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Editorial

"Managing Dengue Syndrome in Children: Challenges for Paediatricians"

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EDITORIAL

Managing Dengue Syndrome in Children: Challenges for Paediatricians

Mirza Md. Ziaul Islam

Dengue is a mosquito-borne viral infection which causes flu-like illness, and occasionally develops into a potentially lethal complication called severe dengue. The global incidence of dengue has grown dramatically in recent decades. About half of the world's population is now at risk. Dengue is found in tropical and sub-tropical climates worldwide, mostly in urban and semi-urban areas. Severe dengue is a leading cause of serious illness and death among children. There is no specific treatment for dengue/severe dengue, but early detection and access to proper medical care lowers fatality rates.

Dengue viruses cause symptomatic infections or asymptomatic seroconversion, thus better termed as "Dengue Syndrome". Symptomatic dengue infection is a systemic and dynamic disease. Paediatrician usually fail to diagnose dengue when a child presents with fever in the first few days, and thus follow-up is missed. A superficial history and physical examination will fail to diagnose early dengue patient thus diagnosis of upper respiratory tract infection or viral fever are usually presumed. These children are more ill and unable to attend school or work, but these questions are missed.

There may be an overload of hospital admissions out of fear and panic among the parents of febrile children which will overwhelm the hospital system with many uncomplicated dengue cases which could be treated as out-patient basis. Clear guidelines for admissions should be followed diligently which may ensure effective gate-keeping in a dengue outbreak. It should be kept in mind that only 2 to 3 percent of dengue patients, the disease could progress very rapidly during the critical phase resulting in shock and death. Admission into the hospital should be limited for those during the febrile period who are unable to manage adequate oral hydration at home and those with co-morbid conditions with other risk factors.

It is a common practice to withheld investigations especially serial complete blood count during early febrile period, to detect the falling platelet count including changes in the level of hematocrit. Key message is a "complete blood count should be done at the first visit during dengue season with repetitions during next few days".

It has a wide clinical spectrum that includes both severe and non-severe clinical manifestations. Due to its dynamic nature, the severity of the disease will usually be apparent around defervescence which often coincides with the onset of the critical phase. For a disease that is complex in its manifestations, management is relatively simple, inexpensive and very effective in saving lives, so long as correct and timely interventions are instituted. Diverse clinical scenarios that arise during the different phases of the disease clearly assessed by the paediatricians leading to a rational approach in case management is key to a good clinical outcome.

The clinical management of dengue is more fraught than that of most other infectious tropical diseases. The uninitiated physician who has managed uncomplicated dengue cases may be lulled into believing that dengue is a "mild disease of thrombocytopenia" that requires no more than intravenous fluid therapy and platelet transfusions for a couple of days. When faced with severe dengue, these same physicians may be unprepared for the changing clinical, biochemical and hematological profiles that accelerate after the first few days of fever and therefore will not step up their vigilance during the critical period. The main hemodynamic elements of septic shock are maldistribution of blood volume resulting from an increased vascular capacitance and

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myocardial suppression, while dengue shock is hypovolemia with decreased vascular capacitance resulting from plasma leakage. Thus, the strategy of aggressive fluid resuscitation of septic shock is not applicable to severe dengue with plasma leakage. Volume replacement in children with dengue shock is a challenging management problem. Aggressive fluid resuscitation may indeed be harmful and should be limited to dengue shock with hypotension. There is a "narrow therapeutic index"; therefore, fluids have to be given timely, at the appropriate volume, rate, of the appropriate type (crystalloids, colloid and/or blood) and for the appropriate duration. Therein lies the challenge to physicians who are not familiar with the important practice of fluid titration through frequent and meticulous assessment. Progression of the disease through the critical phase should be tracked in hours of plasma leakage. Recognizing the cues to discontinue intravenous fluid therapy is just as important as knowing when to start it. Given time and hemodynamic stability, other issues such as thrombocytopenia, coagulopathy and raised liver enzymes will recover spontaneously or with supportive care.

The updated national guideline should be used by the paediatricians, to assess, identify, classify and manage patients. Advice regarding the warning signs and the urgency of seeking immediate medical attention should be clearly conveyed to the patients who are treated as out-patient basis. Furthermore, "stable vital signs" meaning normal blood pressure, urine output should be explained. Shock in the initial stage is difficult to assess unless the criteria is well understood by the treating paediatricians by detecting the cold extremities, feeble peripheral pulses and prolonged capillary refill time which are the earliest changes in shock. In compensated shock, the patient remains in quiet alert state until cerebral perfusion diminishes, and then if not appropriately resuscitated, develops "sudden" shortness of breath and restlessness or seizures followed quickly by a "sudden" collapse due to cardiac arrest and other complications.

Triage and management decision are crucial in determining the clinical outcome. Timely appropriate front-line management response not only reduces the number of undue hospital admissions but also saves the lives.

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LEADING ARTICLE

Impact of COVID-19 on the Symptoms of Asthma in Children and Its Management

Md. Jahangir Alam

Introduction

The current outbreak of coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), started in or around December, 2019, in Wuhan.[1] On January 30th, 2020 the World Health Organization (WHO) declared COVID-19 a pandemic health emergency.[2] Since then, COVID-19 has continued to spread quickly and has now become the most dangerous pandemic in over 100 years. Chronically diseased patients are particularly vulnerable to severe complications and so need special attention to prevent increased morbidity and mortality.[3] Asthma is a chronic disease, and patients may experience decreased access to healthcare due to restrictions on public movements, lockdowns and diversion of healthcare resources to the care of patients affected by COVID-19.[4] Patients with asthma are hypothesised to have high susceptibility to, and increased severity of, SARS-CoV-2 infection due to their impaired immune response and the likelihood of respiratory exacerbation when infected by respiratory viruses, but little evidence has supported this theoretical risk.[5]

Based on the available literature, it is believed that children could be spared from COVID-19 likely due to the highly expressed thymic repertoire and efficiently activated immune response against SARS-COV-2.[6] Out of the total cases, children accounted for only 1.2% in Italy, 5% in the USA and 2% in China.[7]

Several factors have been hypothesized to offer an explanation on the low severity of the disease in the pediatric age group. First, seasonal coronaviruses may give a protective immune response toward SARS-CoV-2.[8] Second, children show low expression or function of the angiotensin-converting enzyme 2 (ACE 2) receptor.[9] Third, in children there are "innate" B cells, called immune naïve cells, that respond to novel antigens, producing effective immune responses against the pathogen and possibly contributing to the lower pathogenicity of SARS-COV-2 in the pediatric age.[10] Fourth, in the pediatric age immature B cells secrete anti-inflammatory cytokines such as IL-10, which may contribute to reducing the immune-mediated tissue damage.[11] Moreover, the lower severity of COVID-19 in children with respect to adults could be explained by a stronger innate immune response and by the lack of co-morbid conditions in most subjects.[7]

Therefore, in asthmatic patients some potential protective mechanisms against SARS-COV-2 have been hypothesized, like type 2 immune response, number of eosinophils, overproduction of mucus, and asthma treatment, along with behavioral factors not strictly related to asthma, such as social distancing, hygiene measures and wearing facemasks, that contribute to reduce the individual susceptibility to SARS-COV-2 infection.

Pathogenesis of COVID-19

SARS-COV-2 necessitates two proteins for entry into the host cell. The virus attaches to the ACE 2 receptor; subsequently, the host trans-membrane protease serine 2 (TMPRSS2) splits up the spike protein, expressed on the viral envelope, into two segments, allowing fusion of SARS-COV-2 to the cellular membrane and its penetration into the cell. The binding of SARSCoV-2 to ACE 2 receptors produces a marked down-regulation of these molecules, whose protective effects on the human body have been recognized. In fact, after its entry into the host cells, the activated innate immune

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response prompts release of pro-inflammatory cytokines, which recruit effector cells like neutrophils, macrophages, etc. In the context of the adaptive immune response, antigen-presenting cells (APCs) present viral antigens to T cells, eliciting differentiation from immature cells to mature cells (Cytotoxic T cells and Natural Killer cells) that might contribute to killing virus-infected cells. If the adaptive immune responses are insufficient, innate immune responses can be reinforced through a cytokine storm that is responsible for severe multi-organ damage.[12,13] In case of low-dose virus infection, efficient T- and B-cells responses and neutralizing antibodies could lead to rapid viral clearance. By contrast, high-dose virus exposure may account for severe disease and delayed viral clearance. This can be attributed to lymphopenia, which determines inadequate T- and B-cells responses, eventually followed by a cytokine storm and multiorgan failure.[14]

Pathogenesis of Asthma

Asthma is a respiratory disease characterized by chronic inflammation of the airways with bronchial hyper-responsiveness to several stimuli, mucus overproduction, recurrent episodes of wheezing, respiratory distress, and cough, associated with reversible airway obstruction. Asthma is one of the most common chronic diseases worldwide, affecting more than 300 million individuals, and the incidence is growing, particularly in developed countries.[15] Asthma remains one of the highest causes for school absence and hospital admissions, imposing a high socioeconomic burden, and impairing quality of life of children and their families.[16,17]

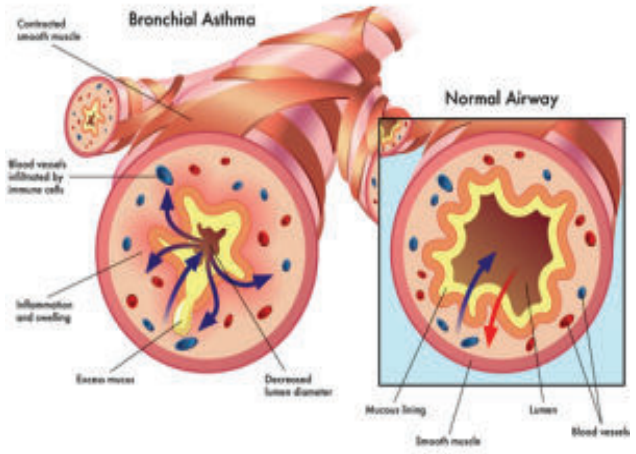

Fig.-1: Airway changes in Asthma

Because of the tendency for disease exacerbation elicited by common respiratory viruses including Rhinovirus, Respiratory Syncytial Virus, Influenza virus, Parainfluenza virus, Adenovirus, human Bocavirus, and Coronaviruses[18] and a deficient antiviral immune response that is evident in asthmatic patients.[19,20] the latter should potentially have increased vulnerability to SARS-COV-2 infection. This could be sustained by the deficient type I Interferon (IFN) responses observed in patients with severe asthma. However, some studies have shown that asthma is not a risk factor in patients with COVID-19.[21] In the study by Zhang et al[22] involving 140 community infected COVID-19 subjects, asthma was not reported by any of the patients. Similarly, Dong et al[23] in a case series of 2,135 pediatric patients with COVID-19, did not report any case of asthma. In the Confidence study, which included 100 pediatric patients with COVID-19, chronic respiratory diseases did not appear as risk factors.[24]

Protective factors against SARS-COV-2 infection in children with Asthma

Some protective factors against SARS-COV-2 infection have been hypothesized in patients with allergic asthma, such as T2 immune response (Fig.-1), overproduction of mucus, and asthma treatment.

Type 2 immune response

The T2 immune response in asthmatic patients might counteract the COVID-19 cytokine storm. According to Kimura et al[25] in airway epithelial cells of patients with allergic asthma ACE 2 is reduced and TMPRSS2 is increased thanks to IL-13 exposure. In addition, patients with activated Th2 immune responses showed decreased expression of ACE 2 in airway epithelial cells, inversely correlated with T2 cytokine levels and Th2 signature molecule expression.[25] In the study by Sajuthi et al[26] nasal airway transcriptome and network co-expression analysis were used to detect cellular and transcriptional factors of ACE 2 and TMPRSS2 genes in a cohort of 695 subjects with asthma and healthy controls between 8 and 21 years of age. They found that Th2 inflammation had a major role in ACE 2 down-regulation as well as in TMPRSS2 up-regulation. The study also showed that ACE 2 expression was marked only in secretory cells and ciliated cells, whereas TMPRSS2 was expressed in all epithelial cell types. Overall, these results suggest that Th2 immune responses may be a protective factor against SARS-COV-2 infection by causing ACE 2 down-regulation.[26]

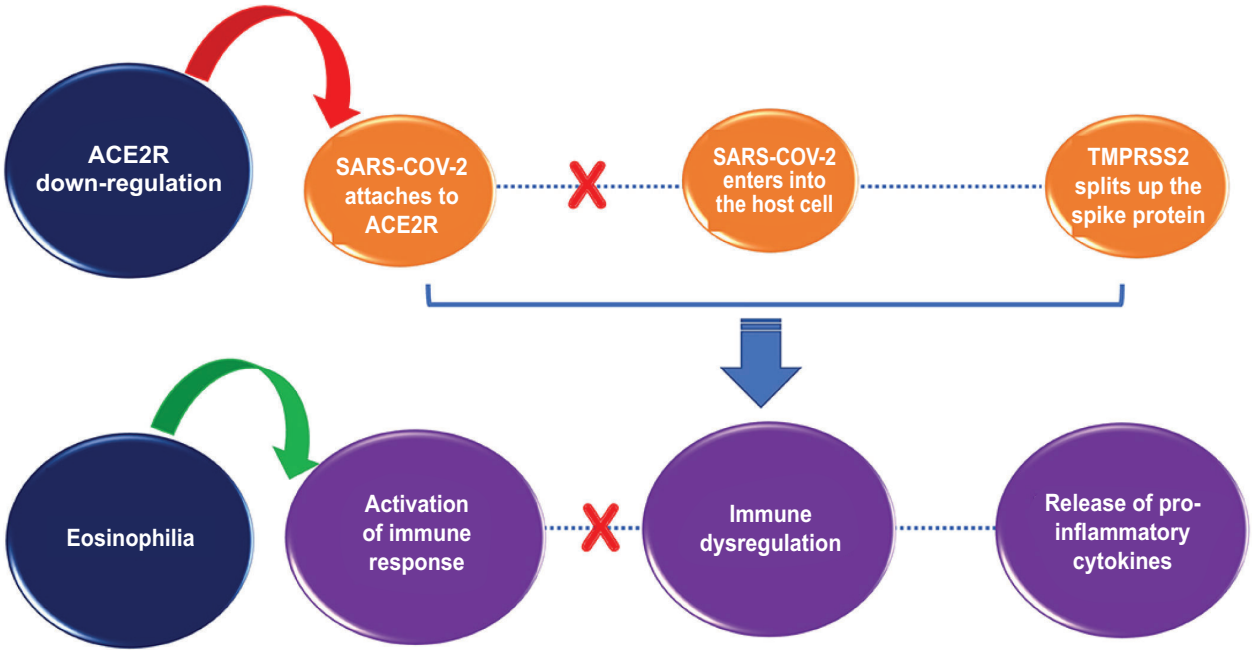

Fig.-2: *T2 immune response*

Additionally, since eosinopenia has been observed in COVID-19 patients, the increased number of eosinophils in asthmatic patients could have a protective role against SARS-COV-2. Though the relationship between eosinophil levels and COVID-19 is still not clear, during the pandemic it is important to monitor eosinophil counts and the clinical course of COVID-19 in patients with asthma treated with biological drugs responsible for decreased eosinophil levels.[27]

Overproduction of mucus

Mucus hypersecretion could be recognized as another hypothetical protective factor against COVID-19 because it acts as the first line of defense against infection, thereby preventing SARS-COV-2 from reaching the distal airways and entry into the alveolar type 2 cells, which predominantly express ACE 2 in the lung. In asthma there is increased expression of MUC5AC,[28] which has been proved to give protection against influenza infection in a murine model. However, not all patients with asthma show mucus overproduction; thus, mucus hyperproduction may only give protection in some patients.

Impact of Asthma treatment during COVID pandemic

Inhaled corticosteroids (ICS) are the first line treatment of asthma. One study hypothesized that ICS could increase antiviral immunity in treated patients.[29] There is also evidence that ICS may down-regulate both ACE 2 and TMPRSS2 expression, thereby decreasing binding of SARS-COV-2 to receptors on the airway epithelium cells.[30] Moreover, ICS suppress virus replication and cytokine production. Additionally, the combination of formoterol, glycopyrronium and budesonide has been shown to inhibit seasonal coronavirus replication and cytokine production.[31]

Allergen immunotherapy (AIT) suppresses T2 immune responses and controls allergic inflammation by stimulating T regulator cell responses and preventing tissue homing and degranulation of mast cells, basophils and eosinophils.[32] Therefore, it could be supposed that AIT might play a role in preventing a cytokine storm. In recent studies, the monoclonal antibody against human IgE Omalizumab has been suggested to have a potential effect on antiviral responses by reducing susceptibility to respiratory virus infections.[29]

Therefore, in light of the abovementioned data and according to the Global Initiative for Asthma Guidelines (GINA) recommendations, children with asthma should continue their treatment to prevent asthma exacerbations due to SARS-COV-2 infection, undergoing pulmonary function tests when needed to guide management.[33]

Impact of the implementation of lockdown measures on asthma outcomes

The ongoing COVID-19 pandemic has had a significant impact on access to and use of health services. Data from US hospital records and online surveys of health-care providers have documented major reductions in emergency room (ER) visits, uptakes of follow-up visits, prescriptions, treatment adherence, and asthma control.[34] Similarly, hospital records analysis in Japan revealed a decrease in asthma hospitalisations during the pandemic.[35] Such reductions likely reflect the combined effects of stay-at-home orders, reassignment of health services, fear of contagion or reduction of severe asthma attacks. A recent multicentre case-control analysis of asthmatic children attending outpatient visits showed improved asthma outcomes and control during the COVID-19 pandemic. Control measures during lockdown likely would have reduced exposures to respiratory viruses that have been associated with 80% of asthma exacerbations in children, with rhinoviruses being particularly important.[36]

Effect of preventable measures of COVID -19 in child with Asthma

In order to mitigate COVID-19 disease transmission, unprecedented disease prevention measures were implemented wordwide. Children have adopted different more hygienic lifestyles such as wearing masks and frequently using disinfectants. Undoubtably, these practices can effectively curb viral transmission. However, there are studies showing that using N95 or KF94 masks increases the risk for chronic disease patients with impaired pulmonary function and that frequent disinfectant usage may affect the respiratory tract of newborns, increasing the risk of pediatric asthma.[37] Zok et al[38] showed that weekly usage of air fresheners may also be a risk factor of severe asthma onset. Considering the fact that 60–80% of allergic asthma cases involve pulmonary asthma, minimizing exposure to allergens should be the most effective method to control asthma. The frequent usage of alcoholic and chlorinated allergic disease prevention materials may be a risk factor of severe asthma attacks, contributing to the increase in the incidence of severe asthma attacks among children during the COVID-19 pandemic. Since certain disease prevention practices such as masks and disinfection are expected to persist even after the pandemic, we have to design ways to minimize the impacts of these measures on pediatric asthma patients so as to achieve effective asthma management.[39]

Conclusion

Based on the available literature, whether asthma could really be considered a protective condition against SARS-COV-2 infection in children is still not clear. Therefore, further studies are required to clarify the impact of asthma on COVID-19 susceptibility and severity, especially in pediatric population where the available evidence is very limited.

