[12] In a study in India, it is observed that women are half as likely to be infected by COVID-19 as men.[14] These above-mentioned results almost matches with our study result (male 64.13% and female 35.86%).

In our study we found, urban population affected more (52.71%) than rural population (47.28%). There may be some explanations linking urban areas and coronavirus, emphasizing densities; connectivity; crowded living conditions; and exposed occupations.

Regarding presentation, in this study, most of the patients presented with fever (63.04%) , cough (45.47%) and shortness of breath (42.39%).The less predominant symptoms were sore throat (4.34%), headache (2.8%) followed by with chest pain, abdominal pain, diarrhea, vomiting, bleeding manifestation and psychosis in a minor of patients. There were 8.33% of asymptomatic patients. In a meta-analysis that included seven articles published from 24th Jan to 16th March, 2020 revealed that fever was the predominant symptom (88.8%) followed by dry Cough(68%) fatigue (33%), productive cough (28.5%), muscle pains (14.4%),diarrhea (4.4%) ,nausea or vomiting (4.1%),

rhinorrhea(3.2%), chest and abdominal pain(0.15%).[15] Similarly, a study in a hospital of Wuhan, China found fever (98%),cough (76%), dyspnoea (55%),myalgia or fatigue (44%),sputum production (28%), headache (8%), haemoptysis (5%), and diarrhoea (3%) as common symptoms.[16] In another meta-analysis, found similar result, where most prevalent clinical symptom was fever (91.3%), followed by cough (67.7%), fatigue (51.0%) and dyspnea (30.4%).[17] These above-mentioned studies closely matched with the result of our study.

Considering comorbidity, 44.24% patients had one or more comorbidities and 55.79% presented in isolation. Common comorbid conditions found were as follows: HTN (17.57%), DM(15.94%), IHD(5.61%), COAD(5.61%) followed by CKD (2.3%), CVD(1.44%), Heart failure(0.54%) and Cancer(0.36%).

In a meta-analysis, as mentioned above revealed hypertension (15.8%) as the most common comorbidity followed by other cardiovascular and cerebrovascular conditions (11.7%) , endocrine disorder primarily diabetes (9.4%), co-existing infection like HIV and Hepatitis B (1.5%),malignancy (1.5%),respiratory system disorder ,e.g. COPD and others (1.4%),renal disorders (0.8%) and immunodeficiency states(0.01%).[15] Almost similar results were found in another retrospective, multicenter cohort study , where 48% patients had comorbidities, with hypertension being the most common (30%), followed by diabetes (19%) and coronary heart disease (8%).[18] In a population-based surveillance for laboratory-confirmed COVID-19–associated hospitalizations in the United States, among 1,482 patients,12% adult patients had one or more underlying conditions; the most common were hypertension (49.7%), obesity (48.3%), chronic lung disease (34.6%), diabetes mellitus (28.3%), and cardiovascular disease (27.8%).[19]

The results of first two studies closely resemble with our study (Hypertension, Coronary artery disease and Diabetes as predominant comorbidities), but the third one revealed obesity as an important comorbidity which was not included in our study.

In our study, 96.8% covid ward patients and 45.34% of ICU admitted patients discharged uneventfully whereas 03.2% covid ward patients and 54.66%of ICU admitted patients expired. These matches with the following two studies.

Approximately 10% of the global population may have been infected by October 2020, with an estimated overall IFR of 0.15% to 0.2% (0.03% to 0.04% in those <70 years of age).20 In another study, roughly 80% of COVID-19-positive cases result in full recovery from the illness without any hospitalizations or interventions.[5]

In our study, death were more in elderly patients (n=43; 72.88%).A total of 75 patients needed ICU support that was 11.96% of total cases; most of them were elderly patients (64 out of 75 i.e. 85.33%).Out of total mortality, death rate was much more higher in ICU than in COVID ward (69.49% vs 30.50%).These results are coherent with the studies done in other centers.

COVID-19 can cause severe disease leading to hospitalization in ICU and potentially death, especially in the elderly with comorbidities. According to the CDC, 8 out of 10 deaths reported in the USA occurred in adults 65 years old and above.[5] According to a report by CDC, data from China have indicated that older adults, particularly those with serious underlying health conditions, are at higher risk for severe COVID-19-associated illness and death than are younger persons. In the same report, COVID-19 cases in the United States, Overall, 31% of cases, 45% of hospitalizations, 53% of ICU admissions, and 80% of deaths associated with COVID-19 were among adults aged ≥65 years with the highest percentage of severe outcomes among persons aged ≥85 years.[21] People <65 years of age have a very small risk of death even in pandemic epicenters, and deaths in people <65 years of age without any underlying conditions is rare.[22] In our study, the mortality rate in ICU was higher in those with one or more comorbid conditions; the predominant comorbidities were hypertension (42.37%) and diabetes (37.28%) followed by IHD,COAD,CKD and CVD. No comorbidity was found in 27.11% of death. In Italy only 12% of death certificates reported direct causality from COVID-19, while 88% of patients who died had at least one comorbidity.[23,24] In New York state, just over 86% of reported COVID-19 deaths involved at least one comorbidity, according to the state's department of health. The leading comorbidity, seen in 55.4% of all deaths, was hypertension. the rest of the 10 most common comorbidities in COVID-19 fatalities were diabetes (37.3%), hyperlipidemia (18.5%), coronary artery disease (12.4%), renal disease (11.0%), dementia (9.1%), chronic obstructive pulmonary disease (8.3%), cancer (8.1%), atrial fibrillation (7.1%), and heart failure (7.1%).[25]

In our study, HTN, DM and COAD patients shows more mortality rates than New York City study. Hyperlipidemia and Dementia were not included in ours.

Conclusion

The coronavirus disease 2019 (COVID-19) has rapidly spread to become a worldwide emergency. Most of the patients presented with fever, cough and respiratory distress in our setting. The elderly patients and those with one or more comorbid conditions reflected poor outcomes. The study highlights the importance of early identification of patients at risk of progression for optimized utilization of medical resource. There are still many facts to be elucidated ,reflecting our uncertainty regarding this disease.

Limitations

The first limitation of this study is the relatively small number of patients included; vast majority of the patients were either treated outside the hospital or were asymptomatic. Secondly, all possible comorbidities were not included in the study.

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Original Article

Seven-years Analyses of Radiotherapy Outpatient Data of CMCH: A Changing Landscape of Cancer.

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ABSTRACT

Background: Globally the cancer landscape is continually evolving owing to changing risk factor patterns and disease classifications, improvements in detection and treatment, and demographic changes, such as ageing and population growth. Monitoring the changes is a key tool for assessing progress, identifying emerging trends and setting priorities to reduce the burden. In this Perspective, we describe trends for major cancer types, and demographic characteristics of the patients attending in a radiotherapy outpatient department of a public tertiary care hospital of Bangladesh.

Method: In this retrospective record review study data of the new cancer patients attending the radiotherapy OPD of Chittagong Medical College Hospital during 2014 to 2020 were extracted from the register. Data included age, sex, residential location and cancer type were extracted. Seven year trendsof demographic and cancer type were analyzed.

Result: The total number of new cancer patients registered was 36189. Total patients ranged from4508 to 5788 per year without any significant upward or downward trends. Regarding age there was a steady increase of the proportion of younger (<50 years) patients with 31% in the year 2014 and 45% in the year 2020. Males were more in all year and proportion of rural patients were the highest in 2020 (38%). There was a steady and gradual decrease in the proportion of lung cancer from2014 to 2020 in male with upward trends in cancer of head and neck region, and cancer of upper GIT. Breast carcinoma was the top most cancer in female followed by carcinoma cervix. There was gradual decline of head and neck cancer and lung cancer in female during this time period.

Conclusion: The study represents a hospital based data regarding trends of cancer over a period. However, establishment of a regional cancer registry system in order to allow the monitoring of cancer trendsand effectively plan cancer control is time needed. Younger population with cancer have upward trend. Proportion of lung cancer is decreasing but cancer of head and neck and upper GIT are increasing in male.Breast cancer is increasing among female.

Keywords: Cancer, Trends, Bangladesh.

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Introduction

Cancer ranks as a leading cause of death and an important barrier to increasing life expectancy in every country of the world. Worldwide, an estimated 19.3 million new cancer cases and almost 10.0 million cancer deaths occurred in 2020. Female breast cancer has surpassed lung cancer as the most commonly diagnosed cancer, with an estimated 2.3 million new cases (11.7%), followed by lung (11.4%), colorectal (10.0 %), prostate (7.3%), and stomach (5.6%) cancers.[1]

The epidemiology of cancer is continually evolving owing to changes in risk factor patterns and disease classification, improvements in detection and treatment, and demographic changes including ageing, population growth and immigration.[2,3] The magnitude and directions of changes in cancer incidence and death rates, however, vary substantially by cancer type, sex, race/ethnicity, socioeconomic status and geographical region. For example, while age- standardized incidences

and death rates are declining for most smoking-related cancers, they are increasing for some obesity-related cancers.[3,4] Furthermore, the total number of cancer cases and deaths recorded each year continues to increase owing to both ageing and population growth, even for many cancers with declining age-standardized incidences and death rates.[4,5] Cancer surveillance in a defined population and geographical area is crucial for measuring the cancer burden and for setting priorities and planning cancer control across the cancer continuum, from prevention to early detection, treatment and survivorship care.

In the absence of population-level surveillance hospital based study could enables preliminary assessments of the effects of interventions and the identification of emerging trends. In this Perspective, we review the changing patterns of cancer occurrence among patients seeking care in radiotherapy OPD of a tertiary care hospital of Bangladesh. We then discuss the implications of these changes for future cancer research, prevention and care priorities.

Method

This retrospective study was conducted in the Chittagong Medical College Hospital, Bangladesh. The Radiotherapy department of this hospital comprises of one inpatient ward and one outpatient day clinic, no changes in administrative routine or structures occurred since 2014. Seven year data was reviewed retrospectively. Data regarding age, sex, residential area and cancer type were retrieved from the register.

The Ethical Review Committee of Chittagong Medical College approved the study protocol. Application of ethical consent form to patients was not considered necessary, since data were collected from the hospital Register. The anonymity of patients and confidentiality of the secondary data is ensured by the researchers and institutions involved in the study. In addition, in this study no individual data is being presented.

Data were tabulated and analyzed using Microsoft Excel for Windows Version 10. Results were presented in appropriate Table and Graphs.

Results

Our study provides single-centre data on a large patient cohort of outpatient and inpatients treatment visits over a time frame of 7 years (2014–2020). The total number of patients registered was 36189. Total patients ranged from 4508 to 5788 per year without any significant upward or downward trends. Regarding age there was a steady increase of the proportion of younger (<50 years) patients with 31% in the year 2014 and 45% in the year 2020. Males were more in all year and proportion of rural patients were the highest in 2020 (38%) (Table 1).

Table 1: Year-wise distribution of demographic characteristics of cancer patients

Year	Total patients	Age group		Sex		Residential location	
		<50 years	>50 years	Male (%)	Female (%)	Rural (%)	Urban (%)
2014	5702	31%	69%	58%	42%	30%	70%
2015	5308	33%	67%	57%	43%	32%	68%
2016	4630	30%	70%	58%	43%	33%	67%
2017	4508	38%	62%	56%	44%	31%	69%
2018	5788	40%	60%	53%	47%	30%	70%
2019	5568	44%	56%	57%	43%	33%	67%
2020	4685	45%	55%	59%	41%	38%	62%

Among different types of cancer, lung cancer predominates in the year 2014 with a proportion of 28%. However, there was a steady and gradual decrease in the proportion of lung cancer from2014 to 2020. In the year it was 12%. On the other hand, cancer of head and neck region shows a steady upward trends in male patients from 2014 to 2020 (11% to 19%) with overall 8% increase. Similar upwards trend was also noticed regarding cancer of upper GIT (Increase from9.2% to 18% in 2020).

