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EDITORIAL

Involving Children in Clinical Research: Ethical Dilemmas and Perspectives

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Progress in children's healthcare can only be achieved through research, which forms the evidence base for interventions to protect them from ill health, disease, and the impacts of disability (1,2). Given the methodological and ethical challenges of research in children, there are tendencies to extrapolate information from adult studies, which often poses several problems. There are differences in disease processes and the effects of interventions between children and adults. The pharmacokinetics of many drugs and their beneficial and adverse events in children are different from those in adults (3). Young children do not tolerate some drugs and dosages and administration of the drugs may be difficult. These differences and the fact that many adult diseases have antecedents in early life and their occurrence in adults can be prevented with effective evidence-based strategies in childhood make clinical research in this age group imperative (4).

In research involving children, the need for the research and whether children need to be involved should be the primary consideration. Balancing the protection of this vulnerable patient population with the need to do clinical research to improve their health and well-being constitutes one of the quandaries of clinical research in children. The core ethics principles (beneficence, nonmaleficence, autonomy, and justice) in research that relate to adults apply equally to children (5). However, research with children gives rise to a wide range of unique and complex ethical challenges and dilemmas (6). The increase in international research collaborations and the context in which research is conducted also constitute critical ethical challenges.

An ethical research must produce reliable and valid data that can be interpreted. Indeed, an underpowered study, a study with a biased endpoint, instrument, or statistical test, and a study that cannot enroll sufficient subjects is invalid and unethical (7). Research that is good for children needs to answer an important question for the research subjects in this age group and carry an acceptable risk to the subjects. Before starting the research, one needs to answer an important question

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for the research subjects in this age group and carry an acceptable risk to the subjects. Before starting the research, one needs to carry out a risk assessment, particularly considering the risks of harm to children and ways to mitigate, monitor, and manage the risks. It is paramount to recognize that children on the age spectrum from the newly born to adolescence have different experiences and roles concerning decision-making and that, when they are ill, the nature and severity of illness may be specifically important as are the wider social and economic factors.

It is well recognized that respect for autonomy (informed consent, truth-telling, and confidentiality) in research related to children constitutes the most challenging ethical requirement to meet giving rise to complex ethical dilemmas (8). As with medical treatment and as far as possible, children should understand the nature and what will be expected of them before taking part in the research. It is important to explain confidentiality to the child before they give their consent (the positive agreement of the parent/guardian). According to the Declaration of Helsinki (9), when possible, the child's consent/assent should be obtained in addition to parental consent. Emancipated minors—working or earning their living, married, parenting—may be allowed to give informed consent or an institutional review board (IRB) may decide a waiver of consent (10).

In addition to the consent of the parent, next-of-kin, or guardian, assent (a child's affirmative agreement to participate in the research) should be sought from all children 12 years of age and above (10). The default threshold age for assent is 7 years in some guidelines, but there are differences, and a flexible criteria for personalized threshold age determination is suggested (11). In institutionalized children, a legally approved guardian may give consent. Assent with waiver of consent may be applicable in research dealing with sensitive issues like drug use and abuse and sexuality to avert problems for the child because of the nature of the study. Children should be given appropriate information based on their level of comprehension irrespective of the complexity of the research procedures. The extent to which the information, however clearly presented, can be received, considered, and understood by parents poses a major challenge in obtaining consent. The process of consent requires that time be available to reflect on whether to agree to participate, but that may often not the case sick children.

In clinical trials, it is exceedingly difficult to explain that a new treatment is unproved but potentially valuable, gain consent for entry into the trial, and then explain that the patient has been randomized to standard therapy, while still maintaining parents' trust (12). As an alternative, the parents may be informed before their child was enrolled in the study and they could refuse permission for their child to take part. With this approach, the potential benefits of research would be maintained, while ensuring that there was minimal risk would be placed firmly on the

researcher and ethics committees. Children should also be protected from bearing more than their fair share of the burden of participation in and be assured of the benefits of research (13)

In the context of developing settings, those who conduct research with children invariably adopt western concepts and approaches that may not largely address the needs of children in these settings. This is a paradox as only a little more than 10% of the world's children live in the developed countries and yet related research is heavily concentrated on children from developing countries (14). Inherent in globalization, much of the penetrating research work is sponsored by external funders applying research paradigm rooted in Western ethos. As emphasized in a study report from Ethiopia, the development of participatory-based paradigms and ethical approval procedures need to guide research with children in the global south (15).

Ethical issues of research with children are embedded in diverse and shifting paradigms. An efficiently administered, effectively performing system with adequate resources to meet ethical and legal standards for protecting children (and adolescents) who participate in research. Pediatricians practicing in Ethiopia, and those particularly working in tertiary care centers, need ethical guidance and training in order to care for critically ill patients while upholding the highest ethical standards and deal with ethically complex situations. The Ethiopian Journal of Pediatrics and Child Health (EJPCH) of the Ethiopian Pediatric Society (EPS) upholds that any research undertaking should be approved by a relevant institutional review board or ethics committee. It observes that ethical considerations are adequately covered in its publications. EJPHD believes, supports, and encourages that due considerations are given to research in children (and adolescents) by pediatricians, researchers, managers, regulators and policy makers.

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Original article

Major postmortem pulmonary histopathological findings in preterm infants in Ethiopia

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Abstract

Background: *Respiratory disorders are the leading cause of death in preterm infants. Postmortem lung histological findings may help to confirm or exclude a clinical diagnosis. This study aims to describe the common postmortem pulmonary histological findings and their potential contributions to preterm neonatal mortality in Ethiopia.*

Methods : *A prospective, multicenter, and cross-sectional clinical study of preterm infants was conducted in five hospitals in three regions of Ethiopia. A total of 4,919 preterm infants were enrolled, and of these, 3,852 were admitted to neonatal intensive care units (NICUs). Within 28 days of postnatal age, 1,109 or 29% of those admitted to the NICU died. Consent was requested from all parents for a complete diagnostic autopsy (CDA) and was obtained in 441 of the preterm neonates who died. A histopathological examination of representative lung tissues was performed .*

Results*: On histopathologic examination of the lungs of these deceased preterm neonates, the major abnormal histological changes observed were hyaline membrane disease (HMD) in 81.6%, pneumonia in 44.7%, pulmonary hemorrhage or diffuse alveolar hemorrhage (DAH) in 39%, and*

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meconium aspiration syndrome (MAS) in 5.9%. A combination of histopathological findings, two or more, were also observed in > 30% of the preterm lungs.

Conclusion : *HMD was the most common pulmonary finding in extremely and moderately preterm infants. The highly prevalent pneumonia and pulmonary hemorrhage, with the frequently observed HMD, might have significantly contributed to their deaths. Histopathological findings, beyond confirming a clinical suspicion, can be used as input in the refinement of clinical and radiological diagnostic parameters to identify respiratory pathologies, particularly pneumonia, in preterm infants.*

Keywords: Postmortem, autopsy, histopathology, pulmonary, preterm

Background

Respiratory disorders are the leading cause of death in preterm infants (1). The major pulmonary pathological findings described in preterm neonates include hyaline membrane disease (HMD), pneumothorax, pneumonia, pulmonary hemorrhage/diffuse alveolar hemorrhage (DAH), meconium aspiration syndrome (MAS), and chronic lung disease (1-5). In some instances, extrapulmonary conditions result in respiratory distress, making it difficult to distinguish them from primary pulmonary pathologies. Moreover, overlapping morphologic features can be seen in different types of primary pulmonary pathologies (6).

HMD, also described as diffuse alveolar damage (DAD), is the most frequently presenting pathology in the lungs of preterm neonates. The risk of HMD is inversely proportional to gestational age (3,5). HMD is histologically characterized by the deposition of pinkish homogenous proteinaceous material along the alveolar lining with associated alveolar collapse and capillary edema. Usually, it is exacerbated by oxygen toxicity-induced epithelial necrosis. HMD is considered an existing phenomenon rather than a primary cause of respiratory failure, but it can determine the course of the illness and both short- and long-term outcomes. HMD can be complicated by pneumonia, pulmonary hypertension, and pulmonary hemorrhage (5, 7).

Pulmonary hemorrhage is difficult to detect while the neonate is alive but is a common postmortem finding in preterm neonates. Pulmonary hemorrhage is considered severe when at least one lobe of the lungs is involved based on gross or histologic examination (8).

Pneumonia is a significant cause of respiratory distress in preterm infants. It is classified as early-onset when it presents before 7 days or late-onset when it presents at or after 7 days of age (1). Clinically, pneumonia may not be easily diagnosed in preterm infants, particularly for cases with congenital pneumonia, where most of the deaths are misdiagnosed as respiratory distress syndrome (RDS) (9). The mortality rate due to pneumonia is inversely

proportional to gestational age (GA) and birth weight (BW) (10). Histomorphologically, pneumonia can present as a patchy or lobular involvement pattern where a conspicuous number of intra-alveolar and/or interstitial acute inflammatory infiltrates associated with edema, fibrin and vascular congestion are present (11).

MAS is not commonly seen in preterm infants except in preterm infants with listeriosis (12). The histologic features of MAS include tiny keratotic squames, lanugo, meconium bodies, and mucus in the bronchi and alveoli to a variable extent. Massive aspiration can be a lethal condition when it is complicated with bronchopneumonia (13,14).

The purpose of this study was to describe the major postmortem histopathological findings of primary pulmonary diseases in preterm infants who were admitted to the neonatal intensive care units of five hospitals in Ethiopia and died.

Methods

Study setting and design

The study was conducted as part of a project entitled "A Prospective Study of Causes of Illness and Death in Preterm Infants in Ethiopia" (SIP) (15,16). This was a prospective multicenter observational study conducted in five hospitals (Tikur Anbessa Hospital, Gandhi Memorial Hospital and St Paul Hospital in Addis Ababa, Gondar University Hospital in the north of Ethiopia, and Jimma University Hospital in southwest Ethiopia) from July 1, 2016 to May 31, 2018.

All preterm infants admitted to the study hospitals with a gestational age of less than 37 completed weeks were enrolled. Three methods of gestational age assessment, ultrasound, last menstrual period (15), and physical examination using the new Ballard score, were used. All deliveries where an induced abortion was performed and for which the gestational age could not be reliably determined using the three GA assessment methods were excluded from the study. The analysis for this paper only included those cases for which a complete diagnostic autopsy (CDA) was performed.

A panel of experts decided on primary and contributory causes of death using the histopathological findings as well as other clinical and investigational parameters. In some cases, the panel might have decided to use other parameters to decide primary and contributory causes of death. Therefore, the numbers may not tally. The details of the findings are published elsewhere (16). This study focused only on analyzing the major histological findings in the lung but not on the causes of death.

CDA Procedures

CDA was performed according to the hospital protocol and guidelines of the involved institutions within 6-12 hours after death in all cases. After dissection of the lungs, liver, brain, and kidneys, representative lung samples from both lungs were taken and fixed in 10% neutral buffered formalin for 24 hours. Paraffin sections were prepared from the fixed tissues and stained with hematoxylin and eosin as per standard procedures.

Data collection, entry, and analysis:

The CDA results were reported using a standardized data reporting format prepared for this study(15). The format included a checklist of major preterm problems and expected histological features of each case, and the pathologist summarized the major findings in the format. All CDAs and histologic slide reviews were performed by experienced pathologists of the respective institutions. Representative histological pictures of major findings were taken using an Infinity HD Lumenera camera fitted on an Olympus BX43F microscope.

Results

The total number of preterm deaths with a CDA was 441 [Figure 1]. Most preterm deaths in the study were between the gestational ages of 28-34 weeks (78.7%).

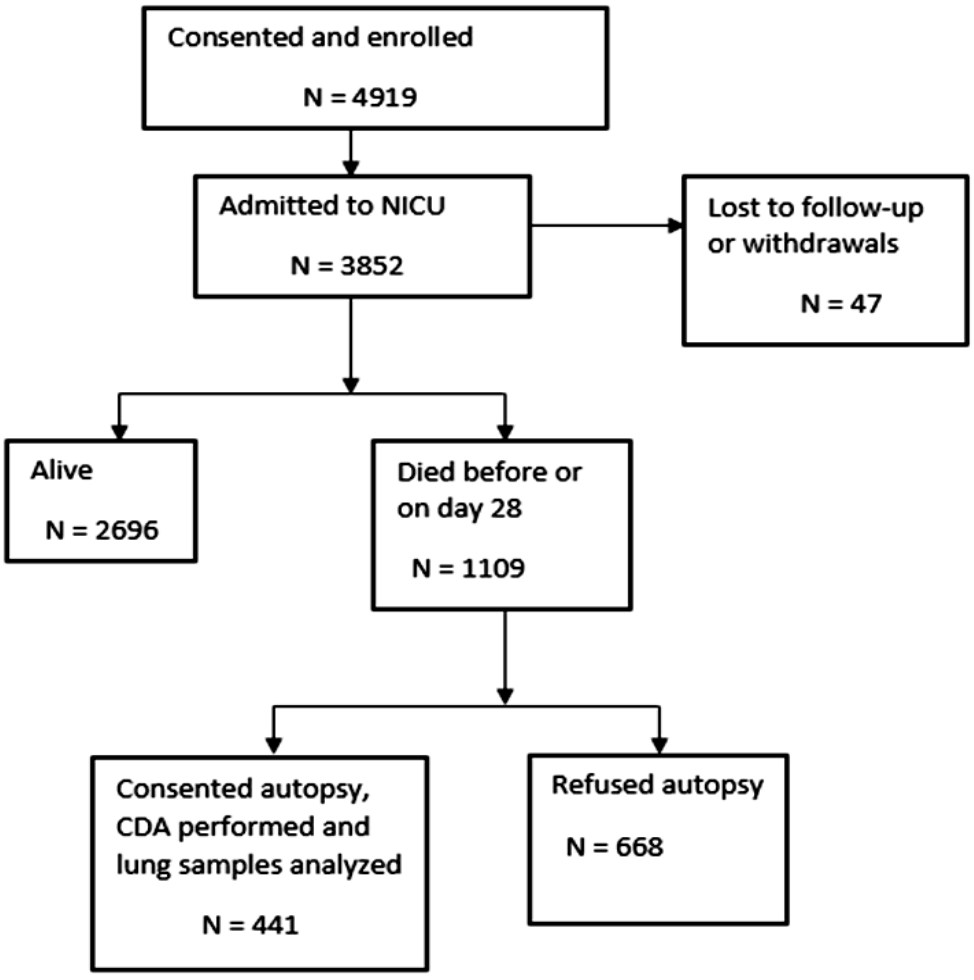

Figure 1: Enrollment flow chart

(NICU-neonatal care unit, CDA-complete diagnostic autopsy)

Of the 441 preterm deaths, a total of 1002 major histopathologic findings were reported. Of these, 758 (75.8%) were found to be primary pulmonary pathologies. (supplemental table)

The major lung primary pulmonary histopathological findings included 360 (81.6%) with HMD, 197 (44.7%) with pneumonia, 172 (39%) with pulmonary hemorrhage, and 26 (5.9%) with MAS. Additionally, diffuse non-exudative alveolar edema with a conspicuous number of hemosiderin-laden macrophages was observed in three cases. Multiple histopathologic findings were observed as HMD with pneumonia in 170 cases (38%), HMD with pulmonary hemorrhage in 152 cases (34%), and pneumonia with pulmonary hemorrhage in 120 cases (27%).

HMD was observed across all gestational age groups with no significant difference in the proportions. HMD was the most prevalent pulmonary pathology finding across all gestational age categories. Although not statistically significant, 87.3% of preterm infants between gestational ages of 32 and 34 weeks had HMD, followed by those <28 weeks, where 82.6% showed pathological findings consistent with HMD. There was no significant difference by sex or birth weight.

Table 1: Gestational age, sex, and birth weight distribution related to the major primary pulmonary pathologies

Pulmonary findings			**HMD**			**Pneumonia**			**DAH**			**MAS**		
Variables	Categories	N	%	OR	P-value	%	OR	P-value	%	OR	P-value	%	OR	p-value
	<28	35	82.60	1.234	0.704	40	0.644	0.309	64.30	0.185	0.002	12.80	0.318	0.305
	28-31	213	78.40	0.927	0.835	44.60	0.778	0.395	34.30	0.577	0.065	4.20	0.476	0.2
	32-34	134	87.30	1.757	0.174	43.30	0.738	0.332	49.20	1.075	0.818	8.20	0.966	0.951
	35 - <37	59	79.70	Ref.	Ref.	50.80	Ref.	Ref.	47.50	Ref.	Ref.	8.50	Ref.	Ref.
Sex	Male	243	79.80	0.758	0.273	44.40	0.795	0.895	38.30	0.975	0.9002	6.90	1.538	0.31
	Female	193	83.90	Ref	Ref.	45.10	Ref.	Ref.	38.90	Ref.	Ref.	4.70	Ref.	Ref.
Birth weight	<1000	59	89.80	1.767	0.326	47.50	0.982	0.962	37.30	0.764	0.498	6.80	0.625	0.503
	1000-1500	201	77.10	0.674	0.35	45.30	0.899	0.741	32.80	0.629	0.156	4.50	0.403	0.119
	1500 -2000	122	83.60	1.02	0.966	41.80	0.781	0.47	47.50	1.165	0.656	6.60	0.604	0.398
	>= 2000	48	83.30	Ref	Ref.	47.90	Ref.	Ref.	43.70	Ref.	Ref.	10.40	Ref.	Ref.

