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ISSN 2309-5393 (online)

ISSN 1013-9923 (print)

Indexed in EMBASE/Excerpta Medica,
Science Citation Index Expanded (SCIE) and
Scopus Full text online at www.hkjpaed.org



Hong Kong Journal of Paediatrics

香港兒科醫學雜誌 (New Series)

An Official Publication of
Hong Kong College of Paediatricians &
Hong Kong Paediatric Society
c/o Hong Kong College of Paediatricians, Room 801,
Hong Kong Academy of Medicine Jockey Club Building,
99 Wong Chuk Hang Road, Aberdeen, Hong Kong.

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Hong Kong Journal of Paediatrics is published by
Medcom Ltd, Flat E8, 10/F, Ka Ming Court,
688-690 Castle Peak Road, Kowloon, Hong Kong
SAR. Tel: (852) 2578 3833,
Email: mcl@medcom.com.hk

Indexed in EMBASE/Excerpta Medica, Science
Citation Index Expanded (SCIE) and Scopus

Website: www.hkpaed.org

ISSN 2309-5393 (online)

ISSN 1013-9923 (print)

Editorial

From Promoting Breast Feeding Practice to Diagnosis and Management of Rapunzel Syndrome, Exchanging Ideas Through a Peer-review Platform

In this issue, we have a good mixture of original articles covering a wide spectrum of paediatric medical, surgical and also child health related studies. That is in line with our mission to promote child health and general paediatric knowledge. We hope that no matter our readers are general paediatricians or subspecialists, they should find our contents useful in their daily clinical practice.

For paediatricians, most if not all of us agree that breast feeding is beneficial and should be the first choice for the baby. But how to promote and implement this practice is another issue, especially when the baby is a premature baby. Providing proper training and education to the nursing mother is essential. The study of Korğalı et al supports this view and it showed that with proper training and support, to either mother alone or the whole family, could lead to a more sustained period of breast feeding and better parent-infant interaction. While it appears that it is a simple logic but when we look at the training program stated in this report, it is comprehensive and requiring a strong commitment from both the paediatricians and the nursing staff involved. The same doctor and nurse actually have to conduct multiple home visits (at 1 week, 1, 2, 4 months after discharge) and spent 2 hours each time for the education. I wonder whether such intensive effort can be sustained after the study is concluded. The other alternative is to train a breast-feeding educational team with hot line that can facilitate consultation and follow-up. No single method is perfect, but the key is that it should be a continuous process with feasible accessibility for advice.

In recent years, the term "acute renal injury" (AKI) has replaced "acute renal failure" to describe the impairment of renal function due to short term adverse events. One of such adversities is caused by severe infection leading to the admission to ICU. Multi-organs dysfunction is predictive of fatality in the ICU setting and whether the severity of acute renal injury can also provide some insight on the mortality prediction has been assessed by 3 critical illness scoring systems. The severity of AKI was defined by the Kidney Disease Improving Global Outcomes (KDIGO) guidelines based on the serum creatinine level and urine output. It was shown that Pediatric Critical Illness Score (PCIS) was better in predicting the mortality risk of paediatric patients with early-stage AKI, whereas Pediatric Risk of Mortality III (PRISM III) was better for paediatric patients with more advanced stage AKI. The result suggested that using multiple assessment tools may be more

accurate in predicting the outcome of patients with AKI in the ICU under different settings.

Though uncommon, deep neck space abscesses can be fatal if diagnosis is delayed. This group of abscesses can be further classified by their anatomical location into retropharyngeal, parapharyngeal, peritonsillar, submandibular, and mixed type. They have different presenting patterns and causes. For example, retropharyngeal and parapharyngeal abscesses are more common in early childhood (<5 years), and peritonsillar abscesses usually occur in older children and adolescent as a complication of tonsillitis. The presenting signs and symptoms are quite non-specific including fever, sore throat, dysphagia, limitations of neck movement and neck swelling. Since young children may not express themselves accurately, therefore high index of suspicion is needed. The main controversial point in deep neck space abscesses is whether to treat conservatively with antibiotics alone or performing surgery early. The report of Duman et al suggested that almost 50% of the patients can be treated conservatively with antibiotics such as Augmentin alone. It was suggested that indication of surgery can be guided by the size of the abscess (surgery if >2.2 cm) and age of patients (surgery if <5 years).

Rapunzel syndrome is a psychiatric disorder and patients with this syndrome tend to swallow their own hair.

Therefore, trichobezoar is formed in the stomach and some may have a long hairy tail that can extend into the upper part of small bowel. Prof. Wu's team from a large regional hospital in Shanghai reported 7 cases of this interesting complication within a 10-year period. This condition is mainly found in girls with the habit of trichophagia. Most complained of abdominal pain and chronic gastrointestinal symptoms. While endoscopic examination is the best diagnostic method, the removal of the trichobezoar usually requires opened laparotomy. The chance of recurrence of this condition is expected to be high if psychiatric assistance in the form of behavioural therapy is not provided.

Even for experienced paediatricians, to catch-up with the changing practice in subspecialty fields can be difficult, such as AKI assessment and approach to deep neck space abscesses. The exposure can be expanded by sharing under different exchange platforms. Our journal can serve as one of these sharing platforms among experts working in the paediatric fields. Then we can minimise the chances of delayed diagnosis and inappropriate management of our patients.

GCF CHAN
Chief Editor

Original Article

The Effects of Education Program Applied to the Families of Moderate and Late Premature Infants on Breastfeeding, Parental-infant Attachment and Parents' Anxiety Levels in the First Year: A Randomised Controlled Trial

EÜ KORĞALI, FŞ ORHON

Abstract

Introduction: To evaluate the effect of education given by home visiting on the families of moderate/late premature infants (MLPI) in respect of exclusively breastfeeding (EBF), complementary feeding and parent-infant interaction up to 1-year. **Method:** MLPI were randomly separated into three groups (n=22) as Standard Care (SCG), Mothers Education (MEG) and Family Education Group (FEG). Four home visits were made to MEG/FEG. They were evaluated at 1-week after discharge and 1/2/3/4/6/9/12 months. Infant-Character-Perception-Scale, Maternal-Attachment-Inventory, Paternal-Postnatal-Attachment-Questionnaire, State-Anxiety-Inventory were used. **Results:** EBF was higher in MEG/FEG than SCG at 3th (respectively 72.7%, 59.1%, 27.3%, p=0.01, OR:7.11; 95% CI; 1.89-26.80 and OR:3.85; 1.01-13.66), 4th (72.7%, 54.5%, 13.6%, p<0.001, OR:16.89; 3.63-78.56 and OR:7.6; 1.73-33.34) and 6th month (68.2%, 54.5%, 27.3%, p=0.02, OR:13.57; 2.99-61.59 and OR:6.3; 1.45-27.73). At 12 months, breastfeeding cessation was higher in SCG (50%) than MEG (18.2%) and FEG (22.7%) (p=0.04). Mothers' baby perception, mother/father-infant attachment were better in MEG/FEG. **Conclusion:** Education program can improve EBF and parent-infant interaction in MLPI.

Key words

Breastfeeding; Parents; Premature infants

Introduction

Moderate and late premature infants (MLPI-gestational week 32^{0/7}-36^{6/7}) constitute 84% of the premature. MLPI has worse breastfeeding results compared to term babies due to low rates of exclusively breastfeeding

(EBF) and breastfeeding rates, early cessation, breastfeeding difficulties, feeding problems, and frequent hospitalisations.^{1,2} On the other hand, increased stress and anxiety levels in MLPI parents decreased social interaction with their babies, which cause the development of an unsafe attachment model and increased risk of insensitive parenting. It is recommended that MLPI families receive extra support at the hospital and after discharge, both for successful and long-term breastfeeding of these babies, as well as for parents to interact appropriately with a healthy mood.³ The most effective intervention for this is the education given to the families.⁴⁻⁶

The majority of studies on breastfeeding have focused on the mother-infant couple. Whereas fathers are often overlooked, they are in the ideal position to help their breastfeeding partners. In many studies, it has been reported that the father's attitudes and approaches towards breast milk have a positive effect on the mother's desire to

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Received February 21, 2021

breastfeed, the beginning and duration of breastfeeding, and the EBF rate.⁷⁻⁹ However, these studies were conducted on term babies and their families, the effect of attitudes and approaches towards breast milk, especially of fathers with MLPI, on breastfeeding results is not clear. At the same time, there are a limited number of studies investigating the effects of both parents' training on baby care on the MLPI and their family.

Aim and Objectives

Our aim in this study is to evaluate the effect of the educational intervention created by the researchers and carried out with home visits on the EBF, breastfeeding status of MLPI and the anxiety levels of the parents and the parent-infant relationship. In order to evaluate the efficiency of fathers, the intervention groups were designed as two different groups in which only mothers participated and mothers and fathers participated together.

The education program aimed to provide emotional and social support to the families based on two main components; 1) to improve the EBF and breastfeeding of MLPI, 2) to ensure that parents with MLPI gain more knowledge and become more sensitive parents.

Primary Objective

To measure the effectiveness of each of two education interventions designed to increase the EBF rate and duration of breastfeeding in MLPI up to 1 year corrected age (CA).

Secondary Objective

To investigate the effectiveness of the interventions on the parents of MLPI in respect of mothers' baby perception, parents' anxiety levels, and parent-infant attachment.

Study Hypotheses

The hypotheses of this study are as follows; with the education program provided;

H1: the duration of breastfeeding and EBF rates would be significantly higher difference in the intervention groups compared control group at first 1 year CA.

H2: the rate of positive perception of the infant by the mother, mother-infant attachment, father-infant attachment and the state-anxiety levels of the parents would be significantly difference between the interventions and control groups at first 1 year CA.

Methods

Design and Setting

This study was conducted as a randomised controlled trial with a 1-year follow-up in an university hospital between June 2015 and July 2017. Approval was obtained from the local ethics committee for the study (no: 2015-05/07, date: 15/05/2015). Approximately 1500 babies are born per year in our hospital. The level 3 Neonatal Intensive Care Unit (NICU) provides hospitalisation of about 800 babies from this city and surrounding cities per year. This study included the parents and infants who were born within the 32-37 weeks with a birth weight appropriate to gestational age and were followed up in the NICU. The data were collected from the parents of MLPI while the infant was during in the NICU, at one week after discharge than at 1, 2, 3, 4, 6, 9 and 12 months CA. The CA was calculated by subtracting the time of premature birth from the chronological age.¹⁰

Participants

In the NICU, suitable MLPI and their parents were determined for the study. Any infants with congenital anomalies, neurological sequelae or chromosome anomaly, those with birthweight <10 percentile or >90 percentile according to gestational week, and multiple births were excluded from the study. Parents with psychiatric or chronic disease, mothers with postpartum depression, those living outside the centre of the province, who were not willing to participate or parents who were living separately, were excluded, together with their infant. Any infants diagnosed with a chronic disease during the follow-up were withdrawn from the study, together with the parents. Written and verbal informed consent was obtained from the parents who agreed to participate.

Randomisation and Sample

After informed consent procedures were completed, the baseline data related to the birth of the infant and follow-up in the NICU were retrieved from hospital records. The parents provided sociodemographic information. The parents were randomly assigned to either a control group or two intervention groups by sequentially numbered, sealed, opaque envelopes containing randomly generated numbers. These envelopes were coordinated by a research assistant who was not involved in any other trial procedure. The groups in the study are formed as follows:

1. Standard Care Group (SCG) (control group); infants and families received routine follow-up in the Paediatric Polyclinic.
2. Mothers Education Group (MEG); the education program applied during follow-up was delivered to the mothers only.
3. Family Education Group (FEG); the education program applied during follow-up was delivered to the mothers and fathers.

Participants and researchers were not be blinded to study groups because of the true nature of this study. However, the study statistician analysed the data independently and hence was be blinded to the allocation of participants to groups.

Intervention

Before the hospital discharge, face-to-face informative briefing about the characteristics and care of premature infants and breastfeeding was given by a paediatrician, and a paediatric nurse in a calm environment to the SCG, to the mothers in the MEG and both the mothers and fathers in the FEG. A written brochure related to premature infant care was given to the MEG and FEG parents on discharge, and they were given the attending paediatrician's telephone number.

The education program was applied in a 2-hour home visit by the same paediatrician and paediatric nurse at one week after discharge than at 1, 2, and 3 months CA of the infant. In the home visit, information was given about the general health of the infant, breastfeeding, feeding, and the parent-infant relationship. Breastfeeding mothers were observed while feeding, as well as parent-infant communication. Solutions to the problems experienced or observed during breastfeeding were investigated. During the home visits, questions of the mothers in MEG and mothers and fathers in FEG were answered. In the period up to 3 months CA, in the weeks where no home visit was made, the mothers in the MEG and FEG were contacted via phone calls, and information was obtained. The subject headings and details of the education program are shown in Table 1. The same paediatrician made the follow-up of the SCG participants at the same time intervals in the Paediatric Polyclinic.