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ORIGINAL ARTICLE

Hepatitis A: Leading Cause of Paediatric Acute Liver Failure in Bangladesh

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Abstract

Background: *Pediatric acute liver failure (PALF) is a multisystem disorder that gives rise to severe liver failure within days or weeks and occurs in children without pre-existing chronic liver disease. The etiology of PALF varies with age group and geographical area.*

Objectives: *This study was aimed to evaluate the etiological factors of PALF in Bangladeshi children.*

Methods: *This observational study was conducted at the Department of Paediatric Gastroenterology & Nutrition, Bangabandhu Sheikh Mujib Medical University, Bangladesh, from 2017 to 2020. Twenty-six PALF patients were included, purposively, excluding the acute-on chronic liver failure cases. Demographic data, vaccination history, and other information regarding etiology and complications were recorded. During hospital stay following investigations were performed: Serum bilirubin, liver enzymes, prothrombin time, serum albumin, serum creatinine and electrolytes. Fisher's exact test determined the association between etiologies of PALF and past histories along with other descriptive statistics using the open-source PSPP software.*

Results: *The average age of the 26 studied patients was 8.6±3.5 years, and 73.1% belonged to 5-12 years of age group. Half of the patients had a history of taking street food or unsafe water. Only six patients had a history of ingestion of herbal medicine. None of the patients had history of vaccination against Hepatitis A. The etiology of PALF patients varied. About 54% of the studied patients had HAV infection, in 23.1% etiology was not determined. About 71.4% of the study patients with HAV infection had a history of taking street food or unsafe water, and this association was statistically significant.*

Conclusion: *This study found that hepatitis A virus infection is the leading cause of paediatric acute liver failure in Bangladesh. Timely preventive measures may help in lowering fatality from liver diseases in children in Bangladesh.*

Keywords: *Paediatric acute liver failure, liver function test, hepatitis A.*

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Introduction

Liver diseases are widely neglected health issues in developing countries, which carry the highest-burden but receive little attention.[1] Acute liver failure (ALF) is a fatal disorder in previously healthy children, despite improvements in intensive care management and the development of other therapeutic modalities.

Hepatitis A virus (HAV) is notorious for being the most typical cause of ALF in children in the developing world, as is evident from the recent study of Sood et al and previous studies in the Indian subcontinent.[2,3] This result is in stark contrast to the western literature, where HAV contributes only 1% to pediatric ALF etiology.[4] The HAV infection fatality ratio is estimated to range between 0.1-2% depending on the age; however, the mortality rate of ALF due to HAV soars to 30-50%.[3] This result poses further importance in our country, where affordability for specialized intensive care and liver transplantation is not available.

Identifying the etiological factors and taking preventive measures might be an effective way to minimize the loss of life from liver diseases in a developing country, like Bangladesh, where resources are limited.

Materials and Methods

This observational study was conducted at the Department of Paediatric Gastroenterology & Nutrition, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh, from May 2017 to February 2020. Twenty-six paediatric acute liver failure (PALF) patients were selected, excluding all the cases of acute-on chronic liver failure (ACLF) patients. Demographic data, vaccination history, and other related information regarding etiology and complications were recorded in a standard data sheet. Serum bilirubin, liver enzymes, prothrombin time, international normalized ratio (INR), albumin, creatinine, electrolytes were carried out to establish the diagnosis and find the complications. Viral markers, screening for Wilson Disease and invastigations to diagnose autoimmune hepatitis were performed to find the etiologies. Collected data were checked manually and processed by open-source PSPP statistical software. Fisher's exact test determined the association between etiologies and patients' past histories. Every ethical concern was discussed with the parents. Parents were informed about the nature and purpose of this study in an understandable local language. Then a written consent was obtained from the parents of each child to be included in the study. Every precaution was taken so that the study will not cause any harm or delay in the treatment.

Results

Twenty-six PALF patients were enrolled in this study. About 65.4% of the studied patients were male, and the rest 34.6% were female. The average age was 8.6±3.5 years. The majority (73.1%) of the studied patients were from the 5-12 years of age group.

Table I

Demographic data, history, etiology and outcome of the studied patients (N=26)

Features		Number	Percentage
Age	<5 years	2	7.7
	5-12 years	19	73.1
	>12 years	5	19.2
Gender	Male	17	65.4
	Female	9	34.6
History	History of taking street food or unsafe water	13	50
	History of ingestion of herbal medicine	7	26.9
	History of vaccination against Hepatitis A	0	0
	Family history of liver disease	4	15.4
	History of vaccination against Hepatitis B	19	73.1
Etiology	Hepatitis A virus	14	53.8
	Indeterminate	6	23.1
	Hepatitis E virus	4	15.4
	Coinfection with multiple hepatotropic viruses	2	7.7
Outcome	Died	14	53.9
	Survived	12	46.1

Half of the patients had a history of taking street food or unsafe water. Only six (26.9%) patients had a history of ingestion of herbal medicine. None of the patients had any history of vaccination against Hepatitis A. Only four (15.4%) patients had a family history of liver disease, and one patient had a history of sibling death by liver disease. Nineteen (73.1%) out of the twenty-six PALF patients had a history of Hepatitis B vaccination. About 81% of the patients had a history of jaundice (Table I).

The etiology of PALF patients varied; infection with Hepatitis A virus (HAV) was the most common cause. About 54% of the studied patients had HAV infection, and the etiology of 23.1% of cases was indeterminate (Table I).

Only four patients had moderate anaemia, and most of the patients had mild anaemia. Physical examination revealed jaundice in majority (65.4%) of the patients. The liver was palpable in 73.1% of patients, and 38.5% of patients had palpable spleen. Only two (7.7%) patients had tense ascites. Clinical features of coagulopathy (bleeding from any site) were present in 23.1% of patients. About 81% of the study patients had grade I & II encephalopathy. Only two (7.7%) patients had grade IV encephalopathy. Among the haematological parameters, an INR of more than 2.3 was found in 69.2% of patients. Among the biochemical parameters studied, serum ALT was raised in 84.6% of patients, and serum bilirubin was high (> 3 mg/dL) in about 81% of the study population (Table II).

Result revealed that there is significant association between a history of taking street food or unsafe water with HAV infection. None of the other past histories had any significant association with HAV infection (Table III).

Table II
Clinical features of the studied patients (N=26)

Features	Number	Percentage
Anaemia		
Absent	3	11.5
Mild	19	73.1
Moderate	4	15.4
Jaundice	17	65.4
Coagulopathy (bleeding from any site)	6	23.1
Encephalopathy	26	100
Palpable liver	19	73.1
Palpable spleen	10	38.5
Ascites		
Absent	8	30.8
Mild	16	61.5
Tense	2	7.7
INR (n=23)		
<1.7	3	11.5
1.7-2.3	2	7.7
>2.3	18	69.2
Serum ALT (IU/L) (n=24)		
Normal (<65)	2	7.2
Raised (>65)	22	84.6
Serum bilirubin (mg/dl)		
>3	21	80.8

Table III
Association between past histories and HAV infection of the studied patients (N=26)

Variable	Etiology of PALF		p value
	HAV (n=14) n (%)	Other (n=12) n (%)	
History of taking street food or unsafe water			
Present	10 (71.4)	3 (25)	0.026*
Absent	4 (28.6)	9 (75)	
History of ingestion of herbal medicine			
Present	6 (42.9)	1 (8.3)	0.081
Absent	8 (57.1)	11 (91.7)	
Family history of liver disease			
Present	1 (7.1)	3 (25)	0.306
Absent	13 (92.9)	9 (75)	

* Statistically significant
Fisher's exact test

Discussion

This study excluded all the cases of ACLF and only included the cases of ALF. Hence, only twenty-six patients were enrolled during this 34 months' study. Among the studied patients, 73.1% of the patients belonged to the 5 to 12 year age group. The mean age was 8.6±3.5 years, with data ranged from 4.0 - 16.0 years. This finding is similar to the finding of a recent study by Mazumder et al in Bangladesh.[5] The mean (±SD) age of the present study population is also very close to the findings of Öztürk et al.[6] This age group (school-going children) is more prone to taking unhygienic street foods and unsafe water. This study found that 50% of the PALF patients had a history of taking street food and unsafe water.

The most common presenting features among the studied patients were hepatomegaly (73.1%) and jaundice (65.4%). Other presenting features were splenomegaly (38.5%), mild to moderate anaemia (88.5%), and ascites (68.5%). These findings are similar to the findings of Lee et al.[7]

According to Squires, children are increasingly exposed to a variety of over-the-counter, prescription, and herbal medications as well as environmental toxins and recreational drugs.[8] The present study also found that 26.9% of patients had a history of ingestion of herbal medicine.

Among the studied patients, 53.8% had an infection with the Hepatitis A virus. Mazumder et al also showed that viral hepatitis was the most common cause of ALF in Bangladeshi children.[5] In a recent study by Sood et al,[2] HAV accounted for 46.5% of acute liver failure, similar to previous studies from India that have shown that HAV is the etiology in 51% of ALF.[3,9-11]

Stravitz et al presented that viral hepatitis A, hepatitis B, and hepatitis E are the leading causes of acute liver failure in developing countries.[12] HAV infection incidence rate is heavily related to socioeconomic indicators and access to safe drinking water. In developing countries with poor sanitary and hygienic conditions, HAV infection is highly endemic. Areas of high endemicity include most of Africa, Asia, and also Central and South America. Conditions that contribute to the propagation of the virus among young children in these areas include household crowding, insufficient sanitation, and inadequate pure water supplies.[13-15] About 71.4% of the study patients with HAV infection had a history of taking street food or unsafe water, and this association is statistically significant. HAV vaccination is not included in the government vaccination program in Bangladesh. These factors could be the underlying causes of increased rate of Hepatitis A virus injection. A contemporary study by Lal et al[16] also found HAV is the commonest cause of PALF. HBV or HCV infection is not found in the studied patients as an underlying cause. Absence of HBV infection may be due to the vaccination program of the country that includes the HB vaccine. As we have excluded all the cases of chronic liver disease, we didn't find any HCV cases.

Poddar et al[17] recommended implementing the HAV vaccine in the universal immunization or targeted immunization based on the endemicity pattern. The Cost-effectiveness of universal HAV vaccination is undoubtedly evident in middle-income countries with intermediate endemicity, and targeted immunization is better suited for low endemicity regions.[18]

With an almost homogeneous population, high endemicity of HAV, and no option for liver transplantation facilities, we suggest that the HAV vaccine should be included in the government immunization program.

Conclusion

HAV infection is the major cause of PALF found in this study. Mass HAV vaccination and awareness about proper hygiene and safe drinking water may be beneficial in this regard.

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ORIGINAL ARTICLE

Hypocalcemic Seizures in Infancy and its Relationship with Maternal Vitamin D Deficiency

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Abstract

Background*: Hypocalcemia accounts for a large number of seizures in infants presented at the emergency department of our hospital.*

Objective*: To evaluate the role of Vitamin D deficiency as the etiology of hypocalcemic seizures in infancy and its relationship with maternal Vitamin D levels.*

Methods*: Cross sectional hospital based study over a period of 35 months from July 2016 to June 2019. Total 60 infants with hypocalcemic seizures were enrolled into the study. Blood samples were taken for serum total calcium, inorganic phosphate, alkaline phosphatase, albumin, 25(OH)D and PTH from the child. Maternal serum 25(OH)D levels were measured as well.*

Results*: The mean age of the studied infants was 3.6 (±1.2) months. All patients had low total calcium (mean 6.5 mg/dl) and most of them had low inorganic phosphate (mean 3.5 mg/dl), while all of them had raised alkaline phosphatase (mean 1093.50 IU/L) and PTH levels (mean104 pg/ml) at presentation. Forty percent of infants were severely deficient and 60% were deficient in vitamin D; none of them were vitamin D sufficient. Among their mothers, none were sufficient, 10% were insufficient, 45% were deficient, and 45% were severe deficient of vitamin D. Neonatal 25(OH)D showed strong negative correlation with their serum PTH levels and strong positive correlations with maternal serum 25(OH)D levels.*

Conclusion*: All infants in our setting presented with hypocalcemic seizures were found due to Vitamin D deficiency and it was mostly related to maternal Vitamin D deficiency.*

Keywords*: Hypocalcemia, seizures, 25-hydroxycholcalciferol.*

Introduction

Seizures are commonly encountered as emergency in pediatric population occurring in 4-7% of infants and children.[1] In the developing countries, hypocalcaemia has been found as a major biochemical cause of seizures in infancy[2,3], which constitutes 25.6% of total afebrile seizures in paediatric age group.[4] Among the notable causes of hypocalcemic seizures, prematurity, birth asphyxia, exogenous phosphate load, magnesium deficiency, hypoparathyroidism, malabsorption syndromes, pancreatitis, hypoalbuminemia (pseudohypocalcemia) and vitamin D deficiency are well documented.[5] Furthermore, hypocalcemia due to vitamin D deficiency constitutes an important cause of infantile seizures in developing countries.

Infants are more vulnerable for vitamin D deficiency because of their high rate of skeletal growth.[2,3,6]

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Vitamin D stores in young infants mostly depend on intrauterine accretion and breastmilk. Breastfed infants born to and nursed by vitamin D deficient mothers found to have low serum 25(OH) D levels.[7,8] Maternal vitamin D deficiency may therefore be an important risk factor for hypovitaminosis D in early infancy, thereby causing in hypocalcemia and seizures in this age group.[9,10]

The role of vitamin D has been found in central nervous system as antiepileptics which are mediated through vitamin D receptors.[11] Due to its prolonged half life serum 25 (OH) vitamin D level is the best available biomarker for the diagnosis of vitamin D deficiency. Vitamin D concentrations of >20 ng/mL (50 nmol/L) are considered as sufficient, between 12-20 ng/mL (30-50 nmol/L) as insufficient and <12 ng/mL (<30 nmol/L) as deficient.[12]

There is paucity of data studying association of hypocalcemic seizures in infants with hypovitaminosis D in Bangladesh. This study was conducted to evaluate the role of Vitamin D deficiency in the etiology of hypocalcemic seizures in infancy and its relationship with maternal Vitamin D levels.

Materials and Methods

Infants aged 15 days to 12 months of age, presenting with seizures at emergency department of Bangladesh Shishu Hospital & Institute, Dhaka were assessed for the study between July, 2016 and June, 2019. Written informed consent was taken from the mothers enrolled in the study.

Only infants of full term deliveries had normal birth weight and without any congenital malformation were recruited. Infants with history of intake of calcium or vitamin D supplementation, infants with other causes of seizures-meningitis, hypoglycemia, dyselectrolytemia, structural brain malformation, history of birth asphyxia and infants of diabetic mothers were excluded from the study. Finally excluding above causes these who were diagnosed as hypocalcemic were included in the study.

Hypocalcemia was considered to be the cause of seizures when total serum calcium level was <8 mg/dL, with normal levels of serum albumin. The study was approved by the Ethical Review Committee of the hospital.

Mothers known to have hepatic, renal or bone disorders, malabsorption or intake of any drugs or supplements known to affect the calcium-vitamin D-PTH axis were excluded from the study. A structured questionnaire was used to obtain relevant information for Infants and mothers. The selected mother-infant pairs underwent necessary clinical, biochemical and hormonal assessment on the first visit.

Blood sample was drawn from the children by venipuncture with all aseptic precautions without using tourniquet for total calcium, inorganic phosphate, alkaline phosphatase, albumin, creatinine, 25(OH)D, PTH and only for 25(OH)D from the mothers. Routine investigation to exclude other causes of seizures in Infants were also performed accordingly. Total calcium, inorganic phosphate, alkaline phosphatase, albumin and creatinine were analysed by BECK MAN COULTER AU-680, whereas 25(OH)D and PTH were analysed with ARCHITECT-1000 plus by Chemiluminescence method. Vitamin D concentrations of >20 ng/mL are considered as sufficient, between 12-20 ng/mL as insufficient, <12 ng/mL as deficient and severe deficiency as levels less than 5 ng/mL.[12,13]

We analyzed data using the Statistical Product and Service Solutions version 26.0 software (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp). The categorical variables were represented as percentages and measurable variables as the mean±standard deviation (SD) or median (interquartile range, IQR). Pearson correlation test was used to see the correlations of neonatal serum 25(OH)D levels with other variables. *P* value <0.05 was considered statistically significant.

Results

Total 60 infants with hypocalcemic seizure were enrolled in this study. The mean age of the studied neonates was 3.6 (±1.2) months, youngest one was 2 months old and oldest one was 8 months old. They consisted of 36 (60%) males and 24 (40%) females. All of our patients were breastfed with 36 (60%) exclusive breastfed. Neither the infants nor the mothers were receiving calcium or vitamin D supplementation. Most of our patients were of middle and lower social classes. All the infants and mothers had history of limited sun exposure.

All patients had low total calcium (mean 6.5 mg/dl) and most had low inorganic phosphate (mean 3.5 mg/dl), while all of them had raised alkaline phosphatase (mean 1093.50 IU/L) and PTH levels (mean 104 pg/ml) at presentation (Table I).

Table I
Characteristics of the studied neonates (N=60)

Variables	Mean ± SD or Median (IQR)	Range
Age (months)	3.6 ± 1.23.5 (3.0-4.0)	2.0-8.0
S. Calcium (mg/dL)	6.72 ± 0.696.80 (6.20-7.38)	5.6-7.9
S. Inorganic Phosphate (mg/dL)	3.39 ± 0.593.50 (3.05-3.80)	2.1-4.5
S. ALP (IU/L)	1222.03 ± 455.821093.50 (977.25-1244.50)	685-2678
S. PTH (pg/mL)	111.25 ± 25.94104.00 (93.25-123.00)	82-187
S. 25(OH)D (ng/mL)	5.35 ± 1.595.65 (4.13-6.28)	1.4-9.8
Maternal S. 25(OH)D (ng/mL)	6.10 ± 3.175.45 (3.90-7.40)	1.5-14.6

Forty percent of neonates were severely deficient and 60% were deficient of vitamin D; none of them were vitamin D sufficient. Among their mothers, none were sufficient, 10% were insufficient, 45% were deficient, and 45% were severe deficient of vitamin D (Fig.-1).

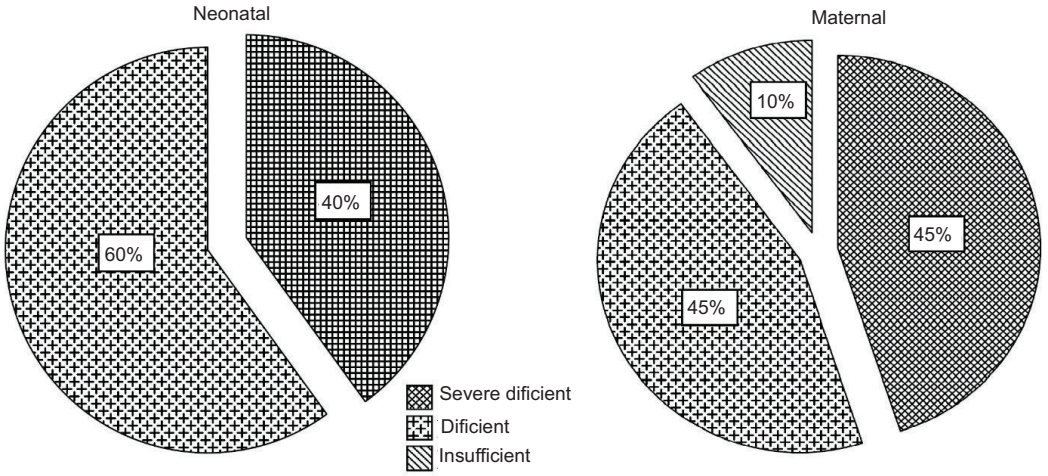

Fig.-1 *Neonatal and maternal vitamin D status*

Correlations of serum 25(OH)D levels with other variables are shown in Table-II. Serum 25(OH)D showed strong negative correlation with their serum PTH levels and strong positive correlations with maternal serum 25(OH)D levels.

Table II
Correlations of neonatal serum 25 (OH) D levels with other variables

Variables	Pearson Correlation	p value
Age (months)	0.110	0.404
S. Calcium (mg/dL)	0.017	0.896
S. Inorganic Phosphate (mg/dL)	0.025	0.851
S. ALP (IU/L)	0.162	0.217
S. PTH (pg/mL)	-0.631	<0.001
Maternal S. 25(OH)D (ng/mL)	0.279	0.031

Simple scatter diagram showing the correlations of neonatal and maternal vitamin D levels (Fig.-2).