Hyaline membrane disease (HMD), pneumonia, diffuse alveolar hemorrhage (DAH), and meconium aspiration syndrome (MAS)

Pneumonia was documented across all gestational age groups, with the highest rate in infants with a GA of 35 to <37 weeks (30/59, 50.8%). However, this result was not statistically significant. A relatively high occurrence was documented in infants with a birth weight <1000 gm (28/59, 47.5%) and >=2000 gm (23/48, 47.9%), which was also not significantly different.

Pulmonary hemorrhage was observed in all gestational age categories. However, it was a rare finding among the <28 weeks gestational age group (14.3% only, p<0.005). There were only 5 cases in this gestational age group.

MAS was largely observed in infants of GA 32 to <37 weeks 16/26 (61.5%). There were no sex differences in the occurrence of HMD, pneumonia, or DAH. However, MAS occurred more frequently in males with an M:F ratio of 2:1.

HMD was predominantly found in preterm infants who died between 24 and 72 hours after birth. Pneumonia was observed in neonates who died between 24 hours and 7 days (132/197, 67%). DAH was commonly observed in infants who died between 24-72 hours postnatal age. MAS was documented in 5 of the 26 neonates who died within 24 hours of birth.

(HMD-hyaline membrane disease, DAH-diffuse alveolar hemorrhage, MAS- Meconium aspiration syndrome)

Histological analysis

Histological analysis was performed for the two most common conditions, i.e., HMD and pneumonia. Waxy-appearing layers of a hyaline membrane composed of fibrin, cellular debris, and red blood cells mostly covered extensive areas of the lungs [Figure 2A], and only in a few cases was a patchy hyaline membrane seen in the organizing phase with hyperplasia of type 2 pneumocytes. [Figure 2B].

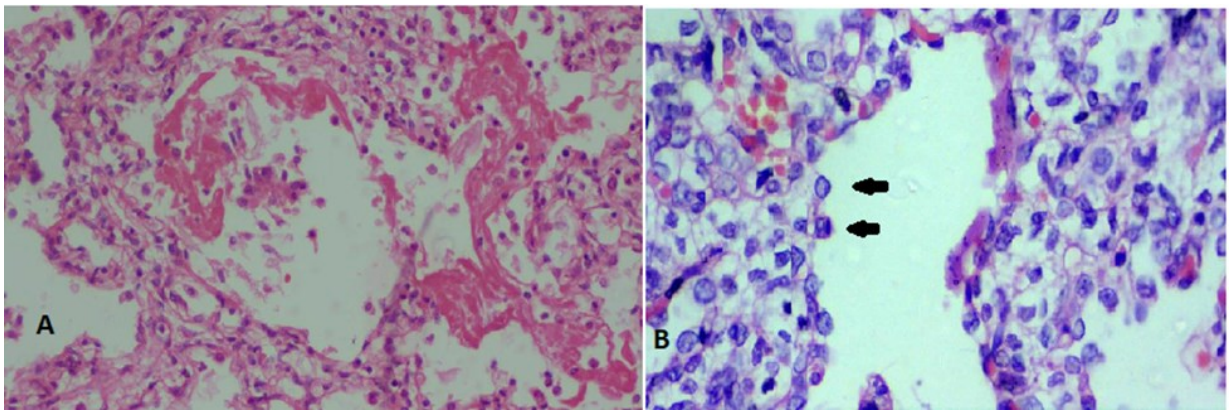

Figure 2. (A) A hyaline membrane in an early phase of HMD in association with epithelial disruption (10x objective). (B) A hyaline membrane in the organizing phase of HMD with a prominence of type 2 pneumocytes (arrows) (20x objective).

Intra-alveolar or interstitial hemorrhage was considered significant or diffuse when it involved a large area of a lobe or more lobes with or without intra-alveolar fibrin or capillaritis [Figure 3 (A)].

Histologically, pneumonia was considered present when a significant exudate with neutrophilic infiltrates and an increase in foamy macrophages were seen in the alveolar spaces, intrabronchiolar, intrabronchial, and interstitium associated with capillary congestion and,at times,an extension of polymorphs into the sinusoids of parabronchial lymph nodes [Figure 3(B)].

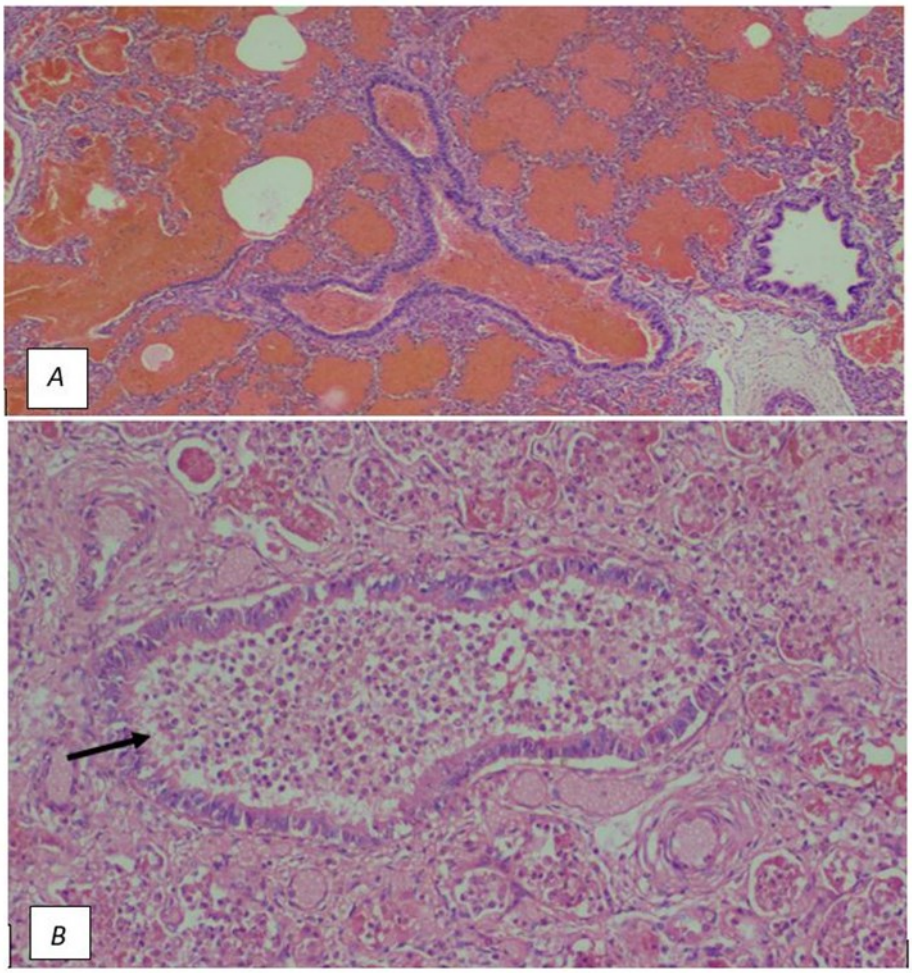

Figure 3: (A) Diffuse intra-alveolar and intrabronchial hemorrhage (10x objective). (B) Classical pneumonia with intra-alveolar and intrabronchiolar neutrophilic exudate (arrow) (10x objective)

Discussion

Respiratory disorders are the most frequent causes of admission to a neonatal ICU and the leading cause of early neonatal mortality in preterm infants (1). Primary pulmonary pathologies are the most common causes of respiratory distress when compared to other secondary causes, such as cardiac anomalies (17,18). In our study, pulmonary pathologies were found to be 3 times more common than non-pulmonary pathologies. The top pulmonary pathologies were HMD, pneumonia, DAH and MAS. There were no significant differences in the frequencies between gestational age groups, sex, and birthweight. However, DAH occurred significantly less often in those infants at <28 Wk gestational age. Out of the observed HMDs among preterm deaths, 86.9% fall in the <35 weeks gestational age categories. This was also observed in a related clinical study (19).

Pneumonia was recorded in nearly half (44.7%) of our cases. This high occurrence is consistent with other studies since preterm neonates are susceptible to infections (20-22). Most of our

cases were early-onset pneumonia, and their occurrence was inversely proportional to GA, which is similar to reports elsewhere (23). The occurrence of pneumonia in 55.8% of neonates at <72 hrs of age suggests congenital pneumonia (11,23,24). A high chance of underdiagnosis of congenital pneumonia has been described in the literature (25).

Patchy or diffuse alveolar hemorrhage was consistently seen in association with HMD and pneumonia in most of the cases and was found in a higher proportion among early to mid-preterm infants. DAH alone occurred only in 8/441 (1.8%) of the cases. Interestingly, DAH occurred at a significantly lower frequency in extremely preterm neonates, which is in sharp contrast to the described literature (26).

Consistent with similar studies, MAS was seen in a minority of the cases (26, 5.9%) (27). However, one might consider this as higher than expected in preterm infants (28,29). MAS occurred in equal proportion in all GA groups in contrast to the expected concentration at later preterm gestational ages (28). MAS is fatal only if meconium is massively aspirated. In all our cases, MAS was seen as a patchy finding, and we presume that it is less likely to be the direct cause of death. However, it is argued in some literature that the amount aspirated may not correlate with severity (29).

This study aims primarily to characterize the major pulmonary histopathologic changes. However, we also found unexpected histologic features that we believe are diagnostically important. However, the major pneumonia histologic findings are classical with extensive fibrinopurulent exudate. In some cases, even with associated pleuritis, the exudate was localized, suggesting focal pneumonia [figure 4] – a situation that can easily be missed, ignored clinically, or called something else.

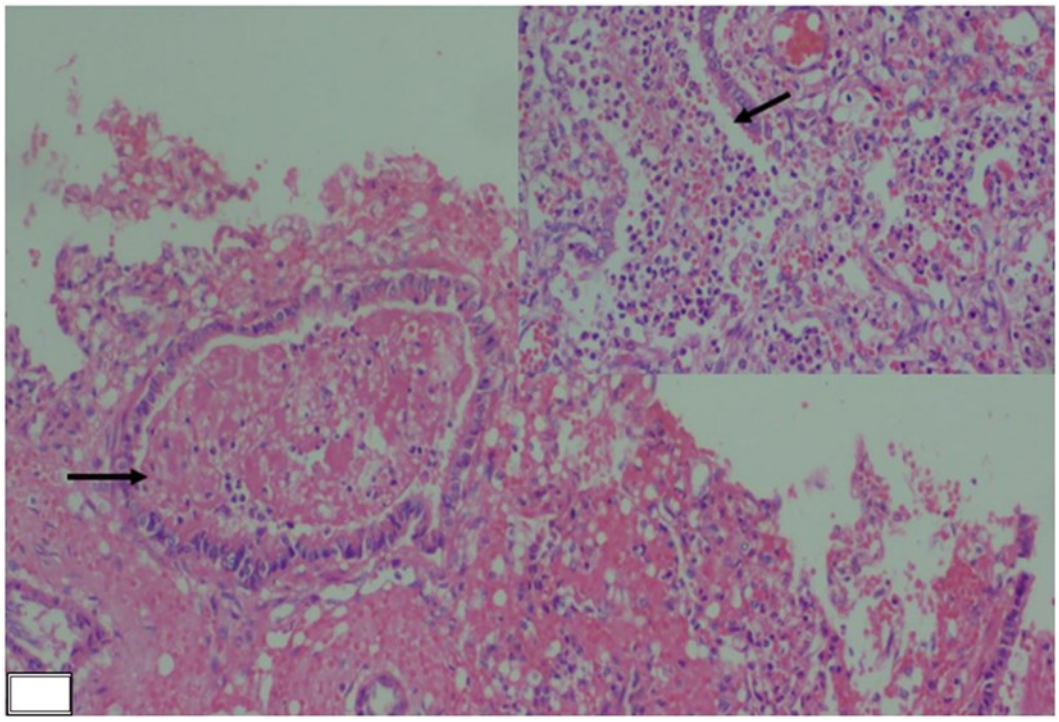

Figure 4. Patchy pneumonia with intrabronchiolar fibrin and neutrophils (arrows, 20x objective)

Additionally, intra-alveolar and intrabronchiolar 'fibrin balls' or fibrin plugs with patchy areas of organization, also described as acute fibrinous and organized pneumonia (AFOP), were consistently seen in the classical pneumonia cases with or without combined features of HMD and DAH but not in isolated cases of HMD [Figure 5]. This histologic pattern of acute lung involvement with largely unknown clinical significance is documented as a distinct clinical entity and is also observed in connective tissue diseases involving the lungs, drug-induced pneumonia, and virus-associated cases of pneumonia such as COVID-19 with good corticosteroid response (30-32). However, we found it to be difficult to put it as a separate disease entity in preterm infants. Rather, we speculate that these features may add to the radiographical clues that can be helpful in differentiating pneumonia from HMD.

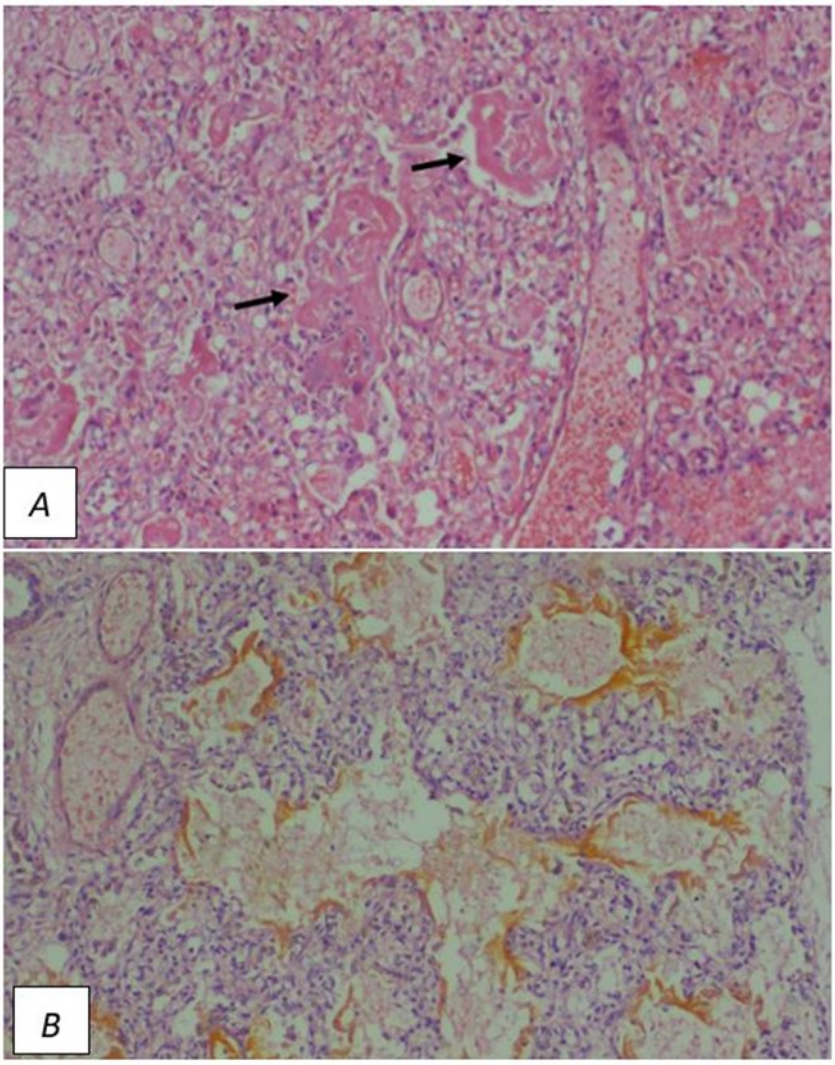

Figure 5. (A) case of pneumonia with fibrin balls (arrow) (20x objective), (B) Yellow/bilirubin-tinged hyaline membrane (10x objective)

The presence of yellow-stained membranes in a few of our cases [Figure 5] may suggest bilirubin-stained hyaline membranes, and we speculate that this may lead to the persistence of HMD, leading to poor respiratory outcomes in these neonates.