Data Collection Instruments and Procedures

Information was obtained from the mother about the nutritional status of the baby (EBF, breastfeeding, formula or complementary foods), feeding method and nutritional

problems at all times during follow-up. The breastfeeding and EBF status and transition time to complementary feeding up to 1-year CA of all infants were recorded. EBF was defined by the World Health Organization (WHO) as infants receiving no food or drink (including water) other than breast milk but includes the use of vitamins, minerals, or medication.¹¹ Whether the time of starting complementary feeding for premature infants should be according to chronological age or CA is a matter of debate.¹² In this study, the appropriate time of starting complementary feeding was accepted as 6 months CA.

Anthropometric measurements of all the infants in the study were performed during systemic examinations at one week after discharge than at 1, 2, 3, 4, 6, 9 and 12 months CA. The physical and neurological development of the infant was interpreted according to CA. All the follow-up examinations of the infants in the SCG, and the follow-up examinations after the home visits for those in MEG and FEG, were performed in the Paediatric Polyclinic.

The parents were evaluated regarding the levels of anxiety, how the mother perceives the infant, mother-infant, and father-infant attachment. The questionnaires for the mother and father were filled at the appropriate time in the polyclinic or during home visits. The flowchart of the study is shown in Figure 1.

The Maternal Attachment Inventory (MAI)

It is used to evaluate the mother's emotions and behaviour towards her baby in the postnatal period.¹³ It is a 26 item; 4 point Likert-type scale whose items range from 'always' to 'never.' The high points indicate high maternal-infant attachment (min: 26, max: 104). The Turkish validity and reliability scale was found suitable for Turkish mothers with babies between 1 to 4 months.¹⁴ In our study, MAI was administered to all mothers at 1, 2, 3 and 4 months CA.

The Paternal Postnatal Attachment Questionnaire (PPAQ)

This scale of 19 items was developed to evaluate father-infant attachment.¹⁵ The scale has three sub-dimensions of "patience and tolerance," "pleasure in interaction," and "love and pride." Each item is scored from 1 to 5, and high points indicate a high level of attachment. The validity and reliability of the Turkish version were studied and found to be suitable for fathers with babies between 6-12 months.¹⁶ In our study, PPAQ was completed by all fathers at 6 and 12 months, CA.

Table 1 Timetable content of education program

Parent Education	Subjects
Before discharge	
General information	Preterm infants' features, feeding, breastfeeding techniques, body heat, dressing, sleeping, bathing, bottom cleaning, routine follow-up, vaccination, awareness of disease markers
Home visits	
General	Getting general information about mother and baby (1-4). Describing the CA, telling that the growth/development of preterm babies will be followed by CA (1,2)
Feeding	
<i>General</i>	Questioning of babies nutrition (frequency, breast milk or formula, feeding method, feeding problems, baby's hunger/satiety signals, signs of adequate nutrition) (1-4)
<i>Breastfeeding</i>	Synthesis and secretion of breast milk (1) Content of human milk, first and last milk (1,2) Relationship between breastfeeding and milk release (1,2) Frequency of breastfeeding, the effect of night breastfeeding (1,2) Importance and benefits of breast milk for babies and mothers (1-4) Importance of exclusively breastfeeding for first 6 months (1-4) Breastfeeding techniques and positions (1-2) Breastfeeding problems and breast care (1-2) Breeding and storage of breast milk (1-4) Perception of mother's own milk (1-4) Effect of fathers on breast milk (1-2) Observation and evaluation of breastfeeding (1-4)
<i>For suckling mothers</i>	Proper nutrition, abundant fluid intake, rest/relaxation, adequate sleep, focus on baby, request support from husband and relatives, participate in social environment (1-4)
<i>Complementary feeding</i>	When and how to get started (3,4) Effects of early or late start (3,4)
Possible problems	Infantile colic and solutions (1-4) Crying reasons and solutions (1-4) Try to understand the baby's clues (1-4) Vomiting and gastroesophageal reflux (1-3)
Cognitive and motor development	Age-appropriate development steps (1-4) Importance of eye contact-verbal communication with the baby (1-4) Baby calming methods (1,2) Sensitive parenting (1-4)
Parent infant relationship	The importance of a healthy parent-infant relationship (1-4) How fathers can support mother and babies (1-4)
Baby's physical examination	Systemic physical examination, anthropometric measurements (1-4) Marking in percentile curve according to CA (1-4) Processing in baby follow-up form (1-4) Informing the family about growth and development of baby (1-4).
Answering the questions of the mother (also the father in the Family Education Group)(1-4)	
Filling in forms for study (1-4)	
Determine the next visit time and terminate the session (1-4)	

CA, corrected age; 1, one week after discharge; 2, 1st month CA; 3, 2nd months CA; 4, 3rd months CA

Infant Character Perception Scale (ICPS)

It was designed to evaluate the perceptions of mothers about their infant's character, based on social attitude principles.¹⁷ The mother is instructed to indicate the most appropriate responses according to the character of their infant in areas defined as easy - difficult, happy - unhappy, peaceful - disgruntled, cries a little - cries a lot, attentive - inattentive, active - passive, easy to look after - difficult to look after. Low points were indicating a positive perception, and high points were indicating a negative perception (min: 7, max: 49). All the mothers in the study completed this scale at one week after discharge, and at 1, 3, 6 and 12 months CA.

The Edinburgh Postnatal Depression Scale (EPDS)

This scale was developed to determine the risk of postnatal depression, and it was adapted to Turkish.^{18,19} The scale was applied to all the mothers while the infant was in NICU and at one week after discharge. Mothers with a score of >12 points were withdrawn from the study and referred to the Psychiatry Clinic.

State Anxiety Inventory (SAI)

It was used to assess the level of state-anxiety and how parents feel at a given time.²⁰ It is a 20-item scale adapted to Turkish.²¹ The total score is between 20-80, and the high score indicates a high level of anxiety. SAI was administered to all parents when their infants were in NICU and at 1, 3, 6 and 12 months CA.

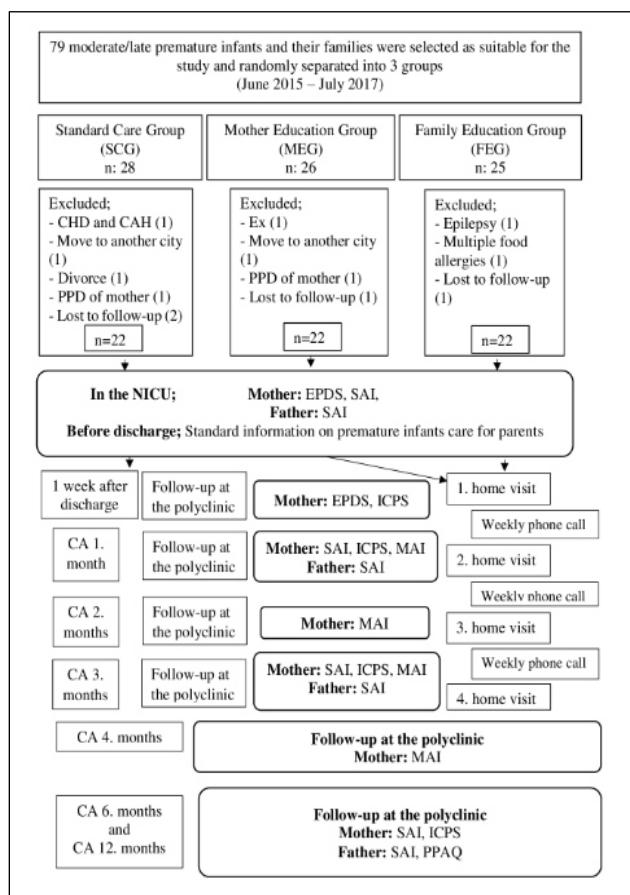


Figure 1 Flow diagram of the study.

Note: CHD, congenital heart disease; CAH, congenital adrenal hyperplasia; PPD, postpartum depression; NICU, neonatal intensive care unit; EPDS, The Edinburgh Postnatal Depression Scale; SAI, State Anxiety Inventory; ICPS, Infant Character Perception Scale; CA, corrected age; MAI, Maternal Attachment Inventory; PPAQ, Paternal Postnatal Attachment Questionnaire

Outcomes

For the MLPI and their parents;

Primary Outcomes

- Duration of breastfeeding
- EBF rate
- Age of introduction of complementary foods

Secondary Outcomes

- Perception of the infant by the mother
- Mother-infant attachment
- Father-infant attachment
- State-anxiety levels of the parents

Statistical Considerations

According to the repeated ANOVA test, with p=0.05 and power value=0.80, by evaluating previous similar studies, by predicting standard deviation=6.0 and by foreseeing after the education program a minimum of 5 units increase in The Maternal Attachment Inventory scores, it was determined that each group should consist of at least 22 infants and their families. The potential exclusion/withdrawal rate is considered 20%.

Data obtained in the study were analysed statistically by using SPSS version 17.0 software. Baseline data were summarised with descriptive statistics. Chi-square tests were used to compare between-group differences, and the ANOVA test was applied for parametric analysis. A value of p<0.05 was accepted as statistically significant.

Results

The study initially enrolled 79 MLPI and their families and was completed with 66 MLPI and the parents (Figure 1). The gestational age, birth weights, APGAR scores, and follow-up characteristics in the NICU of infants were similar in all three groups. There was no significant difference between the sociodemographic characteristics of the parents in the groups (Table 2).

The mothers' time to decide breastfeeding and previous breastfeeding experiences were similar in all three groups ($p=0.094$). However, the rate of mothers who intend to

breastfeed their babies for at least two years was significantly higher in MEG and FEG than SCG ($p=0.014$) (Table 3).

There was no significant difference between the groups in terms of EBF rates at the time of discharge, at one week after discharge, and at 1-month CA ($p=0.242$, $p=0.242$ and $p=0.126$, respectively). EBF rates were significantly higher in MEG and FEG than SCG at 3 months (respectively 72.7%, 59.1% and 27.3%, $p=0.008$), at 4 months (respectively 72.7%, 54.5%, 13.6%, $p<0.001$) and at 6 months (respectively 68.2%, 54.5% and 27.3%, $p=0.022$). According to the results of this study; compared

Table 2 Neonatal and parental sociodemographic characteristics

Characteristics	Standard Care Group (n=22)	Mother Education Group (n=22)	Family Education Group (n=22)	p value
<i>Neonatal Characteristics</i>				
Gestational age (week)*	33.9±1.3	34.1±1.1	34.1±1.5	0.869
Birth weight (grams)*	2050.2±466.6	2086.8±485.9	2086.1±398.5	0.955
APGAR, 1. minute*	6.6±1.4	6.9±0.9	6.6±1.1	0.563
APGAR, 5. minutes*	7.9±0.9	8.1±0.9	7.9±1.0	0.760
Duration of NICU (day)*	16.4±9.9	15.9±11.0	16.1±11.2	0.986
Female sex, n (%)	10 (45.5)	13 (59.1)	10 (45.5)	0.580
NSVD, n (%)	6 (27.3)	8 (36.4)	7 (31.8)	0.811
Mech. vent. (yes), n (%)	6 (27.3)	5 (22.7)	5 (22.7)	0.921
Nasal CPAP (yes), n (%)	12 (54.5)	10 (45.5)	10 (45.5)	0.785
Surfactant (yes), n (%)	6 (27.3)	5 (22.7)	7 (31.8)	0.795
TPN (yes), n (%)	8 (36.4)	7 (31.8)	6 (27.3)	0.811
<i>Maternal Characteristics</i>				
Age (years)*	30.0±6.4	29.1±5.3	28.0±4.9	0.481
Education (years)*	9.3±4.23	9.6±3.7	11.6±3.8	0.118
Housewife, n (%)	16 (72.7)	15 (68.2)	12 (54.5)	0.420
Primipar, n (%)	10 (45.5)	7 (31.8)	13 (59.1)	0.192
<i>Paternal Characteristics</i>				
Age (years)*	35.0±6.9	32.1±6.0	32.9±4.3	0.238
Education (years)*	9.4±3.0	9.6±3.7	11.4±4.2	0.154
<i>Familial Characteristics</i>				
Duration of marriage (years)*	6.4±4.6	8.1±4.9	5.7±5.1	0.240
Number of children*	1.8±0.8	2.2±1.0	1.5±0.8	0.400
Nuclear family, n (%)	16 (72.7)	14 (63.6)	18 (81.8)	0.400
Planned pregnancy, (yes), n (%)	17 (77.3)	12 (54.5)	17 (77.3)	0.166
Monthly income, n (%)				0.290
Income ≥ expense	17 (77.3)	14 (63.6)	18 (81.8)	
Income < expense	5 (22.7)	8 (36.4)	4 (18.2)	