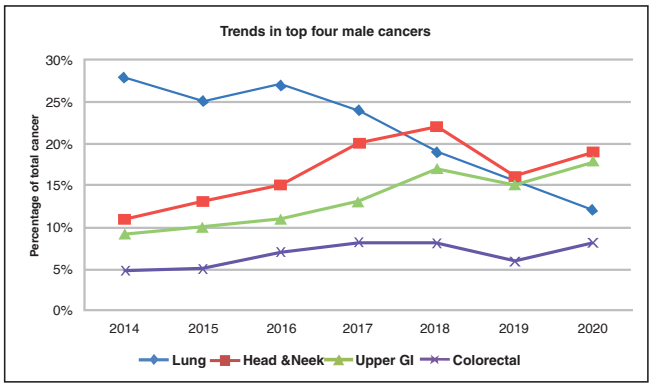

Figure 1: Proportion of top four cancers from2014 to 2020 in male.

Among female carcinoma cervix was the top most cancer in 2014 with a proportion of 24.98% but in theyear 2020 carcinoma breast was the top most cancer (23%). If we consider the trends from 2015 to 2020, Figure 2 shows that, breast carcinoma was the top most cancer in female followed by carcinoma cervix. There was gradual decline of head and neck cancer and lung cancer in female during this time period.

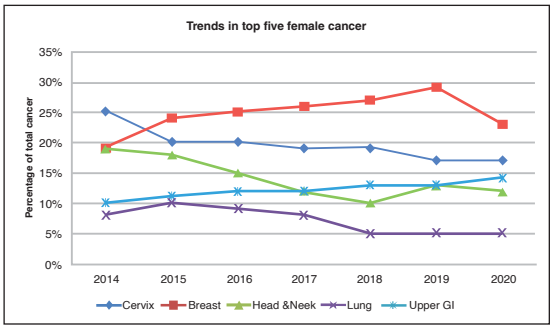

Figure 2: Proportion of top five cancers from2014 to 2020 in female.

Discussion

The no prominent increase in patient numbers is most likely attributed to unchanged characteristics of the study site in terms service provided and manpower. Patients' turn over depends on the service provided and facilities available in a center. During the last seven years there was no major infrastructural and manpower related change in the outdoor and indoor of the Radiotherapy department CMCH. Demographic characteristics of the studied patients demonstrate an alarming trend of increasing. Younger patients with cancer are growing steadily. Similar trends was also noticed in United States decades ago.[6] Probably due to extensive early screening and risk factor modification geriatric cancers are occurring more frequently in early ages.[7]

Another important finding the steady decline of lung cancer among male patients and increase cancer of head and neck region, cancer of upper GIT and colorectal cancer. Over the past three to four decades, industrialized nations have seen large declines in cigarette smoking and, consequently, lung cancer. In contrast, emerging economies and developing countries face many challenges in initiating tobacco cessation campaigns while also addressing environmental risk factors and cultural barriers.[8] A recent study suggests that cases of lung cancer have been on the rise in Bangladesh, with the number of smokers and air pollution levels rising. The report also claimed that from January 2015 to December 2017, a total of 76,543 new patients attended the outpatient department of the National Institute of Cancer Research and Hospital (NICRH).[9] Head and neck cancer (including thyroid lesions) is third most common malignancy seen in both the sexes across the globe but isthe commonest malignancy encountered in Indian males.[10] Bangladesh is advancing fast in the horizon of head, neck and thyroid diseases. Cancer specialties of these regions are becoming much more important as head, neck and thyroid cancer incidences are increasing day by day.[11]

In terms of top five female cancers, there was no significant observable change in the last five years in our study. Carcinoma breast was the top most cancer followed by carcinoma cervix, cancer of upper GI, head and neck cancer and lung cancer. A 2013 study in Bangladesh revealed that, top five leading cancers and the prevalence in last 5 years(2007-2012) in female was breast cancer (32.8%), cervical cancer (26.1%), Lip and oral cavity cancer (6.5%), ovarian cancer (3.2%) and colorectal cancer (2.1%).[12]

Limitations

Single center hospital based study design is the major limitation for the generalizing the results in the community. Retrospective design was another limitation of the study.

Conclusion

Proportion of younger patients with cancer was in upwards trends. In male cancer of head and neck region, upper GIT and colorectal cancer showed upward trend also. In female, breast carcinoma was the top most cancer followed by cancer cervisduring the studied year.

Recommendations

It is necessary to initiate the establishment of a regional cancer registry system in order to allow the monitoring of cancer trends and effectively plan cancer control. In addition, research is needed to elucidate causes for the rising geriatric cancers incidence in young and middle-aged adults.

Disclosure

All the authors declared no competing interest.

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Original Article

Study of Sentinel Lymph Node Biopsy in Patients with Carcinoma Breast with Clinically Non-Palpable Axillary Lymph Nodes

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ABSTRACT

Background: Carcinoma breast is the most common cancer of adult females and is the leading cause of death among cancer patients with more than 300,000 deaths worldwide annually . Breast cancer patients routinely undergo axillary lymph node dissection (ALND). There have been a common practice to stage the axilla using less invasive measures and In order to have more accurate samples of the node; the concept of the sentinel lymph node biopsy (SLNB) was developed. SLNB especially with lymphotropic dye is a safe, less technically demanding and cost effective procedure suitable for a developing country like Bangladesh. The use of SLNB as a diagnostic tool in early breast cancer needs to be reviewed in the context of our country ; especially in assessing its ability to determine which axillary lymph nodes are negative and which are positive for metastasis.

Objectives: To determine the diagnostic accuracy of sentinel lymph node biopsy in patients with carcinoma breast with clinically non-palpable axillary lymph nodes.

Method: The study was a prospective cross-sectional study where female patients with carcinoma breast with clinically non palpable axillary lymph nodes admitted in department of Surgery in Bangladesh Medical College and Hospital (BMCH), Dhanmondi, Dhaka. The Study period was Dec 2012 to May 2013.

Results: Thirty (n=30) female patients with breast cancer and clinically node negative axilla participated in this study. The age of the patients ranged between 26-78 years(Median age±SD-46.50±11.21). Majority of the tumours were found upper outer quadrant of the breast (33%). 93% of the tumours were infiltrating ductal carcinoma. 23 cases where SLNB was successful , there were 12 (52.17%) patients where both SLN and non SLN were negative for metastasis. 6 (26.08%) patients , SLN was positive for metastasis while non SLN was negative. 4 (17.31%) patients had metastasis in both their SLN and the non SLN. 1 patient (4.34%), the SLN was negative while the axilla was positive. False negative rate of the study was ¬9.09%. There were 7 patients (30.4%) in whom methylene blue dye failed to locate the SLN.

Conclusion: Breast cancer management has dramatically evolved towards minimally invasive approaches . SLNB is an easy and cost effective procedure while it has a short learning curve and Methylene blue is radiely available. In this study, albeit with a small study sample; sentinel lymph node biopsy in breast cancer patients showed to have high diagnostic accuracy (95.6%) with low false negative rate (9.09%) .

Recommendation: Breast cancer management has dramatically evolved towards minimally invasive approaches. Hopefully, in the near future, improvements in the SLNB technique should increase its usefulness as a staging technique in Bangladesh.

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Introduction

Carcinoma breast is the most common cancer of adult females and is the leading cause of death among cancer patients with more than 300,000 deaths worldwide annually.[1] As women are becoming increasingly conscious about their breast health; the cancer cases are being presented at earlier stage. This is giving the physicians the chance to treat breast cancer at an early stage thus improving the outcome. So accurate staging is therefore crucial in these patients for planning the right treatment .The axillary nodal status is accepted universally as the most powerful prognostic tool available for early stage breast cancer and is the universal standard.[2]

Breast cancer patients routinely undergo axillary lymph node dissection (ALND) i.e. removal of Level I & II axillary lymph nodes; it is the most accurate method to assess axillary nodal status.[2] Physical examination and imaging technique

such as ultrasonography or mamogram underestimates the presence of axillary lymph nodal involvement in 20-30% of patients with clinically negative axilla.[3] So ALND remains the gold standard for accurate assessment of axillary nodal status.

Unfortunately around 50% of patients staged by axillary clearance develop morbidities that includes lymphaedema , chronic shoulder pain, paraesthesias, damage to sensory and motor nerves, seroma formation, wound infection, drain complications.[2,4] Treatment of these complications are often very difficult. Additionally, the survival advantage of ALND has been challenged due to relatively low incidence of axillary lymph nodal metastasis in early breast cancer as up to 70% of women with small tumours (i.e. T1 or T2) found to have negative lymph nodes after axillary clearance.[4,5] So less extensive methods of evaluating the axillary nodal basin have been sought after.[2]

There have been a common practice to stage the axilla using less invasive measures such as axillary node sampling where only a small number of Level I lymph nodes are removed . Although axillary node sampling is associated with fewer complications, it has been shown to have a high error rate of about 24%.[4]

In order to have more accurate samples of the node; the concept of the sentinel lymph node biopsy (SLNB) was developed. Cells detaching from the primary tumour are likely to arrive at, and be held by, the first node to receive lymph from the involved area.[4,6] This lymph node is termed as sentinel lymph node (SLN) and this node reflects the status of the entire nodal basin.[7]

A lymphotropic dye or a radioisotope (99mTechnetium) labeled radioisotope, or a combination of both, is injected into the breast and its drainage pattern traced. This node can then be removed and tested pathologically to determine whether it is negative or positive for metastatic disease (i.e. staging).[4] Once the sentinel nodes has been identified it can be surgically excised and subjected to pathological analysis. If it contains metastatic cells then the patient will undergo axillary lymph node dissection. But the patients with negative sentinel lymph nodes are spared from the unnecessary axillary dissection and its complications.

Sentinel Lymph Node Biopsy also results in increased sensitivity as a diagnostic procedure, since focused pathologic attention is paid to the lymph nodes that are most likely to harbormetastases, compared to brief pathologic analysis of all excised lymph nodes in an axillary dissection.[4,8]

Sentinel lymphnode biopsy (SLNB) in early stages of breast carcinoma using radioistiope was used by Alex And Krag in 1993.[3,4] Giuliano and colleagues used blue dye as a single agent for SLNB and reported sentinel node identification rates of 98%, without false-negative nodes.[9] Since then it has been picked up and practiced all over the world.

The NSABP-32 trial is the largest multicenter trial to date examining the safety and accuracy of SLNB.[10] The trial randomly assigned women with clinically negative axilla to receive SLNB with an ALND or just SLNB alone . It demonstrated that SLNB is safe and reliable, with false-negative rates of 8% to 10%, and lower morbidity than ALND.[10] Veronesi and colleagues randomly assigned 516 women with early stage breast cancer to either SLNB and ALND or SLNB alone (ALND was performed only for axillary metastases in the SLNB-alone arm).[11] There was less pain and better arm mobility in those who underwent SLNB only. Additionally, there were no differences in local recurrence or survival at follow-up.[12]

SLNB especially with lymphotropic dye is a safe, less technically demanding and cost effective procedure suitable for a developing country like Bangladesh. It has a short learning curve among surgeons making it easy to grasp therefore can be used across the country. The use of SLNB as a diagnostic tool in early breast cancer needs to be reviewed in the context of our country ; especially in assessing its ability to determine which axillary lymph nodes are negative and which are positive for metastasis. This information can then be used to avoid unnecessary removal of lymph nodes and reduce the consequent morbidity of axillary clearance without compromising survival.