Diffuse non-exudative alveolar edema with hemosiderin-laden macrophages was observed in three cases, perhaps the result of underlying cardiac anomalies.

Although this paper presents the largest autopsy series describing pulmonary pathologies in Ethiopia, it has some limitations. The lung pathologies were not correlated with corresponding placenta findings as described in perinatal autopsy guidelines, and the low consent rate may bias the findings.

In conclusion, an autopsy is instrumental in establishing a diagnosis and identifying new findings. This study has demonstrated the high occurrence of pneumonia in preterm infants in a low-resource settings such as Ethiopia. The classic histologic evidence with extensive involvement of lung parts may dictate pneumonia

as a strong contributory factor or perhaps the most important cause of death in the 44.7% of preterm neonates in this study. Therefore, we strongly recommend consideration of infectious conditions such as pneumonia as a contributor to death, in addition to HMD in this setting.

List of abbreviations

HMD	Hyaline Membrane Disease
NICU	Neonatal Intensive Care Unit
DAH	Diffuse alveolar hemorrhage a.k.a. Pulmonary hemorrhage.
MAS	Meconium Aspiration Syndrome
RDS	Respiratory Distress Syndrome
GA	Gestational age
BW	Birth Weight
SIP	Study of causes of illness and death in preterm infants
CDA	Complete Diagnostic Autopsy
OR	Odds Ratio

Declarations

Ethical approvals

The study was approved by the institutional review board of each hospital and at the College of Health Sciences of Addis Ababa University. All clinical procedures were conducted per the hospital protocol. In addition to the consent taken for the main study, separate parental consent was obtained for the CDA.

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Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Author contributions

MAT - Contributed to conception and design; contributed to acquisition, analysis, and interpretation; drafted the manuscript; critically revised the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy

RPP- Contributed to the design, analysis, and interpretation and critically revised the manuscript. RP agrees to be accountable for all aspects of work ensuring integrity and accuracy.

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Original article

Determinants of preterm birth among mothers who gave birth at Shiek Hassan Yabare Referral Hospital in Jigjiga town, Eastern Ethiopia: Unmatched case-control study

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Abstract

Background: *: Complications of prematurity are one of the leading causes of death in children under the age of five across the world. Preterm delivery can cause cognitive impairment, attention deficit hyperactivity disorder, hypoxic-ischemic encephalopathy, neurocognitive deficits, and poor academic performance in children. All of these problems lead to poor quality of life and long-term health effects. Despite significant reductions in neonatal mortality in Ethiopia, preterm birth rates remain high. The objective of the study is to identify the determinants of preterm birth among mothers who gave birth at Sheik-Hassen Yebere Jigjiga University Referral Hospital from June 1 to July 30, 2021 .*

Methods : *An unmatched case-control study design was employed among 381 mothers (127 cases and 254 controls) who delivered at Sheik-Hassen Yebere Jigjiga University Referral Hospital in Jigjiga Town between January 1, 2018, and December 31, 2019. The medical records of eligible participants were randomly selected using a computer-generated simple random sampling method. Both bivariate and multivariable logistic regression models were used, and independent determinants were determined based on adjusted odds ratios with 95% confidence intervals and a p-value of less than 0.05 .*

Results: *A total of 381 charts were reviewed, 127 cases, and 254 controls. The mean gestational age was 32.5+2.57SD and 39+2.57SD weeks for preterm and term respectively. History of less than or equal to 4 ANC visits (AOR 6.43 CI 3.1-13.20), male fetus (AOR 2.04, 95% CI 1.2-5.2), reside in rural areas (AOR 2.51, 95% CI 1.4-6.74), maternal hemoglobin level <11mg/dL (AOR 3.32, 95% CI 1.4- 13.2), neonates who had congenital birth defects (AOR 3.49 CI 1.4.4-8.68) were significantly associated with preterm birth.*

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Conclusion: *Based on the factors that contribute to preterm birth, it is important to encourage pregnant women to regularly take iron and folic acid supplements and to attend their scheduled antenatal care visits. In addition, improving healthcare accessibility in rural regions is crucial.*

Keywords: Preterm birth, Jigjiga town, Determinants, Neonates, Prematurity

Background

Preterm delivery is defined as giving birth before 37 weeks of gestation or fewer than 259 days from the first date of the maternal last menstrual period (1). Every year, 15 million newborns are born prematurely, with over 80% of births occurring between 32 and 37 weeks of gestation. In 2020, 13.4 million preterm births occurred, with over 1 million premature complications resulting in death(2).

The World Health Organization (WHO) has reported that the prevalence of preterm birth in 2020 varies from 4% to 16 % among different regions. However, the burden of preterm birth is significantly higher in low- and middle-income countries, particularly in Sub-Saharan Africa and Asia(3). In these regions, the rate of preterm birth exceeds 10%, which is twice as high as the rate in developed countries. In Ethiopia alone, there are 320,000 premature births each year, resulting in the death of 24,000 children under the age of five due to complications related to preterm delivery(4).

Premature birth is a major contributor to child mortality worldwide, accounting for more than 1 in 5 of all deaths among children under the age of five(1). It can result in various complications such as cognitive impairment, attention deficit hyperactivity disorder, difficulty in feeding, poor body temperature regulation, hypoxic-ischemic encephalopathy, neurocognitive deficits, and academic underachievement in children(5-7). These issues ultimately lead to a diminished quality of life and long-lasting health consequences(8).

Numerous studies conducted globally have identified several risk factors for preterm birth. These include substance use during pregnancy, being pregnant with multiples, short gaps between pregnancies, previous preterm births, short cervixes, pregnancy-related complications like diabetes and hypertension, as well as lifestyle factors like low pre-pregnancy maternal weight(3, 4, 7, 9). However, in many cases, the exact cause remains idiopathic(2).

Despite the World Health Organization (WHO) releasing new recommendations for the care of premature infants, the rates of preterm birth and the mortality rates associated with complications from preterm birth remain elevated. Consequently, it is crucial to prioritize understanding the underlying causes of preterm birth to improve health outcomes for both mothers and infants. There is a lack of research in this field, particularly in the study area, regarding the factors that contribute to preterm birth. Additionally, most studies conducted in Ethiopia have utilized a cross-sectional study design, whereas our study employed a case-control study design. Thus, this

study aimed to identify the determinants of preterm births in Jigjiga, town, eastern Ethiopia.

Methods

Study setting, period, and design

The study was conducted in public hospitals in the of Jigjiga town. Jigjiga is the capital city of the Somali Region and is located 631.4 kilometers from Addis Abeba, Ethiopia's capital. The town has a total of sixteen health facilities, including one regular public hospital, one referral hospital, and 14 health posts. The Jigjiga University Shiek Hassan Yabare Referral Hospital, which is affiliated with the university, serves the populations of the Somali Region and nearby areas. This hospital has 282 beds and provides a wide range of services, including outpatient care, hospitalization, delivery services, and emergency care. An institution-based unmatched case-control study design was employed from June 1 to July 30, 2021.

Population and Eligibility criteria

The study population were women who gave birth at the hospital from January 1, 2018, to December 31, 2019. Cases were defined as women who delivered before 37 weeks of gestation, while controls were defined as women who delivered at or after 37 weeks of gestation. To identify these women, data from various sources such as the Operation Theater, admission and discharge logbooks, and delivery registers was utilized. Only those women whose hospital records contained complete information about their obstetric conditions were included in the study, while charts with incomplete information and women who delivered before 28 weeks of gestation were excluded.

Sample size and Sampling Technique

The sample size was calculated using EPI Info version 7 statistical software for the double population proportion formula by considering multiple pregnancies as an exposure variable with the following assumptions. The proportion of outcome among cases (P= 23.4%), the proportion of outcome among controls (P= 8.4%), 95% confidence level, 80% power, and the ratio of a case to control 1:2(10).After considering 10% non-retrieved cards, the total sample size was 381, with 127 cases and 254 controls.

Between January 1st, 2018, and December 31, 2019, Shek-Hassen Yebere Jigjiga University Referral Hospital undergone 6249 childbirths. Out of these, 601 neonates were born prematurely during this period. To conduct the study, a sample of 381 medical records was chosen, comprising 127 cases and 254 controls. This sample size was allocated proportionally based on the number of preterm births in each of the two years. The selection of all medical records was done through computer-generated random sampling.

Data Collection Tools and Procedures

In this study, data was gathered by reviewing the medical records of the participants. A structured checklist, which was adapted from previous studies [8, 24, 27], was used to collect data on various factors such as maternal socio- demographics , obstetric history,

gynecologic information, medical factors, and infant characteristics. Prior to data collection, a pretest was conducted at Deghabur hospital on 5% of the medical records to identify any variables that were not recorded and these variables were subsequently excluded from the checklist. The data was collected by 5 trained BSc professional midwives who work at private hospitals.

Operational Definition

Preterm birth: refers to the delivery of a baby between 28 and 37 weeks of gestation.

Full-term birth: refers to newborns who are delivered after completing more than 37 weeks of gestation.

Data quality control

A pretest of the questionnaire was carried out on samples (5% of the total sample size) prior to the real data collection. The study's objectives, data collection methods, and data management strategies were covered in a two-day training session for the supervisors and data collectors. The data collectors were closely supervised on a daily basis. The supervisors and the principal investigator ensured that the collected data was consistent and complete.

Data processing and analysis

The collected data were organized, cleaned, and entered into Epi-data version 3.1. They were then exported to SPSS version 23 for further analysis. Descriptive statistics, such as frequency tables, mean with standard deviation, and percentages, were used to present the data. Bivariable logistic regression analysis was conducted to select candidate variables for the multivariable analysis. Variables with a p-value less than 0.25 were considered for the final model. The multivariable analysis aimed to identify the true effects of the predictor variables on preterm birth. Multi-collinearity was assessed using the variance inflation factor (VIF) and tolerance, but no collinearity effect was found. The Hosmer-Lemeshow goodness of fitness test was used to evaluate the model's fit, and the result ($p = 0.63$) indicated that the model was a good fit. Finally, the strength of the relationships between PTB and predictor factors was evaluated using Adjusted Odds Ratios (AOR) with 95% Confidence Intervals. A p-value less than 0.05 was considered statistically significant.

Results

Socio-demographic characteristics

A total of 381 medical records of mothers were reviewed, with 127 being cases and 254 being controls. The mean maternal age was 25.28, with a standard deviation of $\pm$5 years. The majority of participants in both groups were between the ages of 20 and 34. Most of the respondents, 286 (75.1%), lived in urban areas. The mean gestational age was 32.5 weeks with a standard deviation of $\pm$5 2.57 for cases, The majority of the babies were male, with 195 (51.2%) in total, including 70 (55.1%) in the cases group. The mean weight of the neonates was 3063 grams with a standard deviation of $\pm$831.84 for both cases and controls. The minimum weight recorded was 1000 grams, while the maximum was 5000 grams.

For the controle the mean gestational age was 39 weeks with a standard deviation of ±2.57. The majority of the babies among control were also male 125 (44.9%) (Table 1).

Table 1: Socio-demographic factors among mothers and their neonates at Sh. Hassen Yebere Referral hospital between January 1, 2018, and December 31, 2019 in Jigjiga town, Eastern Ethiopia 2021

Variables	Category	Case N (%)	Control N (%)	Total N (%)
Age Group	<19	14(11%)	38(15%)	52(13.6%)
	20-34	99(78%)	198(78%)	297(78%)
	>35	14(11%)	18(7.1%)	32(8.4%)
Place of residence	Rural	38(29.9%)	25(11.4%)	63(24.9%)
	Urban	89(70.1%)	225(88.6%)	314(75.1%)
Sex of neonate	Male	50(39.4%)	35(13.8%)	195(51.2%)
	Female	77(60.6%)	219(86.2%)	186(48.8%)
weight of the neonate	< 2500gm	70(55.1%)	33(13.0%)	103(27%)
	>2500	57(44.9%)	221(87.0%)	278(73%)

Maternal obstetric and medical factors

Approximately 76 (59.8%) of the case group mothers received ANC follow-up. Among them, 39 (30.7%) of the cases had less than 4 ANC visits. Approximately 95 (74.8%) of the case group mothers were multigravida, and a total of 12 (9.4%) had a history of abortion.

Among the participants, 8 individuals (8.25%) were found to have HIV/AIDS, with 5 (9.26%) from the case group. Furthermore, 24 cases (18.9%) had urinary tract infections during their current pregnancy. Regarding the mode of delivery for mothers, 88 (63.9%) of the cases were delivered through spontaneous vaginal delivery (SVD), while 32 (25.5%) underwent cesarean section (C/S). Additionally, 12 (9.4%) of the cases had a history of previous cesarean section.

Among controls, 117 (46.1%) mothers received ANC follow-up, of which 91 (35.8%) had less than 4 ANC visits, and 187 (73.6%) of the control group were multigravida. Only 6 (2.4%) of the control group mothers had a history of abortion.

Additionally, 3 (6.98%) from the control group were found to have HIV/AIDS, and 13 controls (5.1%) experienced urinary tract infections during their current pregnancy. Moreover, 200 (78.7%) of the control group were delivered through spontaneous vaginal delivery (SVD), while 39 (15.4%) underwent cesarean section (C/S), and 27 (10.6%) had a history of previous cesarean section (Table 2).

Table 2 -Maternal obstetric and medical factors among mothers who gave birth at Sh. Hassen Yebere Jigjiga university referral hospital between January 1, 2018, and December 31, 2019 in Jigjiga town, Eastern Ethiopia 2021.

Variables	Category	Case N(%)	Controls N(%)	Total n (%)
ANC visit	Yes	76(59.8%)	117(46.1%)	193(50.7%)
	No	51(40.2%)	137(53.9%)	188(49.3%)
Number of ANC visits	<4 ANC visit	39(30.7%)	91(35.8%)	130(67.4%)
	> 4 ANC visit	37(29.1%)	26(10.2%)	63(32.6%)
Gravidity	Primigravida	32(25.2%)	67(26.4%)	99(26%)
	Multigravida	95(74.8%)	187(73.6%)	282(74%)
Parity	Primipara	41(32.3%)	69(27.2%)	110(28.9%)
	Multipara	86(67.7%)	185(72.8%)	271(71.1%)
Hemoglobin level	<11d/dl	28(22%)	23(9.1%)	51(25.9%)
	≥11d/dl	99(78%)	231(90.9%)	330(74.1%)
History of previous abortion	Yes	12(9.4%)	6(2.4%)	18(4.7%)
	No	115(90.6%)	248(97.6%)	366(96.1%)
Multiple pregnancies	Yes	16(12.6%)	17(6.7%)	33(8.7%)
	No	111(87.4%)	237(93.2%)	348(91.3%)
Current pregnancy complication	Premature Rupture of Membranes	38(38.0%)	29(29.59%)	67(33.84%)
	Preeclampsia	34(34.0%)	40(40.82%)	74(37.37%)
	APH	19(19.0%)	15(15.31%)	34(17.17%)
	Placenta previa	9(9.0%)	14(14.29%)	23(11.62%)
Maternal medical problem	Hypertension	15(27.78%)	10(23.26%)	25(25.77%)
	Diabetes Mellitus	10(18.52%)	17(39.53%)	27(27.83%)
	HIV seropositive	5(9.26%)	3(6.98%)	8(8.25%)
	Urinary tract infection	24(44.44%)	13(30.23%)	37(38.14%)
Mode of delivery	Spontaneous vaginal delivery	88(63.9%)	200(78.7%)	292(76.6%)
	C-section	32(25.5%)	39(15.4%)	71(18.6%)
	Instrumental	7(5.5%)	15(5.9%)	18(4.7%)
Previous C-section	Yes	12(9.4%)	27(10.6%)	39(10.2%)
	No	115(90.6%)	227(89.4%)	342(89.8%)
PROM	Yes	38(29.9%)	57(22.4%)	95(24.9%)
	No	89(70.1%)	197(77.6%)	286(75.1%)

Neonatal outcome factors

Out of all the neonates that were delivered, 57 (44.9%) of the cases and 29(11.4%) of the control neonates experienced fetal distress. Approximately 23(18.1%) of the cases and 18 (7.1%) of the controls had congenital defects. Additionally, about 12 (9.4%) of the cases and 5 (2.0%) of the controls were deliveries with intrauterine growth restriction (IUGR) (Table 3).