*Mean ± standard deviation

NSVD, normal spontaneous vaginal delivery; Mech. vent, mechanical ventilation; CPAP, continuous positive airway pressure; TPN, total parenteral nutrition

Table 3 Breastfeeding and complementary feeding characteristics

Characteristics n (%)	Standard Care Group (n=22)	Mother Education Group (n=22)	Family Education Group (n=22)	p value
<i>When did you decide to breastfeed?</i>				0.345
Before pregnancy	16 (72.7)	17 (77.3)	21 (95.5)	
<i>Breastfeeding experience</i>				0.094
Yes	10 (45.5)	15 (68.2)	8 (36.4)	
<i>How long are you planning to breastfeed?</i>				0.014
≥ 2 years	11 (50.0)	21 (95.5)	20 (90.9)	
<i>Breastfeeding</i>				
<i>Discharge and 1 week after discharge</i>				0.242
Exclusive	19 (86.4)	20 (90.9)	16 (72.7)	
Mixed	3 (13.6)	2 (9.1)	6 (27.3)	
Formula	-	-	-	
<i>1st month, CA</i>				0.126
Exclusive	12 (54.5)	18 (81.8)	13 (59.1)	
Mixed	8 (36.4)	3 (13.6)	9 (40.9)	
Formula	2 (9.1)	1 (4.5)	-	
<i>3rd month, CA</i>				0.008
Exclusive	6 (27.3)	16 (72.7)	13 (59.1)	
Mixed	13 (59.1)	5 (22.7)	8 (36.4)	
Formula	3 (13.6)	1 (4.5)	1 (4.5)	
<i>4th month, CA</i>				<0.001
Exclusive	3 (13.6)	16 (72.7)	12 (54.5)	
Mixed	14 (63.6)	5 (22.7)	8 (36.4)	
Formula	5 (22.7)	1 (4.5)	2 (9.1)	
<i>6th month, CA</i>				0.022
Exclusive	6 (27.3)	15 (68.2)	12 (54.5)	
Mixed	9 (40.9)	5 (22.7)	8 (36.4)	
Formula	7 (31.8)	2 (9.1)	2 (9.1)	
No breastfeeding				
9th month, CA	8 (36.4)	2 (9.1)	3 (13.6)	0.051
12th month, CA	11 (50.0)	4 (18.2)	5 (22.7)	0.046
Complementary feeding, (yes)				
3rd month, CA	1 (4.5)	-	-	0.362
4th month, CA	9 (40.9)	1 (4.5)	1 (4.5)	0.001
5th month, CA	17 (77.3)	3 (13.6)	3 (13.6)	<0.001
6th month, CA	19 (86.4)	22 (100)	22 (100)	0.043
9th month, CA	21 (95.5)	22 (100)	22 (100)	0.362
12th month, CA	22 (100)	22 (100)	22 (100)	-

CA, corrected age

Statistically significant (p<0.05) shown in bold.

to the SCG the probability of infants in the FEG to be fed EBF was higher 3.85 times (OR:3.85, 95 CI 1.01-13.66), 7.6 times (OR:7.60, 95 CI 1.73-33.34) and 6.33 times (OR:6.33, 95 CI 1.45-27.73) respectively at 3, 4 and 6 months CA. Similarly, it has been found that the probability of EBF in the MEG was higher 7.11 times (OR:7.11, 95 CI 1.89-26.80), 16.89 times (OR:16.89, 95 CI 3.63-78.56) and 13.57 times (OR:13.57, 95 CI 2.99-61.59) compared to the SCG, respectively at 3, 4 and 6 months CA.

At 9 months CA, 36.4% of the infants and at 12 months CA 50% of the infants were not receiving breast milk in SCG, and this rate at the 12 months CA was significantly higher than the other two education groups ($p=0.046$) (Table 3).

In our study, one baby at 3 months CA (4.5%), nine babies at 4 months CA (40.9%), and 17 babies (77.3%) at 5 months CA had complementary feeding in the SCG. No

infant had complementary feeding at 3 months CA in the MEG and FEG. The rate of infants who started complementary feeding at 4 and 5 months CA in SCG was significantly higher than the other two groups ($p=0.001$ and $p<0.001$, respectively). While all babies were introduced with supplementary food in MEG and FEG at 6 months CA, this rate was found to be 86.4% in SCG ($p=0.043$) (Table 3).

When the mother's perception of her baby was evaluated, the mothers in both MEG and FEG were determined to have a more positive perception of their infants at all times. However, only the result at 6 months CA was not statistically significant ($p=0.072$) (Table 4).

In the evaluation of mother-infant attachment, the mothers in SCG were found to have the lowest values at 1, 2, 3 and 4 months CA. The MAI scores of the mothers in MEG and FEG were similar and significantly higher than the SCG mothers ($p<0.001$) (Table 4).

Table 4 The mother's perception of the infant, mother-infant and father-infant attachment

Characteristics (Mean±std dev.)	Standard Care Group (n=22)	Mother Education Group (n=22)	Family Education Group (n=22)	p value
Mother's Perception of their infant				
1 wk after discharge	20.3±7.1 ^{a,b}	13.8±4.5	13.7±4.5	<0.001
1st month, CA	20.4±7.4 ^b	16.6±5.7	15.0±6.6	0.026
3rd month, CA	19.5±6.7 ^{a,b}	14.3±6.3	13.8±6.1	0.014
6th month, CA	17.6±7.6	13.1±5.5	13.7±7.2	0.072
12th month, CA	17.9±6.2 ^{a,b}	12.6±4.9	12.8±6.2	<0.001
Mother-infant attachment				
1st month, CA	93.0±6.0 ^{a,b}	100.7±3.4	99.9±6.01	<0.001
2nd month, CA	92.2±6.5 ^{a,b}	98.7±4.2	99.5±3.9	<0.001
3rd month, CA	90.3±7.1 ^{a,b}	99.9±4.4	99.9±4.6	<0.001
4th month, CA	89.3±7.2 ^{a,b}	99.9±4.3	100.1±4.3	<0.001
Father-infant attachment				
6th month, CA				
Patient-tolerance	31.9±5.2 ^b	33.5±4.9	35.9±3.5	0.016
Pleasure in interaction	23.3±4.8 ^b	25.4±3.9	27.2±3.9	0.010
Love-pride	12.6±1.9 ^{a,b}	13.9±1.3	14.0±1.3	0.009
12th month, CA				
Patient-tolerance	32.1±5.6	32.7±5.2	32.1±4.0	0.106
Pleasure in interaction	25.0±4.9	25.8±4.0	26.6±5.7	0.562
Love-pride	13.2±1.6 ^b	13.8±1.7	14.5±0.7	0.004

std. dev, standard deviation; wk, week; CA, corrected age

Statistically significant ($p<0.05$) shown in bold

a: $p<0.05$, compared to SCG and MEG

b: $p<0.05$, compared to SCG and FEG

The father-infant attachment points in all three sub-dimensions were highest in FEG fathers and lowest in SCG fathers at 6 months CA, and the difference was statistically significant ($p=0.016$ for patience and tolerance, $p=0.010$ for pleasure in interaction and $p=0.009$ for love and pride). In the "love and pride" sub-dimension, the points of MEG fathers were significantly higher than those of SCG at 6 months CA. The results of all three groups at 12 months CA were similar, with the only difference was that the significantly higher scores of FEG than SCG in the sub-dimension of "love and pride" ($p=0.004$) (Table 4).

The state-anxiety levels of the fathers were similar in all groups ($p>0.05$), but the highest anxiety level was seen in the SCG mothers. At 3 months CA, the anxiety level of SCG mothers was significantly higher than the mothers of the other two groups, and at 6 and 12 months CA, significantly higher than the level of FEG mothers ($p<0.001$ and $p<0.001$, respectively) (Table 5).

Discussion

It has been determined that MLPI have serious problems in early initiation and maintenance of breastfeeding due to inpatient monitoring in NICU, long-term hospital follow-up requirements, and high re-hospitalisation rates.^{1,5,6} In addition, it has been reported

that breastfeeding is challenging in these babies since they are more hypoactive and hypotonic compared to term babies, they get tired quickly, and their sucking-swallowing coordination is insufficient.²² Goyal et al,⁵ reported that low rates of EBF in late premature infants compared even with early premature infants. The EBF rate of MLPI at the time of discharge was reported between 20% and 60% in several studies.^{2,6,23,24} All infants in our study were on breastfeeding at the time of discharge. The EBF rates at the time of discharge were similar, with over 70% in all three groups. Our breastfeeding rates on discharge were higher than in previous studies. We think that this result is related to the fact that our hospital is a "baby-friendly hospital," as well as the sensitivity of our healthcare staff.

In the current study, although the breastfeeding rates of the groups were similar at one week after discharge and at 1-month CA, it was noteworthy that there was a remarkable decrease in rates of breastfeeding and EBF in the SCG as the infants grew. In our study, one-third of the infants (31.8%) were not on breastfeeding in the SCG at 6 months, CA. In a study performed in late premature infants, the rate of EBF and not receiving any breast milk were reported as 20% and 52% in the 3rd month. In the same study, the rate of breastfeeding and EBF was 24% and 12% in the 6th month, respectively.² In a previous study, EBF rate of premature infants at 2, 4, and 6 months

Table 5 The state anxiety levels of the mothers and fathers

State Anxiety Inventory Scores (Mean±std dev.)	Standard Care Group (n=22)	Mother Education Group (n=22)	Family Education Group (n=22)	p value
Mothers				
In NICU after birth	42.8±11.7	39.8±8.8	42.2±12.2	0.638
1st month, CA	40.0±10.6	33.9±7.6	34.2±10.2	0.065
3rd month, CA	38.3±7.6 ^{a,b}	29.1±7.5	30.9±9.2	<0.001
6th month, CA	38.8 ± 7.3 ^b	34.5±9.2	31.6±8.4	<0.001
12th month, CA	37.5±6.8 ^b	32.4±7.4	32.0±8.5	<0.001
Fathers				
In NICU after birth	39.1±9.6	38.1±10.1	40.2±10.9	0.803
1st month, CA	36.7±8.4	37.4±10.7	35.0±10.2	0.710
3rd month, CA	37.4±7.0	34.7±9.7	31.0±9.7	0.064
6th month, CA	34.6±7.2	33.6±9.1	30.7±8.0	0.260
12th month, CA	34.7±7.6	32.4±8.3	30.4±8.6	0.239

std. dev, standard deviation; NICU, neonatal intensive care unit, CA: corrected age

Statistically significant ($p<0.05$) shown in bold

a: $p<0.05$, compared to SCG and MEG

b: $p<0.05$, compared to SCG and FEG

were reported to be 51%, 37%, and 9%, respectively.²⁵ In another study, the rates were reported as 66%, 38%, and 13% in premature infants at 1, 4, and 6 months, respectively.²⁶ In the literature, educating families and home visits have been shown to contribute positively to EBF and breastfeeding for both term infants and MLPI, similar to our study. Morrow et al,²⁷ reported that the EBF rate in term infants at three months was 67% in the group that was visited six times in the home, while the group that had three visits this rate was 50% and expectedly the group that did not receive any visits the ratio decreased to 12%. Ravn et al,²⁸ also stated that the rate of breastfeeding was 77.3% in the education given group and 63.6% in the uneducated group in MLPI.