Method

The study was a prospective, cross-sectional study to localize the sentinel lymph node for biopsy and then to determine the diagnostic accuracy of the procedure in patients with carcinoma breast with clinically non-palpable axillary lymph nodes.The study was conducted in the Department of Surgery of Bangladesh Medical College & Hospital, Dhanmondi, Dhaka, Bangladesh.. Study period was Six Months (December 2012 to May 2013). And the study populations we Female patients admitted with Carcinoma breast with clinically non palpable axillary lymph nodes in Department of Surgery in Bangladesh Medical College and Hospital (BMCH), Dhanmondi, Dhaka.

Patients who were admitted in the Surgery Department of Bangladesh Medical College and Hospital from December 2012 to May 2013 admitted with carcinoma breast with non palpable axillary lymph nodes.

Criteria for inclusion of patients were Female patients with diagnosed as a case of carcinoma breast with clinically non palpable axillary lymph nodes. And exclusion criterias are Patients with carcinoma breast with clinically palpable axillary lymph nodes, Patients with carcinoma breast with history of neo-adjuvant therapy,Patients with carcinoma metastatic breast cancer.

A total number of 30 female patients diagnosed as carcinoma breast (by FNAC) with clinically non palpable lymph nodes admitted in patients in department of surgery in Bangladesh Medical College and Hospital (BMCH) were chosen by purposive sampling.

After approval from hospital ethics committee and getting informed written consent to participate in the study, 30 female patients aged 26-78 years, admitted with breast cancer with clinically non palpable axillary lymph nodes were chosen; all with the fine needle aspiration (FNAC) proven carcinoma breast.

At the operation table, 5ml of sterilized 1% methylene blue dye was injected in the sub-areolar region (Figure:1.1) . Gentle massage of the breast was done for 5 minutes to increase the uptake of dye by the lymphatic channels (Figure 1.2). Ten-fifteen minutes later, the axilla was explored through a transverse incision made in the lower axilla just below the hair line. (Figure: 1.3).

The subcutaneous fascia followed by the axillary fascia was dissected looking for blue stained channels and lymph nodes.(Figure: 1.4) If found, then the blue stained lymph node(s) were then removed and was demarcated as sentinel lymph node (SLN)(Figure 1.5). All patients underwent simple mastectomy and axillary lymph node dissection up to level II. The dissected axillary specimen was checked again to see whether any blue stained lymph nodes were seen. If found then they were also marked as sentinel lymph node(Figure 1.6). The specimens were then fixed and preserved in formalin and sent to Histopathogy.

The pathological analysis was done by Haematoxilin and Eosin stain. Both the sentinel and non-sentinel lymph nodes examined for metastatic deposit.

Figure 1.1: Injection of methylene blue dye in sub-areolar plexus

Figure 1.2: Gentle massage of breast to increase dye uptake by lymphatic channel

Figure 1.3: Axillary incision given for SLNB

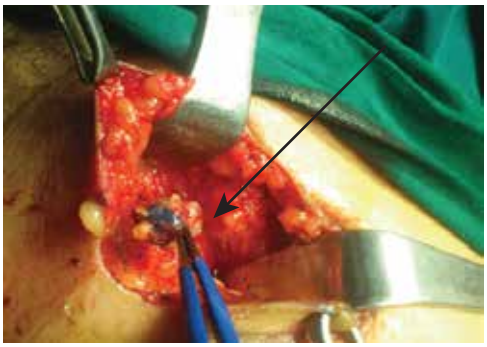

Figure 1.4: Identification of the blue stained lymph node in axilla followed by excision(pointed by arrow)

Figure: 1.5: Sentinel lymph node

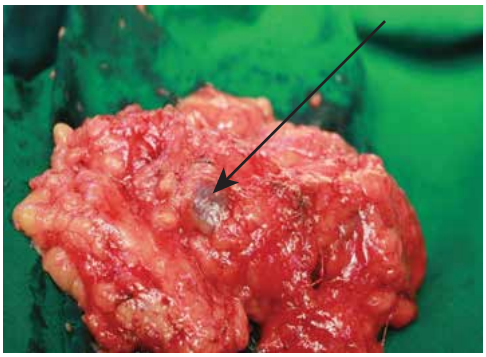

Figure 1.6: Blue stained lymph node the specimen of the axillary tail (pointed by the arrow)

Results

Thirty (n=30) female patients with breast cancer and clinically node negative axilla participated in this study. The age of the patients ranged between 26-78 years(Median age±SD-46.50±11.21).Among them 13 were premenopausal and 17 were postmenopausal. Clinically tumour size ranged between 1.5-6.5 cm. (Median size ±SD = 3 ±1.27) (Table1.1).

Table 1.1: Statistical Profile of Age and Tumour size of the study population

	Age of the patients	Size of the tumour
Range	26-78 years	1.5-6.5 cm
Mean	49.23	3.317
Median	46.50	3.000
Mode	40	2.0
Std. Deviation	11.212	1.2763

All patients were injected with methylene blue dye in the subareolar plexus for sentinel lymph node biopsy followed by mastectomy and axillary clearance up to level II . In 23 of them, sentinel lymph nodes were identified. The number of sentinel lymph nodes(SLN)ranged 1-5 (Median number ±SD = 2.5±1.249) while the number of non-sentinel lymph node ranged between 5-13 (Median number ±SD = 7 ± 4.31) (Table:1.2).

Table 1.2: Statistical Profile of SLN and Non-SLN

Total	SLN	Non-SLN
	22	27
Range	1-5	5-13
Mean	2.68	7.07
Median	2.50	7.00
Std. Deviation	1.249	4.341

Sentinel lymph nodes could not be identified in 7 cases. SLN identification rate increased with surgical experience in the 6 months study period. SLN were detected in 11 (68%) of the 16 cases in first 3 months and 12 (85%) of the 14 cases in the last 3 months. Overall identification rate 76.66%(Table5).

Table 1.3 : SLN Identification rate in breast cancer patients with clinically node negative axilla

Number of cases	30
Number of cases- sentinel lymph node identified	23
Number of cases -sentinel lymph node was not identified	7
Sentinel lymph node identification rate	76.66%

Patient characteristics such as age of the patient, body weight, size of the tumour ,site
of the tumour was recorded. These variable were than correlated with the identification .

Most of the patients (57%)were in 35-50 age group .There were no significant correlation between age group and SLN identification rate (Table:1.4).

Table 1.4: Statistical Relationship between age of the patients and SLN Identification

Age group	SLN identification		Total
N=30	Positive	Negative	
< 35 years	1(33.3%)	2(66.7%)	3(100.0%)
35-50 years	14(82.4%)	3(17.6%)	17(100.0%)
> 50 years	8(80.0%)	2(20.0%)	10(100.0%)
Total	23(76.7%)	7(23.3%)	30(100.0%)
Pearson Chi-square test(χ^2) :3.5			
Degree of freedom(df): 2			
p-value: 0.17*			

*Analysis done by Chi-square test

Most of the patients (40%) were of average body weight. Our study found no significant relationship between SLN identification rate and body weight (Table:1.5).

Table 1.5: Statistical Relationship between BMI of the patients and SLN Identification

	SLN identification		Total
Body weight	Positive	Negative	
Average	11(91.7%)	1(8.3%)	12(100.0%)
Over weight	3(60.0%)	2(40.0%)	5(100.0%)
Obese	5(62.5%)	3(37.5%)	8(100.0%)
Under weight	4(80.0%)	1(20.0%)	5(100.0%)
Total	23(76.7%)	7(23.3%)	30(100.0%)
Pearson Chi-square test(χ^2) :3.21			
Degree of freedom(df): 3			
p-value: 0.36*			

*Analysis done by Chi-square test

Majority of the tumours were found upper outer quadrant of the breast (33%). This study found that there was an association between the tumour site and SLN identification

rate (p-value was <0.05).The SLN identification rate increased when the tumour was located in upper outer quadrant (Table:1.6).

Table1.6: Statistical Relationship between site of the tumour and SLN Identification

Site of the tumour (Dominant)	SLN identification		Total (n=30)
	Positive	Negative	
UOQ(upper outer quadrant)	10 (100.0%)	0 (0)	10(100.0%)
LOQ(lower outer quadrant)	6 (85.7%)	1(14.3%)	7(100.0%)
UIQ(upper inner quadrant)	3(60.0%)	2(40.0%)	5(100.0%)
LIQ(lower inner quadrant)	1(33.3%)	2(66.7%)	3(100.0%)
Central	3(60.0%)	2(40.0%)	5(100.0%)
Total	23(76.7%)	7(23.3%)	30(100.0%)
Pearson Chi-square test(χ^2) :9.5			
Degree of freedom(df): 4			
p-value: 0.048*			

*Analysis was done by Chi-square test

In this study , 60% of the tumours were of the size ranged between 2-4 cm. No specific size of tumour showed significant association with SLN identification (Table:1.7).

Table 1.7: Statistical Relationship between size of tumour and SLN Identification.

	SLN identification		Total (n=30)
size of the tumour	Positive	Negative	
< 2 cm	6(85.7%)	1(14.3%)	7(100.0%)
2-4 cm	14(77.8%)	4(22.2%)	18(100.0%)
> 4 cm	3(60.0%)	2(40.0%)	5(100.0%)
Total	23(76.7%)	7(23.3%)	30(100.0%)
Pearson Chi-square test(χ^2) : 1.1			
Degree of freedom(df): 2			
p-value: 0.57*			

*Analysis was done by Chi-square test

The pathological characteristics of the tumour such as histological type , grade, lympho-vascular invasion, free margin involvement were documented. Nodal status of the axilla was delineated after histo-pathology of the lymph nodes. Statistical analysis was done to see whether there was any correlation between SLN identification and nodal status.

There was no significant correlation between lymph node status and SLN identification. 53% of the patients were found to in No stage (Table:1.8).

Table 1.8: Statistical Relationship between lymph node status and SLN Identification.

	SLN identification		Total (n=30)
Lymph node status	Positive	Negative	
N0(no node metastasis)	10(76.9%)	3(23.1%)	13(100.0%)
N1(0-3 node metastasis)	7(77.8%)	2(22.2%)	9(100.0%)
N2(4-9 lymph node metastasis)	5(83.3%)	1(16.7%)	6(100.0%)
N3:(>10lymphnode metastasis)	1(50.0%)	1(50.0%)	2(100.0%)
Pearson Chi-square test(χ^2) : 0.95			
Degree of freedom(df): 3			
p-value: 0.813*			

*Analysis was done by Chi-square test.

93% of the tumours were infiltrating ductal carcinoma. This study found no significant correlation between histological type and SLN identification (Table 1.9).

Table 1.9: Statistical Relationship between histological sub-type of the tumour and SLN Identification groups.

	SLN identification		Total (n=30)
Types	Positive	Negative	
Infiltrating Ductal Ca	21	7	28
	75.0%	25.0%	100.0%
	91.3%	100.0%	93.3%
Infiltrating Lobular Ca	2	0	2
	100.0%	.0%	100.0%
	8.7%	.0%	6.7%
Total	23	7	30
	76.7%	23.3%	100.0%
	100.0%	100.0%	100.0%
Pearson Chi-square test(χ^2) :0 .662			
Degree of freedom(df): 1			
p-value: 0.582*			

*Analysis was done by Chi-Square test

73% of the tumours were of nuclear grade II (moderately differentiated). Relationship between nuclear grade of the tumour and SLN identification was evaluated. No significant correlation was found between them (Table:2.0).