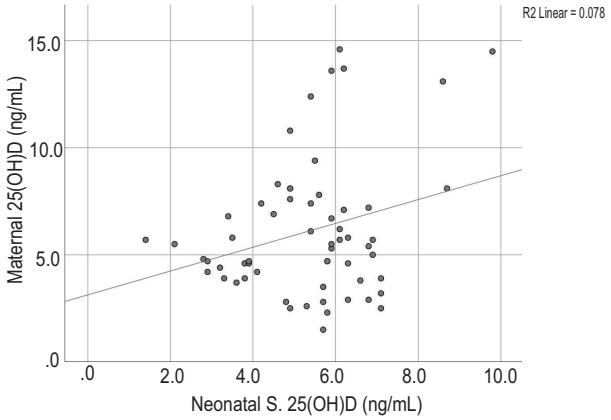

Fig.-2 *Simple scatter diagram showing the correlations of neonatal and maternal vitamin D levels*

Discussion

Neonatal hypocalcaemia (NH) is a common metabolic event in the neonatal period. NH is classified into early and late, based on the time of presentation. The early NH usually manifests within 72 hours after birth, requiring short term calcium supplementation, and it is a frequent co morbidity in high risk neonates. Another entity, resistant or prolonged hypocalcemia is defined as symptomatic hypocalcemia not responding to appropriate doses of calcium supplementation, calcium requirement beyond 72 h of age in neonates or hypocalcemia manifesting beyond 1st week of life.[14] Our patients belong to this group.

Late NH usually results from increased phosphate load (due to cow milk intake or renal insufficiency), hypomagnesemia and hypoparathyroidism.[14] Maternal vitamin D deficiency leading to neonatal vitamin D deficiency is also reported to be a cause of late NH.[15,16]

Vitamin D deficiency in neonatal period has been related to several environmental and maternal factors.[17,18] This study emphasizes the need for the evaluation of infantile and possibly maternal vitamin D status in case of late-neonatal and infantile convulsion due to hypocalcaemia.

All of our patients had hypovitaminosis D with secondary hyperparathyroidism. As mothers' vitamin D level were low, symptomatic early infantile hypocalcemia in these cases can be attributed to the maternal vitamin D deficiency. A strong correlation between child's and mother's vitamin D level is evident in our study. This has been documented in many studies. In Iran 100% of neonates with delayed hypocalcemia were born by mothers with vitamin D deficiency.[19] Some other previous studies showed same results that babies born from mothers having vitamin D deficiency suffering from late onset hypocalcemia and vitamin D deficiency.[20,21] Exclusive breastfeeding without vitamin D supplementation is another risk factor of vitamin D deficiency in early infancy.[22,23] Being all of our infants breastfed with 60% exclusive breastfed supports this finding.

Late onset hypocalcemia is usually caused by high phosphate intake[24] and usually accompanied by raised ALP and PTH.[21] However, Do et al.[25] showed that most of their patients had hypocalcemia and hyperphosphatemia represented normal or near normal ranges of PTH and ALP. In contrast, our patients with hypocalcemia do not have history of high phosphate intake or hyperphosphatemia,rather they have hypophosphatemia with raised ALP and PTH. This hypophosphatemia could be attributable to phosphaturia caused by elevated PTH, though this was not investigated.

According to Avery's disease of the newborn, PTH levels are usually high with hypocalcemia with vitamin D deficiency,[26] which is truly evident in our study and found consistent with another study.[27] However, one study in Korea et al[25] observed no elevation of PTH in neonates with late onset hypocalcemia despite vitamin D deficiency.

Among many factors, skin pigmentation may also contribute to less vitamin D synthesis in our study population as Kreiter et al[28] found that dark skinned individuals produce less vitamin D in response to sunlight.

We have some limitations in this study. First, we didn't obtain detailed information on sunlight exposure of mothers and infants, diet of mothers. Second, this study is not a case-control study and maternal-infant pair was not assessed case by case. Third, we didn't consider rachitic changes among our infants. Regardless of these limitations, the present study is conducted to evaluate the relationship between early infantile hypocalcemia and maternal vitamin D status in Bangladesh using infant-mother sera.

Conclusion

In this study, an important relationship was found between hypocalcemic seizures in young infants and maternal vitamin D deficiency. Assay of vitamin D for young infants and their mothers should be considered in cases of infantile hypocalcemic seizures. Supplementation of vitamin D for mothers and their infants is important to prevent hypocalcemic seizures in this age group.

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ORIGINAL ARTICLE

Outcome of Dengue Patients Admitted in the PICU of Bangladesh Shishu Hospital & Institute

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Abstract

Background: *Recent re-emergence of dengue patient among Bangladeshi children have created a huge burden in the morbidity and mortality of our children.*

Objectives: *This study was designed to document the outcome of dengue patients, admitted in the ICU of Bangladesh Shishu Hospital & Institute (BSH&I).*

Methods: *This retrospective observational study was performed among the children having dengue infection and who were admitted in the PICU of BSH&I from 1st June 2019 to 31st December 2019. All patients who were diagnosed as dengue fever by serological tests (NS1, Dengue IgG & IgM) and those who were admitted in the PICU were included in this study. Total one hundred and twenty-six patients were enrolled. Data were collected from hospital record of the Dengue patients.*

Results: *Mean age of the Dengue patients were 5.91(±3.53) years. Most of the patients suffering from dengue fever were urban dwellers; among them 52.4% were female. Presenting symptoms during admission in the PICU were fever which was present in 119 patients (94.4%), followed by hypotension in 106 (84.1%) patients. Severe dengue (SD) was diagnosed in maximum number of cases (i.e., 62.7%), followed by Dengue fever with warning signs (DFWS) in (20.6%) and Expanded Dengue Syndrome (EDS) in 16.7%. Maximum cases received crystalloid (98.4%), about 51.6% patients received colloid. A good number of patients received blood transfusion (23%), plasma was received in (23%) and albumin was received in (33.3%) cases. Majority of the patients received Oxygen (80.2%); antibiotics were prescribed in 87.3% cases. Fifty-five percent patients received inotropes for the management of shock. The overall outcome revealed 75.4% patients were cured and discharged. Only 21.43% patients died in the PICU despite protocol-based management. Death due to severe dengue was 15(18.9%) out of 79, followed by death due to Dengue Hemorrhagic fever with warning signs which was 8 (30.7%) out of 26 and death in Expanded Dengue syndrome was 4(19.04%) out of 21.*

Conclusion: *This retrospective study found that majority of the Dengue patients admitted in PICU has survived. However the death due to Dengue with warning signs was higher than death in severe Dengue cases. Delayed recognition of warning signs along with delayed referral to PICU may be responsible for such outcome.*

Keywords: *Dengue, Outcome of dengue, mortality in dengue.*

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Introduction

Bangladesh is situated in the tropical and sub-tropical regions like other Southeast Asian (SE) countries and like them has become a suitable habitat for the dengue vector and its increased transmission. Before 2000, only sporadic dengue cases were reported from Dhaka and other parts of the country.[1,2] Dengue caused a serious public health concern, following a sudden outbreak in 2000 where around 5,551 cases and 93 death occurred in the country. During the Dengue outbreaks from 2000-2017, both types of the vectors (*Aedes aegypti* and *Aedes albopictus*) were identified in Bangladesh.[3,4] Recent re-emergence of dengue and emergence chikungunya is found in our country, both spreads by the *Aedes* mosquitoes and have created a huge burden in the morbidity and mortality with insufficient allocation of resources under the CDC Operational Plan (OP) of the Health, Population, and Nutrition Sector Program (HPNSP: 2017–2022).[5] Like other countries, once the virus have emerged in Bangladesh, they are expected to remain in the environment and cause increased public health problems in the near future. Bangladesh first experienced a large outbreak of Dengue in the year 2000 with 5551 cases and case fatality was found 93. The containment of the disease was successfully handled afterwards. Between the years 2007 to 2011 very low number of cases were reported with no death record. From 2015 the incidence of cases started rising with few deaths. This is obviously a change in epidemiology of the disease.[6] The aim of the study was to observe the clinical features, complications and predictors of mortality and outcome of moderate and severe dengue cases admitted in the PICU of Bangladesh Shishu Hospital & Institute.

Materials and Methods

Present study was conducted in Paediatric Intensive Care Unit (PICU) of Bangladesh Shishu Hospital & Institute. This was a retrospective observational study. Data was collected from hospital records. Duration of the study was from 1st June 2019 to 31st December 2019. All the children below 15 years of age having clinical features of dengue and confirmed by IgM, IgG and rapid dengue test NS1Ag were included in the study. Children with other diseases were excluded from the study. Informed consent was taken from parents and the study was approved by Institutional Ethical Committee. Detailed history and examination findings of each patient were collected from hospital record. The patients were classified according to revised WHO guideline as 1) Dengue Fever with warning signs, 2) Severe dengue and 3) Expanded Dengue Syndrome and they were managed appropriately.[7] The requirement of crystalloids or colloids and the use of blood products were also retrieved from hospital records.

The data were entered and analyzed using SPSS (Statistical Packages for Social Science). The presenting symptoms, clinical features, laboratory parameters and outcome of these children were taken for analysis.

Results

Table I shows the demographic characteristics of the patients. Most of the patients suffering from dengue were urban dwellers. Among them 52.4% were female. Mean age of the patients were 5.91±3.53 years. Regarding presenting symptoms during admission in PICU, fever was present in 119 patients (94.4%), followed by hypotension in 106 (84.1%) patients. Other major symptoms that necessitate intensive care admission were narrow pulse pressure, respiratory distress, shock, abdominal pain, and ascites (Table II).

Table I
Demographic profile of PICU admitted Dengue patients (N=126)

Variables	Number	Percentage
13 October Urban	108	85.7
Rural	18	14.3
Gender		
Male	60	47.6
Female	66	52.4
Age		
0-5 years	60	47.6
6-10 years	50	39.7
11 years or above	16	12.7
Mean ± SD	5.91±3.53	
Schooling Status		
School going	66	52.4
Non-School going	60	47.6

Table II
Clinical Features of patients admitted in the ICU

Presenting Symptoms at admission	Number	Percentage
Fever	119	94.4
Hypotension	106	84.1
Narrow Pulse Pressure	91	72.2
Respiratory distress	87	69
Shock	84	66.7
Abdominal Pain	75	59.5
Vomiting	74	58.7
Pleural Effusion	55	43.7
Ascites	45	35.7
Rash	36	28.6
Abdominal Distention	29	23
Headache	20	15.9
Melaena	19	15.1
Bleeding	14	11.1
DIC	13	10.3
Convulsion	13	10.3
Myalgia	10	7.9
Haematemesis	9	7.1
Anuria	9	7.1
Liver Dysfunction	7	5.6
Obesity	4	3.2
Positive Tourniquet test	3	2.4
Eye Congestion	3	2.4
AKI	3	2.4

This study found that 33 (26.2%) patients had both pleural effusion and ascites. Isolated pleural effusion was present in 17.5% (22) cases (Table III).

Table III
Pleural Effusion and Ascites of Dengue patients

Escape of Fluid	Frequency	Percentage
Both Pleural Effusion and Ascites Positive	33	26.2
Pleural Effusion Positive	22	17.5
Presence of Ascites	12	9.5
Absence of Ascites	59	46.8

The admitted patients were classified into three groups according to the WHO. Severe Dengue was diagnosed in maximum number of cases (i.e., 62.7%) followed by Dengue fever with warning signs (20.6%) and Expanded Dengue Syndrome (16.7%) (Table IV).

Table IV
Diagnosis according to WHO guideline

Diagnosis	Frequency	Percentage
Dengue fever with warning sign	26	20.6
Severe Dengue	79	62.7
Expanded Dengue Syndrome	21	16.7
Total	126	100

Table V shows that maximum number of patients received Crystalloid (98.4%), about 51.6% received colloid. A good number of patients received blood (23%), plasma was also received in 23% and albumin was received in 33.3%. Majority of patients received Oxygen (80.2%), antibiotics was received in 87.3% and, anti-ulcerant was received in 92.9%. 55.6% patients received inotropes for the management of shock. A very few number of patients required platelet transfusion (7.1%), and steroid was received in 15.1%.

Table V
Treatment pattern of ICU admitted dengue patien\ts

Treatment	Yes	
	Frequency	Percentage
Crystalloid	124	98.4
Colloid	65	51.6
Blood	29	23
Plasma	29	23
Albumin	42	33.3
Inotropes	70	55.6
Platelet Transfusion	9	7.1
Oxygen	101	80.2
Anti-Convulsant	12	9.5
Antibiotic	110	87.3
Anti-ulcer ant	117	92.9
Steroid	19	15.1

Regarding hospital stay mean duration of hospital stay was 7.83±3.0) days. Sixty-one percent patients (n=77) had an average hospital stay of 6-10 days (Table VI).

Table VI
Duration of Hospital stay of the admitted patients

Days	Number of patients	Percentage	Mean ±SD
1-5 days	27	21.4	7.83 ± 3.0
6-10 days	77	61.1	
11 days or more	22	17.5	

Table VII shows the outcome of the admitted patients. Ninety five i.e., 75.4% patients were cured and discharged and 21.43% (n=27) patients died in the PICU despite protocolized management. Four patients (3.17%) were discharged on risk bond, so the outcome of those four patients is unknown whether they were cured or died.

Table VII
Outcomes of the Dengue Patients admitted in the ICU

Outcomes	Number of patients	Percentage
Cure	95	75.40
Discharged on risk bond (DORB)	4	3.17
Death	27	21.43

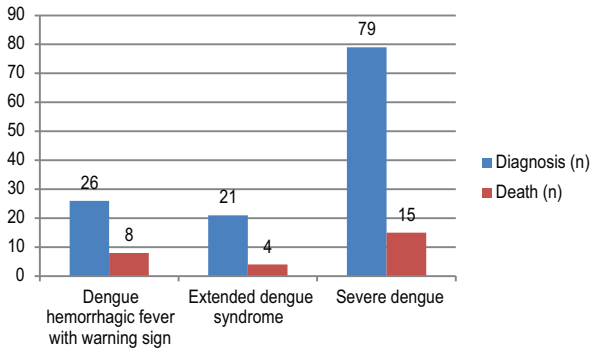

Fig.-1 N*umber of death according to diagnosis (n=126)*

Death due to severe dengue was the highest i.e., 15 cases out of 79, which accounts for 18.9% followed by death due to Dengue Hemorrhagic fever with warning signs 8 out of 26, which accounts for 30.7% and Expanded Dengue syndrome 4 out of 21, which accounts for 19.04% (Fig.1). Among the death cases though the number of deaths is more in SD group but percentage was more in DF with WS group. This occured due to delay in diagnosis and delayed referral to ICU.

Discussion

In this observational study we have found that the male female ratio was 0.9:1. The mean age at presentation was 5.9 (±3.53) years in our study which was similar to Khan et al[8] i.e., 5.6 (± 3.8) years. The commonest age group varied in different studies like 5-10 years observed by Palaniappan.[9-11] Kale et al[12] showed 11-15 years was the most commonly affected age group. Rasul et al[13] showed 10-14 years as most commonly affected age group. In our study Female patients predominated male patients by their number this finding was opposite to the finding by Sultana & Afroze.[14,15] Anker et al[16] explored the sex-related differences in the prevalence of dengue in more detail. They noted that the magnitude of the difference is small and is not consistent in pediatric patients. However, male female differences regarding the use of health services, the use of fully covered dresses by female children, and prioritizing provisions of male children in the society might be reasons for the differences noted in our country.[17, 18]

Dengue patients typically present with the triad of fever, pain, and rash. However, gastrointestinal and bleeding manifestations might occur in variable proportions.[19] The most common bleeding manifestations was epistaxis and melena similar to several previous studies.[20,21]

The common clinical feature we found was fever (94.4%), followed by Hypotension (84.1%), Narrow pulse pressure (72.2%). Pothapregada et al[22] found similar findings like fever in 94.6% cases, conjunctival congestion (89.6%), myalgia (81.9%), coryza (79.7%), headache (75.1%), palmar erythema (62.8%), retro-orbital pain (51.3%), joint pain (28.7%), and rash (17.2%). He also noted common atypical

manifestations of dengue fever at admission were lymphadenopathy (52.3%), splenomegaly (20.7%), epigastric tenderness (16.4%) biphasic fever (15.7%), right hypochondriac pain (8.4%), seizures (6.5%), and febrile diarrhea (6.5%), [Table 1]. The mean duration of fever was 4.8 (1.8) days at admission. Khan et al[8] found 310 cases 63.9540% cases with vomiting next to fever among 310 cases, followed by ascites and rash (21%), pleural effusion (20%) abdominal pain (14%) and shock (12%).

When incidence was observed it was found that the incidence of Severe dengue was 62.7% in our study, whereas severe dengue infection was seen in 102 cases (39.1%) by Pothapregada.[22] Khan found that out of the 310 cases 63.9% cases had dengue fever, 18.7% of Dengue Hemorrhagic Fever I & II and 17.4 % cases of Dengue Shock Syndrome.[8]

In this observation 55.6% patients received Ionotropes. Bhaskar found use of inotropes were 74.2% cases, and they were associated with higher mortality rate (11.5%).[10] Goonasekera et al. reported a mortality of 55.5% patient who received inotropes.[23] Transfusion of blood products were also associated with higher death rates of 23.3%.[10]

In this observation we found that the mean duration of hospital stay was 7.83 (±3.0) days, whereas Vikram et al found that the duration was 5.5 days in Dengue without co-infection and 11.8 with co-infection.[10] Mortality was found to be 21.43% (27 cases) in our study. Haridarshan et al[24] reported only 1 death among 175 cases, Bhaskar et al[10] reported 2 deaths among 29 cases of dengue without co-infection and 1 death among 6 cases of dengue with co-infection.

Conclusion

This retrospective study found that majority of the Dengue patients admitted in PICU has survived. However the death due to Dengue with warning signs was higher than death in severe Dengue cases. Delayed recognition of warning signs along with delayed referral to PICU may be responsible for such outcome.

Limitation of the study

Our study has its limitation due to small sample size but it provided useful information for management of most of the dengue cases. Continuous monitoring, early anticipation of shock, timely use of fluid therapy guided by routine hematocrit values and clinical parameters can all be used successfully to improve the final outcome in dengue patients.