In a review including 73 studies and the information of 74.656 mothers and term babies, it was stated that high background initiation rates of breastfeeding, spousal support, and special education interventions made face-to-face 4-8 times were effective in the improvement of EBF.²⁹ The results of our study, which includes similar features in terms of intervention methods, coincide with the results of term babies. In our study, it was noticed that the EBF rates were significantly higher in the education groups compared to the control group as the baby grows. Especially in the 4th month, this rise is most prominent, and compared to SCG, probability of EBF was found to be 16.89 times higher in MEG and 7.6 times higher in FEG. However, more studies are needed on this subject for MLPI. We believe that solving the breastfeeding problems promptly with the education program and home visits explain the high rates of EBF and breastfeeding determined in our study. On the other hand, in current study although not statistically significant, the rates related to breastfeeding in MEG were better than FEG. This result suggests that the main target of the education provided was mothers and that the effect of fathers on breastfeeding was limited. It has been reported in previous studies that educational interventions on families were the most effective methods in supporting breastfeeding and reducing the risk of cessation of breastfeeding by 10-33%.³⁰

WHO recommends that term infants should be fed with EBF in the first 6 months, and complementary foods with high nutritional value in addition to breastfeeding should be initiated from the 6th month.¹¹ It was reported that early initiation of complementary feeding did not provide additional improvement in the growth of the infant, and even increased the frequency of atopic diseases, gastrointestinal infections, and obesity.^{31,32} On the other

hand, delay of initiation of complementary foods has been associated with increased celiac disease, wheat allergy, type 1 diabetes disease, iron deficiency anemia, eating disorders, and anorexia.³³ These data were achieved from studies subjecting term infants; therefore, it was also discussed whether chronological age or CA would be used for transition to complementary food in premature infants. Norris et al,¹² determined that the initiation of complementary feeding in MLPI was earlier than recommended and that they started supplementary food in an average of 16.3 weeks according to chronological age, and 11.8 weeks according to CA while babies who received EBF were introduced with complementary food later. Fewtrell et al,³⁴ reported that early initiation of complementary foods in premature infants reduces breast milk intake. In our study, the babies in MEG and FEG have introduced with complementary food mostly at 6 months CA, while the initiation of complementary feeding in SCG tends to be earlier or later. Similar to previous studies, lower breast milk rates in SCG may be a reason for the initiation of complementary feeding in the early periods, and early complementary feeding may have reduced breast milk rates.^{12,34}

It has been reported that parents of premature infants had higher levels of anxiety at birth and in the following months compared to parents of term infants.³⁵ In our study, while state anxiety levels of fathers were similar at all times, it was observed that mothers had similar anxiety levels in the first months. However, from 3 months, CA onwards, the lowest anxiety levels were seen in the FEG mothers and the highest in the SCG. In previous studies, it was stated that anxiety in premature baby parents was significantly lower in intervention groups receiving social support, but the difference disappeared as the baby grew.³⁶⁻³⁸ Also, the anxiety levels of parents of MLPI decreased as the baby grew in our study. Our results show that the education and support given to the parents was effective in making a significant difference in the anxiety levels of the mothers, and the participation of fathers in the FEG to the education seemed to play a role in reducing the anxiety of the mothers. The anxiety levels of parents with a premature infant gradually reduce over time, but with social support, this period is shortened.^{39,40}

Preterm delivery is a risk factor for early mother-baby interaction. However, a safe mother-baby interaction and attachment are necessary for both the mother's and child's healthy mood. It has been reported that mothers of premature infants develop severe fears about the safety of their babies and have difficulties in accepting their babies

and establishing harmonious communication compared to mothers of term babies.⁴¹ In order to prevent this situation, education programs starting at the hospital and continuing at home after discharge is the most effective intervention.⁴ In a study, it was shown that the educational training conducted in NICU aiming to increase mother-baby interaction reduces anxiety levels of mothers and provides a more positive mother-baby communication when the babies are two months old.⁴² In another study, the education given after discharge was found to be associated with low anxiety symptoms in parents of premature infants at postnatal 6 and 12 months.³⁶ Newnham et al,³⁷ also showed that early intervention increased the quality of mother-infant interaction and better communication skills in infants with less regulatory problems in premature babies. Recently, it has been shown that educational intervention has positive effects on the mental health of the mother rather than premature babies.^{28,43} In our study, MAI scores were higher in both education groups, and it can be said that mothers performed a healthier attachment with their babies as a result of the intervention. These results may be in association with the mothers' reduced anxiety levels and high rates of breastfeeding.

Positive thoughts of the mother about her baby may also affect the healthy mother-infant attachment. It has been reported that mothers have a negative perception of their premature infants starting from birth and sometimes continuing for years.^{44,45} In a previous study, the premature infants in the intervention group were easier and more approachable by their mothers compared to a control group, and at six months, they were described as more compliant and happy.³⁷ Similarly, the results of the current study showed that mothers in the education group had a more positive perception of their infants. The positive baby perceptions in MEG and FEG started at one week after discharge and continued up to 12 months, CA. When mothers are supported to perceive their baby's tips correctly and respond appropriately, a more sensitive mothering model and a stronger mother-infant attachment can be provided.^{4,37,46-48}

On the other hand, the effects of premature birth on father-infant attachment are controversial, and there are few studies on this subject. A previous study has shown that there was no significant difference between the fathers of MLPI and term infants regarding the bonding model, but the fathers of premature infants were seen to be more hesitant and have a more negative attitude in communication with the infant. Therefore, to avoid the risk

of an unhealthy bonding model, giving information to the parents on the subject of communication with the infant is the most fundamental approach.^{45,49} As a matter of fact, in our study, in the FEG, where fathers also participated in the training program, the PPAQ scores were the highest in all sub-dimensions at six months CA. The father-infant attachment results of the groups were similar as the infant grew over time. These results suggest that the fathers took a more active role in interaction with the infant as time went on. The education given to the fathers seems to be effective in the development of a more potent bonding model with an earlier start. The similarity of the results of the MEG and FEG at six months particularly suggests that mothers indirectly influence the fathers even if they are not included in the education program. Consistent with the findings of previous studies, the results of the current study showed the positive effect of the education on father-infant attachment.^{45,50}

The strong aspects of this study are that it was designed as a randomised, controlled study with a specific group evaluation (MLPI), and the extensive data presented were obtained throughout a long follow-up period. However, for many reasons, the findings should be interpreted with caution. The most important limitation of the study is that the data of the assessment scales are based on the statements of the mothers and fathers.

In conclusion; the educational training program and home visits that were given to families of MLPI had positive contributions to the EBF and breastfeeding of these babies and on the transition to the right time-appropriate complementary nutrition. While the education program provided a significant decrease in anxiety levels of mothers, it also had positive effects on mother-infant and father-infant attachment. In order to reduce the experienced problems by the families of MLPI, a standard education and support program should be applied to this group. For the development of the infant and public health, there is a need for further studies in this area, which include the fathers.

Acknowledgements

The authors thank all the families who participated in the study, Dr. Fatih Bolat and the NICU nurses; Rabia Altun, Nilgün Durmaz and Ayşe Beyaztoprak who undertook the home visits.

Declaration of Interest

The authors declare no conflicts of interests.

Disclosure

This study was given the first prize in oral presentation at the 1st International Eurasian Congress of Social Pediatrics (November 28th -December 1st 2018, İstanbul) by the jury, including Stuart Logan and Nicholas Spencer.

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Original Article

Comparison of Three Critical Illness Scoring Systems for Assessing Septic Acute Kidney Injury

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Abstract

Introduction: Sepsis is the most common critical illness in clinical settings, and septic acute kidney injury (AKI) is a major cause of mortality in paediatric patient. **Methods:** We aimed to investigate scoring systems for determining the severity of septic AKI through mortality prediction using Pediatric Risk of Mortality III (PRISM III), Pediatric Multiple Organ Dysfunction Score (P-MODS), and Pediatric Critical Illness Score (PCIS). The clinical data of 102 paediatric patients with septic AKI admitted to the paediatric intensive care unit from January 2014 to December 2018 were collected. Receiver operating characteristic (ROC) curves were plotted to determine the optimal cutoff values of the scoring systems for assessing mortality. **Results:** There were 25.64% death rates among patients with stage 1 disease, 45% with stage 2 disease, and 58.14% with stage 3 disease, with a significant difference ($\chi^2=8.8409$, $p=0.012$). The cutoff values of the ROC curves of PRISM III, P-MODS, and PCIS were 12, 6, and 82, respectively, in patients with not staged septic AKI; 12, 5, and 84, respectively, in patients with stage 1 septic AKI; 17, 9, and 72, respectively, in patients with stage 2 septic AKI; and 12, 7, and 74, respectively, in patients with stage 3 septic AKI. **Conclusions:** PRISM III was the best mortality risk assessment system for paediatric patients with not staged septic AKI. PCIS was better in predicting the mortality risk of paediatric patients with stage 1 AKI, whereas PRISM III was better for paediatric patients with stage 2 and 3 AKI.

Key words

Acute kidney injury; Pediatric Critical Illness Score; Pediatric Multiple Organ Dysfunction Score; Pediatric Risk of Mortality III; Sepsis

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Received August 10, 2021

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Introduction

Sepsis is a major healthcare problem, affecting millions of people around the world each year.¹ It is a typical complication of severe trauma, burns, shock, and major surgery, and an important cause of mortality in patients with trauma and burns. Statistics show that about 8 million children under the age of five die each year in the world, nearly 70% are due to sepsis caused by infection. Even in the United States, a country with advanced medical technology, 42,000 children have severe sepsis every year, with a mortality rate of up to 10% among them. Meanwhile the mortality rate of paediatric patients with severe sepsis in paediatric intensive care units (PICUs) reaches up to 50% in developing countries.² In China, sepsis among children is also an important concern. An article published in November 2014 in *Pediatric Critical Care Medicine* evaluated the prevalence of sepsis in paediatric patients in Huai'an District of Jiangsu Province in China. The study showed that not only was there a large number of paediatric patients with sepsis but also that the patients were young, with 80% <5-year-old and 36% <1-year-old. The mortality rate among paediatric patients with sepsis was also extremely high (33% died of severe sepsis, 74% died of respiratory failure with or without septic shock), and most patients did not have underlying diseases.^{3,4} In 2013, a prospective multicentre study on paediatric acute kidney injury (AKI) in China was published in *BMC Urology*, which showed that sepsis was the leading cause of mortality in children with AKI, accounting for 34.9% of deaths among paediatric patients.^{3,4}

Severe sepsis is a major cause of death in PICUs in both developing and developed countries, and septic AKI increases the risk of in-hospital death six to eight-fold.⁵ The third generation of the Pediatric Risk of Mortality (PRISM III), published in 1996, is one of the widely used scoring systems for assessing condition and prognosis for critically ill children admitted to PICU.⁶ The Pediatric

Critical Illness Score (PCIS) is the most widely used and effective scoring method for paediatric critical illness in China. The objective of the present study was to compare three paediatric critical illness scoring systems in combination with the staging criteria for AKI diagnosis developed by the Kidney Disease Improving Global Outcomes (KDIGO) Work Group, in order to evaluate the suitability of scoring systems in predicting the mortality of patients admitted in PICU. Receiver operating characteristic (ROC) curves were plotted to compare the predictive effect of the area under the ROC curve (AUC) of each assessment system on the mortality of paediatric patients with septic AKI, in order to select the appropriate critical illness scoring system for different AKI stages.

Data and Methods

Study Populations and Groups

A total of 102 paediatric patients with septic AKI who were treated in the PICU of West China Second University Hospital of Sichuan University from January 2014 to December 2018 were included. This study was conducted in accordance with the provisions of the revised 2013 World Medical Association Declaration of Helsinki.

Methods

Diagnostic Criteria

The diagnosis of sepsis was based on the "Expert Consensus on the Diagnosis and Treatment of Pediatric Septic Shock (2015 edition)".⁷ The diagnosis and staging of septic AKI in paediatric patients were based on the 2012 KDIGO guidelines (Table 1).⁸ The baseline creatinine was derived by urine volume assessment, or according to European Renal Best Practice (ERBP) Working Group recommended that the first recorded serum creatinine value as a baseline.

Table 1 AKI staging in the 2012 KDIGO guidelines

Stage	Serum creatinine criteria	Urine output criteria
Stage 1	1.5-1.9 times baseline or ≥ 0.3 mg/dl (≥ 26.5 μ mol/L) increase	<0.5 mL/kg.h, time 6-12 h
Stage 2	2.0-2.9 times baseline	<0.5 mL/kg.h, time >12 h
Stage 3	3.0 times baseline or ≥ 4.0 mg/dl (≥ 353.6 μ mol/L) increase in or initiation of renal replacement therapy or in patients <18 years decrease in eGFR <35 ml/min per 1.73 m ²	Oliguria (<0.3 mL/kg.h) >24 h or anuria >12 h

AKI, acute kidney injury; KDIGO, the Kidney Disease Improving Global Outcomes

Inclusion and Exclusion Criteria

Paediatric patients who met the diagnostic criteria for sepsis and were diagnosed with AKI based on the 2012 KDIGO guidelines were included. Paediatric patients diagnosed with sepsis but not AKI, or paediatric patients diagnosed with AKI but without clinical manifestations of sepsis were excluded.

Data Collection and Relevant Diagnostic Parameters

The clinical data of all paediatric patients were retrospectively collected, including basic epidemiological data (sex, age of onset), vital signs on admission to the intensive care unit, and results of auxiliary examinations. The disease was evaluated and scored by the bedside clinician using three critical illness assessment systems – PRISM III, PCIS, and Pediatric Multiple Organ Dysfunction Score (P-MODS), and the bedside clinician were blind to the outcome and blinded to the stage of AKI.

Statistical Analysis

Statistical analyses were performed using SAS 9.4 software. Sample size was calculated using the formula for determining the number of samples required for a diagnostic test.⁹ Qualitative data, such as sex, age, AKI, and mortality, were expressed as rate or percentage (%). Differences in rates were compared using the chi-square test. ROC curves were plotted to determine the optimal

cutoff values of the PRISM III score, PCIS, and P-MODS. The cut-off values and the areas under the ROC curve were used to assess the mortality in paediatric patients with septic AKI that had not been staged (not staged septic AKI). Moreover, the best scoring system among PRISM III, PCIS, and P-MODS for predicting mortality in paediatric patients with different stages of AKI was also evaluated. The maximum value of the Youden index was used as the optimal cutoff value.¹⁰

Results

Clinical Data Analysis

Baseline Clinical Data

A total of 102 paediatric patients with septic AKI were included in this study, including 65 boys (63.73%) and 37 girls. The age of onset was 5.32±4.88 years. The youngest patient was 1 month old, and the oldest patient was 17 years old. A total of 62 children (60.78%) were ≤5 years old (Table 2).