Table 3: Fetal factors among mothers who gave birth at Sh. Hassen Yebere Jigjiga university referral hospital between January 1, 2018, and December 31, 2019in Jigjiga town, Eastern Ethiopia 2021

Variables	Category	Case N (%)	Controls N(%)	Total N(%)
Fetal distress	Yes	57(44.9%)	29(11.4%)	86(22.6 %)
	No	70(55.1%)	225(88.6%)	295(77.4%)
Congenital birth defect	Yes	23(18.1%)	18(7.1%)	41(10.8%)
	No	104(81.9%)	236(92.9%)	340(89.2%)
Intrauterine growth re-	Yes	12(9.4%)	5(2.0%)	17(4.5%)
	No	115(90.6%)	249(98.0%)	364(95.5%)

Determinants of Preterm Birth

All variables that had a p-value of less than 0.25 in the bivariate analysis were included in the final model of the multivariable analysis. In the bivariable logistic regression, factors such as congenital birth defects, antenatal care of less than or equal to four visits, rural dwellers, hemoglobin <11mg/dL, antepartum hemorrhage, hypertension, fetal sex, and weight of the neonate were found to be significantly associated with preterm birth.

In the final model of multivariable analysis, variables such as hemoglobin <11mg/dL, being male fetus, having congenital birth defects, antenatal care of less than or equal to four visits, and rural dwellers remained statistically significantly associated with PTB. Accordingly, mothers living in rural areas were twice as likely to have PTB compared to mothers living in urban areas (AOR; 2.512, 95% CI: 1.11, 5.684). Mothers who received ≤ 4 antenatal care visits were six times more likely to have a preterm delivery than mothers who had four or more ANC visits (AOR; 6.426, 95% CI: 3.128, 13.202). Neonates who had congenital birth defects were three times more likely to be delivered prematurely than those who had no congenital birth defects (AOR; 3.491, 95%CI: 1.44, 8.681). Mothers with a hemoglobin level below 11mg/dL were three times more likely to give birth prematurely compared to those with a hemoglobin level of 11mg/dL or higher (AOR; 3.328, 95% CI: 1.459, 7.589). Male newborns were twice as likely to be born prematurely compared to female newborns (AOR; 2.045, 95% CI: 1.042, 4.015) (Table 4).

Table 4: Binary and multivariable logistic analysis of determinates of preterm birth cases and controls in Sh. Hassen Yebere Jigjiga university referral hospital.

Variables	Cases	Controls	Crude OR(95% CI)	Adjusted OR(95% CI)
Congenital birth defects				
Yes	23(18.1%)	18(7.1%)	2.900(1.501,5.602)	3.491(1.4.4, 8.681)**
No	104(81.9%)	236(92.9%)		1
Number of ANC visits				
≥ 4	37(29.1%)	26(10.2%)		1
< 4	90(70.9%)	228(89.8%)	3.605(2.064,6.297)	6.426(3.128,13.20)*
Place of residency				
Rural	38(29.9%)	25(11.4%)	3.313(1.927,5.696)	2.512(1.110,5.684)*
Urban	89(28.3%)	225(88.6%)		1
Hemoglobin Level				
<11 mg/dL	28(22%)	23(9.1%)	2.841(1.595,5.174)	3.328(1.459,7.589)*
≥11 mg/dL	99(78%)	231(90.9%)		1
Antepartum haemorrhage				
Yes	19(15%)	15(5.9%)	2.803(1.372,5.725)	4.154(0.708,10.105)
No	108(85%)	239(94.1%)		1
Chronic hypertension				
Yes	15(11.8%)	10(3.9%)	3.268(1.424,7.500)	4.0 (0.459,7.589)
No	112(88.2%)	244(96.1%)		1
Fetal Sex				
Male	50(39.4%)	35(13.8%)	4.063(2.455,6.726)	2.045(1.042, 5.015) **
Female	77(60.6%)	219(86.2%)		1
Weight of the neonate				
≤ 2500gm	70(55.1%)	33(13.0%)	8.224 (4.958,13.642)	10.624(0.395,20.922)
>2500gm	57(44.9%)	221(87.0%)		1

***Key**: 1= Reference category* *=p-value<0.05, **=p-value<0.001, ***=p-value<0.0001, COR= Crude odds Ratio, AOR= Adjusted Odds Ratio

Discussion

This study identified residing in rural areas, having a maternal hemoglobin level below 11mg/dL, being male, having congenital birth defects, receiving antenatal care of fewer than four visits as a determinant of preterm delivery.

The findings of this study indicate that mothers who were rural dwellers have twice the risk of preterm birth compared to mothers who were urban dwellers. This aligns with previous study conducted in Australia(11). This can be explained by the fact that rural areas have limited availability and access to health services, resulting in delayed initiation of antenatal care during pregnancy. Additionally, women living in rural areas may have inadequate maternal nutrition due to limited access to information about the benefit of dietary diversification during pregnancy.

Mothers whose most recent hemoglobin level below 11gm/dl had a three times higher chance of giving birth prematurely compared to those with a hemoglobin level of 11gm/dl or higher. This finding is in line with similar studies conducted in Tigray, debremarkos , Indonesia, and Malawi(12-16). This could be due to the fact that when a pregnant woman has low levels of hemoglobin, it can induce stress for both the mother and the fetus. This stress can then lead to the release of the cortisol hormone, which can trigger premature birth.

Neonates who had congenital birth defects were three times more likely to be delivered prematurely than those who had no congenital birth defects. This is inline with a study done in the US(17). This could be a result of certain birth defects that impact the structure of the uterus, causing it to be incapable of sustaining a pregnancy until full term. Furthermore, some birth defects can result in pregnancy complications like preeclampsia or abnormalities in the placenta, which can increase the likelihood of premature birth.

Mothers who had less than four antenatal care (ANC) follow-up visits were found to be six times more likely to give birth prematurely. This finding aligns with similar studies conducted in Ghana, Jimma, Debretabor, and Tigray(10, 18-20). The reason for this increased risk may be that mothers with inadequate ANC follow-up miss out on important information, early detection, diagnosis, and treatment that could prevent preterm birth.

Neonatal sex is one factor predisposing to preterm birth. This study revealed that being male neonatal has two times risk to be born preterm than those of females. Our find is consistent with a review conducted by Månsson, Johanna, et al.(21). This could be due to the difference in hormone levels between male and female newborns. Male fetuses tend to have higher levels of testosterone, which may create an unfavorable environment in the uterus and increase the risk of preterm birth.

Conclusion

This study found that factors such as having less than or equal to 4 ANC visits, maternal

hemoglobin level <11mg/dL, being male fetus, having congenital birth defects, living in rural areas, were found to contribute to preterm birth. So, it is important to encourage pregnant women to regularly take iron and folic acid supplements and to attend their scheduled antenatal care visits. In addition, improving healthcare accessibility in rural regions is also crucial.

Declaration

Ethical Approval

The Institutional Health Research Ethics Review Committee (IHRERC) of Jigjiga University granted ethical clearance for the study. Additionally, a permission letter was obtained from the medical director of Shek Hassen Yebere Jigjiga University Referral Hospital to access medical records. To ensure confidentiality, all names and personal identification information were excluded from the data collection record.

Contribution of author

SM conceived the idea for this study, developed the proposal, supervised fieldwork, and was involved with the analysis, interpretation, and writing. SM, EL,ML and DA contributed to the conceptualization of the study, methodology, writing final draft, writing - review & editing of the manuscript.

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Availability of data and materials

All relevant data are included in this study. However, additional data is available from the corresponding author upon reasonable request.

Conflict of interest

There is no conflict of interest

Funding : No funding

Abbreviations

Abbreviations: ANC, Antenatal Care; AOR, Adjusted Odds Ratio; CI, Confidence Interval; COR, Crude Odds Ratio; HIV, human immunodeficiency virus ; PTB, Preterm Birth; PROM, Premature Rupture of Membranes; SPSS, Statistical Package for Social Science; SVD, Spontaneous vaginal delivery ;WHO, World Health Organization.

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Original article

Caregivers' knowledge and practice regarding hypoglycemia prevention in children with type one diabetes mellitus at Saint Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia

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Abstract

Background: *Achieving optimal glycemic control with a stringent preventive interventions targeting hypoglycemia is at the core of diabetic care. Caregivers for pediatric diabetic patients are the primary providers. Therefore, enabling them to have adequate knowledge about hypoglycemia and its prevention is critical.*

Objective: *To assess the knowledge and practice of preventing hypoglycemia among caregivers for diabetic patients on follow-up at a tertiary care at a pediatric endocrine clinic in Ethiopia.*

Methods: *A cross-sectional study was conducted on caregivers for children with type one diabetes patients attending follow-up visits at a tertiary care with a pediatric endocrinology clinic in Ethiopia, from August 16 to October 10, 2021. We collected relevant data using interviews and pretested questionnaire. We analyzed the collected data using statistical Package for Social Science Software.*

Results: *From a total of 101 caregivers, 76.2 % were females, and 23.8% were males. 64.4 % had good knowledge about hypoglycemia. Among 19 caregivers whose child was less than four years old, 10 caregivers had a good practice and 9 had poor hypoglycemia practice and from 75 caregivers whose child was four years and above, 31 caregivers had a good practice and 44 had poor hypoglycemia prevention practice. Overall, 43.6 % had good hypoglycemia prevention practices.*

Conclusion: *Caregiver's knowledge regarding hypoglycemia was satisfactory, but the hypoglycemia prevention practice was poor. Therefore, education about hypoglycemia and its prevention practice should be emphasized during the regular clinic follow-up.*

Keywords: Hypoglycemia, T1DM, Caregivers

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Introduction

Hypoglycemia is a common acute complication in children with type one diabetes mellitus (T1DM). Blood Glucose level of ≤ 3.9 mmol /l or 70 mg /dl is defined as hypoglycemia Common causes of hypoglycemia are insulin therapy, intensive or prolonged exercise, missing main meals and snacks, and ingestion of alcohol in adolescents (1). The signs and symptoms of hypoglycemia are not specific, and the manifestations are different in children and adults (2). Hypoglycemia should be prevented because its occurrence is frequently predictable and often associated with significant psychosocial dysfunction; more importantly, it can rarely lead to permanent long-term squelae and may be potentially life-threatening (1). Approaches known to decrease the risk of hypoglycemia include patient education, dietary and exercise modifications, medication adjustment, careful glucose monitoring by the patient, and surveillance by the clinician (3). Furthermore, knowledge about the symptoms of hypoglycemia is an important step in influencing self-care practices in preventing hypoglycemia as informed people are more likely to exercise better preventive measures (4). Good knowledge about hypoglycemia is positively associated with good practices of hypoglycemia prevention (5). Primary providers for pediatric patients are caregivers, enabling them to have good knowledge and preventive practices for hypoglycemia are parts of core diabetic care.

Hypoglycemia is a common problem in children with type 1 diabetes Because of the challenges of insulin dosing, variable eating patterns, erratic activity, and the limited ability of young children to detect hypoglycemia, it is a frequent problem in children with type 1 diabetes. The infant, young child, and adolescent typically exhibit unpredictable feeding styles, may not eat all the required quantity of food at major meal times and snacks, the interval between meals is unpredictable, , and often overnight fasting is prolonged. (3). Though hypoglycemic episodes tend to be common, evidence suggests that children with type 1 diabetes and their parents fail to recognize hypoglycemic episodes in 40–50% of the time. (6). Failure to recognize hypoglycemia and manage hypoglycemia episodes is dangerous because the recurrence risk increases subsequently, and it causes impaired hypoglycemia awareness (1). Although knowledge about hypoglycemia and its prevention practice is at the core of diabetic care, it is not studied well, especially in the pediatric age group. Therefore, this study aimed to assess the status of knowledge about hypoglycemia and its prevention practices among caregivers of pediatric diabetic patients at the Saint Paul's hospital millennium medical college (SPHMMC) diabetes follow-up clinic.

Methods

The study was conducted at SPHMMC pediatrics and child health department outpatient endocrine clinic. SPHMMC is located in

Addis Ababa Ethiopia. It is one of tertiary hospitals in the country serving population of 8 million. The pediatrics and child health department has inpatient and outpatient services including Neonatal and child intensive care unit.

A hospital-based cross-sectional study was conducted on 101 caregivers of children with T1DM at SPHMMC pediatrics and child health department outpatient endocrine clinic who attended follow-up clinic from August 16 to October 10, 2021. Data was collected at the follow-up clinic using the interview method via a pretested questionnaire after the study got institutional review board approval by the research directorate office of SPHMMC and verbal consent from the caregivers. The study population was all caregivers of diabetes mellitus patients who attended follow-up visits during the study period at pediatrics endocrine clinic. Since patients are coming every 2 to 3 months all the caregivers who attended the follow-up visits during the study period who fulfilled the inclusion criteria were included in the study.

Inclusion criteria: All caregivers of T1DM patients who were above 18 years of age and who were willing to participate in the study during the study period and attended follow-up at pediatric endocrine clinic were included.

Exclusion criteria: All Caregivers of T1DM patients who were unwilling to participate in the study and those who were less than 18 years of age were excluded.

The data was collected using pretested structured interview questionnaire. The questionnaire was first prepared in English then it was translated to Amharic and Afanoromo languages (local languages) and translated back to English . The data was collected by interns who were trained by the principal investigator on the objective, relevance of the study and confidentiality of information before the data collection and it was supervised by the clinical advisor and principal investigator throughout the course. All the data was checked for completeness, clarity and consistency by the principal investigator.

Dependent variables: Hypoglycemia knowledge and prevention practice of hypoglycemia. Independent variables: Socio-demographic variables (age, sex, income, marital status, education, religion, and occupation). Clinical characteristics-related variables (Types of diabetes of the child, duration of illness, type of medication used, frequency of taking medication, having a glucometer, knowing glucose level, history of hypoglycemia, and co-morbidity). The items for the hypoglycemia knowledge and prevention practice were collected from International Society of Pediatrics and Adolescents Diabetes (ISPAD) guideline (1).

For knowledge assessment, twenty-four yes or no questions each with a point score were used. For the practice section a total of seven questions, four yes or no questions each with one-point score, and three questions each with a score of zero to three points were used. Mean was computed using 7 variables for caregivers of children at the age of four years

and above and using three variables for those less than four years. The mean score was calculated by adding each participant's score questions about specific variables (knowledge or practice) and dividing it by the total number of participants using Likert scale which is a psychometeric score scale used to measure opinion, attitude or behavior. The collected data was analyzed using SPSS.

Operational definitions

Knowledge: It is the awareness of the caregivers about hypoglycemia. It is measured by calculating the mean score of the 24 items and categorized as good knowledge (if participants scored ≥ mean score from the knowledge questions on hypoglycemia) or poor knowledge (if participants scored <mean score from the knowledge questions on hypoglycemia).

Practice: The practice of the caregivers in the prevention of hypoglycemia. It is measured by 7 questions using a Likert scale to obtain total mean scores and categorized as good practice or poor practice. All caregivers' answers to practice questions were computed to obtain total mean scores and categorized as good practice (if participants scored ≥ mean score) or poor practice (if participants scored < mean score) (5,7).

Results

Caregivers' Sociodemographic Assessment

A total of 101 caregivers were included in the study. 76.2 % were females. Around 92.1% of the caregivers were their biological parents and 89.1% of the caregivers were married ones. Around 61.4% of the caregivers attended secondary and college level education. All of them had at least one means of health-related information. The majority came from urban areas (91.1%), and only 5.9% came from rural areas (Table 1).

Table 1: Sociodemographic assessment of the caregivers of children with T1DM attending pediatrics Endocrine Clinic at SPHMMC, August 16 to October 10, 2021

Study characteristics	Category	Frequency (%)
Caregivers' relation with the child	Parent	93 (92.1)
	Relative	6 (5.9)
	Legal guardian	2 (2.0)
Caregivers' age	18-34	50 (49.5)
	35-60	48 (47.5)
	>60	3 (3)
Child age in Years	3-5	12 (11.9)
	< 3	24 (23.8)
	6-13	46 (45.5)
	14-17	19 (18.8)
	Mean	8.6±4.7
Caregivers' sex	Male	24 (23.8)
	Female	77 (76.2)
Child sex	Male	48 (47.5)
	Female	53 (52.5)
Religion	Orthodox Christian	61 (60.4)
	Protestant	21 (20.8)
	Muslim	18 (17.8)
	Catholic	1 (1.0)
Marital status	Married	90 (89.1)
	Single	7 (6.9)
	Others*	4 (4.0)
Educational status	No formal education	15 (14.9)
	Primary education	24 (23.8)
	Secondary education	31 (30.7)
	College and above	31 (30.7)
Occupation	Unemployed	51 (50.5)
	Private employ	26 (25.7)
	Government employee	13 (12.9)
	Others**	11 (10.9)
Residence	Urban	92 (91.1)
	Rural	6 (5.9)
	Semi-urban	3 (3.0)
Income per month	<40 USD	57 (56.4)
	40-99 USD	27 (26.7)
	≥100 USD	17 (16.8)

*-separated and widowed ** -Daily laborer and retired #-USD—United States dollar

Caregivers' knowledge of hypoglycemia

The caregivers have attended a regular follow-up at this clinic for a minimum of 6 weeks, a maximum of 13 years, and a mean of follow-up 2.9 years. More than half (51.5%) didn't know the type of diabetes the child was having. Around 82.2% of caregivers received diabetic education 66.3% were educated specifically about hypoglycemia, 71.6% got education at the SPHMMC diabetes clinic, and 11.9% both at Ethiopian diabetes association (EDA) and SPHMMC diabetes clinic.