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ORIGINAL ARTICLE

Risk Factors and Outcome of Neonatal Hyperbilirubinemia: A Case Control Study in a Tertiary Level Paediatric Hospital

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Abstract

Introduction: *Neonatal jaundice is one of the most common morbidities observed during the neonatal period. Several risk factors are responsible for this condition.*

Objective: *This study was aimed to determine the possible risk factors and immediate outcome for jaundice in newborns.*

Methods: *This case control study was performed over a period of 18 months (March 2019 -August 2020) in the Special Care Newborn Unit (SCANU) of Dr. M R Khan Shishu Hospital & Institute of Child Health (ICH). Risk factors for jaundice were evaluated by comparing cases with jaundice and controls having no jaundice.*

Results: *A total of 230 neonates with jaundice and 250 neonates having no jaundice were enrolled. Maternal age between 31-40 years, less than 4 antenatal visits, primi, presence of maternal diabetes, babies born via caesarian section, small for gestational age, prematurity and intra-uterine growth restriction were significantly associated with jaundice in neonates (p value < 0.05). Multi-variate analysis revealed, babies with mothers having <4 antenatal visits were found to have 13 times more risk of developing jaundice than their matched controls (p= 0.00, CI= 0.78-14.9). Mean duration of phototherapy was longer for babies having jaundice due to blood group incompatibilities (4.82 ± 1.94). Most of the patients (91%) were discharged to home.*

Conclusion: *Less than four antenatal visit is a significant risk factor for neonates to develop significant jaundice requiring treatment. Babies with blood group incompatibilities tend to require longer duration of phototherapy wherever most of the babies discharged to home with good recovery.*

Keywords: *Neonatal jaundice; risk factors; case-control, Bangladesh.*

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Introduction

Jaundice is one of the commonest clinical conditions in newborns.[1] It is the yellow discoloration of skin, sclera and mucous membrane which occurs due to accumulation of unconjugated, lipid soluble bilirubin pigment in the skin encountered during the neonatal period, especially in the first week of life.[2-3] The global incidence of neonatal jaundice varies with ethnicity and geography. Incidence is higher in East Asians and American Indians and lower in Africans.[4] The overall incidence of neonatal jaundice in our country is about 33% and reported by various Indian workers varies from 4.6% to 77%.[5]

About 60% of term and 80% of preterm infants develop jaundice during 1st week of life. In neonates it is due to increased break down of fetal erythrocytes which has shortened life span. Hepatic excretory capacity is also low in newborns. These occur more in premature babies than term infants.[6]

There are various causes of neonatal jaundice under the broad umbrella of physiological and pathological types. Physiological jaundice is the most abundant type of newborn hyperbilirubinemia and has no serious consequences.[7] It appears on 2nd/3rd day of life and peaks on 3^{rd}- 4^{th} day of life in term, 5^{th} -6^{th} days in preterm. Gradually disappears spontaneously. Baby is otherwise healthy. Sometimes exaggerated physiologic jaundice can occur where higher bilirubin levels occur earlier and last longer. Prematurity, severe weight loss, maternal diabetes and bruising in infants are the factors behind this condition.[8-9]

Neonates developing jaundice within first 24 hours is always pathological and commonest causes are: Rh incompatibility, ABO incompatibility and Hereditary spherocytosis. Indirect hyper-bilirubinemia which develops after 2 weeks are mostly due to infection, breast milk factors and hypothyroidism. Breast milk jaundice is found in 66% of breastfed babies from 3rd week of life and may persist up to 3 months. Another similar term is breast feeding jaundice that develops in the 1st week of life.[1]

Jaundice is mostly a benign condition. But in 10-15% it may cause significant jaundice and then interventions like phototherapy or exchange transfusion are required. Sometimes different drugs like phenobarbitone, intravenous immunoglobulins (IVIG), metalloporphyrins are also used. High bilirubin levels can be toxic for central nervous system development and may cause behavioral and neurological impairment (Neurotoxicity or Kernicterus) even in term newborns.[10-13]

Neonatal jaundice is an important cause of neonatal morbidity but if remain unaddressed, can lead to mortality and serious long-term sequel. Identification of risk factors is crucial in this regard for early intervention if required. There are several risk factors such as maternal age, weight, BMI, WBC, Hb, PLT, birth in the first pregnancy, numbers of pregnancies and prolonged delivery etc.[14] which are evident in many studies. But these are limited in number, especially in South East Asian countries. So, this study was planned to determine the possible risk factors for jaundice and its immediate outcome in newborns in a pediatric hospital of Asian region.

Materials and Methods

This case control study was performed over a period of 18 months from 1^{st} March 2019 to 31^{st} August 2020 in the Special Care Newborn Unit (SCANU) of Dr. M R Khan Shishu Hospital & Institute of Child Health (ICH), one of the largest Pediatric teaching hospitals of Dhaka city after taking approval from the Ethical Review Committee. All neonates admitted with jaundice and or those who developed jaundice during hospital stay; requiring treatment according to bilirubin nomogram by AAP guideline (American Academy of Pediatrics)[3] were enrolled as case. Gestational age matched neonates without jaundice were taken as controls. Cases, whose parents did not give consent were excluded from the study.

After taking consent from the parents, medical records were observed as well as maternal interview was taken to find out the risk factors. Neonates were examined for detecting visible risk factors such as signs of growth restriction, cephalhematoma, polycythemia etc. Maternal variables including age, occupation, parity, number of antenatal visits, Gestational diabetes mellitus (GDM), hypertension in pregnancy, maternal infection was evaluated in the study. Mode and place of delivery were also observed in both groups. Neonatal variables included gender, gestational age category (appropriate for gestation, small for gestation, large for gestation, intrauterine growth restriction), polycythemia, cephalhematoma, blood group incompatibilities.

Patients were investigated and managed according to departmental protocol. During treatment with

phototherapy or exchange transfusion; AAP guidelines for hyperbilirubinemia in newborn was used thoroughly.[3] Patients were followed up to hospital stay. Outcome of jaundiced neonates were observed with duration of phototherapy and duration of hospital stay according to significant causes of jaundice.

All data were recorded in a data collection form and then analyzed by using SPSS software version 21. Comparison of maternal and neonatal variables was done with univariate and multivariate logistic regression models. Frequency was calculated for qualitative variables, while the mean and standard deviation were calculated for quantitative variables. Chi-square test was used to examine qualitative data, and t-test for non-dependent samples was used to study quantitative data. P-value of < 0.05 was considered significant.

Results

A total of 230 cases and 250 controls were included during the study period. Cases were matched with their controls in terms of gestational age and birth weight (Table I). Mean maternal age was 26.78 ± 4.05 years among cases, which was slightly higher than controls. Other significant variables among case group were maternal age 31-40 years, primi, less than 4 antenatal visits, hospital delivery, born by caesarian section, infant of diabetic mothers (p value <0.05) as shown in Table II.

Table I
Baseline characteristics of neonates with and without jaundice

Variable	Case: Neonates with Jaundice n=230	Control: Neonates without Jaundice n=250	p value
Mean Gestational age (weeks)	36.96±2.55	37.02±2.34	0.81
Mean Birth weight (g)	2696.09±491.57	2656.48±474.85	0.37

Independent sample 't' test

Table II
Distribution of maternal and delivery variables among cases and controls

Variable	Neonates with Jaundice n=230 (%)	Neonates without Jaundice n=250 (%)	p value
Maternal age (years)			
Mean maternal age	26.78±4.05	25.64±3.48	0.004
<20	11(4.8)	46(18.4)	NS
21-30	180(78.2)	183(73.2)	0.03
31-40	39(17)	21(8.4)	0.03
>40	0	0	NS
Housewife	168(73)	158(63.2)	0.00
ANC <4	146(63.4)	116(46.4)	0.00
Primi mothers	140(61)	88(35.2)	0.00
Maternal diabetes	59(26)	25(10)	0.00
Maternal hypertension	4(1.7)	15(6)	NS
Maternal infection	7(3)	15(6)	NS
Mode of delivery			
NVD	53(23)	84(34)	NS
Assisted VD	9(4)	15(6)	NS
LSCS	168(73)	153(61)	0.004
Place of delivery			
Home	30(13)	61(24)	
Hospital	200(87)	189(76)	0.001

Independent sample 't' test and Chi square test

In Table III, neonatal variables were compared between case and control groups which revealed that small for gestational age (p=0.046) and IUGR (p=0.044) neonates developed jaundice more than their matched controls. After adjusting the confounders by multivariate logistic regression, it was found that neonates whose mothers had less than 4 antenatal visits, were at 13 times more risk of developing jaundice (p=0.00; CI=0.78-14.9) as shown in (Table IV).

Table III

Distribution of Neonatal variables with jaundice and their matched controls

Variable	Neonates with Jaundice n=230 (%)	Neonates without Jaundice n=250 (%)	p value
Gestational age category			
AGA	168 (73)	205 (82)	NS
SGA	33 (14.3)	18 (7)	0.046
LGA	6 (3)	15 (6)	NS
IUGR	23 (10)	12 (5)	0.044
Sex			
Male	152 (66)	164 (66)	NS
Female	78 (34)	86 (34.4)	
Polycythemia	3 (1.3)	0	
Cephalhematoma	4 (2)	0	
Sepsis	56 (24)	72 (29)	
Blood group incompatibility	23 (10)	0	NS

Chi square test

Table IV

Multivariate binary logistic regression analysis of risk factors for neonatal jaundice

Variable	β	OR	CI	p value
Maternal age 31-40 years	0.36	1.89	0.55-8.6	NS
Housewife mothers	0.01	3.37	0.00-4.21	
Primi	0.25	1.82	0.00-2.26	
ANC <4	1.89	13.2	0.78-14.9	0.00
LSCS	1.11	3.12	3.12-3.45	NS
Hospital delivery	0.02	1.82	0.00-2.36	
IDM	0.29	0.95	0.59-9.2	
SGA	3.05	4.11	0.00-5.12	
IUGR	0.73	1.22	0.003-1.31	

Regarding the different causes of neonatal jaundice among the admitted cases, exaggerated physiological jaundice was most common cause (33%) followed by infant of diabetic mothers (26%), sepsis (24%) and others as revealed in Fig.-1.

Mean serum bilirubin level was 16.66±4.6 mg/dl. Mean duration of phototherapy was 3.91±1.49 days. Exchange transfusion was required in 7 patients (3%).

In Table V outcome of the jaundiced neonates were observed according to their causes. Babies with blood group incompatibility required longer duration of phototherapy (4.82±1.94 days) and premature babies had longer hospital stay (6.64±1.56 days). Most of the babies were discharged to home (91%) and 9% left hospital against medical advice.

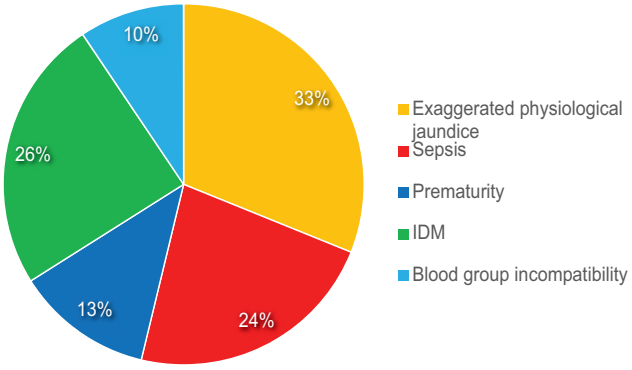

Fig.-1: *Causes of Jaundice among admitted cases*

Table V
Analysis of outcome among cases

Causes of Neonatal jaundice	Mean duration of phototherapy (days)	Mean duration of hospital stay (days)
Exaggerated Physiological Jaundice	3.66±1.00	5.03±1.45
Infant of diabetic mother	3.96±1.44	5.88±2.16
Sepsis	4.18±1.61	6.35±2.47
Prematurity	4.32±1.51	6.64±1.56
Blood group incompatibility	4.82±1.94	6.23±1.74

Discussion

In our study, different maternal, delivery and neonatal variables were compared among neonates with jaundice and no jaundice group. Mean maternal age was found 26.78±4.05 years. It co-relates with the study done by Zhang B et al. where they found peak maternal age 26 years was associated with neonatal jaundice.[15]

The study also observed that maternal age ranging between 31-40 years is a risk factor for developing jaundice. This finding matches with the results of Fetriyah UH et al. where they found mother aged between 20-35 years had neonates with jaundice but not pathological jaundice. Whereas maternal age either <20 or >35 years were at risk of developing pathological jaundice in newborns.[16] In our study, we found jaundice both in 21-30 years and 31-40 years group.

Neonates who were first born child of their parents and who were delivered by caesarian section, they developed jaundice more and this result is similar with other study findings.[14]It has also been reported in previous studies that, mode of delivery is related to jaundice and its severity.

Antenatal visits are planned in such a way so that pregnant women get an idea of caring about her and her upcoming child. Their medical conditions are addressed and treated accordingly so that it cannot affect their health. It is also important to inform mother about the important issues which may develop after birth of her baby. Neonatal jaundice is such a condition which parents need to know from antenatal period. Previous studies on NNJ in Nigeria reported a poor knowledge about its causes, management and complications among pregnant women.[17-22]Interestingly in our study, we found less than four antenatal visits as a significant risk factor for neonates to become jaundiced. The risk is 13 times more among cases which indicate the indirect impact of less visits and parental awareness which eventually lead to delay in admission for phototherapy.

Maternal diabetes is a well-known risk factor for neonatal jaundice and our study finding is also accordant with that (p= 0.00). In some studies, they have described that the incidence of neonatal jaundice in diabetic mothers is three times higher than that in the control group.[23] The increased risk in these babies is well explained and the possible factors evidenced are polycythemia, ineffective erythropoiesis with increased red blood cell turn over, immaturity of hepatic bilirubin conjugation and excretion.

Our study also revealed that, small for gestational age (p=0.046) and intrauterine growth restricted babies (p=0.044) develop jaundice more frequently than appropriate for gestational age and normal birth weight babies. This finding is also consistent with other research works.[24]

Causes of neonatal jaundice usually varies with race and ethnicity. In Asian countries like India and Bangladesh, blood group incompatibilities, breast feeding jaundice, jaundice due to prematurity and sepsis, G-6 PD deficiency are common causes. Although we got patients mostly due to exaggerated physiological jaundice, other causes are not negligible.[25-26]

Regarding the outcome, we found that babies with blood group incompatibilities required longer duration of phototherapy. Study done by Bhat YR also concluded from their study that neonates with hemolysis required phototherapy significantly earlier and for longer than neonates without hemolysis (P<0.001).[27]

Despite a good number of cases with significant results, this study has some limitations. Mothers having hypothyroidism were not included in the study, which is an important risk factor for developing jaundice in newborn. Moreover, in premature babies with jaundice, it was found that they stayed hospital for a longer period. It may be due to completion of treatment or resolution of their complications related to prematurity. These confounders were not excluded and were not analyzed as well.

Conclusion

Less than four antenatal visit is a significant risk factor for developing neonatal jaundice. Babies with blood group incompatibilities tend to require longer duration of phototherapy wherever most of the babies discharged to home with good recovery.

Recommendations

- Early identification and timely screening of neonates having risk factors is essential to decrease the burden as well as severity of jaundice in newborn.
- Attention to be given to improve the rate of antenatal visit of pregnant mothers as indirectly it is delaying the admission of jaundiced babies due to parental ignorance.
- Counseling strategy can be improved in jaundiced neonates as those having blood group incompatibilities and who are premature, tend to require longer duration of phototherapy and hospitalization respectively. This will increase parental understanding of the condition.

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ORIGINAL ARTICLE

Experience of Paediatric Acute Lymphoblastic Leukemia Service in A Newly Established Haemato-Oncology Center in Bangladesh: Opportunities and Challenges

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Abstract

Background: *Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy and its modern management is complex. We are reporting early experience of establishing a paediatric ALL service in a multidisciplinary paediatric hospital in Bangladesh.*

Methods: *This is a retrospective review of children below 18 years of age with confirmed diagnosis of ALL from July 2020 to June 2021 in Dr. M R Khan Shishu Hospital and ICH, Dhaka, Bangladesh, who received treatment adapted from the standard arm of ICICLE (Indian Childhood Collaborative Leukemia Group) protocol. Data were collected which included demographic, clinical, laboratory features of all patients at the time of presentation and also morbidities and outcome during all phases of chemotherapy. Analysis was done using descriptive statistics.*

Results: *Of 51 patients, 16 were newly diagnosed patients, 32 received continuation care and 3 had relapsed disease. Treatment was initiated in 12 (75%) of 16 patients with newly-diagnosed ALL. Median age was three years, 50% were girls, one had T-ALL and 5 (42%) had high presentation leucocyte count (≥50,000/mm^3). Complete cytogenetic testing was available for one patient alone, no patient had Ph+ ALL. Eleven (92%) showed good prednisolone response. All nine patients who completed the induction phase achieved morphological remission, with high minimal residual disease (≥0·01%) in two (22%). At last follow-up (30-06-2021), two patients were midway through induction, two died from sepsis (one each in Induction and Consolidation, both high risk ALL) and eight (67%) are alive in remission, on treatment 2-12 months from diagnosis. Continuation care included intrathecal treatments (n=119) and vincristine-corticosteroid pulses (n=53); 94% patient remained in complete remission, while two (6%) relapsed during the course of treatment.*

Conclusion: *Risk-stratified ALL treatment is feasible in a newly established resource limited setting but limited by availability of high-quality diagnostics, specifically cytogenetics. Our study revealed that, during intensive phase approximately two-third children and during maintenance phase majority of children remained in complete remission.*

Keywords: *Acute lymphoblastic leukaemia, opportunities, challenges, Bangladesh.*

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Introduction

The number of childhood cancer is increasing day by day and 84 % of the cancer cases occur before 15 years of age in the low-income and middle-income countries (LMICs).[1] The age-adjusted incidence rate of leukemia in children and adolescents younger than 20 years is 4.7 per 100,000.[2] The reported incidence of childhood cancer in Bangladesh is 7.8 per million per year out of which leukemia is the commonest cancer (28%) and 84% of the leukemias are acute lymphoblastic leukemia (ALL).[3]

ALL is the most common childhood malignancy accounting for one-fourth of all childhood cancer and almost 72% of all cases of childhood leukemia.[4] ALL is classified as B-lymphoblastic leukemia and T-lymphoblastic leukemia. B precursor cell accounts for 80% of ALL cases, T-cell accounts for 15-20% of ALL cases and mature B cell accounts for 1 to 2% of ALL cases.[5]

Diagnostic and treatment modalities for ALL have seen tremendous advancements over the past few decades. Despite of a higher incidence and constant rise in pediatric cancers in the developed countries, their success stories are ample.[6] Remarkable progress has been achieved in childhood ALL due to adaptation of risk-stratified treatment and improved supportive care.[7,8] With survival rates in developed countries approaching 100%, there is a shift of research focus towards improvement of quality of life, reduction of morbidities and drug toxicities, targeted drug therapies and treatment of drug resistant leukemia.[9]

On the other hand, LMICs like Bangladesh still struggle for optimal results in cancer care. A large proportion of treatment options for ALL is stationed in the superspecialist centers of the country. This reduces the accessibility and feasibility of adequate treatment for leukemic children in the general pediatric hospital. Poverty and lack of parenteral education is the main cause of treatment refusal and abandonment in Bangladeshi children with ALL.[10] Poor socioeconomic conditions, gender discrimination, malnutrition, delayed diagnosis, and referral form some of the important yet modifiable factors attributed to poor outcomes in developing countries.[11] Efforts should be taken to meet the long-term challenge of providing quality care to children with ALL worldwide and improving cure rates globally. This can be passible by increasing collaborative research and international networking so that the therapeutic gains in high-income countries can be translated to patients in low-income and middle-income countries.[9]

Delivery of intensive chemotherapy for ALL requires trained manpower and infrastructure which is usually available in established pediatric haemato-oncology centers in Bangladesh. Challenges for delivering chemotherapy for newly-established pediatric haemato-oncology center are manifold. This study aimed to describe the experience of modern ALL service in a newly setup haemato-oncology unit in a multispecialty pediatric hospital in Bangladesh.

Materials and Methods

This is a retrospective review of children with ALL from July 2020 to June 2021 in Dr. M R Khan Shishu Hospital and ICH, Dhaka, Bangladesh. A total of 51 children below 18 years of age with confirmed diagnosis of ALL who received maintenance chemotherapy in collaboration with TMC (TATA Medical Center), as well as newly diagnosed patients at Dr. M R Khan Shishu Hospital were included in this study.

All patients received treatment adapted from the standard arm of ICICLE (Indian Childhood Collaborative Leukemia Group) protocol.[12] Ethical clearance was obtained from the institutional review board. Informed written consent was taken, and confidentiality of data was maintained. Standard case report forms, specifically designed for this study were used to collect data which included demographic, clinical, laboratory features of all patients at the time of presentation. A follow up case report form was filled for each patient at which recorded morbidities and outcome during induction, consolidation, interim maintenance, delayed intensification, and maintenance phases of chemotherapy.