Among the paediatric patients with septic AKI, 44 (43.14%) died, 26 of whom were ≤5 years old, accounting for 59.09% of all deaths. According to AKI stages, there were 10 deaths (25.64%) among 39 patients with stage 1 disease, 9 deaths (45%) among 20 patients with stage 2 disease, and 25 deaths (58.14%) among 43 patients with

Table 2 Analysis of clinical data of 102 paediatric patients with septic AKI [number of patients (%)]

Group		Died	Survived	x ²	p
n		44	58		
Sex	Male	30 (46.15)	35 (53.85)	2.0399	0.3606
	Female	14 (37.84)	23 (62.16)		
Age	≤5 years	26 (41.94)	36 (58.06)	0.1010	0.9508
	>5 years	18 (45.00)	22 (55.00)		
AKI stage	1	10 (25.64)	29 (74.36)	8.8409	0.012
	2	9 (45.00)	11 (55.00)		
	3	25 (58.14)	18 (41.86)		
Group		Died	Survived	x ²	p
n		44	58		
PCIS	≤82	34 (62.96)	20 (37.04)	17.9025	<0.0001
	>82	10 (20.83)	38 (79.17)		
PRISM III	≥12	33 (75.00)	11 (25.00)	32.0266	<0.0001
	<12	11 (18.97)	47 (81.03)		
P-MODS	≥6	29 (61.70)	18 (38.30)	12.2473	0.0005
	<6	15 (27.27)	40 (72.73)		

AKI, acute kidney injury; PCIS, Pediatric Critical Illness Score; PRISM III, Pediatric Risk of Mortality III; P-MODS, Pediatric Multiple Organ Dysfunction Score

stage 3 disease. The mortality rate significantly increased with higher AKI stages ($\chi^2=8.8409$, $p=0.012$). The mortality rate showed no difference between different sex ($P=0.3606$) and age ($P=0.9508$). The increase in mortality rate was statistically significant when PCIS was <82 , PRISM III score was >12 , and P-MODS was >6 .

Best Scoring System Based on AUC

Evaluation of Each Assessment System for Not Staged Septic AKI

Figure 1 shows the ROC curves of PRISM III, P-MODS, and PCIS for mortality assessment in paediatric patients with not staged septic AKI. The cutoff values were 12, 6, and 82, respectively, and the AUCs were 0.8452, 0.7414, and 0.8184, respectively. Therefore, the best mortality risk assessment system for paediatric patients with not staged AKI was PRISM III.

For paediatric patients with not staged septic AKI, the AUCs for PRISM III, P-MODS, and PCIS were 0.845, 0.741, and 0.818, respectively (Table 3).

The PRISM III score, P-MODS, and PCIS for mortality assessment in paediatric patients with not staged septic AKI showed cutoff values of 12, 6, and 82, respectively. PRISM III had a sensitivity of 75% and a specificity of 81.03%. P-MODS had a sensitivity of 65.91% and a specificity of 68.97%. PCIS had a sensitivity of 77.27% and a specificity of 65.51%. When the three scoring systems were used jointly for assessment, the specificity increased to 96.55% and the sensitivity decreased to 38.64% (Table 4).

Evaluation of Each Assessment System for Septic AKI of Different Stages

In paediatric patients with stage 1 septic AKI, the cutoff values of the ROC curves of PRISM III, P-MODS, and PCIS for mortality assessment were 12, 5, and 84, respectively, and the AUCs were 0.8414, 0.7362, and 0.8810, respectively (Figure 2). Therefore, the best mortality assessment system for paediatric patients with stage 1 AKI was PCIS.

In paediatric patients with stage 2 septic AKI, the cutoff values of the ROC curves of PRISM III, P-MODS, and PCIS for mortality assessment were 17, 9, and 72, respectively, and the AUCs were 0.8232, 0.7576, and 0.6869, respectively (Figure 3). Therefore, the best mortality assessment system for paediatric patients with stage 2 AKI was PRISM III.

In paediatric patients with stage 3 septic AKI, the cutoff values of the ROC curves of PRISM III, P-MODS, and PCIS for mortality assessment were 12, 7, and 74, respectively, and the AUCs were 0.8367, 0.6778, and 0.7822, respectively (Figure 4). Therefore, the best mortality assessment system for paediatric patients with stage 3 AKI was PRISM III.

Discussion

Sepsis is the major cause of critical illness in children. Severe sepsis occurs in approximately 8% of paediatric patients in PICUs. The prevalence of sepsis has decreased

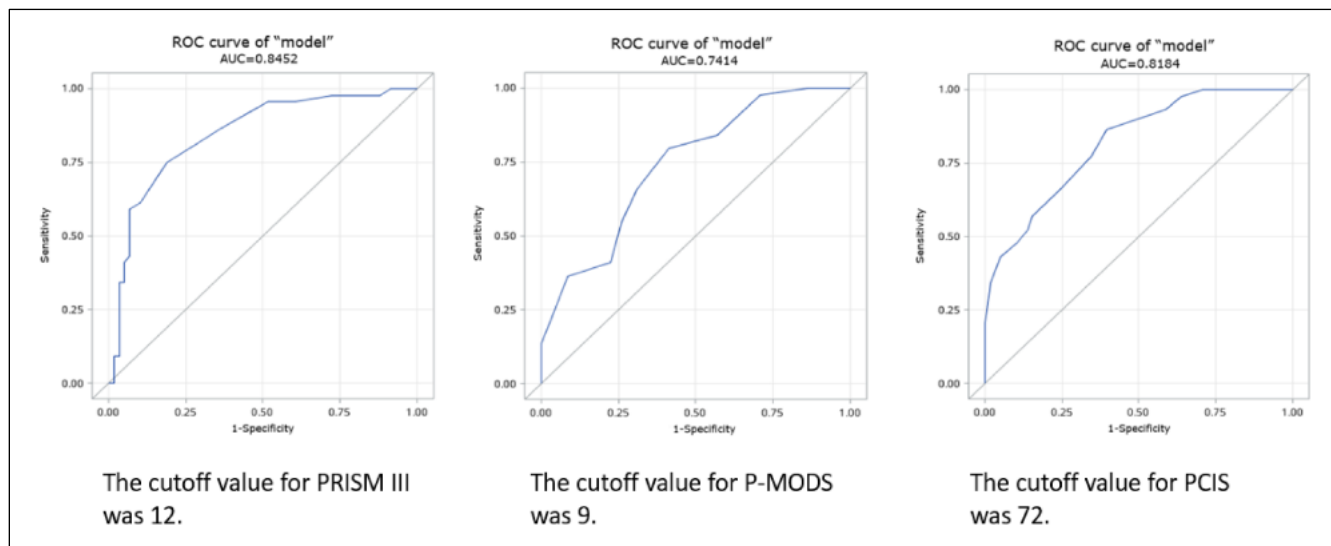


Figure 1 Cutoff values and ROC curves of each assessment system for not staged septic AKI.

owing to relative advances in medical technology and supportive therapies, and sepsis-associated mortality has been greatly reduced. However, it has led to increased attention paid to the organ function and prognosis of surviving children.¹¹⁻¹³ Severe septic AKI is a common comorbidity of sepsis, accounting for more than half of the cases in adult patients. Among paediatric patients with severe diseases in PICUs, AKI occurs in approximately 16%; however, no precise data are available for septic AKI.^{14,15} Many studies have demonstrated an extremely high mortality rate in children with severe sepsis. In PICUs, the mortality rate of critically ill paediatric patients without AKI is 58.7%, whereas that of critically ill paediatric patients with AKI can reach 73.4%. No definitive mortality rate in children with septic AKI has been reported.^{16,17} Given the high mortality rate of septic AKI, early predictive assessment and active strengthening of supportive therapies are needed to reduce the mortality rate of paediatric patients with sepsis and improve the poor long-term prognosis of survivors.

The Physiological Stability Index (PSI) is the first worldwide-recognised critical illness severity scoring method in children; however, it requires the assessment of many parameters and is cumbersome to use in the clinic. In 1988, Pollack et al simplified the PSI and proposed the first generation of PRISM, which has since evolved to the third generation (PRISM III). PRISM III comprises 17 physiological parameters and 26 physiological parameter ranges and is widely used in various parts of the world. It

Table 3 ROC curves of PRISM III, P-MODS, and PCIS for mortality assessment in not staged septic AKI

Assessment system	AUC	SE	P	95% CI
PRISM III	0.845	0.040	0.000	0.767-0.923
P-MODS	0.741	0.048	0.000	0.739-0.836
PCIS	0.818	0.040	0.000	0.739-0.898

AKI, acute kidney injury; PCIS, Pediatric Critical Illness Score; PRISM III, Pediatric Risk of Mortality III; P-MODS, Pediatric Multiple Organ Dysfunction Score

Table 4 Utility of PRISM III, P-MODS, and PCIS for mortality assessment in paediatric patients with not staged septic AKI

Scoring system	Cutoff value	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
PRISM III	12	75.00	81.03	75.00	81.03
P-MODS	6	65.91	68.97	61.70	72.73
PCIS	82	77.27	65.51	62.96	79.17
Joint assessment with the three systems	–	38.64	96.55	89.47	67.47

AKI, acute kidney injury; PCIS, Pediatric Critical Illness Score; PRISM III, Pediatric Risk of Mortality III; P-MODS, Pediatric Multiple Organ Dysfunction Score

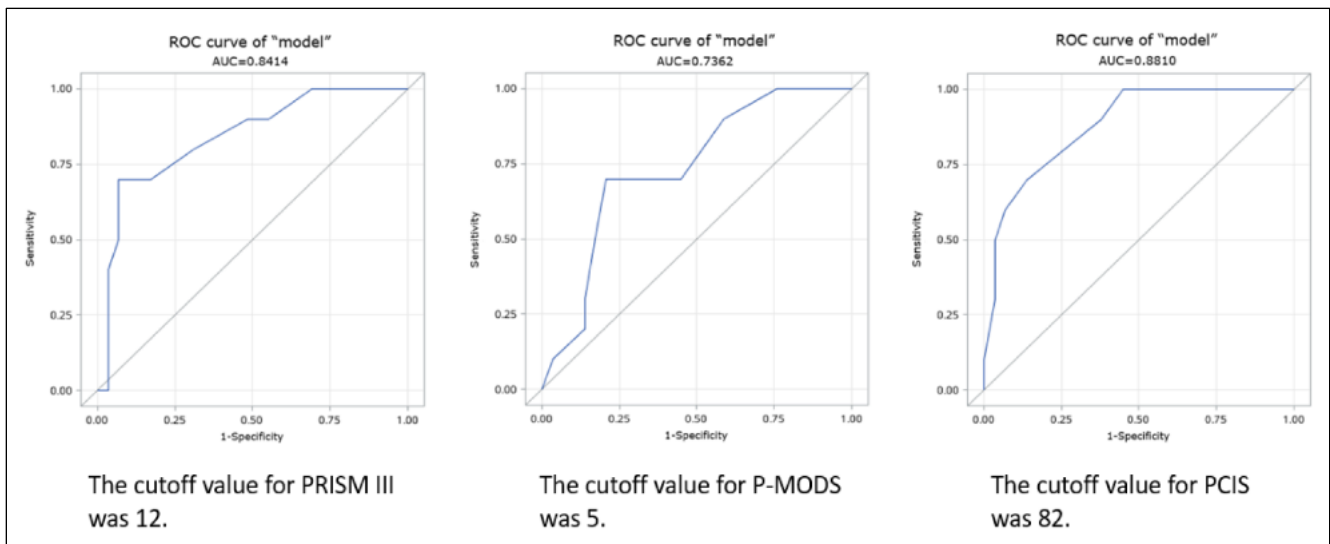


Figure 2 Cutoff values and ROC curves of each assessment system for paediatric patients with stage 1 septic AKI.

has become a standard tool for assessing the condition and prognosis of paediatric patients in PICUs. PCIS was developed by the Emergency Medicine Group of the Chinese Pediatrics Society and the Pediatrics Group of the Chinese Society of Emergency Medicine in 1995. PCIS comprises 10 physiological parameters and is the most widely used and effective paediatric critical illness scoring method in China owing to its simplicity, effectiveness, and compatibility with the national condition. P-MODS is primarily used to assess the degree of organ dysfunction in children by evaluating parameters such as bilirubin, lactic

acid, fibrinogen, urea, and oxygenation index.