Participants were asked about the causes, symptoms, and preventive measures of hypoglycemia. Of 101 participants, 59.4 % can define hypoglycemia correctly based on glucometer measurement. Among the five causes of hypoglycemia listed, inadequate feeding or missing meals and insulin overdose were among the well-known causes of hypoglycemia by 96% and 81.2% of the participants respectively. Alcohol ingestion was the least known cause by caregivers (42.6%). Of the symptoms shakiness, loss of consciousness, and dizziness & unsteady gait were the most commonly known symptoms (94. 1%). Inconsolable crying and nightmares were the least known symptoms, 51.5 %, and 64.4 % respectively (Table 2).

Regarding the prevention of hypoglycemia majority of caregivers (89.1%) believed that hypoglycemia is preventable and 82.2 % knew hypoglycemia was a concern as hyperglycemia. Only 45.5 % knew that the chance of recurrence of hypoglycemia increases even after one episode of hypoglycemia.

Table 2: Knowledge about Hypoglycemia among Caregivers of children with T1DM attending pediatrics Endocrine Clinic at SPHMMC, August 16 to October 10, 2021.

Study characteristics	**Good knowledge response N (%)**	**Poor knowledge response N (%)**
Hypoglycemia definition	60 (59.4)	41 (40.6)
Cause of hypoglycemia		
Giving excessive dose of insulin	82 (81.2)	19 (18.8)
Exercise	65 (64.4)	36 (35.6)
Missing meal/Inadequate feeding	97 (96.0)	4 (4.0)
Alcohol ingestion	43 (42.6)	58 (57.4)
Sleep cause hypoglycemia	61 (60.4)	40 (39.6)
Symptoms of hypoglycemia		
Shakiness	95 (94.1)	6 (5.9)
Sweatiness	91 (90.1)	10 (9.9)
Poor concentration	87 (86.1)	14 (13.9)
Loss of consciousness	95 (94.1)	6 (5.9)
Seizure	92 (91.1)	9 (8.9)
Irritability	76 (75.2)	25 (24.8)
Hunger	86 (85.1)	15 (14.9)
Headache	74 (73.3)	27 (26.7)
Slurred speech	75 (74.3)	26 (25.7)
Dizziness and unsteady gait	95 (94.1)	6 (5.9)
Inconsolable crying	52 (51.5)	49 (48.5)
Nightmare	65 (64.4)	36 (35.6)
Ways to prevent hypoglycemia		
Measuring glucose before exercise	95 (94.1)	6 (5.9)
Giving snacks before intense exercise	84 (83.2)	17 (16.8)
Make avail sugar/snack when child is not around home	46 (45.5)	55 (54.5)
Wearing DM identification in hand	75 (74.3)	26 (25.7)
Ways of initial management of hypoglycemia		
Give sweets (Mirinda, tea, sugar, bread)	61 (60.4)	40 (39.6)
Bring the child to nearby clinic	13 (12.9)	88 (87.1)

26.73 % of the caregivers didn't know what should be done in case of inadvertent over-administration of insulin and the remaining answered that either the child should be brought to the nearby clinic (12.87%) or should be given sweets like Mirinda, sugar, tea and the like (60.4%).

From the 24 yes or no type knowledge questions each with one point, the mean score was 18.82 with a minimum of 9, maximum of 24, and standard deviation of 3.16. Accordingly, 64.4 % had good knowledge and 35.6 had poor knowledge (Table 2).

Caregivers Practice on hypoglycemia prevention

Caregivers Hypoglycemia prevention practice in children less than four years

Twenty caregivers of children less than four years old were assessed. All of them had a glucometer and they monitored the blood glucose level twice and more daily. 19 (95%) of them, their children had experienced hypoglycemia before, and 16 (84.2%) had reported the episode to their physician. Only four caregivers failed to make snacks available when the child was not around home. The majority of the caregivers made snacks available to their children (Table 3)

Table 3: Hypoglycemia prevention practice among caregivers of children < 4 years with T1DM, attending pediatrics Endocrine Clinic at SPHMMC, August 16 to October 10, 2021.

Variables	Frequency	Percentage
Glucometer		
Yes	20	100.0
Frequency of measurement		
Twice	11	55.0
Three times	5	25.0
Four times and more	4	20.0
Total	20	100.0
Hypoglycemic episodes occurred ever		
Yes	19	95.0
No	1	5.0
Total	20	100.0
Report to physicians		
Yes	16	84.2
No	3	15.8
Total	19	100.0
Making snacks available when child is not around home		
Never	1	5.0
Sometimes	3	15.0
Usually,	4	20.0
Always	12	60.0
Total	20	100.0

The practice was assessed by computing a mean score using three variables, regular monitoring (1 point), reporting episodes to physicians (1 point), and making snacks available when the child was not around home (0 to 3 points). It was computed for 19 caregivers who answered all the 3 questions. The mean score was 4.1 with a minimum of 2, a maximum of 5, and a St. Deviation of 1.06. Accordingly, ten caregivers had good practice and 9 had poor practice.

Caregivers Hypoglycemia prevention practice in children four years and above

Eighty-one caregivers of Children four years and above were studied. 79 (97.5%) had a glucometer and 76 monitored the blood glucose level twice and above per day. Seventy-five noticed hypoglycemic episodes before in their children and 67 reported the episode to the physician. The majority of caregivers 76 (93.8%) told the child's DM status to teachers or friends. Nearly half 39 (48.1%) caregivers never measured blood glucose before the child did intense exercise. Twenty-five (30.9%) children were never given snacks before intense exercise and 23 (28.4) were given sometimes. Making snacks available is better practiced regularly by nearly half of caregivers 39 (48.1%). Wearing a DM identification is the least to be practiced 19 (23.5%) (Table 4).

Table 4: Hypoglycemia prevention practice among caregivers of children ≥ 4 years (n= 81) with T1DM, attending pediatrics Endocrine Clinic at SPHMMC, August 16 to October 10, 2021.

Variables	Frequency	Percentages
Glucometer		
Yes	79	97.5
No	2	2.5
Total	81	100.0
Frequency of measurement		
Once	3	3.8
Twice	61	77.2
Three times	12	15.2
Four times and more	3	3.8
Total	79	100.0
Hypoglycemia symptoms occurred		
Yes	75	92.6
No	6	7.4
Total	81	100.0
Report to physicians		
No	8	10.7
Yes	67	89.3
Total	75	100.0
Glucose measurement before exercise		
Never	39	48.1
Sometimes	25	30.9
Usually,	4	4.9
Always	13	16.0
Total	81	100.0
Giving snacks before intense exercise		
Never	25	30.9
Sometimes	23	28.4
Usually,	7	8.6
Always	26	32.1
Total	81	100.0
Making snacks available when child is not around home		
Never	13	16.0
Sometimes	23	28.4
Usually,	6	7.4
Always	39	48.1
Total	81	100.0
Wearing DM ID		
No	62	76.5
Yes	19	23.5
Total	81	100.0
Telling DM status to friends/teachers		
No	5	6.2
Yes	76	93.8
Total	81	100.0

The practice was assessed by computing a mean score using seven variables (regular monitoring, reporting episodes to physicians, wearing DM ID and telling DM status for teachers/friends 1 point for each) and making snacks available when a child is not around home measuring and giving snacks before intense exercise (0 to 3 points for each). It was computed for 75 caregivers who answered all 7 questions. The mean score was 7.17 with a minimum of 2, a maximum of 13, and a St. Deviation of 2.67. Accordingly, 31 caregivers had good practice and 44 had poor practice.

Caregivers practice on primary management of hypoglycemic episodes

Caregivers who witnessed hypoglycemia (symptoms or blood glucose less than or equal to 70 mg/dl) in their children were asked how they managed it using open-ended questions and their answers were as follows. Among 94 caregivers who witnessed hypoglycemia, about 83 did manage it appropriately. Around 69 caregivers said they gave sweets like mirinda, tea with sugar and food, 4 of the caregivers said they give sweets and measure the glucose frequently. One caregiver said she gives sweets then take the child to the clinic and 9 of the caregivers took the children to the clinic. Eleven of the caregivers gave inappropriate answers. Five of them said they only measure the glucose without intervention and 6 of the caregivers said to omit or adjust the next insulindose.

Discussion

In the current study, we discovered that 92.1% of caregivers were their biological parents, with the majority (76.2%) of them being their mothers. We observed also a significant number of caregivers were from urban and they were married and had completed secondary and college level education. Despite these factors which might affect the findings positively, we found that the overall knowledge about causes, symptoms, and preventive measures of hypoglycemia was good only in 64.4% of the caregivers, with a significant portion of them (35.6%) were having poor knowledge.

Generally hypoglycemia in the setting of diabetes is a fundamental area of patient care. Regarding the association between caregivers knowledge and glycemic control, many studies showed that there is a significant association between mothers' knowledge of diabetes and Hemoglobin A1C (HbA1C) level that, higher knowledge ultimately leads to better control of HbA1c level. This fact was demonstrated in many studies , the higher a mother's knowledge, the better metabolic control of children and adolescents with T1DM (8,9,10). The exact incidence of hypoglycemia is difficult to ascertain, but generally mild hypoglycemia is common in children with T1DM (11). In the current study, 94 (93.1%) of the children experienced hypoglycemia, this finding was consistent with a previous study done in T1DM patients in a tertiary hospital at a diabetic clinic in Ethiopia in which 94.3% of them experienced hypoglycemia ever since they were diagnosed with T1DM (12).

Although the finding in the current study regarding the overall knowledge about causes, symptoms and preventive measures was better than other studies a significant portion of the caregivers (35.6%) had poor knowledge. Studies done among adult DM patients in the rural community in India, 63.3% had inadequate knowledge (13). In another study done in India among Type-2 diabetes patients and their caregivers about awareness of symptoms of hypoglycemia, only 38% of diabetic patients had average knowledge about symptoms of hypoglycemia (14). This is a major challenge to address as knowledge about hypoglycemia is an important step to self-care practice because informed people are more likely to have better practice (8). Poor knowledge of hypoglycemia was also observed in other studies. One study done in Sudan, 52% of diabetic patients who were taking insulin had poor knowledge of hypoglycemia symptoms and in another study done in Ethiopia around 51.2% of participants had poor knowledge of identifying symptoms of hypoglycemia respectively (15,16).

In this study, we found that around 82.2% of of the caregivers had received diabetic education, and a considerable number of caregivers had particularly received education about hypoglycemia despite that, a remarkable number of caregivers had poor knowledge about hypoglycemia, this might be the education they received might be less effective as it might lack user friendly teaching materials and because of the high patient burden and a small number of diabetic educators one to one session might not be feasible, Therefore, the caregivers should be thought about every issues related to hypoglycemia using different methods regularly which later affect their practice towards prevention of hypoglycemia.

In our study, although all participants practiced regular blood glucose monitoring, only 59.4 % can define hypoglycemia correctly based on glucometer measurement, which makes subsequent management of hypoglycemia episode difficult and increases the hypoglycemia recurrence rate. As the management of diabetes in the pediatric age depends on the caregivers, it is expected that all caregivers should receive diabetic education regularly.

In the current study, 90% of the caregivers know hypoglycemia can be prevented. Despite this 54.5% of them didn't know the recurrence rate would increase after one episode of hypoglycemia which is highly alarming because, in a previous study done in the same setting, the recurrence rate was also high with a total of 6.9 events of hypoglycemia per patient per year (7). This is a serious gap identified as they are less likely to practice prevention strategies if they didn't anticipate the high chance of hypoglycemia recurrence which needs serious intervention. In addition to this, once hypoglycemia becomes recurring, hypoglycemia fear makes the patients to modify their behaviors and take excess food to decrease hypoglycemia episodes, which in turn could contribute to a poor glycemic control (17). Fear of hypoglycemia should be assessed in children with Type 1 diabetes and their parents on a routine

basis to identify families who may need support or intervention (18). Moreover, symptoms of hypoglycemia tend to be correlated with significantly lower health-related quality of life, lower treatment satisfaction, and higher levels of healthcare resource utilization (19). That is why we need to give much emphasis on the hypoglycemia education in order to decrease its consequences.

In this study, nearly all patients practiced regular glucose measurement and the hypoglycemia reporting rate was satisfying. However, there was a huge gap in practicing preventive measures like measuring blood glucose and giving snacks before intense exercise, and wearing DM identification. And the overall hypoglycemia prevention practice is poor though the practice in those less than four years seems better. This can be due to two factors. First, it could be due to the small number of participants in this group (only 19 caregivers) and another possible explanation is that it might be due to the use of more difficult practices to calculate the mean score in those age group (four years and above) like wearing DM identification, measuring blood glucose and giving snacks before intense exercise.

Regarding prevention practice in one study in South Gondar, Ethiopia, only 21.4% of study participants had good practice in hypoglycemia prevention (16). Another study done in 2019 in the same setting showed significant improvement in terms of knowledge and practice which might be because of certain interventions (20). One study done in Tigray, Ethiopia also showed two-thirds of the study participants were found to have good hypoglycemia prevention practices which was higher than the current study (5). As it was evidenced in one study done in Iran in mothers of children with diabetes from 6-12 years old family or caregivers' empowerment the results showed significant differences in the control and study group in terms of knowledge about DM and its complications and problem-solving ability those who had received empowerment showed better outcomes (7).

In the current study as the caregivers are expected to manage the episodes primarily by their own, the practice of primary management was satisfactory as 83% of the caregivers who witnessed hypoglycemia succeeded in managing it with the administration of sweets immediately with subsequent frequent monitoring or seeking medical care. This behaviour should be encouraged.

In summary, although SPHMMC is one of the tertiary hospitals in the country with specialty care, the prevention practice of hypoglycemia in the current study was not satisfactory. Most patients are from urban areas and they have at least one or more means of getting health information. In addition to that about two-thirds of the patients received diabetic education and had good knowledge. Nevertheless, the prevention practice remained poor. It is quite logical to argue that the condition is highly likely to be worse in patients attending care in low-level setups and in remote parts of the country.

This will have two huge impacts. First, hypoglycemia will be a barrier against optimal glycemic control which is the most essential parameter to decrease the long-term complications. Second, it has a huge financial impact by increasing direct health utilization-related costs and indirect costs (21, 22).

Diabetic education is the basis of diabetic care including hypoglycemia prevention and additionally the use of continuous glucose monitoring is currently highly advocated to decrease the frequency and severity of hypoglycemic episodes in children with T1DM (23 -25).

In conclusion, we recommend healthcare providers to give proper diabetic education focusing on hypoglycemia prevention and management, and empowering families and caregivers to practice prevention of hypoglycemia is also very crucial.

Declaration

Ethical consideration

Ethical approval was obtained from St. Paul's Hospital Millennium Medical College IRB and verbal consent was obtained from the participants of the study.

Conflict of interest

No known competing interests to declare

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Authors' Contribution: NM conceived the study, designed a data abstraction tool, undertook a review, analysis and interpretation of the data, and drafted the initial manuscript. **BF** was involved in topic selection, revised data abstraction tool, supervised data collection and analysis, wrote the final manuscript. **AY** was involved in the data analysis. All authors revised the manuscript and approved the final version.