Table 2.0: Statistical Relationship between nuclear grade of the tumour and SLN Identification

	SLN identification		Total
Grade	Positive	Negative	
Grade I(well differentiated)	1(100.0%)	0(0%)	1(100.0%)
Grade II(moderately differentiated)	18(81.8%)	4(18.2%)	22(100.0%)
Grade III(poorly differentiated)	4(57.1%)	3(42.9%)	7(100.0%)
Total	23(76.7%)	7(23.3%)	30(100.0%)
Pearson Chi-square test(χ^2) : 2.122			
Degree of freedom(df): 2			
p-value: 0.346*			

* Analysis was done by Chi-Square test.

Presence of lympho- vascular invasion and the free margin involvement was compared against SLN identification rate (Table 2.1-2.3). No significant correlation was found between them.

Table 2.1 : Statistical Relationship between presence of lymphatic invasion and SLN Identification

			SLN identification		Total (n=30)
			Positive	Negative	
Lymphatic channel invasion	Positive	Count	4	2	6
		% within Lymph node invasion	66.7%	33.3%	100.0%
		% within SLN identification	17.4%	28.6%	20.0%
	Negative	Count	19	5	24
		% within Lymph node invasion	79.2%	20.8%	100.0%
		% within SLN identification	82.6%	71.4%	80.0%
Total		Count	23	7	30
		% within Lymph node invasion	76.7%	23.3%	100.0%
		% within SLN identification	100.0%	100.0%	100.0%
Pearson Chi-square test(χ^2) : 0.419					
Degree of freedom(df): 1					
p-value: 0.4333*					

*Analysis was done by Chi-Square test

Table 2.2: Statistical Relationship between presence of vascular invasion and SLN Identification

			SLN identification		Total
			Positive	Negative	
Vascular invasion	Positive	Count	7	4	11
		% within Vascular invasion	63.6%	36.4%	100.0%
		% within SLN identification	30.4%	57.1%	36.7%
	Negative	Count	16	3	19
		% within Vascular invasion	84.2%	15.8%	100.0%
		% within SLN identification	69.6%	42.9%	63.3%
Total		Count	23	7	30
		% within Vascular invasion	76.7%	23.3%	100.0%
		% within SLN identification	100.0%	100.0%	100.0%
Pearson Chi-square test(χ^2) : 1.648					
Degree of freedom(df): 1					
p-value: 0.2*					

*Analysis was done by Chi-Square test

Table 2.3: Statistical Relationship between free margin involvement and SLN Identification.

			SLN identification		Total
			Positive	Negative	
Margin of the tumour	Involved	Count	3	2	5
		% within Margin of the tumour	60.0%	40.0%	100.0%
		% within SLN identification	13.0%	28.6%	16.7%
	Free	Count	20	5	25
		% within Margin of the tumour	80.0%	20.0%	100.0%
		% within SLN identification	87.0%	71.4%	83.3%
Total		Count	23	7	30
		% within Margin of the tumour	76.7%	23.3%	100.0%
		% within SLN identification	100.0%	100.0%	100.0%
Pearson Chi-square test(χ^2) : 0.932					
Degree of freedom(df): 1					
p-value: 0.329*					

*Analysis was done by Chi-Square test.

Among the 23 cases where SLNB was successful , there were 12 (52.17%) patients where both SLN and non SLN were negative for metastasis . So SLNB was accurate in staging the axilla as negative for metastasis (table:15). These cases are as defined True Negatives which is defined by a negative SLNB and a negative axilla after ALND.

In 6 (26.08%) patients , SLN was positive for metastasis while non SLN was negative.

4 (17.31%) patients had metastasis in both their SLN and the non SLN . In all 10 of these patients SLNB was successful in determining that axillary metastasis was indeed present . These are true positives which is defined as a positive SLN with or without a positive axilla.

While in 1 patient (4.34%), the SLN was negative while the axilla was positive , indicating that the SLNB could not accurately predict the axillary status in this case . This is a false negative case which is defined as negative SLN but with positive lymph nodes in ALND.So SLNB could not accurately predict the axilla in this case.

Based on these definitions there were no false positives in these study.

Table 2.4: Histological Examination Findings of Sentinel and Axillary Lymph nodes.

	Histological Negative axillary nodal metastasis (Standard Test)	Histological Positive axillary nodal metastasis (Standard test)
Histological Negative SLN	12 (true negative)	1(false negative)
Histological Positive SLN	0 (false positive	10 (true positive)

False negative is considered an important marker for the accuracy of SLNB. False negative rate of our study was 9.09%.

Sensitivity is defined as the probability that a test result will be positive when the disease is present (true positive rate). =True Positive / (True Positive + false negative).

Specificity is defined as the probability that a test result will be negative when the disease is not present (true negative rate). = false positive/false positive + true negative.
Based on these parameters , the sensitivity and specificity of this study was 91% and 100% respectively.

Positive predictive value (PPV) is the probability that the disease is present when the test is positive. = true positive/ (True Positive+ False Positive).

Negative predictive value (NPV) is the probability that the disease is not present when the Standard test is negative. = True negative / (True Negative + False Negative).

So PPV and NPV of this study was found to be 100% and 92% , respectively.

The diagnostic accuracy is calculated by the following formula: True Positive +True negative /Number of patients where SLN could be successfully identified , which was 95.6 % in our study.

Table 2.5: Various Parameters of the study

Standard test (Histo-pathology of ALND)				
		Metastasis Negative	Metastasis Positive	
Index test SLNB histo-pathology	SLNB Outcome Negative	True negative 12	False Negative 1	Negative Predictive Value (NPV)= Σ True Negative / Σ Test Outcome Negative = 92%
	SLNB Outcome Positive	False Positive 0	True Positive 10	Positive predictive value(PPV)= Σ True Positive / Σ Test Outcome Positive =100%
		Specificity: ΣTrue Negative/Σ Condition Negative =100%	Sensitivity: Σ True Positive /Σ Condition Positive = 91%	

Discussion

Screening methods and increased awareness about breast health are helping physicians to diagnose early breast cancer . The challenge is now to accurately stage the patients and treat them accordingly. The complications of ALND are extremely distressing to the patient and very difficult for the surgeons to treat. The most distressing of them , is lymphedema. Patients undergoing ALND also frequently suffers from chronic shoulder pain, stiffness, limited movement of the shoulder.[16] The effect of such complications severely hamper the quality of the patients life.
The concept of sentinel lymph node biopsy was developed in patients with early breast cancer in order to define the axillary status without having to go through extensive dissections; unless they are needed.SLNB was designed to minimize the side effects of lymph node surgery but still offer outcomes equivalent to axillary dissection.[27] Over the years various studies confirmed that post-operative morbidities significantly decreases in patients undergoing SLNB then those undergoing ALND.[20,21,23]

There have been multiple studies conducted regarding the efficacy and the rate of complications between SLNB and ALND. Two of the largest studies are NSABP- B32 in USA and the ALMANAC trial conducted in UK. NSABP –B32 study after long term follow up, found that over all survival, disease free survival and regional control were statistically equivalent between two groups (one underwent SLNB and ALND and the other group underwent SLNB only) and SLNB alone is a safe and effective treatment for early breast cancer with clinically negative axilla.[10] The ALMANAC trial compared the rate of morbidity outcomes between SLNB and ALND and concluded that sentinel lymph node biopsy is associated with reduced complications and better quality of life than standard axillary treatment and should be the treatment of choice for patients who have early-stage breast cancer with clinically negative nodes.[25] Currently SLNB has already been accepted as a standard protocol in early breast cancer in UK and US.[22,26]

There are various studies that are being conducted through out the world on many aspects of SLNB but most of them are in western settings. Despite the huge burden of breast cancer patients in this region, only a handful of studies are found in the setting of our subcontinent let alone our country.
In our neighboring country India , at the 8th Annual Women's Cancer Initiative – Tata Memorial Hospital (WCI-TMH) Conference the panel recommended that a full axillary clearance that includes level III lymph nodes be undertaken as a standard procedure in breast cancer surgery in developing countries.[28] The panel noted the relative abundance of large, non-screen-detected cancers and locally advanced breast cancers in these regions, with a high possibility of axillary nodal involvement being an important factor in this recommendation. The panel also recommended that the sentinel lymph node technique could be considered in carefully selected patients with early breast cancer and clinically negative axilla in centers that have this expertise. However, the panel recommended that in order to establish the safety of this procedure in developing countries, centers that undertake these procedures should regularly audit their outcome with adequate patient follow-up.[28]

In this study, methylene blue dye was used for SLNB due to the widespread availability of the agent in the local setting. It was successful in revealing sentinel lymph nodes in 23 out of 30 (76.66%)ofcases in this series. It is higher than the findings of Guiliano and collegues9 who reported 65.5% identification rate using vital blue dye ; but lower than Golshan et al[29], who reported identification rate of 96.5%

using methylene blue dye alone. Many other investigators also found excellent result using blue dye30,31;their identification rate exceeded 90% compared to the 76.6% of our study. But the high sensitivity (91%) and diagnostic accuracy(95.6%) of the present study are similar to the findings of above mentioned studies.[29-31]

There were 7 patients (30.4%) in whom methylene blue dye failed to locate the SLN. There are many factors that are linked to SLN failure such as, increased age, body mass and tumour palpability and size has been linked to an increased incidence of SLNB failure.[24,47] Many studies found that age of the patientssignificantly affect the ability to identify SLN , where the SLN identification rate significantly decreased in women over 50 years of age.[13,24,32,33] Increased body mass is also implicated as a risk factor for SLNB failure, where localization rate decreased in women with increased body mass.[14,34] However there were no significant correlation found in this study between SLNB localization and these risk factors. The tumoursite was found most commonly in the upper outer quadrant of the breast (33%) . There was a significant correlation between the tumour site and SLN identification rate .The SLN identification rate increased when the tumour was in upper outer quadrant. This is similar with the findings of Goyal et al and Mcmasters et al, where authors reported a increased SLNB identification rate where tumour was located in upper outer quadrant.[13,33]
The tumour characteristics such as size, histological type, number of nodes involved in metastasis , lympho-vascular invasion , margin involvement of the tumour were recorded in this study. In some literature , the tumour size is delineated as a potential risk factor SLNB localization.[5,20,32] SLNB is discouraged in patients where the tumour size is more than 5 cm.[22] No such correlations were obtained from this study. The rate of false negative rates defines the accuracy of SLNB[15,19] as if thenegative sentinel node is removed while the positivenode remains in the axilla, the disease will be understaged,leaving the patient at risk for recurrence.[15] In our study , we had only one false negative case among the 23 cases where SLN were localized . and the over all false negative rate was 9.09%. Although this is lower than the study conducted by Parmar et al 48 who reported a false negative rate of 16.6%; but it is slightly higher than recommended rate which is equal or less the 5%.[17,22]