In the present study, the mortality rate of paediatric patients with septic AKI was 43.14%. This result was similar to the epidemiological results from a survey using claims data of the National Health Insurance system in Taiwan between 2006 and 2010, which showed that the incidence of AKI in critically ill paediatric patients was 1.4%, of which 46.5% of the AKI cases was caused by sepsis. The survey also showed that the rate of mortality associated with critical illness was 44.2%. In addition, Julie et al reported that septic AKI was an independent risk

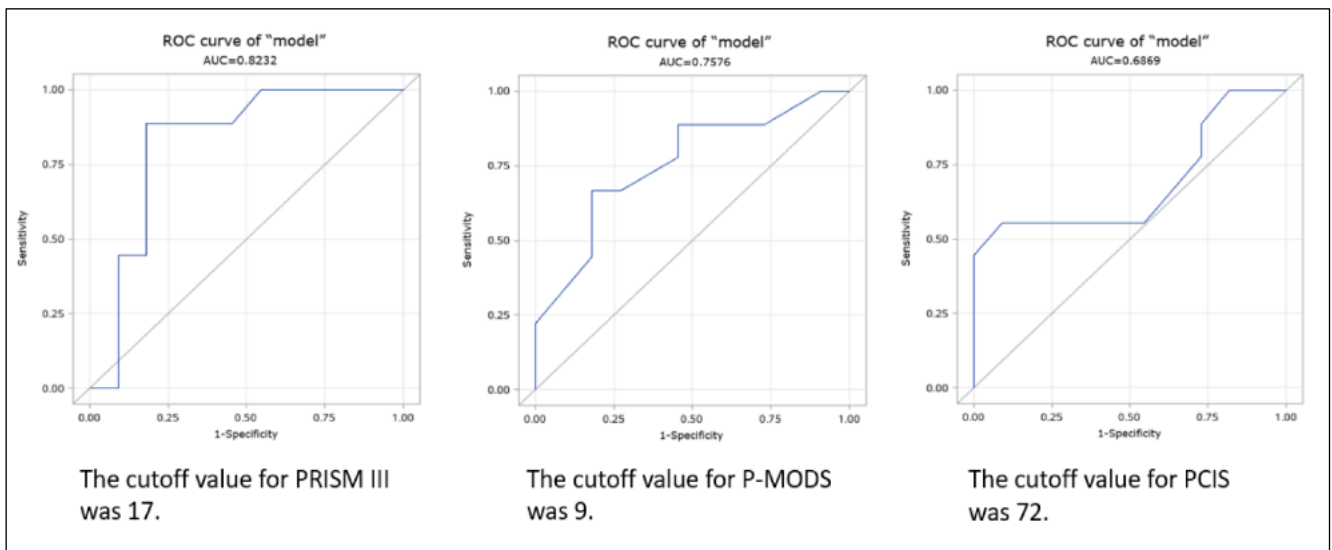


Figure 3 Cutoff values and ROC curves of each assessment system for paediatric patients with stage 2 septic AKI.

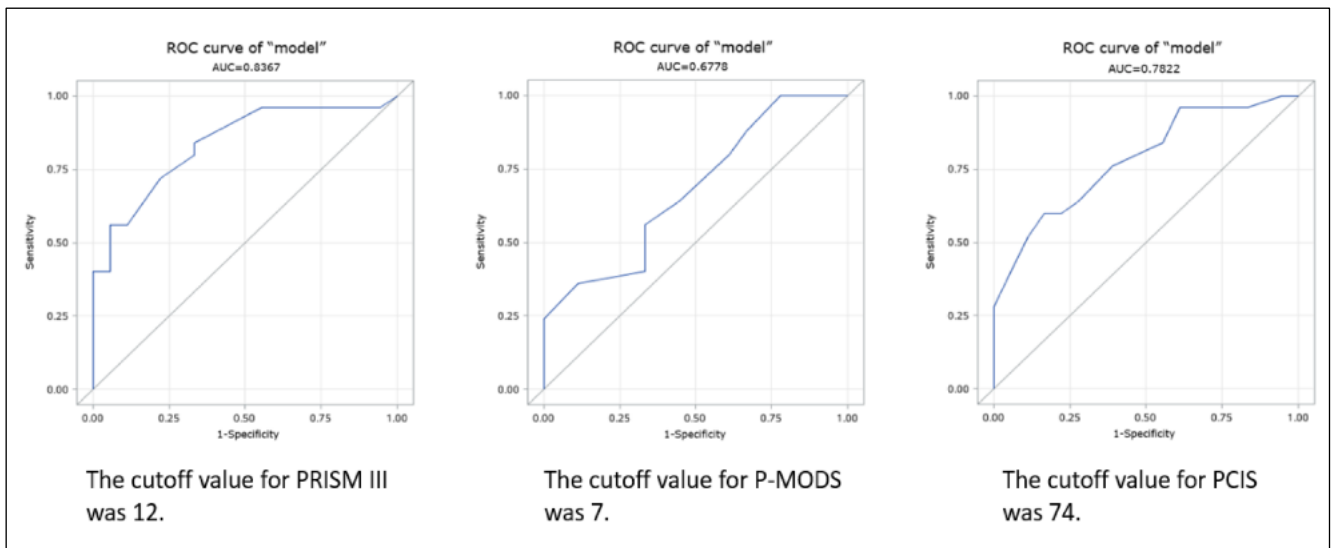


Figure 4 Cutoff values and ROC curves of each assessment system for paediatric patients with stage 3 septic AKI.

factor for death in paediatric patients with severe sepsis.¹⁶ The mortality rate increased with higher AKI stages. Through ROC curve and AUC analyses, we showed that the AUC of PRISM III was 0.845 when the cutoff score was 12, whereas the AUCs of P-MODS and PCIS were 0.741 and 0.818, respectively, which were lower than the AUC of PRISM III. Thus, PRISM III was the most useful system for mortality prediction in paediatric patients with septic AKI.

A study by Kaur et al has reported that PRISM III score has excellent capacity to discriminate between survival and mortality. PRISM III score can be used to predict length of stay among survivors.⁶ A prospective observational cohort study by Graciano et al showed that P-MODS scores could be objectively reflected organ dysfunction and predict the risk of death accurately.¹⁸ Another study showed that PCIS was a protective factor (OR: 0.88; 95% CI: 0.86-0.90) for paediatric AKI.¹⁹ Up to now, few studies have been made to compare three systems in predicting mortality in paediatric patients with different stages septic AKI. In this study, we compared the performance of PRISM III, P-MODS, and PCIS for the prediction of mortality risk in paediatric patients with septic AKI of different stages. For stage 1 septic AKI, the mortality rate was 25.64%. Our result shows that PCIS performed better in predicting mortality risk in paediatric patients with stage 1 septic AKI, and the mortality risk of paediatric patients increased when the PCIS was <84. For stage 2 septic AKI, the mortality rate was 45.0%. Our study suggested that PRISM III performed better than P-MODS and PCIS in predicting mortality risk in paediatric patients with stage 2 septic AKI. When the PRISM III score was >17, the mortality risk of paediatric patients increased with higher scores. For stage 3 septic AKI, the mortality rate was 58.14%. When the PRISM III score was >12, the mortality risk due to stage 3 septic AKI significantly increased. PRISM III performed better than the other two systems in predicting mortality in paediatric patients with stage 3 septic AKI. The P-MODS score can be used to evaluate five body functions, namely, circulation, breathing, liver function, blood coagulation, and kidney function. Because the P-MODS score does not include an assessment of the nervous system, its prognostic value in children with conditions related to the nervous system diseases may be limited. So that there are limitations in predicting prognosis in P-MODS score. For the PRISM III score, data for the following 16 variables: temperature, systolic blood pressure, heart rate, partial pressure of arterial oxygen (PaO₂), partial pressure of arterial carbon

dioxide (PaCO₂), Glasgow Coma Scale (GCS) score, pupillary reaction, prothrombin time (PT) and activated partial thromboplastin time (APTT), serum creatinine, serum urea nitrogen, serum potassium, blood glucose, and serum bicarbonate levels, white blood cell and platelet counts. Therefore, PRISM III score is relatively accurate in predicting prognosis. The PCIS scoring system included more electrolytes, and the scoring was greatly affected by electrolytes. There were few electrolyte disturbances in patients with stage 1 septic AKI. So that PCIS performed better in predicting mortality risk in paediatric patients with stage 1 septic AKI.

Prediction models of mortality provide great insight to health care administrators regarding the prognosis of the patient and may greatly benefit the decision process as well as the outcome of the patient. The conclusion of our study can help in-charge physician to choose more suitable scoring systems to better predict the clinical outcomes in children facing different stages of septic AKI. Choosing suitable scoring systems according to different stages, physicians can assess the survival chances of the patient. In settings where there is a shortage of medicines and staff, such models enable physicians to decide how and where to direct their limited resources.

In summary, this study retrospectively compared the results of three critical illness scoring systems (PRISM III, P-MODS, and PCIS) for mortality assessment in paediatric patients diagnosed with septic AKI. Our results showed that PRISM III had the best assessment performance in paediatric patients with not staged, stage 2, and stage 3 AKI, whereas PCIS performed better in predicting mortality risk in paediatric patients with stage 1 AKI. However, our study is limited by the small sample size and single centre. Moreover, the urinary assessment was not accurate because the urine output may not be measured precisely in infant which have the risk of mixing the urine with stool. In addition, baseline creatinine value can be a bias as patient may already develop AKI on PICU admission. In next study, we will increase the sample size and collect data from a multi-centre. Furthermore, we will find a better way to measure the urine output. And we will try our best to get the baseline creatinine value from the healthy period of the patient.

Declaration of Interest

The authors declare no conflicts of interests.

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Original Article

Paediatric Deep Neck Space Abscesses: Experience of a Tertiary Care Hospital

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Abstract

To evaluate children diagnosed with deep neck space abscesses (DNSAs) between January 2011 and January 2020, a retrospective chart review was performed. Demographics, clinical manifestations, laboratory and radiological investigations, antibiotic choice, need for surgery, operative reports, length of hospital stay and prognosis were recorded. Sixty-two patients were enrolled. The most common presentation was fever and the most common location was parapharyngeal abscess. Patients who were surgically treated had larger abscess diameters on contrast-enhanced computed tomography compared to those who received conservative treatment ($p: 0.025$) but we did not find any difference in laboratory data, antibiotic duration and length of hospital stay. Surgical treatment was more common in patients aged 0-5 years compared with those >5 years ($p<0.001$). Although there is still a lack of consensus on the optimal management or timing for surgery, conservative treatment with close follow-up can be successfully applied in selected cases.

Key words

Children; Deep neck space abscess; Surgery

Introduction

Deep neck space abscesses (DNSAs) are defined as infection in the potential spaces and fascial planes of the neck.¹ Although they remain rare in children in the

antibiotic era, an increase in incidence has nevertheless been seen.^{2,3} Based on the anatomical sites of infection, DNSAs can be categorised as retropharyngeal, parapharyngeal, peritonsillar, submandibular, mixed type, and other abscesses.⁴ They may occur in distinct spaces in different age groups. Retropharyngeal and parapharyngeal abscesses are more common in early childhood, with a peak between the ages of 2 and 5 years, because there is regression in the lymph nodes by age. Peritonsillar abscesses usually occur due to the spread of the infection from acute tonsillitis, so they are primarily seen in older children and adolescents.⁵ Deep neck space abscesses often present with nonspecific symptoms such as upper respiratory tract infection, fever, decreased oral intake, neck pain, swelling of the cervical lymph nodes, limitations of neck range of motion, or trismus, which makes the diagnosis difficult; accurate diagnosis remains a challenge to paediatricians because of insidious signs.⁶⁻⁸ They are associated with life-threatening complications including airway obstruction, mediastinitis, jugular vein thrombosis, cranial nerve dysfunction, and sepsis/septic shock, leading to potential morbidity and mortality.^{9,10} Because DNSAs show rapid onset and cause serious

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Received November 17, 2020

complications when neglected, early diagnosis and adequate management are crucial. The diagnosis is based on clinical evaluation and radiological imaging modalities such as ultrasonography (US), contrast-enhanced computed tomography (CECT), or magnetic resonance imaging (MRI).¹¹ Although CECT has become the most accurate and widely used imaging technique, there are still controversies about its diagnostic value and utility in assessment of DNSAs.¹² The mainstay of treatment is antibiotics and surgical drainage, if required. There is still a lack of consensus on the optimal management of paediatric DNSAs. Some authors advocate immediate surgical drainage because of shorter hospital stay, false negative radiological findings, and the possible rapid spread and life-threatening consequences. In contrast, recent studies support the use of conservative approaches alone if there is no evidence of failure to clinically improve with antibiotic treatment or if there is a complicated clinical course that includes airway compromise or multiple sites of abscesses.^{9,13-15} Wong et al reported that patients with smaller abscess size (maximal diameter less than 25 mm) or younger age could be successfully managed conservatively as first-line treatment.⁹ In another study, it was reported that smaller abscess size could predict favourable outcomes of conservative treatment of peritonsillar abscesses.¹⁶ There is also a debate on the timing of the surgical approach. It is unknown whether delaying surgical drainage has a relatively negative effect on outcomes.¹⁷

The aim of the present study was to evaluate the demographic data, clinical features, laboratory and radiological characteristics, management, and outcomes of children diagnosed with DNSAs in order to identify predictors of need for surgery and prognosis in a tertiary level hospital.