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Original Article

Clinical characteristics of children with congenital anomalies of kidney and urinary tract and predictive factors for Chronic Kidney Disease in a tertiary hospital, Addis Ababa, Ethiopia

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Abstract

Background: *Congenital anomalies of the kidney and urinary tract (CAKUT) are the leading causes of chronic kidney disease (CKD) in childhood. Determining the clinical course, outcome, and prognostic factors of this heterogeneous group of diseases is important to provide appropriate management and follow-up. Therefore, we aimed to identify the risk factors of CKD in CAKUT and the differences in clinical courses between subtypes of CAKUT.*

Methods*: a retrospective cross-sectional study was done in 134 patient records diagnosed with congenital kidney and urinary tract anomalies. They were categorized with subtypes of CAKUT and a chi-square test and logistic regression analysis were done to determine risk factors for CKD and the result is presented in tables.*

Results*: Among the 134 patients, males were 107 (79.9%) and the commonest subtypes of CAKUT were posterior urethral valve in 42 (31.3%), ureteropelvic junction obstruction in 28 (20.9%), multicystic dysplastic kidney in 24 (17.9%). The median age of the study population at the time of diagnosis was 2.5 yrs. Among available 50 prenatal ultrasounds, the most frequent diagnoses were hydronephrosis in 38 patients (28.4%) and MCDK in 9 patients (6.7%). A total of 21(15.7%) patients had CKD and 6 of them (4.5%) progressed to end-stage kidney disease (ESRD). The multivariate logistic regression analysis identified proteinuria on follow-up as an independent risk factor for CKD. (p=0.004)*

Conclusion: *Posterior urethral valve is the commonest congenital anomaly of the kidney and urinary tract and proteinuria is an independent risk factor for CKD.*

Keywords*: CAKUT, chronic kidney disease, proteinuria, end-stage kidney disease*

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Introduction

Congenital anomalies of the kidney and urinary tract (CAKUTs) are some of the most common birth defects in newborns. CAKUT is characterized by structural and functional abnormalities of the kidney, collecting system, bladder, and urethra (1-7). The overall prevalence of congenital anomalies of the kidney and urinary tract in live and stillborn infants is 0.3 to 1.6 per 1000 (2)

CAKUT has been identified in 20% to 50% of all fetal congenital anomalies in some populations, but the causes remain unclear. Although children with CAKUT are often asymptomatic, CAKUT is estimated to be implicated in 30% to 60% of cases of childhood-onset chronic kidney disease (CKD) in different populations. (3) The incidence is higher in offspring with a family history of CAKUT and a maternal history of either kidney disease or diabetes (3, 4).

CAKUT are the most common cause of end-stage renal disease (ESRD) in children accounting for 50–70% of those who begin renal replacement therapy (RRT) worldwide (4-6). The severity of kidney function impairment at the time of presentation, and the presence of co -morbidities at birth like pulmonary hypoplasia, infection, and associated genetic abnormalities were prognostic indicators of progression to CKD. The great majority are diagnosed prenatally or within the first months of life. Most challenging is the early management of these infants with bilateral and severe CAKUT who have significant renal compromise at birth (4-6) The natural history of severe neonatal CAKUT remains incompletely understood concerning the demographic and biological "predictors" of progression to CKD (4-13).

Most cases of CAKUT are diagnosed from antenatal ultrasound imaging, which examines the kidneys, the outflow tracts, and most importantly the amniotic fluid volume (5, 7-13). After the 18th week of gestation, amniotic fluid is primarily composed of urine produced by the fetal kidneys. Antenatal ultrasounds correctly diagnose CAKUT in 60%–85% of infants, especially if imaging is performed in the third trimester (5, 7-13). The remaining cases of CAKUT are mostly diagnosed after an infant or child presents with a urinary tract infection prompting ultrasound and other imaging studies to examine the kidneys and outflow tracts (5). Individuals born with one or two kidneys, but low nephron number, may not exhibit any signs or symptoms until adolescence or adulthood when early onset hypertension or CKD may be diagnosed (5).

Malformed kidneys that are small by length measurements on ultrasound are classified as hypoplastic kidneys; whereas those that are small, hyperechoic, and with/without cysts are described as dysplastic kidneys (5). Although renal hypoplasia/dysplasia refers to the histologic appearance of the kidney, this type of CAKUT is rarely diagnosed by kidney biopsy partly because the small kidney size and/or the

coexistence of a dilated ureter may increase complications from the biopsy(5).

The genetic diagnosis is complex due to the numerous genes involved and the variable genotype-phenotype-correlation. More than 20 genes are currently known in which mutations can cause monogenic CAKUT. Nevertheless, in most cases, genetic defects responsible for the abnormalities cannot be identified. There is still a lack of knowledge about how to assess different patient's aspects because the phenotypes and genotypes of patients with CAKUT are so diverse (6).

The prognosis of the patients varies considerably as in some patients the ultrasound findings return to normal after some time. On the other hand, CAKUT accounts for about 40% of causes of ESRD in childhood and adolescence. Up to now, little is known about which factors influence the outcome of children and adolescents with CAKUT (6, 7). Hence, the objective of this study is to identify the subtypes of CAKUT and risk factors of CKD in CAKUT.

Methods and materials

Study area

Tikur Anbessa Specialized Hospital (TASH) is the largest referral hospital in the country, with more than 700 beds. TASH is now the main teaching hospital for clinical and preclinical training in most disciplines. It is also an institution where specialized clinical services not available in other public or private institutions are rendered to the whole nation. The Department of Pediatrics and Child Health runs 9 subspecialty clinics, including the renal clinic. The clinic delivers outpatient follow-up services twice weekly and there are 25-30 attendees per clinic day.

Study period

This study was conducted from May 2022 up to September 2022 and records of patients who were on follow-up and treatment for the years 2021-22 were reviewed

Study design: Hospital-based retrospective cross-sectional study design was applied.

Population

Source population: The source population was all patients seen at TASH and renal clinics in the pediatric unit during the study period.

Study population: The study population was all pediatric patients diagnosed with congenital kidney and urinary tract anomalies in the study period.

Inclusion criteria: All pediatric patients up to 18 years old who had confirmed congenital anomalies of the kidney and urinary tract treated at TASH and were on follow-up during the study period for a minimum of 1 year and had complete records were included.

Exclusion criteria: All incomplete records and without definitive diagnosis were excluded.

Sample size and sampling technique

For the infinite population, taking a 95% confidence interval our "z" value will be 1.96, according to local data, CAKUT contributes to 26.8% of all kidney patients (8), making a p-value of 0.268, the margin of error 5%, and

the sample size will be 121. The sample size adjusted to account for 10% of the missing data will be 133.

Operational definition

Chronic kidney disease: is defined as an e-GFR <60 ml/mn/1.73m^2

Data collection

A structured questionnaire in the English language was prepared to collect data. All records of patients obtained from the kidney follow-up registry of patients treated for congenital kidney and urinary tract anomalies during the study period, at TASH and the renal clinic were reviewed and trained interns and residents filled out questionnaires. The first author closely supervised data collection.

Data analysis

Statistical Package for the Social Science (SPSS) version 25 was used for data analysis. A chi-square test was applied to assess the patients' demographic features. Mean values, medians, interquartile ranges (IQR), and standard deviations (SD) were calculated based on the clinical and laboratory results. Factors with a P-value less than 0.05 on univariate analysis were considered in multivariate analysis to determine the independent predictors of CKD.

Results

A total of 134 children with the diagnosis of CAKUT were included and 107 of them were males. The age of the study patients ranged from 33 days to 17 years and the mean age was 3.7 years. The majority 101/134 (75.4 %) were under five years of age and the 2 most common causes of healthcare visits were urinary symptoms and antenatal U/S abnormality in 59 (44%) and 40 (29.9%) patients respectively. The diagnosis was made with antenatal ultrasound in 50/134 (37.3%) of the patients but for 84 patients (62.7%) the diagnosis was made after birth. In 68 patients (50.7%) had at least one urological operation, 36 of which occurred in the first year of life. Fifteen patients with PUV underwent valve ablation, 14 patients vesicostomy, and 10 patients both vesicostomy and valve ablation. One patient underwent cystoscopy ablation and bilateral ureteral implantation. Two patients of PUV had not yet undergone surgical intervention during data collection. From 21 patients (15.6%) that developed CKD, 9 patients (42.9%) were stage 3 and 6 patients (28.6%) were at end-stage kidney disease. Of these CKD patients, 18 (85.7%) had a urological intervention, and 8 patients (17.4%) were under 2 years of age when surgical intervention was done (Table 1).

The most common subtypes of CAKUT were posterior urethral valve (PUV) in 42 (31.3%) of the patients, ureteropelvic junction obstruction (UPJO) in 28 (20.9%), and multicystic dysplastic kidney (MCDK) in 24 (17.9%) of the patients as shown in table 2.

The imaging modalities used for diagnosis were U/S examination, voiding cystourethrography (VCUG), intravenous pyelography, and for 2 patients diagnostic cystoscopy was done in addition to U/S examination.

Table 1: Demographic and clinical characteristics of 134 children who were diagnosed to have CAKUT, in a tertiary referral hospital, in Addis Ababa, Ethiopia

Characteristics	Number	Percent (%)
Sex		
Male	107	79.9
Female	27	20.1
Age		
<1year	35	26.1
1-5 years	66	49.3
>5-17 years	33	24.6
Time at diagnosis		
During ANC	50	37.3
After birth	80	59.7
Unknown	4	3.0
Reasons for 1st healthcare visit		
Antenatal U/S abnormality	40	29.9
Pain during urination	59	44.0
Abdominal pain	10	7.5
Abdominal pain and pain during urination	4	3.0
Other	21	15.7
Timing of proteinuria detected		
At first presentation	4	3.0
During follow up	12	9.0
No proteinuria	118	88.1
Time to CKD		
6 months to < 1 year	3	2.2
1 year to 5 years	7	5.1
After 5 years	11	8.2
No CKD	113	84.3
Stage of CKD		
Stage 2	3	2.2
Stage 3	9	6.7
Stage 4	3	2.2
Stage 5	6	4.5
Age at surgical intervention		
< 6 months	20	14.9
6-12 months	16	11.9
>12 months <24 months	13	9.7
24-36 months	9	6.7
>36 months	10	7.5
No surgery	66	49.3

Table 2: Subtypes of CAKUT and sex distribution among 134 study subjects in a tertiary referral hospital, Addis Ababa, Ethiopia

Type of CAKUT	Number (%)	Male number (%)	Female number (%)	CKD number (%)	ESKD Number (%)
PUV	42 (31.3)	42 (31.3)	-	14 (10.4)	3 (2.2)
UPJO	28 (20.9)	25 (18.7)	3 (2.2)	3 (2.2)	-
MCDK	24 (17.9)	13 (9.7)	11 (8.2)	2 (1.5)	1 (0.7)
Ectopic kidney	17 (12.7)	9 (6.7)	8 (6.0)	1 (0.7)	1 (0.7)
Horseshoe kidney	5 (3.7)	4 (3.0)	1 (0.7)	-	-
Solitary kidney	4 (3.0)	3 (2.2)	1 (0.7)	-	-
Mega ureter	2 (1.5)	2 (1.5)	-	-	-
UVJO	2 (1.5)	2 (1.5)	-	-	-
Others	10 (7.5)	7 (5.2)	3 (2.2)	1 (0.7)	1 (0.7)
Total	134 (100)	107 (79.9)	27 (20.1)	21 (15.7)	6 (4.5)

CAKUT; congenital anomaly of the kidney and urinary tract, CKD: is chronic kidney disease, EKD: end-stage kidney disease, PUV; posterior urethral valve, UPJO: ureteropelvic junction obstruction, MCDK: multicystic dysplastic kidney, UVJO: ureterovesical junction obstruction

Others: such as solitary kidney, hypoplastic kidney, renal agenesis, megaureter

On univariate regression analysis, the age of the child at first presentation (less than 6 months), antenatal ultrasound abnormality, proteinuria, and urological operation done in less than one year of age had a statistically significant association with CKD ($p<0.05$) but on multiple regression analysis only proteinuria had a statistically significant association with CKD ($p=0.004$) (table 4).

Table 3: Predictive factors of chronic kidney disease in 134 children with CAKUT in a tertiary referral hospital, Addis Ababa, Ethiopia

Predictive factors for CKD	Univariate			Multivariate		
	OR	95 % CI	P	OR	95 % CI	P
Proteinuria in follow-up	0.66	0.18-0.247	0.000	11.959	2.160-66.218	0.004
Urological operation	7.56	2.107-27.12	0.002	30.470	0.754-1231.734	0.070
Age of operation when <6 months	21.0	3.85-114.549	0.000	0.054	0.001-3.522	0.171
Age of operation >6 mo & <1yr.	9.00	1.325-61.138	0.025	0.041	0.001-2.309	0.120
Antenatal U/S abnormality	0.234	0.65-0.840	0.026	0.178	0.023-1.394	0.10
Age of the child at 1st presentation when <6 months	0.164	0.044-0.610	0.007	11.917	0.379-375.130	0.159

Discussion

In our study, a total of 134 CAKUT patients were included. From this male predominance of 107 (79.9%) was evident with an approximate male-to-female ratio of 3.96:1. In a study done in Egypt with a cohort of 107 patients, the male-to-female ratio was 2.3:1 as reported by Soliman et.al (14). In a study done in Pakistan, in children from birth up to 18 years and out of their 140 cohorts, the male-to-female ratio was 3:1 (15). In another study done in India by Kuma Ravel et.al, out of their 81 cohorts, 70 (86%) were males (16). In a report from Turkey by Cetin Kaya et al., out of their 300 patients with CAKUT, the male-to-female ratio was 203/97 (17). In all the reported studies including ours, the male predominance is partially attributed to PUV predominance.

Our study's median age at presentation was 3.7 years but ranges between 33 days to 17 years and 75.4% were under five years of age. In a report from Turkey, the age at diagnosis ranged between 4 months to 13 years, most of which were under five years (17). In another Indian study by Radhakrishna V et.al, out of their patients, 41% presented between 1-5 years and the oldest was 12 years old (18). In our study, the oldest age at presentation was 17, indicating late presentation at diagnosis. In a study done on 160 Iraqi children with CAKUT, 48.8% of children were diagnosed under five years of age (19) but in a similar study in South Africa by N C Okoronkwo (20), the median age of presentation was 8.4 years and the age ranged between 2 weeks to 18 years. This is similar to our study.

The major cause of health facility visits in our patients 63/134 (47.0%) was symptoms of UTI, 29.9% presented with an antenatal US abnormality. In a study done in Iraq, 58.1% presented with symptoms of UTI, 48.1% presented with fever, and 25.6% with abdominal pain (19). The main cause of presentation to a health institution in many studies is also symptoms of UTI (19-23). In all children with symptoms of UTI, US examination is done for screening and the diagnosis of CAKUT is made unless an ante-natal diagnosis is made by US scanning.

In our study, the most common CAKUT subgroup was PUV in 42/134 (31.3 %), UPJO in 28/138 (20.9%), and MCDK in 24/134 (17.9%) respectively. This is similar to a study done in Ethiopia by Kebede et.al (8) and in Egypt (15) and also in South Africa (20). In other studies, by Sriram et.al in India, the prevalence of UPJO was (20.1%) and MCDK (16.6%) as the second and third most common respectively preceded by primary vesicoureteral reflux (17). Compared to a study by Kumaravel in India, the most common CAKUT subgroup was UPJO (40%) (18). Geographic differences and genetic predisposition might play a role in the formation of CAKUT.

Abdominal ultrasound was the most common imaging modality used for diagnosis in our patients followed by VCUG in 39.5 % of cases. In many of the studies US examination is the

preferred initial imaging modality either during ANC or the first urinary tract infection (17-23).

In this study 50/134 patients (37.3%) diagnoses was made during ANC which is lower than compared to a study done in India when 80.4% were diagnosed during ANC as reported by Sriram (17), while in Iraq ANC diagnosis was made in only 13/160 (9.4%) of cases (19).

In our study, all patients do not have a family history of similar illness and only one patient had a consanguineous marriage which is much lower than studies reported in Egypt (15) and Iraq (20). This could be because of religious reasons as Christianity does not allow consanguineous marriage in Ethiopia and the majority of the study population are Christians.

In 68 patients (50.7%) had urological operations; cystoscopy ablation being the most common procedure done in 26 patients (19.4%). This is slightly higher than studies done in Turkey as reported by Renda (14.5 %) and another report by Cetinkaya (21.3%) respectively (17, 23). This is because PUV is the most common urological abnormality in our patients and the treatment modality is cystoscopic ablation.

Proteinuria on follow-up, urological operation, age of operation when age less than 1-year-old, antenatal ultrasound abnormality, and age of the child at first presentation when less than 6 months showed statistically significant association in univariate logistic regression analysis to develop CKD, but in multiple regression analysis, only proteinuria was found statistically significant predictor of CKD (p=0.004 (2.160-66.218). This is also consistent with a study in Turkey in 2020 as reported by Cetinkaya (17). In our study diagnosis of PUV and oligohydramnios were not statistically significant associations in multivariate analysis. as compared to the survey reported by Cetinkaya (17). Different studies have compared different parameters to predict the progression to CKD and have come up with different results (14,16,17,19). This could be because of the objectives and methodology differences in these studies as well as geographic differences.

Among the study participants, 21 patients had progressed to CKD in our study (16.15%) which is higher than studies done in Turkey as reported by Renda (7.5 % of patients developed CKD) (23) and Cetinkaya (8% of patients developed CKD) (17). Of those 21 patients who developed CKD, 6 patients had progressed to end-stage renal disease. This could be because of late diagnosis and recurrent urinary tract infections in our patients before diagnosis.