Confirmation of diagnosis of acute lymphoblastic leukemia was done when 20% lymphoblasts or more were present in the bone marrow (BM) aspirate/ trephine biopsy. Flowcytometry was done for the immunophenotypic classification into B -cell ALL and T-cell ALL. Participants were classified into standard risk and high risk according to NCI classification using age and WBC count. Standard risk was defined as WBC count $<50 \times 10^9$/L and age one to 9.99 years, while high risk was defined as WBC count $\geq 50 \times 10^9$/L at any age or age >10 years with any WBC count at presentation. Then clinical risk factors were determined by extramedullary disease features and

genetic risk was determined by cytogenetics. Cytogenetic studies include fluorescence in situ hybridization (FISH) assays for ETV6-RUNX1; BCR-ABL1; KMT2A rearrangements; iAMP21; TCF3-HLF was done for all maintenance patient whose treatment were initiated at TMC.[13]As complete cytogenetic testing by FISH is not available in Bangladesh, we did only RT-PCR method for BCR-ABL in newly diagnosed patient at our center. Only one of newly diagnosed patient had done cytogenetic studies for other translocations including t (12;21), t (9;22), t (4;11) and t (1;19) from abroad. Diagnostic lumbar puncture was done to determine CNS involvement & patien ts were classified as CNS1,2 and 3 categories based on standard criteria. Other investigations at the time of diagnosis included liver function test (LFT), renal function test (RFT), LDH levels, chest X-ray for mediastinal mass, 2D echocardiography and serology for HIV, Hepatitis B and C virus.

Early treatment response was determined by prednisolone response (prednisolone good responder [PGR] and prednisolone poor responder [PPR] if they had <1000 blasts/μL in peripheral blood and >1000 blasts/μL in peripheral blood after 1 week of steroid prephase respectively) and minimal residual disease (MRD) estimation after 5 weeks of induction treatment. Patients were labeled to be in morphological remission if there were less than 5% blasts in the marrow with normal trilineage hematopoiesis and MRD negative if values were <0.01%. All through the patient management a collaboration was established with TMC, Kolkata in the form of knowledge sharing and monitoring of tolerance and treatment adherence. Information about all the patients were discussed weekly with the TMC team about maintenance drugs dose adjustments, management of toxicities and provision for administration of intrathecal chemotherapy locally. This included newly diagnosed patients also and was not limited to the patients receiving continuation care.

Data was analyzed using Microsoft Excel. Categorical variables were given in the form of frequency table. Analysis was done using descriptive statistics.

Results

A total of 51 patients diagnosed as ALL were included in the study. Out of them, 32 patients were diagnosed and had their intensive phase of treatment in TMC and got shared care and 19 were newly diagnosed at Dr. M R Khan Shishu Hospital. Out of the newly diagnosed children with ALL, 3 patients were diagnosed as relapsed ALL and 4 patients were referred to another center (financial constraints).

Among the 12 frontline ALL patients, 50% were male and 50% were female. A total of 92% children were <10 years of age with a median age of 3 years (IQR 2-4.5). A total of 8% children had T cell lineage and 92% patient had B cell lineage leukemia; 58% had NCI Standard-Risk and 42% had NCI High-Risk disease. The highest WBC count ≥50,000/mm^3 was observed in 42% of the cases. The cytogenetics was ETV6-RUNX1 in one patient whose cytogenetics were tested from abroad, others were BCR-ABL (RT-PCR method) negative, but others cytogenetics were not known. Only 1 patient had poor Prednisolone response (8%). At the end of induction all patients achieved complete morphological remission, but 22% patient (n=2) had MRD positive (≥0.01%) disease. One patient died during induction and one died during consolidation. Both had high risk B ALL and both died due to sepsis. At last follow-up (30-06-2021), 2 patients were midway through induction, 2 died from sepsis and 8 (67%) are alive in remission, on treatment 2-12 months from diagnosis. Maintenance cycles were started for 2 of newly diagnosed patients.

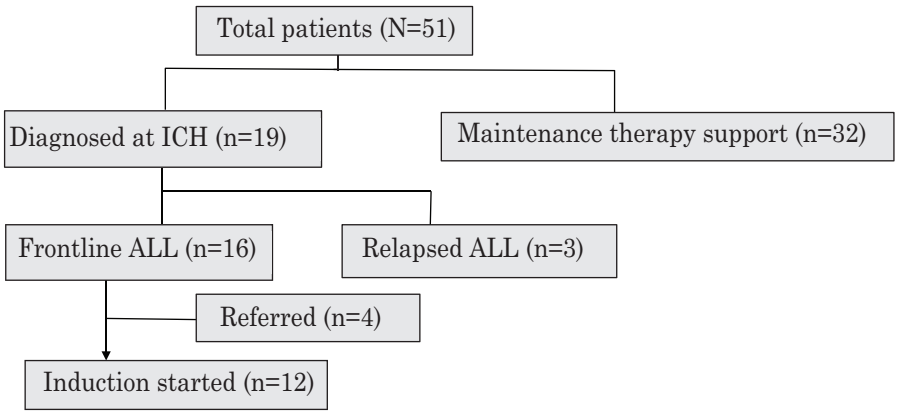

Fig.-1 *Distribution of children with ALL*

Table I
Demography of Frontline ALL patient

Parameter	Number	Percentage
Age in year (n=12)		
Less than 10	11	92
More than or equal 10	1	8
Median	3	
IQR	2-4.5	
Gender (n=12)		
Male	6	50
Female	6	50
Lineage (n=12)		
B cell	11	92
T cell	1	8
Highest White Blood cell (n=12)		
<50000/ mm^3	7	58
≥50000/ mm^3	5	42
NCI Risk (n=12)		
Standard	7	58
High	5	42
B Cell Cytogenetics (n=11)		
ETV6-RUNX1	1	9
Negative BCR-ABL	11	100
Final Risk (n=9)		
Standard	0	0
Intermediate	5	56
High	4	44

Table II
Outcome of Frontline ALL patient

Parameter	Number	Percentage
Prednisolone response (n=12)		
Good	11	92
Poor	1	8
End of induction complete morphological response (n=9)		
Yes	9	100
No	0	0
End of Induction MRD (n=9)		
More than equal 0.01%	2	22
Less than 0.01%	7	78
Event (n=12)		
Relapse	0	0
Induction death	1	8
Consolidation Death	1	8

Table III
Demography and outcome of Maintenance patient

Parameter	Number	Percentage
Diagnosis		
B Cell ALL	26	82
T Cell ALL	3	9
Relapsed ALL (B ell)	3	9
Age in year		
Less than 10	20	62
More than equal 10	12	38
Median	7.6	
IQR	6-12.8	
Sex		
Male	17	53
Female	15	47
Maintenance Type		
Standard maintenance	27	84
Vincristine dexamethasone pulse	5	16
Outcome		
Complete remission	30	94
Relapsed	2	6

Discussion

Treatment and outcome of ALL is one of the success stories in modern medicine with the overall survival reaching >90%.[14,15] However, overall survival (OS) for the St. Jude Total Therapy Study XVI (94.3%) was similar to that for the Total Therapy Study XV (93.5%).[16] But the treatment is complex and long duration and access to modern therapies is limited in developing countries like Bangladesh. In this study we wanted to show the early experiences of our newly established Hematology and Oncology unit.

Cancer treatment is more challenging for children in Bangladesh. There are multiple reasons like financial burden, absence of skilled human resources in laboratories, lack of paediatric oncologists at hospitals, and parents who can afford it, take their children to neighbouring country for diagnosis and treatment as there is a general lack of faith in local diagnostic reports.[17] Tahura S found in her study

that poverty and lack of parenteral education is the main cause of treatment refusal and abandonment in Bangladeshi children with ALL.[10] In our study treatment was not started for 4 (25%), out of 16 newly diagnosed children due to financial burden of family and were referred to Government Hospital for further management.

In our study, out of 51 patients, treatment was initiated in 12 (75%) of 16 patients with newly-diagnosed ALL. We found the median age of child with newly diagnosed ALL was 3 years and a total of 92% children was <10 years of age and 50% were girls. Diba F et al found in her study that most of the patients were 1 to 9 years of age (87.4%), which is almost similar to our study.[18] Sampagar A et al reported that male to female ratio of newly diagnosed ALL was 1.15:1.[19] In our study male to female ratio of newly diagnosed ALL was 1:1.

In our study, 1 child (8%) had T cell lineage and 92% patient was B cell lineage which is comparable to another Bangladeshi study where among 87 analyzed patients, 93.1% were B-cell ALL and 6.9% were T-cell ALL.[18]

In our study the highest WBC count ≥50,000/ mm^3 was 42%. These counts were higher when compared to studies in the west but in concordance with studies from other Low-and Middle-income countries (LMIC), where baseline white blood cell (WBC) count of >50,000/mm^3 was seen in 23-37%.[20,21] The probable reason for this could be delayed presentation.

Complete cytogenetic testing was available for 1 patient alone in frontline ALL children, no patient had Ph+ ALL in our study. Incidence of Philadelphia chromosome was much lesser than its known incidence in childhood ALL (12%) probably due to small sample size.[20,22]

In this study, eleven (92%) children showed good prednisolone response and 8% patient had poor prednisolone response, which is comparable to another Indian study, where the day 8 prednisolone response was poor in 9.72%. [19]

Our Induction outcome based on morphological and MRD assessment showed promising results. All 9 patients (100%) who completed the induction phase achieved complete morphological remission, which is higher than another Bangladeshi study where 87% went into complete remission.[23] Morphological remission is similar to an Indian study done by Sampagar et al[19] Minimal residual disease is currently the most powerful prognostic indicator in ALL. and it was positive in 22% of the patients which is higher than the established centers.[19] There is no study from Bangladesh commenting on the MRD post induction earlier than our study.

Our induction mortality rate of 8% is higher than that seen in HIC.[24] Review of Indian data in ALL by RS Arora et al covering 3761 children reported a death rate of 2-13% during induction.[19] In this study, all deaths were due to bacterial infection and its complications which is corresponding to another Bangladesh study.[23] Bacterial sepsis is indeed the leading cause of mortality during induction.[25]

In this study, 32 children received maintenance chemotherapy, whose treatment was initiated in TMC, India and received their intensive phase of treatment there, but they got the maintenance chemotherapy support to our newly established center in Bangladesh. We successfully continued maintenance phase of treatment including administration of IV vincristine and intrathecal methotrexate without any notable adverse effects. Tuong et al[26] showed, there was 16.7% relapse of the 156 newly diagnosed ALL in between 2012 to 2018, out of them 53.8% cases were relapsed during the maintenance phase. In our study among the maintenance patient 94% remained in complete remission, but 6% (n=2) had relapsed during the course of treatment.

Any inference on the outcome is limited by the very small sample size with short follow up. It is painful to note here that we could not test the cytogenetics for all patients, because the FISH probe testing for cytogenetics is still unavailable in Bangladesh. We could do this test only for one patient by sending the sample to India which was expensive and not bearable for other patients. The best we could do is to test for BCR-ABL by RT-PCR method for other patients.

Conclusion

This study revealed during intensive phase of treatment, approximately two-third children and during maintenance phase majority of children remained in complete remission in ALL. So, Risk-stratified ALL treatment is feasible in a newly established resource limited setting, but there is limitation of availability of high-quality diagnostics, specifically cytogenetics.

Recommendation

Partnership with a specialist cancer center in treatment of the same group of patients allows sharing of expertise and experience. The collaboration could alleviate the anxiety of distant care and be helpful in building confidence of patient to get treatment in their own country with long term reduction in patient exodus.

Acknowledgment

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ORIGINAL ARTICLE

Spectrum of Upper GI Endoscopy in Children: A Tertiary Centre Experience from Bangladesh

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Abstract

Background: *Upper gastrointestinal endoscopy is an essential, safe and sensitive investigation for diagnosing pediatric gastrointestinal diseases. In resource-limited countries like Bangladesh, the practice of pediatric endoscopy remains rudimentary, lacking in trained pediatric endoscopists and appropriate-sized endoscopes. There is limited study on paediatric upper GI endoscopy in our country.*

Objectives: *The aim of the study was to find out the indications, common endoscopic findings and immediate post procedure complication of UGI endoscopy in children.*

Methods: *This is a retrospective study; the records of all the patients whose age is less than 18 years and who underwent endoscopy in the last 6 years were studied.*

Results: *Among the total of 384 children (age <18 years), the most common indications were recurrent abdominal pain in 133 (34.7%) patients followed by hematemesis±melena in 99 (25.8%), esophageal varices (follow up with eradication) in 67 (17.5%), recurrent vomiting in 31 (8.1%), foreign body, CLD screening, suspected celiac disease, isolated splenomegaly, corrosive injury, and weight loss. The most common abnormal findings were gastritis in 103 (26.9%) children followed by esophageal varices in 73 (19.2%), duodenitis in 26 (6.8%), foreign body, esophagitis, hiatus hernia, esophageal stricture, esophageal ulcer, gastric ulcer, duodenal ulcer etc. Minor adverse events occurred in 7.0% of children.*

Conclusion: *The commonest indication for Pediatric UGI endoscopy was recurrent abdominal pain and the commonest endoscopic feature was gastritis. No significant post procedure complication was noted in the study.*

Keywords: *Bangladesh, Child, Upper GI endoscopy, Indication, Complications*

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Introduction

Gastrointestinal diseases like esophageal varices, peptic ulcer disease, inflammatory bowel disease etc. are important health related problems worldwide especially in pediatric age group.[1] Upper gastrointestinal (UGI) endoscopy is the most sensitive investigation for diagnosing upper GI diseases.[2] After the introduction of flexible endoscopy by Hirschowitz in 1950's, use of upper GI endoscopy has become a routine GI procedure.[3] Later on, fiberoptic endoscopy for children developed in 1970's and upper GI endoscopy has now become a standard diagnostic procedure for many gastrointestinal problems in children.[4-6]

Initially, pediatric endoscopy was mainly used for the identification of superficial lesions, which were not seen on radiographic contrast studies, and for diagnosing specific causes of UGI bleeding. Esophagogas-troduodenoscopy (EGD) can now be done at any age because of the development of flexible endoscopes with a small caliber and proper training of operators especially in developed countries.[7] According to international guidelines, diagnostic pediatric EGD is usually safe and complications are rarely encountered.[8-10] Complications mostly occur due to sedation and anesthesia administered during the procedure.[11] However, therapeutic endoscopy in children can have multiple complications de-pending upon the nature of intervention and expertise of the endoscopist, with the reported complication rate of less than 1% when EGD is done by expert pediatric endoscopists.[7,10]

In contrary, the picture of developing countries are not same. Upper GI endoscopy is still an under-utilized tool and information regarding its efficacy is scanty in most of the developing countries. This is mainly due to lack of awareness about the role of this important diagnostic modality in children which prevents referrals of these children to a center where this facility is available.[1] In resource-limited countries like Bangladesh, the field of pediatric endoscopy remains rudimentary and only limited to a few centers due to lack of trained pediatric endoscopists and appropriate-sized endoscopes. Furthermore, there are only very few studies and lack of data regarding the appropriate indications and complications of endoscopy in children. Therefore, we carried out this hospital-based retrospective study to find out the common indications, endoscopic findings and complications of Pediatric upper GI endoscopy in our setup, to raise awareness regarding use of upper GI endoscopy amongst pediatricians in diagnosing upper GI problems in our country.

Materials and Methods

The study was carried out in the department of Pediatric Gastroenterology, Hepatology & Nutrition, Bangladesh Shishu Hospital & Institute, Dhaka, Bangladesh. The medical records of all patients under the age of 18 years who underwent upper GI endoscopy (both inpatient & outpatient department) from January 2016 to December 2021 were reviewed retrospectively. All of the pediatric patients (total 384) on whom upper GI endoscopy was performed during the study period were included in the study. The need for endoscopy was decided by the paediatric gastroenterologist as well as by the general paediatricians. Informed consent was taken from parents/patients before the procedure after careful explanation of procedure details and potential complications. Prior to the procedure, the children remain fasted for at least 6 hours. All pediatric upper GI endoscopies were performed by the faculty members.

The majority of the endoscopic procedures were done with video endoscopes (OLYMPUS GIF-Q190; Olympus, To-kyo, Japan) for ≥2 years of age. In children less than 2 years or weighing less than 10 kg, endoscopy was performed with a pediatric video endo-scope (OLYMPUS GIF-XP190; Olympus) with a diameter of 5.8 mm.

Mode of anesthesia was decided by performing faculty member depending upon patient's age, level of cooperation and physicians comfort level. Parenteral Midazolam (0.05-0.1 mg/kg IV, maximum single dose of 4 mg) with or without Ketamine (1 mg/kg I/V) was used as sedatives. In some adolescents, endoscopy was done without sedation/an-esthesia but under local xylocaine spray or jelly.

Endoscopic findings were documented for each patient and biopsy materials for histopathology were taken. Patients were kept in observation room to see the immediate post procedure complications. Patient's demographic data including age, sex and length of hospital stay were recorded. For descriptive purpose patients were divided into three age groups. Indications for upper GI endoscopy, findings and post endoscopic complications were recorded for each patient.

All data on categorical variables were presented as frequencies and percentages. Data of various indications, endoscopic findings and complications were entered into the SPSS (statistical package for social science) Version 24.0 statistical program and statistical analyses were carried out at 5% level of significance and $P<0.05$ was considered statistically significant.

Results

Over a period of 6 years (2016-2021), a total of 384 children underwent upper GI endoscopy. Mean age of patients was 9.6 years with a minimum age of 2 months and a maximum of 18 years. Older children aged >10 years had highest frequency of upper GI endoscopy, *i.e.* 50.2% (n=193), followed by younger children (5-10 years of age), in which frequency of endoscopy was 32.3% (n=124). The frequency of endoscopy in youngest children between 0-5 years of age was 17.5% (n=67). Male were 207 (53.9%) and female were 177 (46.1%). The Male female ratio was 1.1:1. Out of 384 children, 171 (44.6%) were from outpatient department and 213 (55.4%) from admitted patient. No sedation were required in 75 (19.6%) children especially from >10 year age group. Only parenteral midazolam was given in 257 (66.9%) children whereas parenteral midazolam plus ketamine were required in only 52 (13.5%) sensitive children (Table I).

Table I

Characteristics of study population (N=384)

Variable	No.	Percentage (%)
Age		
<5 years	67	17.5
5-10 years	124	32.3
>10 years	193	50.2
Sex		
Male	207	53.9
Female	177	46.1
Patient status		
Outpatient	171	44.6
Inpatient	213	55.4
Sedation		
No Sedation	75	19.6
Midazolam	257	66.9
Midazolam+Ketamine	52	13.5
Biopsy obtained		
Yes	147	38.2
No	237	62.8

The most common indications were recurrent abdominal pain in 133 (34.7%) patients. Hematemesis±melena was the next cause (25.8%) of the procedure. In 17.5% patients upper GI endoscopy was done due to esophageal varices kept in follow up for surveillance. Other less common indications were recurrent vomiting (8.1%), foreign body ingestion (5.4%), suspected celiac disease (1.9%), isolated splenomegaly, corrosive injury and explained weight loss (Fig.-1).

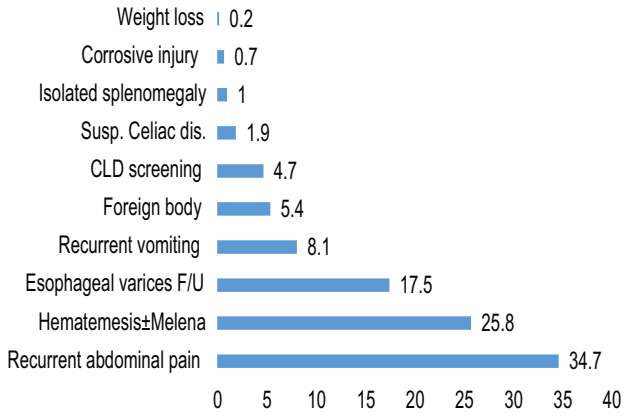

Fig.-1: *Indications of Upper GI Endoscopy (N=384)*

The abnormal endoscopic findings were found in 66% patients. Among them, gastritis was the most common histopathological finding on biopsy, seen 26.9% (n=103) cases. Esophageal varices was found in 19.2%, duodenitis in 6.8%, foreign body in 5.4%, esophagitis in 3.4% and endoscopic findings were normal in 34% cases (Table II & Fig. 2).