There are several reasons attributed for the false-negative results encountered in the studies of SLNB. The surgical learning curve is an important factor influencing SLN localization rate and the false negative rates.[13,35,36] In the present study SLN were detected in 68% of the total cases done in first 3 months which then improved to 85% of cases done in the last 3 months. Coxet al, suggest that increased volumes of cases lead to decreased failure rates35. It is currently recommended that surgeons perform at least 20-30 cases of SLNB with a documented false negative rate before abandoning ALND completely.[13,20,22] This is why in this study , both SLNB and ALND was performed in each patients to ensure the accurate staging of the patient and document the false negative rates of SLNB.
Multifocal tumours or prior excisionof the primary tumour ; such cases may be incapable of intra-operative lymphatic mapping. It is because ofunexpected drainage by one or more lymphatic channels or impaired lymphatic flow.[19,22] In this study, the patient who had the false negative SLNB had previous surgery in the breast for fibroadenoma. In fact she was the only patient in this series who had previous surgery in the breast. Many investigators also reported the incidence of skip metastases to the upper levels in the axilla [5,19]; which is also a disadvantage of SLNB using blue dye . In a meta-analysis done by Kim et al, it was found that The false negative rate was significantly lower in the studies that included more than 100patients (6.7%) compared with the studies thatincluded less than 100 patients.[49] So our small sample population is also another the reason behind our slightly higher false negative rate than the recommended rate. Some studies found that there may be an increased risk of false negativity if blue dye alone is used.[13,37] Somashekhar et al,reported that combination of radio-isotope and blue dye yields higher identification rate and lower false negative rate and this is supported in many other studies.[37-39] But in many cases , methylene blue dye use facilitated the visual detection of SLNs which were neither hot on lymphoscintigraphy nor suspicious at palpation40,41.But many authors found high diagnostic accuracy in using blue dye alone and concluded that is safe and effective in early breast cancer.[29-31,40,42]

Out of the 23 cases , SLNB was able to delineate the axillary status accurately in 22 cases. The sensitivity was 90% and the positive predictive value was 100%. This is similar to the result by Krag and Veronesi in their studies.[11,18] In twelve patients , where both SLN and Non SLN both were free from any metastases. These patients were ideal candidates for SLNB where unnecessary axillary dissection can be avoided. In ten patients where SLN contained metastasis , four of them had non SLN metastases also. Therefore, in these are the patients, ALND is justified for both staging and loco-regional control . The concept of SLNB is that if it contained metastasis then the patient should undergo full axillary dissection; if the facility of per-operative frozen section is available then the decision for ALND can be taken immediately . If per-oprative frozen section is not available then after permanent histology by Hematoxylin-Eosin staining ; the patient has to under go a second procedure. Our institution like many other, does not have the facility for frozen section biopsy. Although many studies report a high sensitivity of frozen section biopsy of lymph nodes[43,44] but the permanent histology with Hematoxylin and Eosin staining still remains the gold standard. This is because current intra-operative sentinel lymph node (SLN) tests have reportedly high false-negative rates[45] leading to second operations when metastases are identified postoperatively by permanent-section hematoxylin and eosin (HE) or immunohistochemistry (IHC).

Canavese etal,performed a study in 2010 , where the authors concluded intra-operative SLN pathology can be safely omitted in T1-N0 tumour but recommended to be used in T2 tumour.[46] Delayed definitive breast surgery offers improved accuracy of SLN diagnosis as well as the possibility of performing this technique even in hospitals without a resident pathologist. The obvious disadvantage of this latter approach is that all patients end up with two operations instead of only the small minority with pathological false negative intra-operative node assessment who require delayed ALND 19.

Fortunately none of the patients in this study series developed any complications of axillary dissection; only one patient developed wound dehiscence. None of the patients reported any anaphylactic reactions to methylene blue dye. Although the sample population of this series is very small, but the results are very much encouraging. It shows that sentinel lymph node biopsy using methylene blue dye can be performed safely and effectively in our local settings. But there is a learning curve for the surgeons and careful selection of patients along with meticulous surgical technique and proper pathological evaluation is important to yield the best result.

Conclusion

In this study, albeit with a small study sample; sentinel lymph node biopsy in breast cancer patients showed to have high diagnostic accuracy (95.6%) with low false negative rate (9.09%) . SLNB procedure showed to have a sensitivity of 91% and specificity of 100%.

Limitations

There were some limitations to our study, most important of them is the small study sample. As only breast cancer patients with clinically non palpable axillary nodes were selected for this study ; it significantly reduced our study sample . Also it was conducted in a single institution within a six months period, the sample population was chosen to be minimum thirty(30) patients. Studies with larger population with longer period of follow up is needed to evaluate sentinel lymph node biopsy on a wider scale.

The technical aspect of the study was also taken into consideration. But the procedures in this study were followed according to the international protocols; which was found easy to grasp and quite doable.

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Original Article

Clinical Presentations, Postoperative Complication and Histologies of Parapharyngeal Tumors in Tertiary Care Hospital

Bhuiyan MMKH [1]

ABSTRACT

Background: Parapharyngeal tumors challenge to the surgeon as they are large and intimately related to carotids and lower cranial nerves at the time of presentation,

Objective: To find the clinical presentations and histologies of parapharyngeal tumors after surgery in tertiary level hospital

Method: The present, retrospective study included 53 patients who underwent surgery for primary parapharyngeal tumors between January 2018 and December 2019 in Department of ENT Shaheed Tajuddin Ahmed Medical College. Informed consent was obtained from the patients prior to their inclusion in the study. In regard to histologic type, there were 33 cases of neurogenic and 20 of salivary gland origin tumors.

Result: The most common symptoms of neurogenic tumors were a neck mass 14 (26.42%),Feeling foreign body in the throat 7(13.21%), hoarseness 5 (9.43%) and pharyngeal pain 3 (5.66%) and abnormal sensation of the pharynx 4 (7.55%). Majority 32 (59.52%) were found schwannoma, followed by 15 (28.57%) were pleomorphic adenoma, 03 (4.76%) were Paraganglioma. First bite syndrome, Lower lip palsy, Horner syndrome and Tongue palsy were common post operative complications.

Conclusion: Majority pathological diagnosis was found schwannoma, first bite syndrome, lower lip palsy, homer syndrome and tongue palsy were common post operative complications. Neck mass and feeling of foreign body in the throat are the common presentation.

Key word: Parapharyngeal tumors; Surgical approach; Schwannoma: Salivary tumors; Cranial nerve palsy

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Introduction

Parapharyngeal tumors are uncommon and a challenge to the surgeon as they are large and intimately related to carotids and lower cranial nerves at the time of presentation.[1]

Parapharyngeal space is a triangular fat-filled compartment of the suprahyoid neck, lateral to the pharynx. It is described as an inverted pyramid with the floor of the pyramid at the skull base and the apex at the level of the greater cornu of the hyoid bone.[2] Parapharyngeal tumors are rare pathologies that comprise approximately 0.5% of all head and neck tumors.[3] Eighty percent-of them are benign, and 20% are malignant. The most common lesions arise from the salivary. glands, followed by neurogenic tumors.[4]

Patients often present with locally advanced tumors which are intimately associated with important neurovascular structures like carotids, vagus & hypoglossal nerves. These tumors can extend higher into masticator space and can be intimately associated with facial nerve and skull base. They can compress the airway and present with stridor. Some of them can secrete vasoactive amines and can be part of a

syndrome involving multiple sites. Some of these tumors may be associated with cranial nerve palsies at the time of presentation.[5] Surgery of these locally advanced tumors is challenging and requires expertise and experienced surgeon and anesthesiologist.[6] Though the outcome of treatment of benign parapharyngeal tumors is good with regard to survival, serious complications and morbidity can result due to treatment.

Method

The present, retrospective study included 53 patients who underwent surgery for primary parapharyngeal tumors between January 2018 and December 2019 in Department of ENT Shaheed Tajuddin Ahmed Medical College. Informed consent was obtained from the patients prior to their inclusion in the study. In regard to histologic type, there were 33 cases of neuro-genic and 20 of salivary gland origin tumors. The following data were evaluated: Preoperative symptoms, histological type, surgical approach and complications Patients were evaluated following a laboratory examination. Enhanced CT and MRI scans were used to confirm the location and size of the tumor as a preoperative diagnosis. In particular, the following aspects were evaluated: Tumor shape and the tumor margin, the association of the tumor location with major vasculature, surrounding tissue and the deep lobe of the parotid gland (DLPG), & whether the tumor localization was pre-or poststyloid. Preoperative imaging was also used to estimate the origin of the tumor, the extent of malignancy and tumor vascularity. For the examination of the histology of the tumor, fine needle aspiration cytology (FNAC) was performed in the majority of cases. Fine needle aspiration biopsy (FNAB) or incisional biopsy was required in certain cases when the histological results were unclear and there was a suspicion of malignancy. In the case of malignancy, additional imaging examination was performed to find out the selection of a treatment plan. Where tumors exhibited the possibility of paraganglioma, angiography or CT-angiography was performed to evaluate the vasculature associated with the carotid artery. All patients enrolled in the study underwent surgical treatment.The plan for the surgical approach was selected according to the tumor location, histological findings, the relationship to anatomical structures and the suspicion of malignancy. The approach of wide resection and reconstruction was selected in cases where malignancy was confirmed.

Results

Table 1: Age distribution of the study population (n=53)

Age in years	Number	Percentage
20-30 yrs	6	11.32
31-40 yrs	11	20.75
41-50 yrs	19	35.85
51-60 yrs	12	22.64
>60 yrs	5	9.43
Mean±SD=48.67±15.72	53	100

The mean age group was 48.67 minimum age was 23 and maximum age was 67 years .

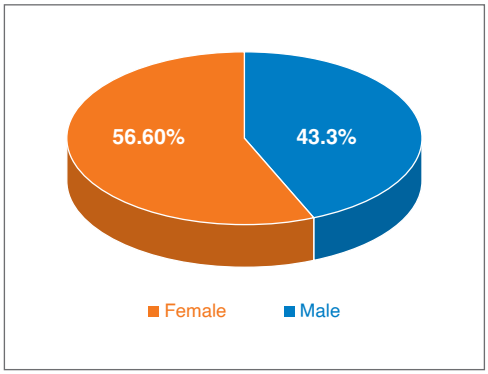

Figure I: Sex distribution of the study population
Female was predominate 56.6% and male was 43.4%.

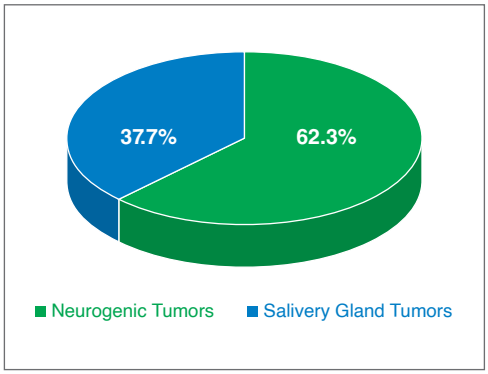

Figure II: Distribution of patients according to tumor origin (n=42)
According to tumor origin Neurogenic tumor was 62.3% and salivery gland tumor was 37.7%

Table 2: Incidence of preoperative symptoms in parapharyngeal tumors (N=53)

Symptoms	Number	Percentage
Neck mass	14	26.42
Feeling foreign body in the throat	7	13.21
Hoarseness	5	9.43
Abnormal sensation of the pharynx	4	7.55
Pharyngeal pain	3	5.66
Pharyngeal mass	3	5.66
Tongue palsy	1	1.89
No symptoms	16	30.19
Total	53	100

Regarding sign and symptoms, the most common symptoms of neurogenic tumors were a neck mass 14(26.42%), Feeling foreign body in the throat 7 (13.21), hoarseness 5 (9.43%) and pharyngeal pain 3 (5.66%) and abnormal sensation of the pharynx 4 (7.55%).

Table 3: Tumor location and size measured by CT and MRI of the study patients (n=53)

Tumor Location	Number	Percentage
Poststyloid	34	64.29
Prestyloid	14	26.19
Prestyloid-poststyloid	5	9.52
Total	53	100

Size of the Tumor	Number	Percentage
2.0-3.0 cm	9	16.67
3.0-4.0 cm	24	45.24
4.0-5.0 cm	20	38.10
Total	53	100

Preoperative CT or MRI imaging was used to evaluate the location of each tumor. A total of 34 tumors were located in the Poststyloid, prestyloid space cases were located 14(26.19%) and 5(9.52%) in the pre-and poststyloid. The size of each tumor was measured with CT or MRI imaging. The most frequent range for tumor size was 3.0-4.0 cm (24 cases; 45.24%) followed by 4.0-5.0 cm (20 cases; 38.10%).