Of 16 patients who had proteinuria, 11 patients progressed to CKD (68.75%). Proteinuria is considered an important predictor of CKD in CAKUT. Proteinuria has also been shown as an unfavorable factor in renal survival in patients with CAKUT. In agreement with existing literature data, we demonstrated that proteinuria on the follow-up was an independent predictor for CKD, and therefore should be

Conclusion

The current study gives a general perspective in children with the diagnosis of CAKUT who applied to a tertiary clinical center in Ethiopia. Proteinuria on follow-up was found to be an independent predictor of CKD on multivariate logistic regression analysis. Surgical intervention did not prevent the development of CKD in this study. Future studies with large sample sizes and prospective studies should be done to better delineate associations and to act accordingly.

Limitations of the study: as this is a retrospective chart review, documentation might be incomplete and some variables like time of the surgical intervention have been missed.

Declarations

Data availability

The datasets used or analyzed for the current study are available upon reasonable request.

Conflict of interest

The authors declare that there is no conflict of interest.

Authors contribution

MA: proposal development, data collection, and analysis and write-up, DS: proposal development and proposal review, final write-up, HL proposal review, data analysis, BA: proposal review, AM: proposal review and review of the final write-up

Acknowledgment

We want to acknowledge the Department of Pediatrics and Child Health for allowing us to do the study.

Ethical clearance

The research was conducted after obtaining approval from the ethical review board of the Department of Pediatrics and Child Health, Addis Ababa University. Patient consent was not needed as this is a retrospective study but patient information confidentiality was maintained.

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Original article

Parental knowledge, attitudes and practices regarding safe handling and disposal of alcohol-based hand sanitizers and surface disinfectants in urban Sri Lanka

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Abstract

Introduction: *Hand sanitizers were increasingly used in most households during the COVID-19 pandemic. This study aimed to assess knowledge and practices regarding the safe handling and disposal of alcohol-based hand sanitizers and surface disinfectants in urban Sri Lanka.*

Methods: *A cross-sectional study was performed including parents of children admitted to North Colombo Teaching Hospital for a period of one year in August 2021. Data were collected regarding parental knowledge about the safe handling and disposal of hand sanitizers, and their health hazards by paediatric post-graduate trainees. All data were analyzed using SPSS 17.0. Chi-square test was used to find the association of overall knowledge and attitude scores with potential socio-demographic determining factors.*

Results*: A total of 153 parents were recruited. The majority of mothers (126, 82.4%) and fathers (133, 86.9%) had attended up to secondary school. Approximately 113(73.9%) parents believed that pre-school children were the most vulnerable for accidental ingestion of sanitizers and 40 parents (26.1%) did not believe that sanitizer solutions can be accidentally inhaled by toddlers. Only 132 parents (86.2%) knew how to disinfect their home premises safely and 29 parents (18.9%) didn't know how to store cleaning products safely. Overall, lower knowledge scores correlated with lower maternal education ($p<0.05$) and lower socio-economic status ($p<0.05$). The gender ($p = 0.06$) and age of the parent (>35 years versus <35 years) ($p = 0.21$) did not show a significant association. Attitude scores positively correlated with parental education ($p<0.002$) and socio-economic status ($p<0.03$). The gender ($p = 0.12$) and age of the parent (>35 years versus <35 years) ($p = 0.07$) did not show a significant association.*

Keywords*: safe handling; sanitizers; surface disinfectants; parental knowledge attitude and practice*

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Conclusion :*Overall knowledge and attitude scores in parents were associated with education level of parents and the level of socio-economic status. Gender and parental age did not show a significant association.*

Introduction

Hand sanitizers were increasingly being used by many people during the COVID-19 pandemic [1]. The sanitizers are effective products that reduce microorganisms on the skin surfaces, but ingestion or improper handling can be associated with increased health risks. Hand sanitizers are classified as over the counter drugs by the U.S. Food and Drug Administration (FDA) [2]. Most of the hand rubs contain about 60%-95% ethanol or isopropyl alcohol by volume, and are frequently combined with fragrances that can be attractive to young children [3]. Some hand sanitizers contain variable amounts of methanol which can be significantly toxic if ingested either accidentally or deliberately by children and young people [4]. Unsafe storage and use of sanitizers are increasingly associated with local and systemic effects on children and can rarely lead to severe complications including death. Therefore, caregivers need to be aware of the potential risks and dangers associated with improper use of hand sanitizer products among children.

Previous studies that have assessed the safe use and storage of hand sanitizers and participants' knowledge, attitudes, and practices during the COVID-19 Pandemic reported that knowledge scores were high among participants who reported that they knew how to clean and disinfect their homes safely, were able to clean and disinfect safely, and were able to store cleaning products safely than among those who did not agree with these statements [5]. Similarly, respondents who agreed that they knew where to get information on safe cleaning behaviours had higher knowledge scores than those who did not agree. Respondents who agreed that misuse of household cleaners and disinfectants can result in injury had higher scores than those who did not agree [5].

Another study that evaluated the use of hand sanitizers and access to children reported that alcohol-based hand sanitizer (ABHS) exposure was most common whilst isopropanol ABHS exposure was minimal. Primarily exposed route was through ingestion, followed by ocular contamination. These children needed medical advices and OPD (out-patient department) treatments as well as some hospital admissions. Unintentional exposures accounted for highest number of the cases [6].

While it is important to use hand sanitizers to prevent cross-infections, the safety should be taken into consideration as this may be hazardous in children. Studies have shown that the increase use, misuse and unsupervised availability of alcohol-based hand sanitizers during the Covid 19 pandemic resulted in adverse events in children such as skin irritation, dryness, cracking and peeling [7].

Unintentional or intentional ingestion of hand sanitizers in children under the age of 12 years may occur because of the colour, smell and flavour added to it [3]. Consumption of alcohol in children may result in hypoglycaemia, apnoea and acidosis [3]. This allows the invasion of other bacterial and viral infections. Children may also rub their eyes with sanitized hands and cause ocular injury [3]. Children can be exposed to sanitizers and subsequently poisoned in communities where the parents are not practicing safety measures and precautions whilst handling, storing and disposing sanitizers. However, knowledge, attitudes, and practices are shown to be highly variable in different populations and there were no studies performed in Sri Lanka on this aspect of children's safety.

Objectives

To assess parents' knowledge, attitudes, and practices on use of sanitizers and access of these sanitizers to children. and potential hazards of using alcohol-based hand sanitizers and surface disinfectants

Methods

This observational cross- sectional hospital-based study was conducted recruiting parents of children admitted to North Colombo Teaching Hospital, Sri Lanka. North Colombo teaching hospital functions as main and the only tertiary care center for Gampaha district and receives a population of varied ethnicities and socio-cultural backgrounds. All parents of children admitted to North Colombo teaching hospital were selected as the study population. The study was conducted within ward settings once children were admitted for acute medical conditions. Parents were recruited prospectively to the study over a period of one year from 01/08/2021 to 01/08/2022.

All parents of children who were between the ages of 18 months and 12 years and considered as at risk for accidental and deliberate self-ingestions of sanitizers were recruited to the study. Parents of children suspected or confirmed COVID 19 infection were excluded due to difficulties in direct interviewing of parents. North Colombo Teaching Hospital serves a population of approximately 100,000. Sample size of 150 was calculated using "Qualtrics" sample size calculator available at https://www.qualtrics.com/blog/calculating-sample-size/ (margin of error - 0.08 and significance- $p<0.05$). Participants were selected by simple random sampling.

An interviewer administered questionnaire was used for collection of data. Part 1 of the structured questionnaire contained demographic data (age and gender of parents, parental education levels and socio-economic status of the family). Socio-economic status was defined for the study based on monthly household income – low (less than 300 USD, medium (300-500 USD) and high (over 500 USD). Knowledge was assessed in a 27-item questionnaire and a score was calculated out of the correct responses provided for each of

the 27 questions. A cumulative score of less than 50 percent for the knowledge domain was considered as a poor knowledge score. The attitudes were assessed with an 18-item questionnaire. A similar score was calculated out of the correct responses provided for each of the 18 questions. The practices were assessed using a 7-item questionnaire. Questions were asked in participant parents' native language. The questionnaire was subjected to psychometric analysis and pretesting prior to the study. Administrative approval was obtained prior to collection of data from the Director, North Colombo teaching hospital. Ethical clearance for the study was granted by the ethical review committee, Sri Lanka College of Paediatricians.

All data were collected by post-graduate medical trainees and medical graduates trained for data collection by the investigators of the study. Data were analysed using SPSS 17.0. The respective descriptive data were compared with demographic variables and parental practices in use, and disposal of hand sanitizers.

Chi-square test was applied to find the association of overall knowledge and attitude scores with potential determining factors such as socio-economic status (low socio-economic status versus medium/high socio-economic status), age (> 35 years versus < 35 years) and gender of the parents and the educational background of parents (secondary or equivalent above education versus below secondary education level).

Results

One hundred and fifty-three attendant parents were recruited to the study. The majority of mothers (126, 82.4%) and fathers (133, 86.9%) had received education at least up to secondary school. 124 parents (81%) had been using hand sanitizers at home regularly. Most mothers were housewives (113, 73.8%) whilst the majority of fathers were semi-skilled workers (drivers, salesmen, farmers, security and defence workers, and clerks) (74, 48.4%). Socio-economic status as assessed based on the monthly household income was low in the majority of participants (88, 57.5%) as compared to medium (51, 33.3%) and high (14, 9.2%) socio-economic status.

Assessment of knowledge

Only 113(73.9%) parents believed that preschool children were the most vulnerable for accidental ingestion of sanitizers and 40 parents (26.1%) did not believe that sanitizer solutions can be accidentally inhaled by toddlers. Knowledge was poor regarding occurrence of potential symptoms and side effects of sanitizer poisoning such as sore throat (56, 36.6%), irritation of eyes (30, 19.6%), breathing difficulties (40, 26.1%), high heart rate (72, 47%), aspiration (43, 28.1%) and low blood sugar (108, 70.5%) (Table 1). Only 132 parents (86.2%) knew how to clean and disinfect their home premises safely whilst 29 parents (18.9%) didn't know how to store cleaning products safely. Sixty-four parents (41.8%) were unaware regarding how to get

information on safe cleaning practices. In the majority of parents, the main source of education regarding sanitizer safety was social media (134, 87.5%).

Table 1: Pattern of inaccurate knowledge regarding possible symptoms of sanitizer poisoning

Clinical manifestation/complication	Number (%) with inaccurate response
Drowsiness	17 (11.1%)
Loss of consciousness	32 (20.9%)
Vomiting	8 (5.2%)
Sore throat	56 (36.6%)
Irritation to eyes	30 (19.6%)
Haematemesis	92 (60.1%)
Malena	103 (67.3%)
Breathing difficulties	40 (26.1%)
High heart rate	72 (47%)
Aspiration to lungs	43(28.1%)
Low blood sugar	108 (70.5%)
Loss of balance	68 (44.4%)

Mean knowledge score was 14.1 (range – 7-23). Overall, lower knowledge scores correlated with lower maternal education (Pearson chi-square - 9.48, p=0.004) and lower socio-economic status (Pearson chi-square - 4.58, p=0.045). The gender (Pearson chi-square - 3.12, p = 0.06) and age of the parent (>35 years versus <35 years) (Pearson chi-square - 0.71, p = 0.21) did not show a significant association.

Assessment of sanitizer handling related practices

Forty-two parents (27.4%) kept sanitizer bottles within easy access to children whilst 85 parents (55.5%) had been storing sanitizers in unlabelled bottles. Ninety-eight parents (64%) were not keen to read the signage alerts in sanitizer storage bottles. Only 25 parents (16.3%) safely disposed sanitizer bottles. Thirty-three parents (21.6%) put sanitizer bottles together with food items in carriage bags from supermarkets.

Seventy-eight (51%) had been used to buy sanitizers with no description about the containing chemicals. Only 41 parents (26.8%) attempted to find out what chemicals were contained in hand sanitizers they used whilst only 119 parents (77.8%) took measures to keep sanitizer bottles out of reach to their children. Thirty parents (19.6%) said that they will make their own sanitizers at home whilst 49 parents (32%) said they would dispose sanitizer bottles to kitchen waste bin as a means of reducing access of sanitizer bottles to children at home. Parental practices regarding use and storage of hand sanitizers are illustrated in Table 2

Table 2. Parental practices regarding use and storage of hand sanitizers

Item relevant to assessment of practices related to use and disposal of sanitizers	Number (%)
I do not label the sanitizer bottle if I store them in an unlabelled bottle	85 (55.5%)
I do not read signage alerts of the hand sanitizer bottle label whenever I use	98 (64.0%)
I regularly re-fill the hand sanitizer bottles	34 (22.2%)
I store sanitizer bottles together with food items	33 (21.6%)
I dispose sanitizer bottles to kitchen waste bin	49 (32.0%)

Assessment of attitudes related to use of sanitizers

Sixty-three parents (41.1%) believed that soap and water are not a good substitute for sanitizer solution. Fifteen parents said that they will not take any action if their child ingests sanitizers accidentally as they are harmless. Parental attitudes regarding use and storage of hand sanitizers are illustrated in Table 3.

Table 3. Parental attitudes regarding use and storage of hand sanitizers

Item relevant to assessment of attitudes related to use of sanitizers	Number (%)
I do not care about chemicals that are contained within hand sanitizers at time of purchase	108 (70.6%)
I buy hand sanitizers with no clear description about its containing chemicals	75 (49.0%)
I do not attempt to keep the sanitizer bottle out of reach of young children?	34 (22.2%)
Soap and water are not a good substitute for hand sanitizers	63 (41.1%)

Parents also admitted that they will practice home remedies if their child is to ingest hand sanitizers and they included: insertion of finger in mouth (48,31.4%), induce vomiting by soap water (9,5.9%), cow's milk (7,4.6%), coconut milk (23,15%), and water (36,23.5%) (Table 4).

Table 4. Parental attitudes regarding harmful first-aid practices for induction of emesis following potential sanitizer ingestion

Method of emesis induction	Number (%)
Insertion of fingers	48 (31.4%)
Forceful administration of coconut milk	23 (15.0%)
Forceful administration of water	36 (23.5%)
Forceful administration of cow's milk	07 (4.6%)
Forceful administration of soap water	09 (5.9%)

A number of parents believed that following measures would prevent accidental ingestions of sanitizers at home premises (Table 5).

Table 5. Parental opinion regarding preventive measures for potential sanitizer ingestion

Method of prevention	Number (%)
Making them taste bad	105 (68.6%)
Introducing screw capped lids	132 (86.3%)
Safe storage	143 (93.5%)
Using sanitizers only when soap is not available	103 (67.3%)

Mean attitude score was 9.3 (range: 6-16). Attitude scores positively correlated with parental education (p=0.002) and socio-economic status (p=0.03). The gender (p = 0.12) and age of the parent (>35 years versus <35 years) (p = 0.07) did not show a significant association.

Discussion

Hand sanitizers are increasingly being used both in healthcare and household settings following the COVID-19 pandemic and concurrently with this practice worldwide, there were a number of reports of poisoning with hand sanitizer solutions [8,9,10]. In order to plan preventative measures for poisoning with hand sanitizers, specially by children, it is important that actions are taken to improve existing knowledge, attitudes and practices with regard to safe use and disposal of hand sanitizers by the general public.

The current study noted gaps in knowledge among the parents regarding possible clinical manifestations and complications of sanitizer poisoning and safe use of hand sanitizers. Further, the study noted that gender was not a determining factor for overall knowledge scores. Similar observations were made in a study performed in Ethiopia [11]. Although there are a number of studies performed to assess knowledge, attitude and practices of use and disposal of hand sanitizers amongst health care workers and students, similar studies on general public are limited [12,13]. These studies have shown that both age and gender were not determining factors for overall knowledge or attitude scores. Interestingly, our study showed that knowledge scores negatively correlated with lower maternal education and lower socio-economic status.

Availability of reliable information sources are vital in informing the public about potential hazards of a toxic agent. Importantly, they should be available in native languages for easy access. Previous research has shown that videos published on social media can potentially give false information to the public. According to a study, most videos published on social media platforms failed to describe labelling storage containers, whilst others encouraged use of oils, perfumes and colouring agents to be more attractive for use among children specifically [14]. The current study observed that majority of parents had acquired knowledge on use of hand sanitizers from social media platforms highlighting the need for improved awareness regarding reliable and valid information sources. Practices with regard to unsafe storage of hand sanitizers seen in the current study were similar to studies conducted in developed

countries[5]. These studies have highlighted the importance of tailored communication strategies specially for those with poor understanding of safety.