Materials and Methods

Study Design

This was a single-centre retrospective chart review performed in the paediatric emergency department of the Dokuz Eylul University Faculty of Medicine, a tertiary level hospital. The study was approved by the Institutional Review Board of the Dokuz Eylul University Faculty of Medicine.

Children aged 0 to 18 years who were referred to the paediatric emergency department and diagnosed with DNSAs between January 2011 and January 2020 were

included. We used the International Classification of Diseases (ICD) codes for DNSAs to identify patients. We obtained information from the computer database, electronic medical records, medical charts, and nursing records. Patients with superficial infections, phlegmon/cellulitis, lymphadenitis, infections due to trauma, foreign body or surgery, immunocompromise, tuberculosis, congenital cervical anomalies, thyroid gland infections, malignancies, and insufficient data were excluded. All data were investigated and recorded by a paediatric emergency fellow and two paediatric residents.

The following data were also obtained: demographics; duration of symptoms and antibiotic use before arrival at the emergency department; clinical manifestations; laboratory data including blood cultures, white blood cell (WBC) count, absolute neutrophil count (ANC), erythrocyte sedimentation rate (ESR), and serum C-reactive protein (CRP) levels; the radiological imaging technique preferred; US, CT, or MRI findings; and the maximal diameter of the abscess formation. The site of infection was categorised into 5 groups as follows: parapharyngeal, retropharyngeal, peritonsillar, submandibular, and mixed type of abscesses.⁴ Abscess was defined as the presence of a hypolucent or hypointense mass with complete or near-total rim enhancement.¹⁸ Abscess formation in the space surrounded by the palatine tonsils, limited externally by the superior pharyngeal constrictor muscle, was defined as peritonsillar abscess. Parapharyngeal abscess is localised medially to the space surrounded by the pharynx, the carotid sheath posteriorly, and the muscles of styloid process laterally. Retropharyngeal abscess is confined posteriorly to the pharynx, bounded by the buccopharyngeal fascia anteriorly, the prevertebral fascia posteriorly, and the carotid sheaths laterally. Submandibular abscess is bounded by a superficial layer of deep cervical fascia inferiorly and by the lingual mucosa superiorly. If there were two or more compartments of infection, it was defined as the mixed type of abscess.^{4,7} The determination of the location of DNSAs was based on clinical manifestations and/or radiological investigations. Antibiotic choice, the duration of antibiotic treatment, need for surgery, operative reports, and, if obtained, pus culture specimens were recorded. Subjects were divided into three groups according to treatment approaches: immediate surgical drainage, delayed surgical drainage, or treatment with antibiotics alone. Delayed surgical drainage was defined as a time interval to surgery of more than 24 hours from the start of first intravenous antibiotic treatment

or failure of medical therapy.¹⁷ The following were investigated as complications of DNSAs: airway obstruction, jugular vein thrombosis, mediastinitis, emphysema, pericarditis, cranial nerve dysfunction, and sepsis/septic shock.^{9,10} Recurrence was defined as the reappearance of the infection after one month of clinical remission.¹⁹ Finally, the need for admission to the ward or PICU, total length of stay in the hospital, prognosis, and mortality were recorded. During the study period, there was no standardised protocol for the management of DNSA patients; the decision for surgical intervention was reserved for the judgement of individual surgeons.

Statistical Analysis

All statistical analyses were performed using SPSS 22.0 for Windows. Categorical and continuous variables were reported as frequencies and percentiles, means with standard deviations (SD), or medians with interquartile ranges (IQRs). The Mann-Whitney U test was used to compare non-parametric variables and Student's t test was used for parametric data. Correlations were assessed with Spearman's rank correlation coefficient. To determine the cut-off diameter of abscesses to predict surgical intervention, receiver operating characteristic (ROC) curve analysis was performed and sensitivity and specificity were calculated. Values of $p < 0.05$ were considered statistically significant.

Results

Study Population

A total of 62 patients were enrolled during the study period. The median age was 6.0 years (IQR: 3.0-10.0). Seventeen patients (27.4%) were under five years of age. Of the patients, 35 (56.5%) were male and 27 (43.5%) were female (Table 1). The most common presentations were fever, sore throat, limitations of neck range of motion, neck swelling, and dysphagia. Frequencies of all signs and symptoms are shown in Table 2. At the time of admission, 40 patients (64.5%) presented with ongoing upper respiratory tract infection, with symptoms having started a median of 4.0 days earlier (IQR: 4.0-7.0), and 26 (41.9%) patients had received enteral or parenteral antibiotic treatment 4.4 ± 2.3 days prior to the referral. The most often prescribed antibiotic was amoxicillin clavulanate (57.7%), followed by ceftriaxone (15.4%), ampicillin sulbactam (11.6%), clindamycin (7.7%), gentamicin (3.8%), and cefdinir (3.8%). Patients had an

initial mean WBC count of $20200 \pm 9200/\text{mm}^3$, ANC of $15300 \pm 8200/\text{mm}^3$, ESR level of 59.4 ± 28.4 mm/h, and CRP value of 107.5 ± 79.4 mg/L, which were consistently increased and showed a status of inflammation (Table 1). Blood cultures were obtained from 21 (33.9%) patients and, of those, only one was positive (mixed type of bacteria). Pus specimens were obtained from 26 (41.9%) patients and 10 (38.5%) of them resulted in positive cultures. Of the 10 positive specimens, the most common microorganisms were *Streptococcus pyogenes* (40.0%) followed by *Streptococcus viridans* (10.0%), *Streptococcus parasanguinis* (10.0%), coagulase-negative Staphylococcus (10.0%), Haemophilus influenzae (10.0%), gram-negative Bacillus (10.0%), and anaerobic bacteria (10.0%).

Radiology

Ultrasound was performed for 14 (22.6%) patients and CECT for 52 (83.9%). Thirteen (20.9%) patients were evaluated with both US and CECT together. The most common abscess location was parapharyngeal (n: 23, 37.1%), followed by peritonsillar (n: 17, 27.4%), submandibular (n: 9, 14.5%), mixed (n: 7, 11.3%), and retropharyngeal space (n: 6, 9.7%) (Table 1). Peritonsillar abscess was more common in patients aged >5 years (n: 16, 35.5%) than 0-5 years (n: 2, 11.7%) ($p < 0.001$). In 13 (20.9%) cases, repeated radiological images were obtained in order to evaluate response to treatment or to guide the surgical planning for the patients. Of those, 9 (69.2%) were repeated with US, 3 (23.0%) with CECT, and one (7.7%) with MRI.

Management

Of the patients, 29 (46.8%) were treated with antibiotics alone and 33 (53.2%) underwent surgery with antibiotic treatment. Of the 33 undergoing surgery, 3 (9.1%) underwent immediate and 30 (90.9%) underwent delayed surgery. The most preferred antibiotics were clindamycin alone (n: 38, 61.2%), a combination of ampicillin sulbactam + clindamycin (n: 14, 22.7%), and a combination of ceftriaxone + clindamycin (n: 10, 16.1%). Among the 33 patients who were surgically treated, 24 (38.7%) of them underwent a transoral approach and 9 (14.5%) had open surgery with drainage of the abscess through cervicotomy. The overall time interval between admission and surgery was a median of 2.0 days (IQR: 0.0-12.0). Closed drainage was classified as a surgical treatment and was performed by surgeons in our study. Evaluating patients who underwent surgical treatment, we

compared closed versus open drainage but there was no difference in age ($p: 0.077$), duration of antibiotic therapy ($p: 0.090$) and, total length of stay in the hospital ($p: 0.849$). There was a change in treatment strategy for 4 patients (6.4%) in the study; all but one of them underwent surgery. The first antibiotic which was started for these 4 patients was clindamycin. One patient, who was a 2.5-year-old boy with a parapharyngeal abscess of 2.5 cm on

CECT, was successfully treated with a change in antibiotics as being ceftriaxone 48 hours after admission. Among 3 patients who underwent surgery, the first case was a 6-year-old boy with a 2 cm of parapharyngeal abscess on CECT who underwent surgery on the 5th day of admission. The second patient was a 2-year-old girl with a 3.5 cm of submandibular abscess and she underwent surgery on the 7th day of admission. The third patient was

Table 1 Demographics, laboratory/radiological features, and management of the patients in the study

Variable	n: 62
Sex (n, %)	
Male	35 (56.5%)
Female	27 (43.5%)
Age in years [median (IQR)]	6.0 (3.0-10.0)
At the time of admission	
Upper respiratory tract infection (n, %)	40 (64.5%)
Symptom duration (days) [median (IQR)]	4.0 (4.0-7.0)
Received antibiotics (n, %)	26 (41.9%)
Antibiotic duration (days) (mean±SD, min-max)	4.4±2.3 (7.0-34.0)
Laboratory data [mean±SD (min-max)]	
WBC count (cells/mm ³)	20200±9200 (6300-51700)
ANC (cells/mm ³)	15300±8200 (2000-43300)
ESR (mm/h)	59.4±28.4 (7.0-120.0)
CRP (mg/L)	107.5±79.4 (5.0-427.0)
Radiology (n, %)	
CT	52 (83.9%)
US	14 (22.6%)
CT and US together	13 (20.9%)
Localisation (n, %)	
Parapharyngeal	23 (37.1%)
Peritonsillar	17 (27.4%)
Submandibular	9 (14.5%)
Mixed	7 (11.3%)
Retropharyngeal	6 (9.7%)
Management (n, %)	
Antibiotic alone	29 (46.8%)
Antibiotic + surgery	33 (53.2%)
Timing of surgery (days) [median (IQR)]	2.0 (0.0-12.0)
Antibiotic choice (n, %)	
Clindamycin	38 (61.2%)
Ampicillin sulbactam + clindamycin	14 (22.7%)
Ceftriaxone + clindamycin	10 (16.1%)
Antibiotic duration (days) [mean±SD (min-max)]	17.4±6.3 (7.0-34.0)
Length of stay in the hospital (days) [mean±SD (min-max)]	9.6±3.9 (3.0-21.0)

WBC: white blood cell, ANC: absolute neutrophil count, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, US: ultrasound, CT: computed tomography.

a 6-year-old boy with a 1.5 cm of mixed abscess and he underwent surgery on the 3th day of admission. All three patients who underwent surgery was successfully treated without any complications. Patients who were surgically treated had larger abscess diameters on CECT compared with patients receiving conservative treatment (2.60 ± 0.94 cm versus 1.95 ± 0.95 cm) ($p: 0.025$), but we did not find any differences in WBC count, ANC, ESR, or CRP levels. Antibiotic duration and total stay in the hospital also did not differ between surgical and conservative treatment groups (Table 3). To predict the abscess diameter for surgery, ROC analysis was performed and the area under the curve (AUC) was 0.697 (95% confidence interval (CI): 0.533-0.860). At a cut-off level of 2.4 cm, the sensitivity and specificity of abscess diameter for need for surgery were respectively 52.0% and 68.0% (Figure 1). Surgical treatment was more common in patients aged 0-5 years ($n: 10, 58.5\%$) compared with >5 years ($n: 23, 51.1\%$) ($p<0.001$). The mean duration of antibiotic treatment (intravenous + oral) was 17.4 ± 6.3 days and length of stay in the hospital was 9.6 ± 3.9 days. Antibiotic duration had a negative correlation with age ($p<0.001, r: -0.452$) and a positive correlation with initial WBC count ($p: 0.003, r: 0.389$) and ANC ($p: 0.020, r: 0.311$) but not with ESR or CRP levels. There was no correlation between any laboratory data (erythrocyte sedimentation rate, CRP levels, WBC count, or ANC) and need for surgery. The mean length of stay in the hospital was 9.3 ± 4.2 days in the surgical treatment group and 9.9 ± 5.8 days in the conservative treatment group; there was no difference

between these groups. Length of stay in the hospital was negatively correlated with age ($p: 0.003, r: -0.382$) and had a positive correlation with initial WBC count ($p<0.001, r: 0.491$) and ANC ($p<0.001, r: 0.441$) but not with ESR or CRP levels. No patients developed any complications or recurrences and no deaths were observed in our study.