Table 4: Final pathological diagnosis

Pathological diagnosis	Number	Percentage
Schwannoma	32	59.52
Pleomorphic adenoma	15	28.57
Paraganglioma	3	4.76
Neurofibroma	1	2.38
Carcinoma in pleomorphic adenoma	3	4.76
Total	53	100

Regarding pathological diagnosis, it was observed that majority 32(59.52%) was found schwannoma, followed by 15(28.57%) were pleomorphic adenoma, 3(4.76%) were Paraganglioma.

Table 5: Post operative complication of the study patient (n=53)

Complications	Number	Percentage
First bite syndrome	9	16.98
Lower lip palsy	6	11.32
Total facial nerve palsy	3	5.66
Pharyngeal pain	2	3.77
Homer syndrome	11	20.75
Tongue palsy	10	18.87
Vocal cord palsy	9	16.98
Pharyngoparalysis	3	5.66
Total	53	100

First bite syndrome 9 (16.98 %) , Lower lip palsy 6 (11.32) , Horner syndrome 11 (20.75%) and Tongue palsy 10 (18.87 %) were common post operative complications.

Discussion

In this study observed that the common age group was found 41-60 which (58.49%) minimum age was 23 and maximum age was 67 years . The mean age was 48.67(+15.72) years. Majority of the patients in our series were in the 3rd decade of life and a few about 50-years-of-age. Other studies in literature also have reported maximum incidence of parapharyngeal tumors in the age group of 40 years to 47 years.[7] The mean age of patients treated for PPS tumors ranges from 53 to 42 years; however, some authors include patients under 18 years of age in the analysis. Their population mean age was 52 years.[8,9]

In current study showed that female was predominate 56.6% and male was 43.4%. Rzepakowska et al.[3] reported there were 46 (67.6%) women and 22 (32.4%) men with a mean age of 52.2 years (age range 33-92 years).

Regarding sign and symptoms, the most common symptoms of neurogenic tumors were a neck mass (26.42%), Feeling foreign body in the throat 7(13.21), hoarseness (9.43%) and pharyngeal pain (5.66%) and abnormal sensation of the pharynx (7.55%). Tjichi K and Murakami10 study reported that the most common symptoms of neurogenic tumors were a neck mass (37.5%),hoarseness (12.5%) and pharyngeal pain (12.5%).[10] The most common symptoms of salivary gland tumors were the presence of a mass on the neck (30.8%) and abnormal sensation of the pharynx (15.4%).The most frequent symptom in the cohort of the present study was a neck mass,followed by pharyngeal mass; this is comparable with other studies.[11] Dysphasia and pain have also been reported to be common symptoms.[11,12] Rzepakowska et al.[13] studied in 2018, Reported a feeling of an obstacle in the pharynx, hoarseness, speech disorders, tongue numbness and nasal congestion. Rzepakowska et al.[3] studied in 2020 symptoms on admission were present in 43 (63.2%) patients. Most of them had foreign body sensations in the throat (35/68), difficulty swallowing (33/68), a neck mass (29/68) or symptoms of Eustachian tube dysfunction (15/68). Thirty-two percent of patients (22/68) were asymptomatic and were diagnosed incidentally.

This study showed that preoperative CT or MRI imaging was used to evaluate the location of each tumor. A total of 34 tumors were located in the poststyloid, prestyloid space cases were located 14(26.19%) and 5(9.52%) in the pre-and poststyloid. The size of each tumor was measured with CT or MRI imaging. The most frequent range for tumor size was 3.0-4,0 cm (24cases; 45.24%) followed by 4.0-5.0 cm (20 cases; 38.10%). Gupta et al[1] reported that the average size of parapharyngeal space tumor was 6 cm + 3 cm. This was similar to most studies which reported average diameter of 5 cm.[14] Few of our patients presented with tumors of massive size (10 cm x 12 cm). In Rzepakowska et al.[3] study, the majority of tumors (39, 57.4%) were located in the prestyloid space. There were 11 (16.2%) postyloid tumors and the same number of tumors involving both localizations. They identified

that neurogenic tumors were more likely to be located in the poststyloid area than other types of tumors. The concealed location of PPS tumors and their slow growth contribute to the rather large volume at diagnosis.In Rzepakowska et al.[13] study, only 25% of the tumors were smaller than 4 cm, and tumors larger than 5 cm accounted for 33.8%. Most authors present only the measures for the largest tumors in their series but do not analyze the cumulative influence of tumor size on the outcomes; for example, Sun et al. found that the longest mean diameter of PPS tumors was 5.6 cm, Changet al. reported a largest tumor size of 6.8 cm among their 51 cases, and Presutti et al. described an 8 cm diameter as the largest.[15,16]

In present study regarding pathological diagnosis, it was observed that majority 32(59.52%) was found schwannoma, followed by 15(28.57%) were pleomorphic adenoma, 03(4.76%) were paraganglioma. In the Ijichi and Murakami study, >50% of the cases were schwannoma. The most frequent origin nerves of the schwannomas were the sympathetic and vagus nerves. Liu efal10 corroborated this observation, reporting that the sympathetic and vagus nerves were the most common nerves of origin in head and neck schwannomas.[17] A study by Tryggvason et al[18] revealed that schwannomas arise in nerves with a sensory component and are associated with sensory ganglia. In addition, it was reported that the majority of sympathetic chain schwannomas are associated with the superior cervical ganglion.[18]

In this study showed that first bite syndrome, Lower lip palsy, Homer syndrome and Tongue palsy were‘common post operative complications. In the Ijichi and Murakami study, FNMB palsy typically occurred following surgery to remove tumors of salivary origin, as the surgery was performed close to the mandible. The second most common complication in these previous studies was the presentation of FBS. FBS also occurred in the present study, following prestyloid tumor surgery.[10]

Conclusion

Majority pathological diagnosis was found schwannoma, first bite syndrome, lower lip palsy, homer syndrome and tongue palsy were common post operative complications.

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Original Article

Depression Among Nurses in Rajshahi Medical College Hospital, Rajshahi

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ABSTRACT

Background: Nursing is a stressful, demanding, and taxing profession. Job stress is linked to higher rates of depression. Many of the factors that impact an individual's mental health, including significant stress, an odd sleep schedule, and lack of support. It is a normal part of a nurse's profession. In fact, nurses often experience these challenges at a higher level. Every day, nurses experience a great deal of stress. They face many problems at work, people relying on them for their care, and also tons of responsibilities piling up at home. Psychological stress is very common in hospital ward and associated with depression. Only few studies are done concerning mental health of Nurses in Bangladesh.

Objective: The study was carried out with a view to find out the prevalence of depression among nurses at Rajshahi Medical College Hospital, Rajshahi , Bangladesh.

Method: A cross sectional, questionnaire-based survey was carried out among the 200 nurses of Rajshahi Medical College Hospital, Rajshahi. The study was conducted between March to September 2020. The depression levels were assessed using Zung depression scale. Nurses were asked to complete the questionnaire and then the depression levels calculated.

Results: Out of the 200 questionnaires distributed to nurses 193 were returned completed, giving a response rate of 96.5 %. Out of the 193 respondents, 139 were females and 54 males. The mean age of study subjects was 40.67 years and a range of 26 to 55 years. Overall prevalence of depression in nurses was found to be 5.03 % in female and 3.7% in male nurses. The incidence of depression was found to be more among female nurses versus male nurses.

Conclusion: The overall prevalence of depression among the nurses was 4.66 percent. The prevalence of depression was 5.03 percent among female nurses versus 3.7 percent in male nurses.

Key Words: Depression, Nurse, Zung depression scale

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Introduction

Depression is common in our country. It is one of the most commonly diagnosed mental disorders. According to the World Health Organization (WHO), about 300 million people suffer from depression worldwide, which represents one of the leading causes of disability and global burden of diseases.[1] Even veteran nurses can find themselves feeling overwhelmed by their work. Nearly all healthcare professionals, regardless of their rank, are haunted by the fear of making a medical error. Unfortunately, many nurses are unable to leave this stress at the door when their shift is over, meaning it becomes a central part of their lives even when they are off the clock. Nurses are known to be the victims of tremendous mental stress. The personal and social sacrifice they have to make in order to maintain a good patient care result in a highly stressful environment puts them under a lot of stress. Depression imposes a considerable economic burden on the society; therefore, prevention plays an important role in saving resources and improving quality of life.[2] By 2030, depression is expected to become the second cause of disability and co-morbidities in developing countries [3], profoundly impacting people's performance and quality of life. Furthermore, an anticipation of age-of-onset is expected .[4]

From an etiopathogenetic standpoint, hereditary genetic and biochemical causes can cause depression, disturbing communication between nerve cells.[5] Social and family problems and employment conditions can be among the causes of depression.[6] This disease severely impairs familiar and social sphere, as well as professional working, leading, in some cases, to suicide.[7] Doctors, nurses, and other hospital service providers are among a group at high risk for developing depression. Doctors, nurses, and other hospital service providers are among a group at high risk for developing depression.[8] It is estimated that depression has a greater impact on job performance than chronic diseases, such as arthritis, blood pressure, backache, and diabetes.[9] Nursing is among occupational groups at high risk for depression due to harsh working conditions.[10] Several studies have examined the prevalence of depression among nurses. In 2 studies conducted in the USA, the prevalence of depression was reported to range from 18% to 41%.[11,12] However, only few studies are done in nurses of Bangladesh. Thus, we carried out a 20 questionnaire based cross sectional study to find out the prevalence of depression in nurses.

Method

The Study was a descriptive cross sectional study conducted at Rajshahi Medical College Hospital, Rajshahi, Bangladesh during the period of March 2020 to september 2020. 200 nurses were included in the study after randomized sampling. The recruited nurses were informed about the purpose of study and explained about the general instructions. Informed consent was taken prior to the study. The nurses were allowed to respond in their own time and privacy. The participation was entirely voluntary. The study was approved by the Research Ethical Committee. Then they were given the questionnaires which comprised of personal data, Zung Depression Inventory & stress inducing factors.

- Personal Data: This included age, sex, religion and home district.
- Zung Depression Scale: It is a 20 itemed self rated questionnaire which assess the level of depression symptoms.[13] It has already been used in primary care and community settings and as a screen for depression.[14] It contains 10 positive questions for e.g. “I eat as much as I used to” and 10 negative questions for e.g. “I notice that I am losing weight”. Answers thus obtained are scored between one to four for each question with a total score ranging from 20 to 80. A score less than 50 were considered to represent a case with no depression while a score ≥50 was considered to represent a case with depression.
- Stress inducing factors: After in-depth literature review and peer consultation, five most important stress inducing factors were selected. The nurses were asked to strike the factors they thought to be important from the following.
    a) Hospital stress
    b) Relationships problem
    c) Hectic lifestyle
    d) Future concerns
    e) Familial problem

Data were analyzed by using SPSS software (Version: 16) and then the results were interpreted.

Results

Out of the 200 questionnaires distributed to nurses 193 were returned completed, giving a response rate of 96.5 %. Out of the 193 respondents, 139 were females and 54 males. The mean age of study subjects was 40.67 years and a range of 26 to 55 years. Overall prevalence of depression in nurses was found to be 5.03 %. The incidence of depression was found to be more among female nurses versus male nurses which is shown in table.