Table II

Endoscopic findings of studied children (N=384)

Findings	No.	Percentage (%)
Normal	131	34.1
Gastritis	103	26.9
Esophageal varices	73	19.2
Duodenitis	26	6.8
Foreign body	21	5.4
Esophagitis	13	3.4
Hiatus hernia	07	1.8
Esophageal stricture	03	0.8
Esophageal ulcer	02	0.5
Gastric ulcer	02	0.5
Duodenal ulcer	01	0.2
Duodenal growth	01	0.2
Duodenal polyp	01	0.2
Total	384	100

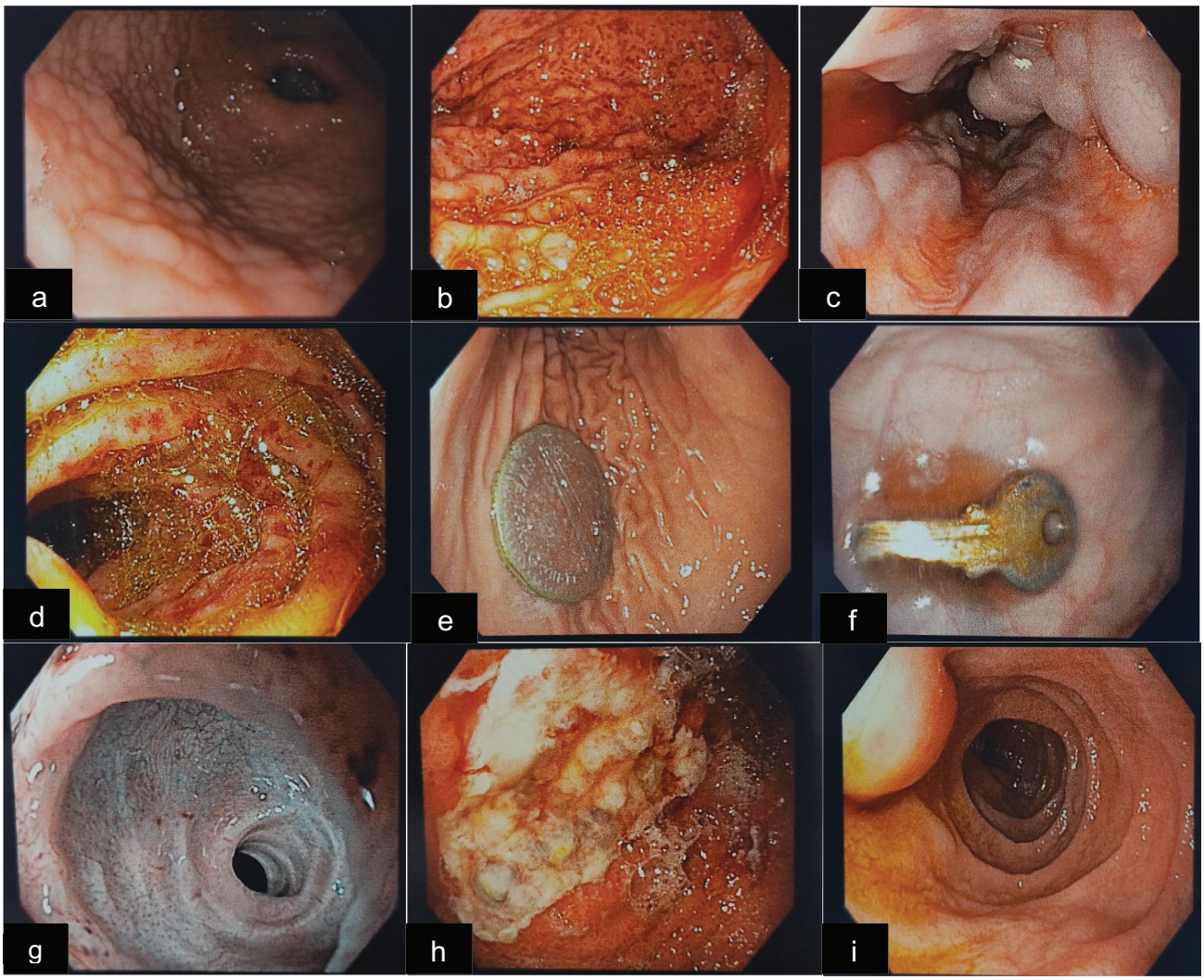

Fig.-2: *Various endoscopic views: (a) Gastritis without bleeding, (b) Gastritis with bleeding, (c) Esophageal varices, (d) Duodenitis, (e) Foreign body, coin, (f) Foreign body, key, (g) Corrosive injury, (h) Gastric ulcer, (i) Duodenal growth*

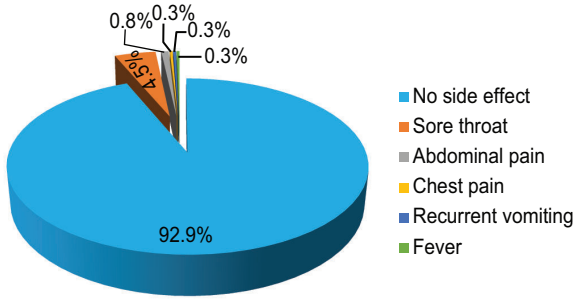

Fig.-3: *Complications of Upper GI Endoscopy (n=384)*

No side effects were observed in near 93% of children following endoscopy procedure. A total of 23 (7.0%) adverse events were recorded. Seventeen (4.5%) patients complained of sore throat, 3(0.8%) patients had abdominal pain and 1(0.3%) patient each had complained of chest pain, recurrent vomiting and fever. All of them were minor and did not affect the overall survival and hospital stay (Fig-3).

Discussion

Upper GI endoscopy is one of the most specific, prompt, conveniant and cost effective diagnostic tool for a wide variety of gastrointestinal disorders in children, especially under the circumstances when other investigations are often remain inconclusive. In addition to its diagnostic use, upper GI endoscopy also has an established therapeutic role and various disorders like upper GI bleeding, Mallory Weiss tear; gastric erosions can be effectively treated by

endoscopy.[12-13] Therefore, despite changing indications over a period of time, the disorders requiring upper GI endoscopy for diagnostic or therapeutic purposes in children have shown a rising trend.[14]

In the present study, older children aged >10 years had highest frequency of upper GI endoscopy with 50.2%. Same phenomena were observed in Mazumder et al[2] (40%) from Bangladesh, Khan et al[1] (40%) from Pakistan, Wani et al[7] (66.2%) from India, Kumo et al[15] (80.2%) from Nigeria, Isa et al[16] (35.8%) from Bahrain and Altamimi et al[17] (35.8%) from Jordan. Less fear and much more gastrointestinal diseases in older children probably the possible causes. The Male female ratio was 1.1:1. Other studies gender ratio were same from different countries.[2,7,15-17] No gender differences regarding incidence of pediatric gastrointestinal diseases may be the possible cause. No sedation were required in 75 (19.6%) children especially from >10 year age group. Another study from Bangladesh, Mazumder et al[2] (66%) and Wani et al[7] (30.4%) from India did upper GI endoscopy without sedation in the older children. Appropriate counseling and good co-operation of older children probably the possible etiology. Mild sedation with intravenous midazolam was given in 66.9% children whereas midazolam plus ketamine were required in only 13.5% sensitive children. In different studies from Bangladesh[2], India[7], Nigeria[15], Bahrain[16] and Jordan[17], midazolam was commonly used as a sedative agent during endoscopy as it is safe, short acting, rapid onset with minimal side effects. In 14.8% patients, Wani et al[7] using general anesthesia like developed countries. Due to unavailability of anesthetic support and inadequate number of experienced pediatric anesthesiologist, conscious sedation is the key for developing countries.

In the present study, the most common indications were recurrent abdominal pain in 34.7% patients followed by Hematemesis±melena (25.8%) and esophageal varices with follow up for surveillance (17.5%). Recent studies from Nigeria[15] (47.7%), Bahrain[16] (40.9%) and Jordan[17] (45.1%) also observed the commonest indication was pain abdomen. From previous study of Bangladesh [2] (41%) and India[7] (19%) esophageal varices with follow up for surveillance was the commonest cause. Recent trend of spicy diet, frequent use of nonsteroidal anti-inflammatory drugs as a pain reliever and smoking habits among adolescents may be the possible etiology of pain abdomen nowadays. In the literature from most of the developing countries, recurrent abdominal pain has been reported to be the commonest indication of upper GI endoscopy ranging from 8% to 43%.[18-20]

About one third of the children (34%) who underwent upper GI endoscopy in our study had normal endoscopic findings. Another study from Bangladesh[2] (36%), India (26.7%)[21] and Pakistan[1] (46%) stated the similar results. The abnormal endoscopic findings were found in 66% patients. Among them, gastritis was the most common (26.9%) histopathological finding on biopsy followed by esophageal varices was found in 19.2%, deodenitis in 6.8%, foreign body in 5.4% and esophagitis in 3.4% cases. In the recent study, Isa et al. [16] (29.3%) from Bahrain and Altamimi et al[17] (22.1%) from Jordan also stated that gastritis were the commonest findings on pediatric endoscopy. On the other side, esophageal varices was the commonest one in Mazumder et al[2] (40%) from Bangladesh and Wani et al[7] (23%) from India. Non-specific findings (30.5%) in Khan et al[1], Pakistan and foreign body in Gadgade et al[21] (25.3%) from Karnataka, India were the superior one. Different studies from different geographic areas have shown different indications & findings but the overall pattern is almost similar.[7]

Adverse events were observed in 7% cases, which was similar to Wani et al[7] (7.3%) f rom India. In the present study, Seventeen (4.5%) patients complained of sore throat which was similar to Indian[7] (3.64%) and Nigerian[15] (1.2%) study. All the adverse events were minor and did not increase morbidity or mortality.

Limitations of the study

This study's primary limitation is that it was a single-center study. Furthermore, its retrospective nature may have resulted in inaccurate findings regarding underreporting of adverse events in OPD patients.

Conclusions

Abdominal pain followed by upper GI bleeding was the most typical indication, and gastritis followed by esophageal varices were the most common abnormal findings of pediatric upper GI endoscopy. No significant premedication or procedure-related complications were found. We observed that upper GI endoscopy is beneficial and can be safely used in

children of all ages, which helps in early diagnoses and managing various GI conditions.

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ORIGINAL ARTICLE

Complications of Paediatric Ventriculoperitoneal (VP) Shunt: Experience in A Tertiary Care Hospital

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Abstract

Background: *Ventricloperitoneal (VP) shunt is the most commonly used shunt procedure in children because of the capacity of the peritoneum to resorb fluid like Cerebrospinal fluid (CSF). Primary and subsequent peritoneal catheter placement is relatively easy procedure to be done. VP shunt procedures are associated with varieties of complications.*

Methods: *A prospective study was done from July 2017 to June 2021 in Faculty of Paediatric Surgery, Bangladesh Shishu Hospital & Institute. A total number of cases underwent VP shunt surgery were 192. We had analyzed 82(42.71%) patients of VP shunt surgery who had various shunt related complications and analyzed the predisposing risk factors and spectrum of complications.*

Results: *The mean age was 16±14 months and median age was11.75 months. Out of 82 patients 56 (68.29%) were male and 26(31.71%) were female. Seventy (85.37%) patients had single complication and 12(14.63%) had more than 1 complications. Twenty four (29.27%) patients had infective complication and 58(70.73%) had mechanical complication. Infective complications (24, 29.27%) include shunt tract abscess (41.66%), CSF leak (16.67%) exposure of shunt tube through anus (16.67%), wound infection (16.67%). Mechanical complications were present in 58(70.73%) cases and 40(48.78%) had ventricular end malformation, 24(29.27%) peritoneal end and 18(21.95%) had both end malformation.*

Conclusion*: With this prospective study of complications of VP shunt, age at initial shunt surgery, insertion and important patient-related predictors of shunt failure. The different predominant etiological factors the interval between the age of initial shunt placement and onset of complications were the most responsible for early and late shunt failure were infective and mechanical complications respectively.*

Keywords*: Paediatric hydrocephalous, VP shunt, complication.*

Introduction

Hydrocephalus (HCP) is defined as excessive accumulation of cerebrospinal fluid (CSF) within the ventricular system of brain due to imbalance between CSF production and absorption or due to obstruction in the CSF pathway.

The complications of VP shunt surgery may be broadly divided into (a) mechanical complication and

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(b) infective complication. Mechanical complications include obstruction, disconnection or migration of any component of the ventricular or peritoneal catheter.

Infective complications include shunt tract abscess, skin necrosis overlying the shunt device and exposure of shunt tube followed by ventriculitis most commonly. Other complications are seizure, subdural effusion, craniosynostosis, inguinal hernia or hydrocele, ascites, CSF pseudocyst formation, perforation of a viscus or gut extrusion or prolapse of shunt through anus, intestinal volvulus and obstruction.[1] We studied 82 patients of VP shunt procedure who presented with various shunt related complications and analyzed the predisposing causes and spectrum of complications.

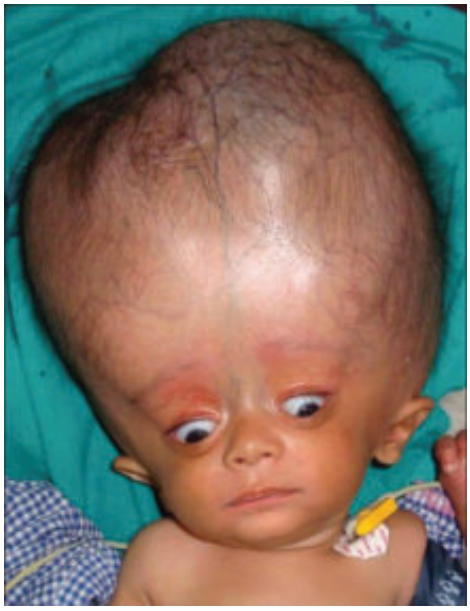
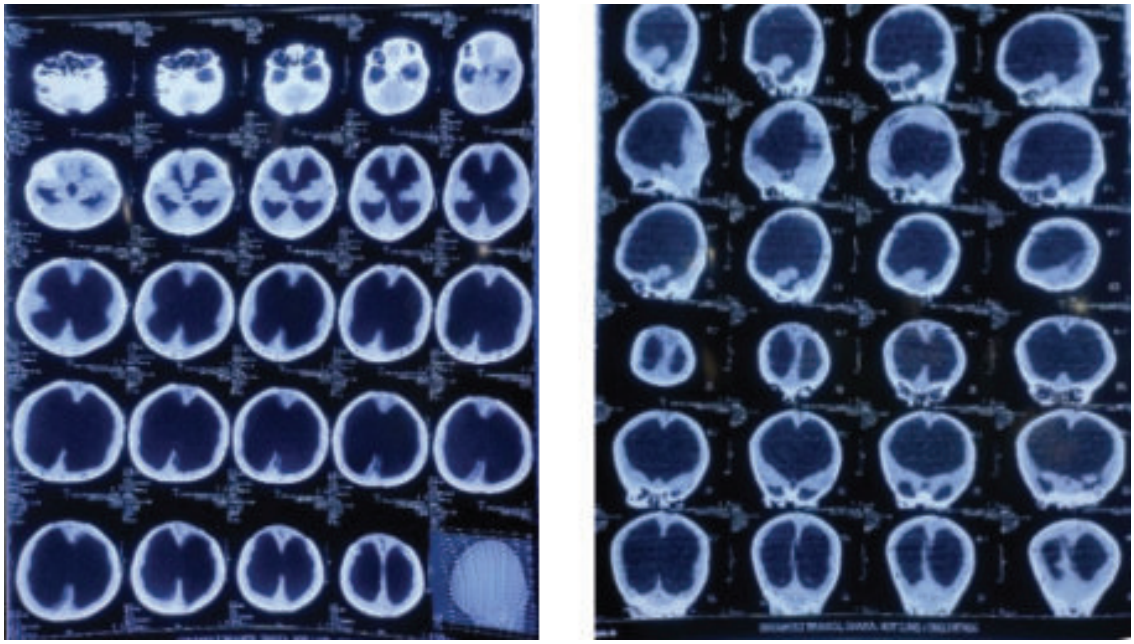


Fig.-1: *A baby with hydrocephalous*

Materials and Methods

This study included 82 patients out of 192 patients of hydrocephalus (HCP) who underwent VP shunt placement and had complications. The study was conducted in Faculty of Paediatric Surgery, Bangladesh Shishu Hospital & Institute (BSH&I) from July 2017 to June 2021.

A total number of patients were 192 and all of them underwent VP shunt surgery were evaluated. In all patients medium pressure Chabra's silastic shunt were used for hydrocephalus and 82 patients were presented with various shunt-related complications due to the causes other than intracranial tumour. All patients who presented with complications were recorded and thoroughly analyzed by clinical examinations, laboratory tests and imaging studies like plain x-ray to establish shunt location, computed tomography (CT) scan of brain and ultrasonography (USG) and CT scan of abdomen.



a) Axial view b) Sagittal & coronal view

Fig.-2: *CT scan of brain*

Early and late shunt complications were defined according to the duration between the initial shunt placement and appearance of first complication. Those occurring within 2 years were early and more than 2 years were considered as late complications.[2] The patients whose shunt were completely non-functioning, revision shunt procedure were performed once or more than one occasions whenever applicable.

Results

During the study period, a total of 82 (42.7%) patients presented with different patterns of complications were analyzed. The mean age was 16±14 months and range was 2 to 30 months. Median age was 11.75 months sex incidence were male 56(68.29%) and 26 (31.71%) female. Out of 82 patients 70(85.37%) had single complication and the rest 12(14.63%) had multiple complications (Table I).

Table I
Distribution of baseline data of study cases

Parameter		Value	Percentage
Age (month)	Mean ±SD	16±14	
	Range	2-30	
	Median	11.75	
Sex	Male	56	68.29
	Female	25	31.71
VP shunt	Single	70	85.37
complication	Multiple	12	14.63
Mortality			6.17

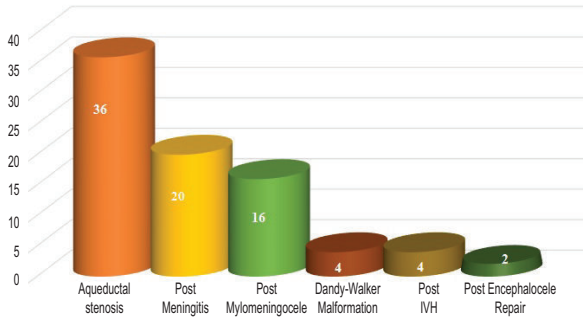


Fig.-3: *The etiology of HCP*

Aqueductal stenosis (36, 43.90%), post meningitis (20, 24.39%), post mylomeningocele (16, 19.51%), Dandy Walker malformation (4, 4.88%), post IVH (4, 4.88%) and post encephalocele repair (2, 2.44%) were the causes of hydrocephalous (Fig.-3). Infective complications include shunt tract abscess (10, 41.66%), CSF leak (4, 16.67%), exposure of shunt tube through anus (2, 8.33%), seizure (4, 16.67%), wound infection (4, 16.67%), scrotal swelling (2, 8.33%) (Fig.-4).