The current study revealed several unhealthy practices and attitudes among parents regarding safe use and disposal of hand sanitizers. Over 40% of respondents believed that soap and water are not a good substitute for hand sanitizer and a notable proportion was having a higher threshold for action following a potential sanitizer ingestion. There was a high prevalence of unhealthy parental attitudes regarding harmful first-aid practices for induction of emesis following a potential sanitizer ingestion. It is therefore, important that the public is provided with accurate information in their native languages regarding potential harmful effects of these first aid measures and safety information of hand sanitizers. Promotion hand washing and increase of hand washing facilities important for preventing inadvertent harmful effects of hand sanitizers [15].

In the light of observations made in current study, the use of hand sanitizers in general needs to be revised in both children and adults. Other interventions on lowering the risk of adverse events because of misuse of hand sanitizer need to be encouraged more often. These include promoting washing of hands over sanitizers where possible, training children on how to use hand sanitizers and creating awareness of the dangers if ingested or in contact with the eyes.

Conclusion

The findings of this study inform that knowledge in parents regarding safe use of sanitizers can further be improved specially, in areas of local and systemic effects of sanitizer poisoning and information resources of safe cleaning practices. As a number of parents used and disposed hand sanitizers unsafely, the effectiveness of awareness programs to improve safety practices among parents should be evaluated. Overall knowledge and attitude scores in parents were correlated with education level of parents and the level of socio-economic status.

Declarations

Authors' contribution

KD designed the study, performed literature survey, analysed data and wrote manuscript. HP collected data and wrote manuscript. EKND collected data and wrote manuscript. VT collected data and wrote manuscript. SJSD collected data and wrote manuscript. All authors approved the final version of the manuscript.

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Conflict of interest

All authors declare that there are no conflicts of interest.

Ethical approval

Ethical approval for the study was granted by the Ethical Review Committee of Sri Lanka College of Paediatricians.

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Case Report

Bladder plexiform neurofibroma in a 4-year-old male child with neurofibromatosis type 1: A case report

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Abstract

Bladder plexiform neurofibroma (PN) is a rare disease entity that is challenging to treat. We report a 4 year old male child who had presented with a suprapubic abdominal swelling and irritative voiding symptoms of one year duration. The child had a palpable suprapubic mass, multiple café au lait macules over his body. The father had similar skin lesions. Imaging revealed diffuse asymmetric thickening of the bladder wall. The diagnosis was confirmed by immunohistochemistry. Selumetinib was offered as a treatment option.

Key words: Bladder, plexiform, neurofibroma, child, Ethiopia

Introduction

Neurofibromatosis type 1 (NF-1) is a well-characterized autosomal dominant genetic disorder presenting with a diverse range of clinical manifestations. It affects roughly 1 in 2,600 to 1 in 3,000 individuals [1]. Plexiform neurofibromas are benign peripheral –nerve sheath tumors that occurs in up to 57 % of NF-1 pediatric cases [2]. Genitourinary involvement in NF1 is rare, with less than 80 cases reported in literature to date [1]. We report a 4 years old male child diagnosed to have a bladder plexiform neurofibroma, at the largest tertiary hospital in Ethiopia Tikur Anbessa Specialized Hospital (TASH). TASH receives referrals from government and private medical institutions, nationwide.

Case presentation

A 4-year-old male child presented with progressively increasing lower abdominal swelling, frequency, hesitancy, dysuria and hematuria of one year duration. The child had these voiding symptoms a few weeks prior to the abdominal swelling. The abdominal swelling started to rapidly increase in size one month prior to presentation at the institution. The child has

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no symptoms of urinary retention or previous catheterization.

The examination revealed a well-nourished and comfortable child with stable vital signs. He had a 4x4 cm suprapubic firm, non- tender palpable mass, multiple café au lait macules (CALMs) most greater than 5mm, particularly on his trunk, and a huge hyperpigmented patch on his right buttock (Figure 1, Supporting file). His father had CALMs as well. Complete blood count and urine analysis were non-revealing.

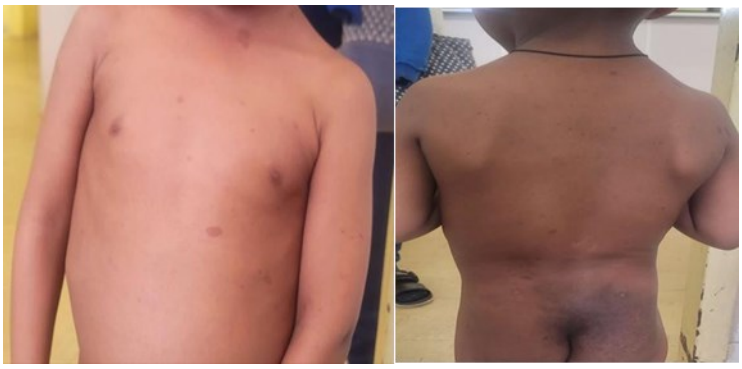

Figure 1: The presence of CALMs on the trunk.

The CT imaging demonstrated contrast enhancing diffuse asymmetric circumferential thickening of the urinary bladder wall measuring 2.2cm with evidence of mild bilateral pelvicalyceal dilatation. The renal parenchyma has normal thickness with symmetric contrast enhancement and excretion. The lumbosacral vertebral bones have normal CT findings (Figure 2 and 3, supporting files).

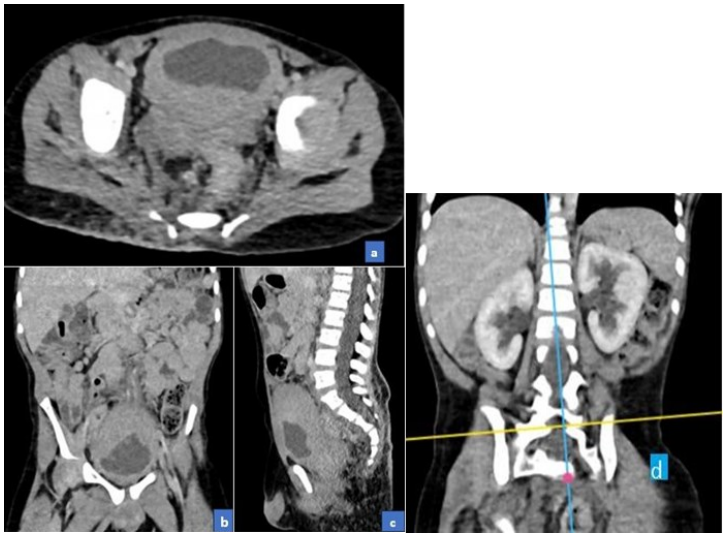

Figure 2: Post contrast abdominal-pelvic CT in axial (a), coronal (b) and sagittal (c) sections depicting homogenous diffuse asymmetric circumferential urinary bladder wall thickening. (d)Post contrast CT scan with coronal 3D MPR image depicting mild bilateral hydronephrosis

Gross specimen: one core needle fragment, 0.4x0.3cm.

Microscopic examination: small tissue composed of cellular nodules of myxoid degeneration and wavy spindle cells interspersed between skeletal muscle fragments forming a plexiform like architecture (Figure 3a and 3b, Supporting file).

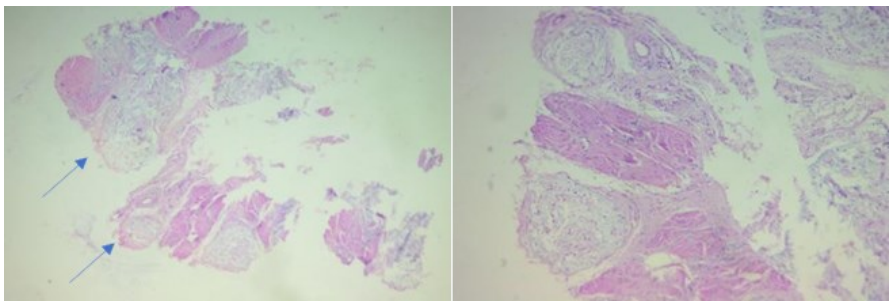

Figure 3a: Low Power (4x objective magnification) of submitted tissue showing plexiform like architecture (Arrow) B. 10x objective showing the schwann cells and myxoid stromal background.

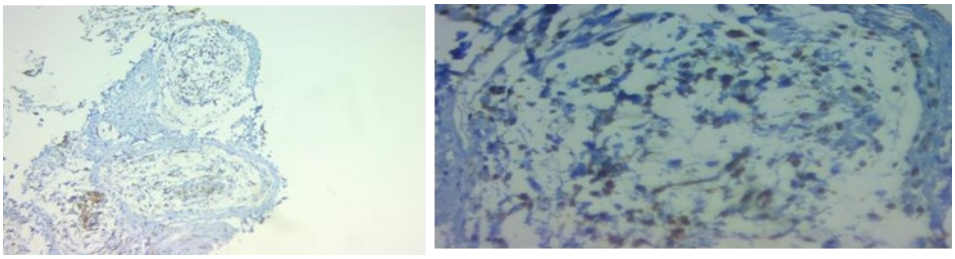

Figure 3b: S-100 stain showing cytoplasmic and nuclear staining in the schwann cells (10x objective) and B. 40x objective showing similar staining

Discussion

The presence of a bladder plexiform neurofibroma (BPN), CALMs in the child and the father fulfills the diagnosis of NF-1 [4]. Histology and immunohistochemistry have verified the diagnosis. Bladder involvement in NF1 is very rare and mostly affects the age group of 7 to 28 years with a ratio of 3:1 male predominance. It often arises from the nervous ganglia of the bladder wall, especially the vesicoprostatic plexus [9]. The clinical features of BPN include irritative voiding symptoms and hematuria due to recurrent urinary tract infections [5]. On imaging, BPN can manifest as a focal mass or as diffuse bladder wall thickening [3]. There is no definitive criteria for BPN. In contrast to our case, BPF without stigmata of NF-1 may be the initial presentation of NF – 1 [3,9]. The incidence of neurofibroma undergoing malignant transformation is 30% [10]. Bladder neurofibromatosis is almost always a benign process and malignancy has been reported in 5%–10% of the literature [9]. Radical cystectomy with urinary diversion is indicated for urinary obstruction with hydronephrosis or malignant transformation [5].

The diffuse and asymmetric nature of the bladder wall thickening makes our case inoperable. He was offered selumetinib, a MEK inhibitor. It works by inhibiting the molecule MEK, which plays a role in the Ras downstream signaling pathway and thus affects the cell proliferation in NF1-associated tumors. Gross et al reported 34 (68%) of 50 children with inoperable PNF had size reduction and improved symptoms. [8]. The child has not been started on treatment for financial reasons. Currently, he is on follow-up at the pediatric hematology/ oncology clinic. In conclusion, bladder PN should be suspected in the setting of irritative voiding symptoms, hematuria and bladder wall thickening, in the presence of NF-1. Inoperable BPN can benefit from selumetinib.

Declaration

Consent for publication

Verbal consent was obtained from the mother of the child and the mother also approved the publication of anonymized photo of the child. All personal data of the child were anonymized.

Conflict of interest

None to declare

Authors contribution

HA conceived the idea, compiled the child's history, physical findings, photo of the skin lesions and lab reports. AD involved in framing the idea, provided the pathology images and did the reporting. SS examined the imaging results did the radiology report. All authors involved in the write up of the manuscript, read the manuscript and approved the submission of manuscript.

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Guidelines for Authors

The Ethiopian Journal of Pediatrics and Child Health (EJPCH) is the official Journal of the Ethiopian Pediatrics Society (EPS) and devoted to the advancement and dissemination of knowledge pertaining to the broad field of medicine in Ethiopia and other developing countries. Prospective contributors to the Journal should take note of the instructions of Manuscript preparation and submission to EJPCH, as outlined below.

Article Types accepted by EJPCH

- Original Articles (vide infra) on experimental and observational studies with clinical relevance.
- Brief Communications
- Case Series
- Case Reports
- Systematic Review
- Teaching Articles
- Editorial
- Correspondences/Letters to the Editor
- Monographs or set of articles on specific themes appearing in Special Issues of the Journal

N.B. Articles are acceptable only if NOT previously published or submitted elsewhere in print or electronic format, except in form of abstracts in proceedings of conferences.

Content and format of articles:

1. **Original Art**

- 2500 words, excluding Abstracts, References, Figures and Tables. The manuscript of the Article, should appear under the following headings:
  - **A) Abstract** (vide infra)
  - **B) Introduction:** should provide necessary information and Background of the topic. It should not be a review of the subject
  - **C) Patients or (Materials) and Methods**: should contain details to enable reproducibility of the study by others. This section must include a clear statement specifying that a free and informed consent of the subjects or their legal guardians was obtained and that the study was approved by relevant institutional and/ or national ethics review board. For manuscripts on clinical trials, a copy of an ethical approval letter from the concerned body should be submitted with the manuscript. Photos of patient s should be disguised or have a written consent.

D) Results: should present the experimental or observational data in text, tables or figures. The data in Tables and Figures should not be described extensively in the text.

E) Discussion: The first paragraph should provide a summary of key finding that will then be discussed one by one in the paragraphs to follow. The discussion should focus on the interpretation and significance of the Results of the study with comments that compare and describe their relation to the work of others (with references) to the topic. Do not repeat information of Results section in this section.

- **Abstract**: The Abstracts of an Article is prepared on a separate page and contain 250 words; it should be structured under the titles: a) Background; b) Methods; c) Results; d) Conclusions. Briefly summarize the essential features of the article under above headings, respectively. Mention the problem being addressed in the study; how the study was conducted; the results and what the author(s) concluded from the results. Statistical method used may appear under the Methods paragraph of the Abstract, but do not insert abbreviations or References in the Abstract section.
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  - Type the references on a separate sheet, double spaced and keyed to the text.
  - Personal communications should be placed NOT in the list of references but in the text in parentheses, giving name, date and place where the information was gathered or the work carried out(e.g. personal communication, Alasebu Berhanu, MD, 1984, Gondar college of Medical Sciences). Unpublished data should also be referred to in the text.
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- Gilbert C, Foster A. Childhood blindness in the context of Vision 2020: the right to sight. Bull World Health Org 2001; 79:227-32
- Teklu B. Disease patterns amongst civil servants in Addis Ababa: an analysis of outpatient visits to a Bank employees' clinic. Ethiop. Med J 1980; 18:1-6
- Tsega E, Mengesha B, Nordenfelt E, Hansen B-G; lindberg J. Serological survey of human immunodeficiency virus infection in Ethiopia. Ethiop Med J 1988; 26(4):179-84
- Laird M, Deen M, Brooks S, et al. Telemedicine diagnosis of Diabetic Retinopathy and Glaucoma by direct ophthalmoscopy (Abstract). Invest Ophthalmol Vis Sci.1996; 37:104-5

Books and chapters from books:

- Henderson JW. Orbital Tumors, 3rd ed. Raven Press New York, 1994
- Clipard JP. Dry Eye disorders. In Albert DM, Jakobiec FA (Eds). Principles and Practice of Ophthalmology. Philadelphia: W.B Saunders: 1994. pp. 257-76

Website:

David K Lynch; laser History: Masers and lasers.

http://home.achilles.net/-jtalbot/history/massers.htmAccessed 19/04/2001

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- Tables and Figures up to five.
- References (Vide supra- Original Article)

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- Abstracts of up to 200 words; unstructured; (vide supra)
- Statistical statements here are expressed as 5/8 (62.5%)
- Tables and Figures: no more than three
- References: maximum of 20

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Report on a rare case or uncommon manifestation of a disease of academic or practical significance.

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- Tables and Figures up to 8

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- All pages should be numbered consecutively in the following order: Title page; abstract and keywords page; main manuscript text pages; reference pages; acknowledgement page; Figure-legends and Tables.
- The Metric system of weights and measures must be used; temperature is indicated in degrees Centigrade.
- Generic names should be used for drugs, followed by propriety brand name; the manufacturer name in parenthesis, e.g. diazepam (Valium, Roche UK).
- Statistical estimates e.g. mean, median proportions and percentages should be given to one decimal place; standard deviations, odds ratios or relative risks and confidence intervals to two decimal places.
- Acronyms/Abbreviations should be used sparingly and must be given in full, at all first mention in the text and at the head of Tables/ foot of Figure, if used in tables/ figures. Eg. Blood Urea Nitrogen (BUN). Intestinal Lung Disease (ILD).
- Use the binomial nomenclature, reference to a bacterium must be given in full and underlined-underlining in typescript becomes italics in print (e.g. Haemophilus influenzae), and later reference may show capitalized initial for the genus (e.g. H. influenzae).
- In the text of an article, the first reference to any medical phrase must be given in full, with the initials following in parentheses, e.g. blood urea nitrogen (BUN); in later references, the initials may be used.
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