Table 1: Distribution of the respondents by sex of the nurses

N=193	Total	Percentage (%)
No. of depressed Male	2	3.7%
No. of depressed Female	7	5.03%

Table 2: Distribution of the respondents by stress inducing factors

Factor	Total	Percentage (%)
Hospital stress	5	2.5%
Relationships problem	4	2.07%
Hectic lifestyle	4	2.07%
Future concerns	5	2.5%
Familial problem	3	1.55%

Discussion

The response rate of 96.5 % renders an adequate sample of population studied to fulfill the objectives of the study. The findings show the prevalence of depression (4.66%) in Rajshahi Medical College Hospital, Rajshahi . In another study conducted in China, the prevalence of depression among nurses was 38%.[15] Also in two studies conducted in Taiwan, the prevalence was 52.5% and 27.7%, respectively.[16,17] Canada, France, and the USA reported a prevalence rate of 10% to 40%.[18,19,20,21] Various factors, such as differences in personality, cultural, social, and working conditions may explain differences in the prevalence of depression among nurses in different countries around the world. Moreover, different methodological designs and different tools used for assessing depression could play a role in explaining these discrepancies. In our study, the prevalence of depression was found to be less in the nurses. This finding could be due to less hospital, familial and relationship stress . In Bangladesh a rural community-based study showed an overall prevalence of psychiatric disorders as 16.5%; notably, half of the sufferers had depressive disorders (8%) and a third had anxiety disorders (5%).[22] On the other hand, another study on females in a rural setting reported 16.4% had mental disorders with depression being

the single most common disorder (8.9%).[23] In table no: 01 we found that a gender difference regarding the association with depression was noted where female nurses reported a higher. This gender variation in depressive status in nurses could be the reflection of usual trend of high prevalence of depression in females as in the general population. However, the study has been able to throw some light about the mental health of nurses.There were several limitations to the study. Our study only included 193 respondents due to unavailability. Other stressors were not assessed. To achieve optimal health in registered nurses, it is crucial that occupational health nurses properly identify depression and additional risk factors for this disease. Because depression is complex and often associated with other chronic conditions, it may also be advantageous for occupational health nurses to form interdisciplinary health care management teams to strengthen early identification and treatment. It is vital for occupational health nurses to understand the implications behind these findings and create pathways to better health and workplace wellness.

Conclusion

The results revealed a picture of the prevalence of depression in nurses in Rajshahi Medical College Hospital in Bangladesh. They should be supported by counseling. By identifying the symptoms of depression and the stress inducing factors at an early stage hopefully the psychological morbidity among nurses can be prevented and the ones in morbid state can be helped to seek the professional.

Conflict of Interest

There is no conflict of interest (COI) among the authors in relation profession, financial or any other condition.

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Review Article

Remdesivir as a Possible Therapeutic Option for the COVID-19.

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ABSTRACT

A recent outbreak of coronavirus disease 2019 (COVID-19) caused by the novel coronavirus designated as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) started in Wuhan, China, at the end of 2019. The clinical characteristics of COVID-19 include respiratory symptoms, fever, cough, dyspnea, and pneumonia. The mortality rate has greatly increased in Italy, Spain and USA. However, there is no specific treatment against this new virus. Therefore, it is urgently necessary to identify effective antiviral agents to combat the disease and explore the clinical effect of antiviral drugs. No drugs or biologics have been proven to be effective for the prevention or treatment of COVID-19. Numerous antiviral agents, immunotherapies, and vaccines are being investigated for development of potential therapies. The antiviral agent remdesivir, nucleotide analogue prodrug, has broad-spectrum activity against viruses from several families. Having demonstrated potent antiviral activity against coronaviruses in preclinical studies, remdesivir emerged as a candidate drug for the treatment of the novel coronavirus disease COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, during the current global pandemic.

Keywords: Remdesivir, COVID-19.

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Introduction

Coronaviruses are non-segmented, enveloped, positive-sense, and single-stranded RNA viruses that commonly exist in mammals.[1] Human and animal coronaviruses comprise four genera, named α, β, γ, and δ. β-Coronaviruses include those that cause Middle East respiratory syndrome (MERS), severe acute respiratory syndrome (SARS), and coronavirus disease 2019 (COVID-19).[2] Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) interacts with pulmonary and parabronchial epithelial cells to enter through the epithelial cell membrane.[3] The virus primarily spreads through saliva droplets or discharge from the nose of an infected individual after coughing or sneezing and is the causative pathogen of COVID-19,[3] which appears to have a spectrum of clinical presentations that ranges from asymptomatic to severe respiratory failure.[4,5,6] SARS-CoV-2 caused an outbreak of novel pathogenic viral pneumonia in December 2019, which subsequently became a global pandemic.[7] Several preventive strategies were then implemented by governments worldwide in an attempt to control the spread of the virus, including but not limited to the shutting of air and sea borders, case identification and tracking, quarantining individuals with suspected infections, travel restrictions, big data integration, and facemask policies.[8,9,10.11] Furthermore, many drugs have been proposed to control and treat COVID-19.[12,13,14] SARS-CoV-2 enters cells through direct interactions between the viral S protein and the cellular receptor angiotensin-converting enzyme 2.[15,16] After entering a cell, the virus releases its genome, which is translated into viral replicase polyproteins and cleaved into functional proteins by proteases. Viral genome replication is mediated by the viral replication complex, which includes RNA-dependent RNA polymerase (RdRp).[17,18] Viral nucleocapsids are assembled from the packaged viral genomes and translated to form viral structural proteins, which are then released by exocytosis.[19 20, 21, 22]

Based on the currently understood mechanisms, many therapeutic drugs are being investigated and developed to

fight SARS-CoV-2 during the current COVID-19 pandemic. Several ongoing clinical trials are testing the efficacy of single and combination treatments.[23,24] Many different drugs are under evaluation,[25] including antiviral nucleotide analogs such as remdesivir,[26, 27, 28, 29, 30] antiviral nucleoside analogs such as favipiravir[31] and ribavirin,[32] protease inhibitors such as lopinavir/ritonavir,[33] antimalarials such as chloroquine and hydroxychloroquine alone[34] or combined with azithromycin,[35,36] biologics such as tocilizumab,[37] corticosteroids[38,39] colchicine,[40] nonsteroidal anti-inflammatory drugs such as indomethacin[41,42] and convalescent plasma.[43]

Based on several clinical trials and reports on its compassionate use, remdesivir is considered by many to be the most promising drug for the treatment of COVID-19.[44, 45, 46] Remdesivir is a prodrug of an adenosine analog, and its triphosphate form can be used as a substrate for many viral RdRp complexes.[47,48] It has been reported to inhibit viral RNA synthesis by a specific mechanism of delayed chain termination for MERS-CoV, SARS-CoV, and SARS-CoV-2.[49]

To date, there are no Food and Drug Administration (FDA)-approved drugs for COVID-19, however, in the USA, the FDA has authorized the emergency use of remdesivir to treat hospitalized adults and pediatric patients with suspected or laboratory-confirmed SARS-CoV-2 infection and severe COVID-19. Remdesivir has also been made available in the UK through the Early Access to Medicines Scheme (EAMS) after a positive scientific opinion from the Medicines and Healthcare Products Regulatory Agency. Similar arrangements have already been made by regulatory authorities in Japan. The EAMS scheme provides patients with COVID-19 and life-threatening or seriously debilitating conditions access to drugs that have not yet received licensing approval.[50] Additionally, several large-scale clinical trials on the compassionate use of remdesivir have been published with varying results.[26,27,28,30] In the current study, a PubMed search using a combination of the keywords “COVID-19” “SARS-CoV-2” and “remdesivir” was performed.

Remdesivir

Remdesivir is an investigational nucleoside analog that acts as a competitive inhibitor of viral RNA-dependent RNA polymerase.[13] It is a prodrug with a molecular formula of C27H35N6O8P and an exact mass of 602.[23] Da. In the body, remdesivir is transformed into an active molecule known as GS-441524, with a molecular formula of C12H13N5O4 (291.10 Da). Remdesivir was previously proposed for the treatment of Ebola [29,30,44] and is yet to be approved or licensed by the US Food and Drug Administration (FDA) or any other drug regulatory authority worldwide. The antiviral activities of remdesivir on RdRp have been reported against Ebola virus[36,37] MERS-CoV,[33] SARS-CoV,[33,34] and other coronaviruses such as CoV-OC43, CoV-229E, and PDCoV.[5]

Evidence from in vitro studies

In 2015, a study showed that remdesivir is an effective inhibitor of the Ebola virus.[29] Its half-maximal effective concentration (EC50), the drug concentration that induces a response halfway between the baseline and maximum after a specified exposure time, varied between 0.07 and 0.14 μM in Ebola-infected cells such as HeLa, HFF-1, HMVEC-TERT, and Huh-7.[30] Studies on the inhibitory effects of remdesivir against various viruses have been conducted using seven virus families, namely, filo-, paramyxo-, pneumo-, bunya-, arena-, rhabdo-, and flaviviruses.[31]Another study showed that phosphorylated GS-441524, the active molecule of remdesivir, inhibited feline infectious peritonitis in CRFK cells, with a half maximal inhibitory concentration (IC50; the drug concentration at which half of the peak inhibiting effect of the drug against a specific viral function is achieved) of 0.78 μ M.[32]

The RdRp sequences of SARS-CoV-2 and SARS-CoV display more than 80% similarity.[49,50] Therefore, it was suggested that remdesivir could potentially exert antiviral activities against SAR-CoV-2. Remdesivir was found to have an EC50 of 0.77 against SARS-CoV-2 in Vero E6 cells .[17] This activity of remdesivir was higher than that of the other drugs used in the study, such as ribavirin, penciclovir, favipiravir, nafamostat, nitazoxanide, and chloroquine, which showed EC50 values of 109.5, 95.96, 61.88, 22.50, 2.12, and 1.13 μ M, respectively.[17] Another study in Vero E6 cells also revealed that remdesivir inhibited the replication of SARS-CoV-2, with an EC50 of 23.15 μM, showing the strongest antiviral activity among the tested drugs.[39] In this study, the viral load was fit in a logarithmic scale under increasing remdesivir concentrations, rather than a linear scale reported previously.[17] These initial studies suggest that remdesivir inhibits the replication of SARS-CoV-2 and has the potential to be used in the treatment of COVID-19.