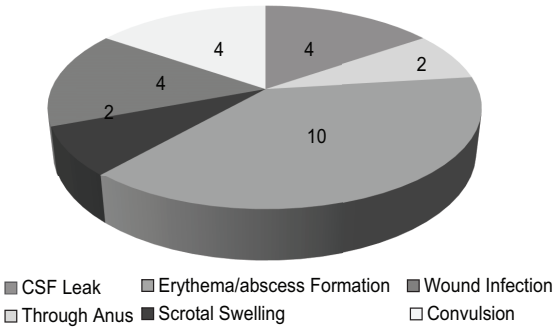
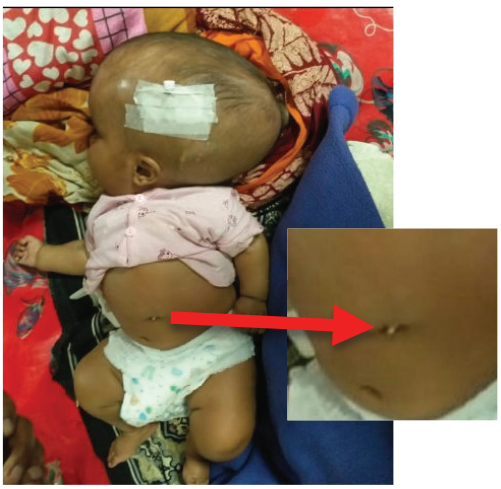
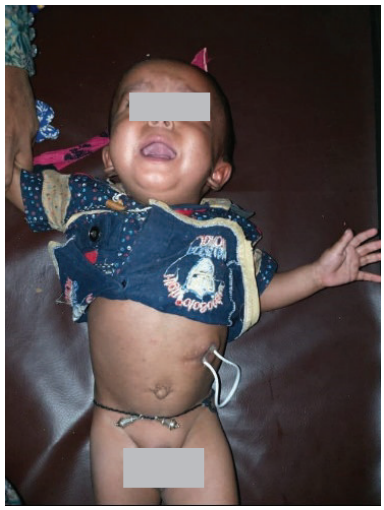


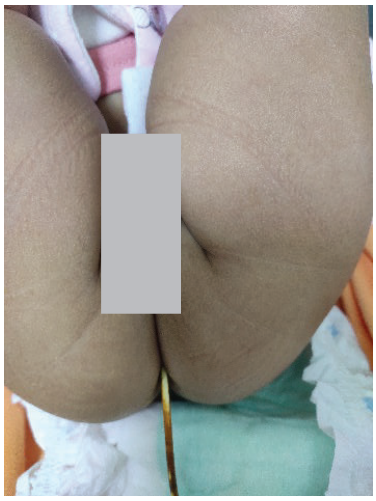
Fig.-4: *Infective implications of VP shunt*



a. CSF leakage from abdominal wound



b. Extrusion of VP shunt through abdominal wound



c. Prolapse of shunt through anus

Fig.-5: *Few complications of VP shunt is shown by photograph*

Patients with meningitis and convulsion had shunt malfunctioning and developed septicemia. The few other follow-up cases of post-encephalocle and post-myelomeningocle repaired HCP developed septicemia and subsequently ventriculitis.

Twenty patients had a history of shunt revision, out of which 14(70%) had undergone revision of shunt once, 2(10%) had undergone revision twice and 4(20%) patients had undergone multiple shunt revision. Fourty (48.78%) patients had ventricular end malfunction and 24 patients had ventricular end malfunction, 18 patients had both ventricular and peritoneal end malfunction. Patient of early infective complications were 20(24.39%) and late infective complications were 4(4.88%). Moreover, numbers of early and late mechanical complication were 22(26.83%) and 36(43.9%) respectively. On analyzing the nature of complication in respect to infective shunt complication interval, 8(34.14%) of patients with shunt related complication presented within 6 months of initial shunt placement and 16(65.86%) presented within 2 years. Mean shunt complication interval in patients with infective complication was 15.8±14.35 (median 18.35) months compared to 48.55±32.75 (median 38.6) months in patients with mechanical complication (Table II).

Table II

Distribution of data of VP shunt complication

Shunt malfunction	Ventricular end	40	48.78
	Peritoneal end	24	29.27
	Both ventricular & peritoneal end	18	21.95
Shunt complication	**Infective**	24	29.27
	Early	20	24.39
	Late	4	4.88
	Mechanical	58	70.73
	Early	22	26.83
	Late	36	43.9
Shunt revision	Single	14	70
	Twice	2	10
	>Twice	4	20
Shunt complication	**Infective**		
interval (month)	Mean ±SD	15.8±14.35	
	Median	18.35	
	Complications within 6 month	8	31.14
	Complications within 2 years	16	65.86
	Mechanical		
	Mean±SD	48.55±32.75	
	Median	38.6	

Discussion

VP shunt placement for hydrocephalus is a well known and popular procedure. VP shunt is significantly associated with complications like malfunction and infection.[16] VP shunt malfunction can occur anytime from hours to years after the placement of shunt. Overall shunt infection rate was 5% to 8% in literature.[1] In our study it was 15.63% which was in a higher rate. The role of age at the time of shunt placement has been evaluated previously in several observational studies. DI Rocco et al[2] reported increased shunt failure in patients who had undergone shunt placement at age <6 months. Piatt and Cariso et al[3] had similar results in patients <2 years of age. Similar observation was made by Liptak and McDonaid[4] in children <1year of age. Our present study also revealed that patient age at the time of shunt placement is an important predictor of shunt function and malfunction. In this study, the majority of patients who had shunt failure primary shunt placement were done during initial 2 years of age. On the other hand there was some studies showing no effect of age on the incidence of shunt infection.[5] Brage et al[6] shown a higher incidence of infection in children older than 2 years.

In our series, 33.33% were mechanical, and 15.63% were infective complications. Similar findings were seen in the study done by Kanesha et al were 32% mechanical and 14.6% infective cause, whereas Lee et al shown 12.2% shunt blockage and 4.1% infection.[5,7] Peacock and Career in their study found a shunt blockage rate of 20%.[8]

Lohani et.al shown 12.07% had shunt malfunction and 7.92% had shunt infection.[16]

In our study, 34.14% of patient had shunt related complications presented within 6 months of initial shunt placement and 51.21% presented within 2 years of shunt placement. On several literature reviewed, event free survival at 1 year ranged from 62% to 80%[9,10] and at 10 years from 35% to 48%.[9,11] The most common pathogen isolated in our study from CSF culture sensitivity reports was staphylococcus aureus followed by methicillin-resistant staphylococcus. Staphylococcus aureus was mentioned in literature.[12,13]

The shunt related mortality was 20% in the study by Kalasha et al[5] whereas in our study, it was 4.17%. The different studies available in literature shown a mortality rate in nontumorus hydrocephalus ranging from 8.6%[14] to 13.7%[15]. The figure varies as per the duration of follow-up in these studies.[14,15] We have a thought from the discussion to decrease the postoperative mortality and morbidity by improving strict technical and sterilization procedure in our setup.

Conclusion

With this prospective study of complications of VP shunt surgery, age at initial VP shunt placement and the interval between age of primary shunt placement and onset of complications were the most important patient related predictors of shunt failure. The different predominant etiological factors responsible for early and late shunt failure were infective and mechanical complications respectively.

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REVIEW ARTICLE

Effect of Intrahepatic Cholestasis of Pregnancy (ICP) on Neonatal Outcome

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Abstract

Intrahepatic cholestasis of pregnancy is a condition unique to pregnancy characterized by pruritus and elevated serum bile acids and/or aminotransferase levels. It usually manifests during second or third trimester of pregnancy and improves after delivery. But neonates are at increased risks of still birth, prematurity, respiratory distress syndrome and metabolic problems. Timely identification and appropriate intervention can reduce the adverse neonatal outcomes.

Keywords: *Obstetric cholestasis, neonatal outcome, effects.*

Introduction

Intrahepatic cholestasis of pregnancy (ICP) is the most common pregnancy related liver disease.[1] It is typically a reversible cholestatic disease presenting in the second to third trimester of pregnancy and is characterized by pruritus in the absence of a skin rash with abnormal liver function tests. There are elevated serum aminotransferases and/or elevated serum bile acid levels (>or = 10micromol/L) with spontaneous relief of laboratory abnormalities and symptoms promptly after delivery but no later than one month postpartum.[2] Untreated ICP carries potential risks for mothers and their newborn infants. It is associated with adverse obstetrical outcomes, which includes stillbirth, spontaneous preterm delivery, respiratory distress syndrome, meconium aspiration syndrome and fetal asphyxia.[3] It is important to have a clear idea about this cholestatic condition in pregnancy. A brief knowledge on its various effects in fetus and neonates, can guide physicians to diagnose timely as well as to eliminate the risks in the newborn infants during the perinatal and postnatal period. So, this narrative review has been planned to enlighten obstetricians and neonatologists with a detail information on this topic.

Incidence and Epidemiology

Different epidemiologic surveys have found significant regional variation in the incidence of ICP. It varies from 0.1 to 1.5% of pregnancies in Europe and 1 to 5% in China.[4] In comparison with the overall prevalence of ICP which is 0.7%, the white population has a low occurrence of 0.62%, while this number is 1.46% in the Pakistani population and 1.24% in the Indian population.[5] Neonatal risks have also been demonstrated in many clinical studies which revealed that, ICP may lead to preterm delivery in 19-60%, fetal distress in 27-33% and fetal loss in 0.2-4.1% of patients.[6]

Etiopathogenesis

There is still much to be explored about the exact causes of ICP and its manifestation, but it is thought to be multifactorial, including genetic, hormonal and environmental factors.[7] The causes are likely to be due to a number of different factors, including:

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- **Genetic predisposition** - The exact mechanisms causing intrahepatic cholestasis during pregnancy are still unknown; but two adenosine triphosphate binding cassette genes *(ABCB4* and *ABCB11*) have been identified as contributors in some women.[8] Certain genetic mutations, and certain unknown factors, cause a rise in serum bile acids.[9]
- **Hormones** - Pregnancy hormones such as estrogen and progesterone have an effect on the liver's ability to transport certain chemicals, including bile acids. The flow of bile acids is significantly reduced and leads to the bile acids building up in the blood that causes the symptoms. Women carrying multiples, women who have IVF treatment and women who have prior liver diseases also appear to have a higher risk of cholestasis.[10]
- **Environment -** More women were diagnosed as Intrahepatic Cholestasis of Pregnancy (ICP) during the winter months. Although the exact reason is not clear, it is suggested that there is an environmental trigger for the condition, such as reduced exposure to sunlight or change in diet.[11]

Identifying pregnant women with ICP

The symptoms of Intrahepatic cholestasis of pregnancy (ICP) can vary based on its severity and type. But commonly encountered features are itching all over, but often more severe on palms and soles of the feet. The itching can be recurrent or constant. Many women find that it is worse at night and it disturbs their sleep. Dark urine and/or pale stools (grayish in color), jaundice (rare) may also be present. Risk factors may be present in some cases like family history of obstetric cholestasis, multiple pregnancy, carriage of hepatitis C and presence of gallstones etc. During searching the cause behind this, elevated liver enzymes and bile acids can also favor the diagnosis of ICP.[12]

Current guidelines state that a diagnosis of ICP can be made if serum bile acid levels are above 10 mmol/L. When levels reach 40 mmol/L, the case is considered severe and risk of adverse outcomes is increased.[13,14] When levels reach 100 mmol/L, the risk of adverse fetal outcomes is increased further, with a 3.44% risk of stillbirth.[15] Although the diagnostic criteria are focused on bile acid levels, other liver function parameters such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin are used to obtain a complete picture and to rule out the cases in which other liver diseases are present.[16]

Effect of ICP on Mother and Newborn

Maternal

The maternal and fetal consequences in ICP have been studied in different populations. A study done in Sweden showed that women with ICP have almost 3 times more chances of developing gestational diabetes, pre-eclampsia, and preterm labor.[17] Whereas, other studies showed a benign maternal outcome with increased postpartum hemorrhage. Vitamin K deficiency is found only in severe persistent ICP with high levels (>40 μmol/L) of circulating bile acids.[18]

Neonatal

Some neonatal conditions are strictly associated with maternal ICP. The fetal complications includes fetal distress, meconium staining of amniotic fluid at delivery, preterm delivery meconium aspiration syndrome, pneumonia, respiratory distress, major congenital anomalies, hyperbilirubinemia, sepsis and still birth.[19] ICP have influence on long term effects on babies like obesity and diabetes. The findings add strong evidence that the environment that the babies are exposed to in the womb is a major cause of metabolic disease in adults.[20]

Evidences with effect of ICP on neonatal outcomes

Respiratory Distress Syndrome

Maternal intrahepatic cholestasis increases the risk for Respiratory Distress Syndrome. In studies, RDS rate was found three times higher among neonates of the cholestasis group. Zecca et al, in a case-control study (matching on gestational age) showed a risk of RDS in newborns of ICP mother is 2.5 times higher than in control infants (28.6% vs 14%), regardless of BA level.[21] The elevated bile acids are thought to interfere with the formation of surfactant which allows the lungs to expand after birth.[21] Hypothesis to explain increased neonatal morbidity among case infants include a direct effect of bile acid on neonatal lung, which could be induce a "bile acid pneumonia".[21]

Fetal Distress

Placenta plays a major role in protecting the fetus from the adverse effects of potentially toxic endogenous substances such as bile acid.[22] Increased levels of bile acid in maternal circulation, enhances placental transport and facilitate the generation of certain placental hormones which leads to significant constriction among chorionic vessels and resulting fetal distress.[23]

Meconium Aspiration

Sometimes meconium is expelled into the amniotic fluid prior to birth, or during labor due to stress. Meconium may also pass earlier in cholestasis due to increased motility of fetal colon with increased bile acid level. If the baby then inhales the contaminated fluid, respiratory problems may occur. In pregnancies affected by cholestasis, meconium is often passed prior to birth.[24]

Preterm labor

There is an increased risk of spontaneous preterm labor, as many as 60% of deliveries in some studies, however with active management most studies report rates of 30%-40%. This is due to high level of bile acid make the uterus more sensitive to oxytocin that causes uterine contractions· Earlier presentations of Intrahepatic Cholestasis of Pregnancy (ICP) seem to carry an even greater risk of preterm labor, as well as twin or triplet pregnancies.[25]

Stillbirth

Stillbirth tends to occur in the last few weeks of pregnancy. The reason this occurs is not completely understood although it is thought to be due to a cardiac arrhythmia caused by the elevated bile acids. With bile acids remaining under 100 µmol/L, the risk is less than 0.28% and similar to a normal pregnancy. When bile acid level is over 100, the risk of stillbirth increases to over 3%.[26]

Metabolic diseases

Increase in fats and excessive cholesterol transport in placenta from mothers with cholestasis, consistent with a disruption in the metabolism of fats. The researchers propose that this shift in the nutrients supplied by the mother is likely to affect the energy balance in the unborn baby, something that could continue after the baby is born, resulting in an altered metabolism in adult life that could give rise to diseases such as obesity and diabetes. The exact mechanisms of how the increase in bile salts in the mothers' blood programs the unborn baby towards metabolic disease not exactly known yet but it seems likely that epigenetics plays a role.[12] A study done in Sweden showed that women with ICP have almost 3 times more chances of developing gestational diabetes, pre-eclampsia, and preterm labor.[13] However, other studies predict a benign maternal outcome with increased postpartum hemorrhage and vitamin K deficiency only in severe persistent ICP with high levels (>40 ìmol/L) of circulating BA.[14]

Others

A study done by Mullally and Hansen showed that congenital malformations and abortions had no association with ICP, and birth weight of babies born to such mothers was also sufficient.[27] Maternal bile acid especially above 40 ìmol/L, increases the chances of preterm delivery, IUFD, poor Apgar score, and NICU admissions significantly. A large case-control study in the UK showed that women with severe ICP (based on BA levels) had significantly high chances of preterm delivery (OR 5.3, 95% CI: 4.1-6.9), still birth (OR 2.5, 95% CI: 1.0-6.4), and NICU admissions (OR 2.6, 95% CI: 1.9-3.6**)**.[26]

Ways for improving neonatal outcomes

Since the disease is relatively rare and symptoms are often nonspecific, it is important for healthcare practitioners to be aware of the signs and symptoms of the disease to help reduce or prevent adverse outcomes. Following measures can be taken in this regard:

- Women should be informed of the increased risk of perinatal morbidity and maternal morbidity
- Women should be followed up to provide appropriate counseling and to ensure that liver function test returned to normal.
- The current standard of care for ICP patients is a combination of ursodeoxycholic acid by mouth and early delivery between weeks 34 and 38, depending on peak bile acid levels and individual patient circumstance, as the risk of stillbirth due to ICP increases in the last weeks of pregnancy.[28] Ursodeoxycholic acid (UDCA) improves pruritus and liver function in women with obstetric cholestasis. It displaces of more hydrophobic endogenous bile salts from the bile acid pool. This protects the hepatocyte membrane from the

damaging toxicity of bile salts, enhance bile acid clearance across the placenta from the fetus. The results of a meta analysis also suggest that UDCA therapy is beneficial for fetal outcome. No side effects of UDCA have been reported for mothers or babies.[29]

- The other part of management is with proper timing of delivery. Delivery recommendations are based on bile acid levels as risks increase as bile acids become more elevated. For bile acids greater than 100 μmol/L, delivery is at 36 weeks. There is consideration for earlier delivery in these cases with other factors. For levels under 100 μmol/L, delivery is recommended at 36 -39 weeks with delivery earlier in the window if levels reach 40 μmol/L.[30]
- Antenatal corticosteroid administration to mothers who are at risk of preterm delivery is also required to reduce the incidence as well as to reduce the detrimental effects of respiratory distress syndrome (RDS) in newborns.
- Reassurance to parents about the lack of long-term sequelae for mother and baby and discussion of the high recurrence rate (45-90%) and the increased incidence of obstetric cholestasis in family members.[31]
- Team work is required with the neonatologists before and during delivery, so that early intervention can be provided for complications of newborns soon after birth.

Conclusion

Intrahepatic cholestasis of pregnancy is not uncommon. Rather it is associated with adverse maternal and neonatal outcome. There is no specific method of antenatal fetal monitoring for the prediction of fetal death. Therefore, appropriate diagnosis, timely treatment and delivery of the pregnant women with ICP may eliminate the risks in the newborn infants during the perinatal and postnatal period. So, a combined effort is needed between the obstetricians and the neonatologists.

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DS (Child) H J 2021; 37(2): 140-142

CASE REPORT

Pulmonary Tuberculosis: Atypical Presentation

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Introduction

Tuberculosis (TB) is a major global health problem. In 2016, there were an estimated 10.4 million TB cases and 10% of this was in children younger than 18 years of age.[1] Pulmonary tuberculosis is caused by Mycobacterium tuberculosis when droplet nuclei containing bacilli are inhaled.[2-5] The course of the disease depends on the interaction between the host defence and the virulence of the organism. The major host defense is cell-mediated immunity, which is effected primarily by macrophages and T lymphocytes.[6] The pathologic form is classified as primary or postprimary.[2-5] Primary tuberculosis appears as consolidation in the lower lobes, hilar and mediastinal lymphadenopathy, pleural effusion and miliary disease. Postprimary tuberculosis appears as a nodular and linear areas of increased opacity or increased attenuation at the apex of lung.[3-5,7,8] Common intrathoracic manifestations of tuberculosis include mediastinal or hilar lymphadenopathy and pulmonary parenchymal lesions. Lymph nodes may caseate or necrose, entering into the airway leading to bronchopneumonia.[9] The most common symptoms include cough and mild dyspnea. Systemic complaints like fever, night sweats, anorexia and decreased activity occur less often. Some infants and young children have localized wheezing or decreased breath sound due to bronchial obstruction.[10] It is a rare complication and occurs in approximately 2%-4% of patients with pulmonary tuberculosis.[8] Airway compromise may result from compression of bronchi by enlarged lymph nodes or less commonly, from bronchostenosis due to tuberculous granulation tissue within the bronchial mucosa.[11] The net effect of obstructive lymphadenopathy is the appearance of segmental atelectasis or obstructive emphysema.[12] Extra-thoracic manifestations comprise 20-40% of TB cases. The most commonly involved extra-thoracic sites are the peripheral lymph nodes and the central nervous system.[9] Unlike confirmation of active TB in adults,which is mainly bacteriologic, diagnosis in children is usually epidemiologic and indirect. A history of recent exposure to an infected adult is critical in the absence of positive cultures, and supporting evidence is derived from tuberculin skin testing, the chest radiograph, and physical examination.[13] For early diagnosis, a high index of awareness of this disease is required. The eradication of Mycobacterium tuberculosis and the prevention of airway obstruction are two most substantial treatment goals.