Evidence from in vivo studies

In 2016, an in vivo study was conducted using Ebola-infected rhesus monkeys (a non-human primate) and various doses of remdesivir intramuscular injections.[30] Post-exposure revealed that remdesivir exerted protective effects by inhibiting viral replication.[30] The concentration of form of remdesivir, was 10 μM in peripheral blood mononuclear cells after administration of 10 mg/kg remdesivir.[30] A study in Nipah virus-infected African green monkeys showed the protective effects of remdesivir: half of the remdesivir-treated monkeys (n = 4) developed mild respiratory symptoms and the other half recovered; those in the control group developed severe respiratory disease.[40]

Remdesivir has also been shown to exert antiviral activity against coronaviruses. Remdesivir treatment was found to reduce the viral load in MERS-CoV-infected Ces1c–/–hDPP4 mice and was phenotypically associated with improved pulmonary function and decreased likelihood of acute lung injury development in infected animals.[41] In addition, remdesivir inhibited MERS-CoV replication in the pulmonary organs of rhesus macaques and led to a reduction in lung lesions.[42] Remdesivir also reduced the viral load in the lung and improved the respiratory function of SARS-CoV MA15-infected mice.[34] A recent study showed that remdesivir administration to SARS-CoV-2-infected rhesus macaques improved pulmonary lesions, according to radiographs; reduced viral titers in bronchoalveolar lavage after 12 h of treatment; and reduced the viral load in the lungs after 7 days

of treatment. Moreover, the remdesivir-treated animals did not show any signs of pulmonary disease.[43]

Results from patients with COVID-19 and clinical trials

Historically, remdesivir was tested to treat patients with Ebola in a randomized clinical trial in the Democratic Republic of the Congo in 2018.[44] In 2020, remdesivir was included in the "Solidarity" international clinical trial conducted by the World Health Organization in an attempt to find an effective treatment for COVID-19.[51] As a timely response to the pandemic, patients with COVID-19 have been treated with remdesivir in emergency protocols. In the first patient with COVID-19 treated with remdesivir, a 35-year-old from Washington, pneumonia improved after 7 days of treatment.[45] In Seattle, USA, remdesivir was used as a compassionate drug to treat seven critically ill patients.[46] A larger study found that, following a 10-day course of remdesivir treatment (intravenous administration at 200 mg on day 1, followed by 100 mg daily), 68% (36 of 53) of patients with COVID-19 showed clinical improvement; however, there was no control group in this study.[47] Therefore, this information is insufficient to confirm the efficacy of remdesivir in treating patients with COVID-19.

To adequately assess the efficacy of remdesivir, clinical trials are ongoing in countries such as USA, Norway, Canada, France, and China. Although the length of treatment differs slightly, the dose of remdesivir is similar: 200 mg on day 1, followed by 100 mg for the rest of the treatment period.

The first randomized, double-blind, placebo-controlled, multicenter clinical trial was reported on April 29, 2020.[48] The study was conducted in China with 237 patients (158 in the remdesivir group and 79 in the placebo control group), and the primary endpoint was the time taken to achieve clinical improvement. The study revealed that treatment with remdesivir did not lead to a significant reduction in the time taken to achieve clinical improvement. In addition, mortality and viral clearance time in patients with severe COVID-19 were not significantly different from those in the placebo group, suggesting that remdesivir had poor clinical benefits. This further suggests that in COVID-19, viral propagation is not the main factor responsible for disease severity. On this account, the antiviral properties of remdesivir will not be beneficial. The severity of COVID-19 has been associated with the cytokine release storm,[52] suggesting that host immune responses play an important role in this event. Therefore, a combination of remdesivir with immunosuppressants (for example sarilumab, an IL-6 the inhibitor) and/or other antiviral agents might potentiate the antiviral activity of remdesivir and mitigate the immunopathological injury caused by excessive immune effectors.[52]

Nonetheless, during the same trial,[52] in remdesivir-treated patients with COVID-19, especially those treated within 10 days of symptom onset, faster clinical improvement was observed than that in the placebo group. Unfortunately, the study was terminated prematurely owing to the occurrence of more frequent adverse events in the remdesivir group than in the placebo group.[52] Considering these findings, the small sample size, and because the study was unexpectedly terminated, it may be insufficient to elucidate the efficacy of remdesivir.[53] Furthermore, the pharmacokinetics of remdesivir and its active metabolite in the respiratory tracts and/or other infected organs remain largely unknown in patients with COVID-19.[36]

The pharmacokinetic profile of remdesivir, particularly the concentrations of the active metabolite, GS-441524, in the respiratory tract or other infected tissues in patients with severe COVID-19 are unknown.[48] In addition, currently available data on remdesivir are lacking, in particular those in drug–drug, drug–gene, and drug–disease interactions. This information is important in predicting possible negative outcomes that may arise during treatment.

Conclusion

Remdesivir is a nucleotide analog prodrug that inhibits SARS-CoV-2 RdRp. Its viral activities against SARS-CoV-2 have been shown in both in vitro and in vivo studies. Remdesivir has been used in several countries as an emergency drug for patients with COVID-19, and some patients showed improved clinical outcomes.

Recommendation

However, large-scale clinical trials should be conducted to confirm the efficacy of remdesivir in treating patients with COVID-19.

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Case Report

Value of Duplex Ultrasound Scan to Assess IVC Obstruction and Arterial Insufficiency due to Liver Abscess

Hossain M M [1], Hosen M M A [2], Ahsan M S [3], Begum N [4], Ahmed P [5], Ahmed T [6], Alam S N [7].

ABSTRACT:
Liver abscess presenting with bilateral ankle edema is an unusual clinical presentation. Recently we have made such an unusual diagnosis of a patient as AKI with ascites due to vascular occlusive disease by an unusually very large liver abscess with the help of duplex ultrasound modality who was presenting with fever with upper abdominal pain and distention along with bilateral ankle edema in a tertiary level academic hospital.

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Introduction

Duplex ultrasound denotes the B-mode ultrasound scan along with Doppler study by which we can easily determine the anatomical abnormality of any internal organ as well as vascular flow and any obstruction by a real time imaging method.Ultrasound can reliably diagnose liver abscess (85% sensitivity).[1] Unusually a very large liver abscess may cause complete IVC occlusion and markedly reduced arterial flow which may produce AKI, ascites and bilateral ankle edema. In the recent past we have diagnosed such an atypical case by the help of duplex ultrasound. The patient was also treated by ultrasound guided aspiration with the help of alternating dilution of abscess cavity by normal saline solution and was cured within a one month follow up period. This is a rare clinical presentation in our experience and this report describes the importance of duplex study in rapid management planning of such a rare case.

Case report

A 37 years old male patient was admitted in medicine department of Rajshahi Medical College Hospital, a tertiary level medical college hospital of Bangladesh with the complaints of fever for 15 days and upper abdominal pain for the same duration. The patient was non-hypertensive, non-diabetic, non-anemic nor any previous cardiac illness. After hospital admission his urine R/M/E showed (+) albumin but no sugar and pus cell was 6-8 / HPF. Routine blood count reveals neutrophilic leukocytosis with normal RBC and Platelet counts. ESR was 35 mm in 1st hour and SGPT was 304 U/L. On the same day Ultrasound reveals a large liver abscess (about 17 x 16 cm) along with bilateral renal parenchymal disease and mild ascites and CxR shows right sided mild pleural effusion. The patient's RBS was 4.5 mmol/L with high serum creatinine level (5.0 mg/dl) and ultimately diagnosed as AKI due to septicemia with liver abscess and mild ascites. Only 200 ml pus could be aspirated from the abscess under USG guidance. Culture of the pus showed no growth. Subsequently his serum creatinine level was gradually high up (5.8 mg/dl) on the next day and the patient's condition was deteriorated. Then the patient was transferred to nephrology department for better management and the patient was sent for Doppler study of lower limbs from the Nephrology department. The patient was very ill looking and cachectic. On physical examination we found bilateral ankle edema (more on right) with tense and tender abdomen along with rapid respiratory movement. Doppler study showed markedly reduced arterial flow with luminal narrowing of all lower limb arteries but no atherosclerosis nor any evidence of PVD. Markedly dilated deep veins were also noted without any DVT. Subcutaneous tissue over and above the ankle joints was thick and edematous without any sign of cellulitis. Depending upon these Doppler findings we scanned the abdomen and found a large liver abscess which occupy almost entire right lobe and maximum part of left lobe that pressing over the inferior vena cava (IVC) and abdominal aorta (AA). The abscess completely occluded the IVC lumen without any venous return along with severe arterial narrowing and markedly reduced abdominal aorta flow due to pressure effect.

Figure-I: Shows a large liver abscess and bilateral ankle edema with ill looking face of patient before ultrasound guided aspiration of liver abscess.

Subsequently we found bilateral enlarged, swollen and hypoechoic kidneys consistent with acute renal parenchymal disease with mild ascites and right sided moderate pleural effusion. During this time Echocardiogram showed good LV systolic function without any cardiac abnormality. The pathophysiology of all these multi-system involvement was due to pressure effect of liver abscess on AA and IVC that causes markedly reduced blood flow through the abdominal aorta beneath the liver abscess to below onwards and complete venous obstruction but not due to septicemia. Pleural fluid study showed no malignant cell nor any Gram (+)ve or Gram (-)ve bacteria. Then the abscess was re-aspirated under USG guidance and by alternative use of normal saline dilutions. The abscess was multiloculated. About 3995 ml pus was aspirated from the abscess cavity by a total of 7 consecutive days. About 240 ml normal saline was used alternatively for dilution of abscess cavity. The patient was on conservative treatment during this intervention technique. Serum creatinine was gradually came to 3.8 mg/dl just after 1st day of aspiration then 1.7 mg/dl after 4th day and ultimately 1.1 mg/dl after 5th day of aspiration. After 7th aspiration day abscess cavity was almost empty and within this time about 2780 ml straw colored fluid was aspirated from right sided pleural effusion. Ultrasound scan after the final aspiration day revealed normal size kidneys with normal echogenicity without any ascites. Within this aspiration time patient's ankle edema was disappeared with normal respiratory rate without any crepitation or rhonchi. Abdominal pain and fever was also completely subsided. Patient became well. So, the patient was discharged from the hospital about 1 month after admission.

Figure-II: shows the complete disappearance of ankle edema with a well looking face after a consecutive 7 days ultrasound guided aspiration of liver abscess.

Following 7 days of discharge the patient was again came to us and about 1300 ml pleural fluid was aspirated from right side of chest and only 45 ml pus was aspirated from the abscess cavity. Follow up USG after 1 month of 1st aspiration revealed the abscess cavity was almost absent with very minimum amount of pleural effusion on right side and the patient was quite normal clinically and biochemically with normal S.creatinine level without any albumin in urine.

Discussion

Diagnostic ultrasound is a hazardless modality that can help both in rapid diagnosis as well as in treatment.Duplex ultrasound denotes the B mode ultrasound scan along with Doppler study by which we can easily determine the anatomical abnormality of any internal organ along with vascular flow and any obstruction in a real time imaging method. A liver abscess is defined as a pus-filled cavitary lesion in the liver that can develop from injury to the liver or an intraabdominal infection disseminated from the portal circulation.[2] Unusually a very large liver abscess may cause complete IVC occlusion and markedly reduced arterial flow by pressure effect which may produce AKI, ascites and bilateral ankle edema. B-mode diagnostic ultrasound alone cannot tell the vascular flow abnormality which may give the clue of primary route of pathophysiology. Duplex ultrasound scan is highly effective for the diagnosis of any vascular flow abnormality by which we can easily detect vascular occlusive disease.With refinement of image-guided techniques in recent years, needle aspiration has emerged as an appropriate alternatives to open drainage, providing similarly high success rates but with the advantages of a minimally invasive approach.[3] Ultrasound guided needle aspiration is believed to be as effective and safe as catheter drainage, but simpler and quicker to perform, with decreased risk of procedural complications and post-procedural sepsis.[4] The prognosis of pyogenic liver abscess (PLA) is dependent on the time of diagnosis.[5] Moreover, repeated aspiration incrementally increases the likelihood of management success following each aspiration.[6] Duplex study can give us the clue of diagnosis at the initial stage thereby we can avoid the delay of diagnosis and initiate appropriate treatment at an earlier stage, as it has a high risk of mortality in untreated patients (upto 19%).[7]

Conclusion

In conclusion, we can say immediate screening of each and every patient in emergency medical department presenting with fever, upper abdominal pain and ankle edema by duplex ultrasound can reduce the morbidity and mortality of patients as well as reduce treatment cost and save the time. Moreover, normal saline dilution during USG guided aspiration of multiloculated large liver abscess will be more fruitful of aspiration.

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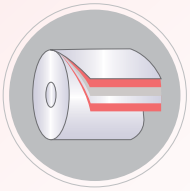

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