Case Report

Morium, a 5 months old girl, the only issue of a non-consanguinous parent, hailing from Dhaka, admitted with the complaints of low grade fever for 15 days and cough for the same duration. Her fever was continued in nature. The highest recorded temperature was 100^0F, subsided by antipyretic, which was not associated with chills and rigor. With these complaints the child was consulted by a local physician and took some oral antibiotics without any

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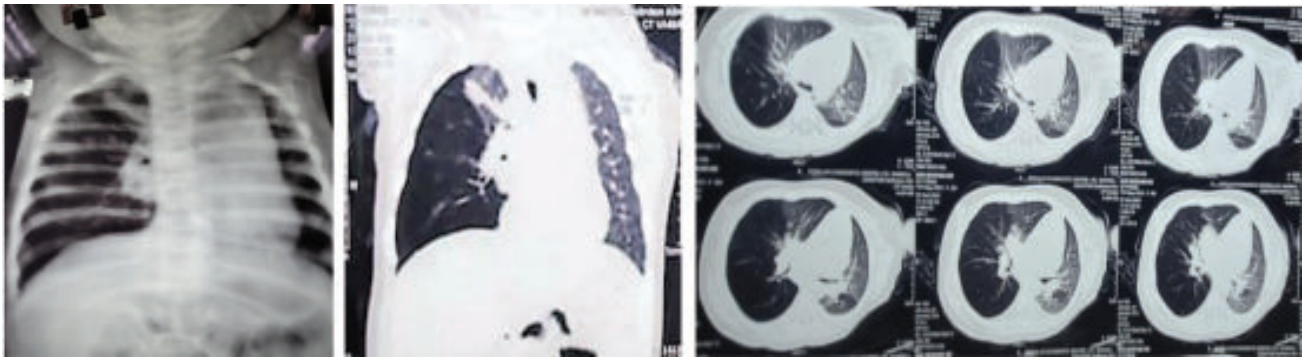

A B C

Fig.-1: *(A) Shows Chest x-ray, (B & C) Shows, CT Scan of chest.*

improvement then she was referred to Bangladesh Shishu Hospital and Institute for further evaluation and better management. On query, the mother stated that, her child had history of similar type of illness at the age of 2 months. In that episode, the child was hospitalized and was treated by injectable antibiotic for 7 days and was completely well at that time. She had history of significant weight loss but no history of contact with any patient with tuberculosis, measles, convulsion, alteration of bowel-habit, history of foreign body inhalation or cow's milk ingestion. Her birth history was uneventful. She was on exclusive breast feeding and was developmentally age appropriate.

On examination, the child was dyspneic, febrile, H/R-100 /min, R/R-55/min. There was no lymphadenopathy and BCG mark was present. Weight was 6.8 kg, Length was 69cm. The child was moderately wasted and mildly under weight. Her chest-wall was bulged on right side. Mediastinum was shifted to left side. On percussion right chest was hyper-resonant and breath-sound was diminished on the same side. Left side was normal. Therefore, our provisional diagnosis was right sided pneumothorax due to pneumonia. After admission the child was treated by injection Ceftriaxone and injection Flucloxacilin for 7 days but no improvement was noticed.

Her investigation revealed Hb-11.1g/dl, TWBC-9580/cu mm, Neutrophil-24 %, Lymphocyte-69%, total platelet count-233000/cu mm. CXR revealed right sided long lobar emphysema with pneumonia. The CT scan of chest was suggestive of congenital lobar emphysema/congenital emphysematous bulla involving all segments of right lung except a part of anterior segment of right upper lobe with a focal consolidation or enlarged right hilum in the right parahilar region.

Then we consulted with Pulmonology Department and they advised us to exclude TB. We also consulted with a thoracic surgeon who had advised us to go for surgery. We also did MT which was MT>20mm and Gene Xpert detected MTB from sample of gastric lavage and stool. RBS, CRP, LFT, serum electrolytes and serum calcium all reports were within normal limit.

Finally we diagnosed the case as right sided obstructive emphysema due to Pulmonary TB. We started treatment with 4-FDC and pyridoxine. Within a few days, we observed significant clinical improvement.

Discussion

TB usually presents with nonspecific symptoms, including fever, cough, wheezing, or diminished breath sounds and these lesions are not evident on chest radiographs.[14] In this case Morium has low grade fever and cough. Fever is usually low grade but may become marked with advanced cavitory disease.[15] Cough is the most common symptom and present in 70–80% of the patient.[16] In this case BCG mark was present which co-inside neonatal BCG vaccination have reported protection rates greater than 80%.[17,18] Tuberculin Skin Test was used for universal screening of the general population and periodic screening of high-risk populations.[19,20] In this case MT was >20 mm, means positive. More than half the cases of airway obstruction present in <35 years of age and has a slight female preponderance.[21] In this case Morium was a girl.

Chest X-ray shows right lung was involved. Emphysema is a major pathological feature in chronic obstructive pulmonary disease (COPD). The most important aspects of emphysema are sustained oxidative stress and cell damage mediated by macrophages and other cells of the innate and adaptive immune systems, leading to epithelial cell death.[22] In this case emphysema was found. TB with Emphysema in children was not reported in Bangladesh. Other studies also showed that, the right upper and right main bronchi were involved most frequently. Addition of steroids to appropriate ATT seems to relieve the features of airway obstruction to some extent.[23] After appropriate treatment all the patients recovered.

Conclusion

Early diagnosis and aggressive treatment with antituberculous chemotherapy is necessary in the management of TB and to prevent complications like airway obstruction. Steroid therapy is effective in some extent to prevent the features of broncho-stenosis.

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ABSTRACTS FROM CURRENT LITERATURE

Clinical spectrum and predictors of severity of dengue among children in 2019 outbreak: a multicenter hospital-based study in Bangladesh

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BMC Pediatrics 2021;**21**:478

Background: The mosquito-borne arboviral disease dengue has become a global public health concern. However, very few studies have reported atypical clinical features of dengue among children. Because an understanding of various spectrums of presentation of dengue is necessary for timely diagnosis and management, we aimed to document the typical and atypical clinical features along with predictors of severity among children with dengue during the largest outbreak in Bangladesh in 2019.

Methods: We conducted a cross-sectional study between August 15 and September 30, 2019. in eight tertiary level hospitals in Dhaka city. Children (aged < 15 years) with serologically confirmed dengue were conveniently selected for data collection through a structured questionnaire. Descriptive, inferential statistics, and multivariable logistic regression were used to analyze data.

Results: Among the 190 children (mean age 8.8 years, and male-female ratio 1.22:1) included in the analysis, respectively 71.1 and 28.9% children had non-severe and severe dengue. All children had fever with an average temperature of 103.3 ± 1.2 F (SD). Gastrointestinal symptoms were the most common associated feature, including mostly vomiting (80.4%), decreased appetite (79.5%), constipation (72.7%), and abdominal pain (64.9%). Mouth sore, a less reported feature besides constipation, was present in 28.3% of children. Atypical clinical features were mostly neurological, with confusion (21.3%) being the predominant symptom. Frequent laboratory abnormalities were thrombocytopenia (87.2%), leucopenia (40.4%), and increased hematocrit (13.4%). Age (AOR 0.86, 95%CI 0.75–0.98, $p = 0.023$), mouth sore (AOR 2.69, 95%CI 1.06–6.96, $p = 0.038$) and a decreased platelet count (< 50,000/mm^3) with increased hematocrit (> 20%) (AOR 4.94, 95%CI 1.48–17.31, $p = 0.01$) were significant predictors of severity.

Conclusions: Dengue in children was characterized by a high severity, predominance of gastrointestinal symptoms, and atypical neurological presentations. Younger age, mouth sores, and a decreased platelet with increased hematocrit were significant predictors of severity. Our findings would contribute to the clinical management of dengue in children.

Early Predictors of Mortality in Children with Severe Dengue Fever: A Prospective Study

Sachdev Anil, Pathak Divyank, Gupta Neeraj, Simalti Ashish, Gupta Dhiren, Gupta Suresh, Chugh Parul

The Pediatric Infectious Disease Journal. 2021;40:797-801.

Objective: The aim of the study was to identify early predictors of mortality in children with severe dengue fever admitted to pediatric intensive care unit (PICU).

Materials and Methods: All consecutive children with laboratory-confirmed severe dengue fever were enrolled in this prospective observational study. Besides demographic data, disease severity and organ dysfunction scores, laboratory investigations and interventions are done in PICU were recorded and analyzed.

Results: During the study period of 42 months, 172 patients with dengue fever were admitted to PICU. A total of 78 (45.3%) patients with severe dengue fever were included and analyzed. There were 20 (25.6%) deaths. There were significant differences in disease severity and organ dysfunction scores, transaminases, blood lactate level and serum creatinine between survivors and nonsurvivors. A significantly higher number of nonsurvivors required interventions in first 24 hours of admission. Platelet counts (*P* value 0.22) and hematocrit (*P* value 0.47) were not statistically different in 2 groups. There was a significantly high vasopressor-inotrope score (VIS) (<0.001) and positive fluid balance >10% (0.002) in nonsurvivors. Multivariate stepwise logistic regression analysis identified serum glutamic pyruvic transaminases (≥284 IU/L; odds ratio [OR] 1.002, 95% confidence interval [CI]: 1.001-1.003), blood lactate level (≥2.73 mmol/L; OR 2.08, 95% CI: 1.354-3.202), Pediatric Risk of Mortality score at 12 hours (e"14.5; OR 1.35, 95% CI: 1.077-1.693), VIS (e"22.5, OR 1.129, 95% CI: 1.059-1.204) and positive fluid balance >10% (OR 22.937, 95% CI: 2.393-219.84) at 24 hours of admission as independent predictors of mortality.

Conclusion: Disease severity, hyperlactatemia at admission, need for multiple vasoactive drugs and positive fluid balance are predictors of mortality in severe dengue infection in children admitted to PICU.

Dengue Management in Triage using Ultrasound in children from Cambodia: a prospective cohort study

Timothy Gleeson, Yos Pagnarith, Eang Habsreng, Robert Lindsay, Michael Hill, Alexandra Sanseverino, Viral Patel, Romolo Gaspari.

The Lancet Regional Health - Western Pacific 2022; 19: 100371. https://doi.org/10.1016/j. lanwpc. 2021.100371

Background: Dengue is a mosquito-borne viral infection with increasing global prevalence. It is endemic in more than 100 countries, with a heavy burden in Asia. Ultrasound findings including gallbladder wall thickening, ascites, and pleural effusions secondary to plasma leakage have been described in dengue. We aimed to determine if the presence of point-of-care ultrasound findings early in suspected dengue could predict clinical worsening in ambulatory pediatric patients.

Methods: We did a prospective, single-blinded, observational cohort study at a children's hospital in Siem Reap, Cambodia during periods of dengue outbreak. Ambulatory patients were screened and children ages > 3 month and d" 16 years with suspected acute, non-severe dengue were enrolled. Subjects had chest and abdominal ultrasound exams. Independently, subjects were evaluated by a blinded physician who determined a treatment plan as per usual practice. Follow-up was conducted 7-10 days after the initial visit. Analysis of ultrasound findings was performed to determine their relationship with outcome measures including need for unplanned hospital visits or admissions.

Findings: A total of 2,186 children were screened during periods of national dengue outbreak in Cambodia in consecutive years 2018-2019, and 253 children met eligibility criteria. Results showed patients with gallbladder wall thickening (> 3·0 mm) who were discharged had a significantly more likely need for unplanned visit or hospitalization than those with normal gallbladder wall, 67% (95% CI 44-84) versus 17% (95% CI 12 - 24), $p < 0.0001$. Subjects with any abnormal ultrasound finding were more likely to be directly admitted versus discharged upon initial presentation, 62·2% (95% CI 46.1 - 76.0) versus 19.5% (95% CI 14.8 - 25.4), $p < 0.0001$.

Interpretation: Point-of-care ultrasound findings, particularly gallbladder wall thickening, in suspected early dengue can help predict disease progression in ambulatory patients. Ultrasound has potential to help guide management of suspected dengue patients and resource management during periods of dengue outbreak.

Clinical Characteristics of COVID-19 Among Hospitalized Children in Bangladesh: A Multi-Center Study

Hussain M, Muaz SSA, Anwar S, Begum N, Mamun MAA, Noman F, Chowdhury AS, Sarker AMS, Farzana F

Korean Journal of Clinical Medi-cine. 2021;1: 1-5.

Background: Initially few cases of COVID19 in children be-ing reported but the number of infected children identification isincreasing day by day. In Bangladesh 3% of children <10 yearswere identified as COVID-19. Though over 90% of the cases weremild or moderate in nature but many of them required hospitaladmission.

Objective: To observe the Clinical characteristics of COVID-19 among hospitalized children in Bangladesh.

Methods: This retrospective multicenter study was conductedfrom May 2020 to November 2020 in Dhaka Shishu (Children)Hospital (DSH), Dhaka Medical College Hospital (DMCH),Mugda Medical College Hospital (MMCH) and Kurmitola Gen-eral Hospital (KGH). Data were collected from hospital records.Clinical characteristics laboratory tests and radiography findingsof COVID-19 infected children were noted. Data were analyzedby using SPSS version 22.

Results: Among 553 COVID-19 hospital admitted cases malewere 58.77% and male female ratio was 1.43:1. Children of allages were affected and 30.74% were <1 year of age, 25.68% were1-5 year belong to age group, 21.34% belongs to 6-10 years and22.24% belongs to 11-15 years' age group. Among COVID-19children 41.41% admitted with mild to moderate symptoms,33.98% with severe symptoms and 20.61% with critical symp-toms. Regarding clinical characteristics majority of the childrenadmitted with fever (94.92%), cough (79.69%), dyspnea (59.77%)and desaturation (62.11%). Regarding investigation findings leu-kopenia was present in 41.02%, lymphopenia in 41.79%, raisedCRP in 28.91%, ground glass opacity in chest X-ray in 3.52%,local patchy shadow in 46.88% and bilateral patchy shadow in28.52% cases. Overall mortality was 4.52%.

Conclusion: This study found that large number of hospitalized children with COVID-19 presented with severe and criticalsymptoms. Majority of the children admitted with fever, cough,dyspnea and desaturation. Leukopenia, lymphopenia, raised CRP,localized patchy shadow and bilateral patchy shadow in CXR werealso common. Mortality was 4.52% among hospitalized childrenwith COVID-19.

INSTITUTE NEWS

Bangladesh Institute of Child Health (BICH) was the academic wing of Dhaka Shishu (Children) Hospital. It was established in 30 January 1983. It was affiliated with Dhaka University, Bangabandhu Sheikh Mujib Medical University (BSMMU) and Bangladesh College of Physicians and Surgeons (BCPS). Recently the name of BICH has been changed, its new name is Bangladesh Shishu Hospital & Institute. In this Institute different basic science departments were established in the year 2006. It has been conducting different courses e.g. FCPS (in General Paediatrics and also subspeciality like FCPS Neonatology, Paediatric Nephrology, Paediatric Haemato-oncology, Paediatric Neurology and Development, Paediatric Pulmonology, Paediatric Cardiology under BCPS), MD Residency Course in General Paediatrics and Neonatology and Nephrology under BSMMU, MD Non residency course under Dhaka University and BSMMU, MS (Paediatric Surgery) Residency Course under BSMMU, MS (Paediatric surgery) non residency course under Dhaka University, DCH course under BSMMU. The Institute is also conducting Diploma in Paediatric Nursing course under Bangladesh Nursing Council, BSc in Health Technology course under Dhaka University. It conducts 3 months certificate course in Paediatrics and 15 days Intensive course for MCPS examinee. It organizes different programme, seminars and symposium on Paediatrics. The Institute conducted its regular classes, academic activities, symposium, seminars etc. during COVID-19 pandemic.

Library facilities

The library of the Institute has a rich collection of updated medical texts and reference books and reputed Medical Journals from home and abroad. Institute has introduced Broad Band facilities which are open to all students, teachers/ consultants of hospital. Facilities of library are also improved by HINARI. Students can download 2230 Medical Journals & more than 50 Paediatric Journals.

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Postgraduate Courses and Training in Paediatrics in Bangladesh Shishu Hospital & Institute

1. BSH&I has course for FCPS in General Paediatrics (2nd part): Students can be registrared twice in a year, in the month of January and July.
2. BSH&I is a recognized center by BCPS for training in FCPS (Paeditric Medicine and Surgery).
3. It is a recognized centre for course and training in different subspeciality of Paediatrics like Neonatology, Paediatric Nephrology, Paediatric Haematology and Oncology, Paediatric Pulmonology, Paediatric Neuroscience and Paeditric Cardiology.
4. There is MD Residency program in General Paediatrics, Neonatology, Paediatric Nephrology and MS Paediatric Surgery. Phase A commences in the month of March every year. There is also MD Paediatrics and MS Paediatric Surgery. Non Residency Courses commences in the month of January and July.
5. DCH course: Once in a year in the month of July.
6. Other courses conducted by BSH&I are
   - Paediatric Nursing.
   - BSc in Health Technology.
   - Three months certificate course: Every year the institute conducts 3 months certificate course in Paediatrics for general practitioners & other post graduate candidates e.g. MCPS.
   - Training programme on Essential Newborn Care for doctors and nurses, KMC (Kangaroo Mother Care) training, ETAT (Emergency Triage, Assessment and Treatment) training, IMCI (Integrated management of childhood illness), newborn and paediatric standard use of oxygen therapy for hypoxemia management etc. are conducted by BSH&I.

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Students Qualified from Bangladesh Institute of Child Health (At present BSH&I)

Student qualified from BSH&I till December 2021

Course	Number
DCH	375
MD Paediatrics	115
MS Paediatrics	105
FCPS Paediatrics	16
MD Neonatology	11
MD Pediatrics Nephrology	05
Total	627

Foreign student qualified from BSH&I till December 2021

Course of origin	Course	Number
Nepal	DCH	23
	MS (Paediatric Surgery)	02
	MD (Paediatrics)	01
India	DCH	01
Iran	DCH	01
Iraq	DCH	01
Somalia	DCH	01
Sudan	DCH	01
Total		31

Present Students (till December 2021) of BSH&I

Name of Courses	Number of Students
MD (General Paediatrics) Phase-A	25
MD (Neonatology) Phase-A	04
MD (Paediatric Nephrology) Phase-A	04
MS (Paediatric Surgery) Phase-A	22
FCPS (Paediatric) Part-II	02
MD (Paediatrics) Part-III	01
FCPS (Paediatric Cardiology)	01
FCPS (Paediatric Nephrology)	01
MS (Paediatrics Surgery) Part-III	21
DCH	26
MD (General Paediatrics) Phase-B	19
MD (Neonatology) Phase-B	05
MD (Paediatric Nephrology) Phase-B	02
MS (Paediatric Surgery) Phase-B	20
Total	134

INSTRUCTIONS FOR AUTHORS

Dhaka Shishu (Children) Hospital Journal is the official organ of Bangladesh Shishu Hospital & Institute (BSH&I). It is a peer reviewed, open access journal published twice a year since 1984. This journal is recognized by Bangladesh Medical and Dental Council (BMDC) which is the highest body for the recognition of medical journals in Bangladesh. All parts of the journal are indexed/ tracked/covered by DOI/CrossRef and BanglaJOL. The present Editorial board has decided that the cover design will be in accordance with the subjects of editorial in each issue. The editor welcomes articles to be published to the journal as leading article, original article, review article, case report, current issues of child health, short report and junior's page where trainee doctors are encouraged to publish their topic of interest.

Original papers written in English will be considered for publication provided these have not been published previously and are not under consideration for publication elsewhere.

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Manuscripts should be submitted in the following order.

- All scientific units should be expressed in System International (SI) units. Authors are referred to Annals of Internal Medicine 1987;106:114-29 for guidance in the use of SI units. All drugs should be mentioned in their generic form.
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Director
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