Discussion

Deep neck space abscesses are uncommon but still remain a serious problem with life-threatening consequences in the paediatric population. They often present with nonspecific symptoms, which may make the

Table 2 Symptoms and signs of the patients at the time of admission

Variable	n: 62 (%)
Fever	44 (71.0%)
Sore throat	37 (59.7%)
Limitations of neck range of motion	28 (45.2%)
Neck swelling	27 (43.5%)
Dysphagia	19 (30.6%)
Lymphadenopathy	13 (21.0%)
Neck pain	12 (19.4%)
Trismus	6 (9.7%)
Cough	5 (8.1%)
Torticollis	5 (8.1%)

Table 3 Demographics, laboratory/radiological features, and outcomes of surgical and conservative treatment groups

Variable	Surgical treatment (n: 33)	Conservative treatment (n: 29)	p value
Male gender (n, %)	19 (56.5%)	16 (43.5%)	0.565
Age in years [median (IQR)]	7.0 (2.0-11.5)	5.5 (3.0-9.3)	0.555
At the time of admission (n, %)			
Upper respiratory tract infection	19 (57.6%)	18 (62.0%)	0.362
Received antibiotics	15 (45.5%)	11 (37.9%)	0.811
Abscess size (cm) [mean±SD (min-max)]	2.60±0.94 (1.0-4.5)	1.95±0.95 (0.7-4.0)	0.025
Laboratory data [mean±SD (min-max)]			
WBC count (cells/mm ³)	19340±7730 (8600-48800)	21640±10880 (6300-51700)	0.511
ANC (cells/mm ³)	14750±7170 (5900-43300)	16480±9870 (2000-42300)	0.263
ESR (mm/h)	60.6±29.0 (7.0-120.0)	56.5±31.7 (17.0-120.0)	0.743
CRP (mg/L)	106.7±67.8 (5.0-283.0)	112.6±98.5 (6.2-427.0)	0.684
Antibiotic duration (days) [mean±SD (min-max)]	17.7±6.9	17.3±5.8	0.765
Length of stay in the hospital (days) [mean±SD (min-max)]	9.3±4.2 (3.0-21.0)	9.9±5.8 (5.0-20.0)	0.487

diagnosis a challenge for paediatricians, so a high index of suspicion is crucial. The most common presentations in the present study were fever, sore throat, limitations of neck range of motion, neck swelling, and dysphagia, in agreement with those reported in the literature.⁶⁻¹⁰

Deep neck space abscesses may occur in specific locations according to the patient's age. Previous data showed that peritonsillar abscesses predominated in older children and adolescents but retropharyngeal and parapharyngeal abscesses were more common in younger children.⁵ In the present study, peritonsillar abscess was more common in patients aged >5 years, whereas retropharyngeal and parapharyngeal abscesses predominated in children aged 0-5 years, consistent with previous data.^{7,14,19}

The most commonly employed radiological modalities to identify DNSAs were CECT and US in our study. Contrast-enhanced computed tomography has become the most widely used imaging technique. The detailed anatomical information provided by CECT is helpful for surgical planning of patients who require surgical intervention.⁷ Meyer et al recommended performing CT for all children with a concerning diagnosis for DNSAs, because no factor appeared to be predictive of abscess on CT. In addition, the duration of symptoms did not predict the finding of an abscess on CT.²⁰ However, the sensitivity and specificity ranges respectively vary between 63% and 95% and between 45% and 65% in the literature, and CT has some limitations in differentiating abscesses from cellulitis along with high radiation exposure. Ultrasound was reported to provide useful information for superficial lesions but it offers poor visualisation of deeper neck space collections. In addition, the use of US depends on the skill level of the radiologist. As the first-line choice, MRI was considered reasonable; it provides higher contrast resolution in pus detection and avoids exposure to ionizing radiation.^{9,13,14,21,22} However, it was not preferred as the first-line imaging modality in our study due to the need for sedation, and it may not be readily available in some cases in our hospital. It was stated that radiological examination could be delayed for 48 hours if there was no airway compromise or signs of complications, so MRI could be preferred to achieve more accurate imaging in the management of paediatric DNSAs.²³

Researchers recommend clindamycin, penicillin with a β -lactamase inhibitor, or a β -lactamase-resistant antibiotic with a drug against most anaerobes as empirical treatment.^{5,24} The most preferred antibiotics in our study were clindamycin alone, a combination of ampicillin

sulbactam + clindamycin, and ceftriaxone + clindamycin, in accordance with the literature. The mean duration of antibiotic treatment was 17.4 ± 6.3 days, which was longer than recent findings recommending a 14-day antibiotic course, representing a more strict conformity to indications.²⁵

There still remains uncertainty about which patients can be managed successfully without surgical intervention. In a study including both adult and paediatric patients, a clinical score with sensitivity of 73.7% and specificity of 92.3% was proposed to determine the need for surgery. Positive peripheral rim enhancement on CT scan, CRP level of >41.25 mg/L, sedimentation rate of >56 mm/h, and neutrophil-to-lymphocyte ratio of >8.02 were identified as major factors associated with surgical intervention.²⁶ Çetin et al evaluated paediatric DNSAs and concluded that patients with a baseline WBC count of $\leq 25200/\text{mm}^3$, with two or less than two cervical compartments, and without complications on admission could be treated successfully with conservative treatment.²⁷ In three paediatric studies including 178, 101, and 93 cases, abscess diameters of >2.2 cm, >2 cm, and >2.5 cm were found to predict the need for surgery.^{13,18,28} In a review evaluating paediatric DNSAs, indications for surgery included airway compromise, presence of complications, no clinical improvement after 48 hours of intravenous antibiotic treatment, abscess diameter of >2.2 cm on CT, age of <4 years, and intensive care unit admission.⁵ In another paediatric review, it was stated that the pooled success rate of conservative treatment in avoiding surgery was 0.517 (95% CI: 0.335-0.700), and when patients with immediate surgical intervention were excluded, the success rate was 0.991 (95% CI: 0.851-1.051), suggesting that conservative management could be a safe alternative to surgery.²⁹ In another trial, age less than 51 months was identified as a predictor for surgery.²⁸ In our study, we found that an abscess diameter greater than 2.4 cm was associated with surgical intervention. Although surgical management was slightly more common in patients younger than five years, we did not find any difference in age or any laboratory data between the surgical and conservative treatment groups. However, mean WBC count, ANC, ESR, and CRP levels were consistently increased and showed a status of inflammation. Likewise, Wilkie et al¹⁸ and Raffaldi et al³⁰ concluded that age, WBC count, and CRP were not predictive of requirement for surgery.

Our results support the findings of previous studies as nearly half of the patients were successfully treated with antibiotics alone.^{18,25,28} There is still debate on the timing of

the surgical approach. We found no difference in length of stay in the hospital comparing patients who underwent immediate or delayed surgery, as previously reported by Johnston et al.³¹ Cramer et al¹⁷ highlighted that there was no association between timing of surgery and morbidity and mortality in children, although they found delayed surgical drainage to increase morbidity and mortality in an adult population. The overall time interval between admission and surgery was a median of 2.0 days (IQR: 0.0-12.0) in our study, which means that some of our patients underwent surgery in the first 48 hours. Surgery was recommended for patients with complications, larger abscesses, and no clinical improvement after a 48-h period of intravenous antibiotic treatment.⁵ Thus, we wonder whether surgical intervention could be delayed until the 48 hours of the antibiotic course are completed.

Of all pus specimens, 38.5% resulted in positive cultures, a rate that was lower than expected. In a recent study, Donà et al²⁵ reported a 64.3% rate of positive pus specimens in paediatric DNSAs. This may be explained by the fact that many of the patients received antibiotics before referral at our hospital and all patients received antibiotic treatment from diagnosis to time of surgery.

Complications of DNSAs were calculated with an incidence of 2.2%.²⁸ Another trial reported a complication rate of 9.4% and concluded that higher complication rates were observed in younger children with retropharyngeal abscesses. *Staphylococcus aureus* was also more likely to be identified as the causative microorganism in children who developed complications. In another study, *Staphylococcus aureus* was identified more commonly in children aged <1 year.^{3,28,32} Fortunately, we encountered no complications in the present study. There was no difference in length of stay in the hospital in our patients who were managed medically or surgically, consistent with the literature. This may be explained by conservative management being indicated for patients without complications or with smaller abscess size. We think it is reasonable to encourage a more conservative treatment strategy. Length of stay in the hospital was negatively correlated with age and had a positive correlation with initial WBC count and ANC but not with ESR or CRP levels in our study. Likewise, Bolton et al³³ reported that higher WBC count was associated with longer stay in the hospital.

The limitation of our study lies in its retrospective nature. We used ICD codes to identify patients, but missing data may lead to the underestimating of the real number of cases. Furthermore, the data were obtained from a single

medical centre, so the sample size was relatively small due to the low prevalence of the disease.

In conclusion, DNSAs may present with a wide range of nonspecific symptoms and signs and serious complications may develop, so a high index of suspicion and prompt management are crucial. Surgical treatment was more common in patients aged <5 years. The abscess size was determined as the most important factor to help the physician select the treatment strategy. Although a lack of consensus on the optimal management or timing for surgery still remains, conservative treatment with close follow-up can be successfully applied in selected cases. Further research should focus on proposing a standardised management protocol for paediatric DNSAs.

Acknowledgements

None.

Declaration of Conflicting of Interests

The authors declare no conflict of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Original Article

Surgical Management of Rapunzel Syndrome: A Retrospective Report from Two Children's Medical Centres

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Abstract

Background: Rapunzel syndrome is a stomach trichobezoar with a long hairy tail that extends into the duodenum and small bowel. Endoscopy, often followed by laparotomy, and psychological intervention were all part of traditional treatment. The purpose of this study was to discuss our experience with seven cases of trichobezoars in the gastrointestinal tract. **Materials and methods:** A retrospective review of all cases of trichobezoar at two children's hospitals from 2010 to 2020 was performed. Demographic data, presenting complaints, imaging, surgical treatment, and subsequent management were collected. **Results:** All 7 patients were female, ages 4 to 13 years (mean, 9.3 years). Although multiple imaging modalities were necessary for preoperative diagnosis, most patients were accurately diagnosed without endoscopic evaluation (71%). All patients required an exploratory laparotomy for definitive treatment. At laparotomy, 3 patients were found to have post-pyloric extension of the trichobezoar (43%). No surgical complications or recurrences were discovered. **Conclusions:** Rapunzel syndrome should be diagnosed with a high degree of clinical suspicion, which can be established with a comprehensive history and radiographs, and laparotomy should be indicated. To avoid additional trichophagia and trichobezoars, psychiatric evaluation and management are essential.

Key words

Acute abdomen; Intussusception; Rapunzel syndrome; Trichobezoar; Trichophagia

Introduction

Rapunzel syndrome is a type of trichobezoar that is extremely rare. It was called after a lovely story about a young woman penned by the brothers Grimm in 1812.¹ It

mainly affects young women under the age of 20 and causes abdominal pain, nausea, vomiting, bloating, early satiety, weight loss, diarrhoea, and constipation. In delayed and neglected cases, complications such as anaemia, haematemesis, gastric ulcers, intestinal obstruction, perforation, and peritonitis were frequently reported.²⁻⁴

Despite the fact that a history of hair eating can aid with diagnosis, patients frequently present to the ER with abdominal pain, making preoperative diagnosis challenging. Abdominal X-rays reveal a nonspecific mass, while computed tomography scans reveal heterogeneous masses containing trapped air.⁵ Trichobezoars can be distinguished from other probable epigastric mass aetiologies (such as pseudocyst, duplicated cyst, or tumour) with a computed tomographic (CT) scan.⁶ For diagnosis, endoscopy is useful. Endoscopic removal of the bezoar, on the other hand, is rarely a permanent solution. Furthermore, endoscopic bezoar fragmentation can result

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Received November 19, 2021

in small bowel blockage. Despite several publications describing laparoscopic techniques to treatment, traditional laparotomy has remained the mainstay of treatment for bezoars that do not flow into the peritoneal cavity.^{7,8}

The purpose of this study was to summarise the clinical manifestations, physical examinations, radiological examination, and surgical outcomes of seven cases of Rapunzel syndrome and discuss the merits of current practice patterns.

Materials and Methods

From January 2010 to December 2020 in Shanghai Xinhua Hospital and Hangzhou Children's Hospital, seven consecutive cases of gastrointestinal tract (GIT) trichobezoars were reviewed after taking permission from the Hospital Institutional Review Board. Demographic data, elements of presentation, imaging, surgical treatment, and subsequent management were reviewed.

Results

There were seven female patients and no male patients identified. The median age at the time of presentation was 11 years old (range 4-13 years old). Table 1 summarises demographic information and characteristics. Stomach pain, abdominal distension, and vomiting were all common presenting symptoms in our study (Table 1). Five patients (71%) presented with acute symptoms as a result

of complications (intestinal obstruction in 4 patients and intussusception in 1). A history of trichophagia was mentioned in 5 (71%) of the patients. A palpable abdominal mass was the most prevalent physical examination finding. Only two individuals reported with bilious vomiting and intestinal blockage on radiographs. An abdominal scan revealed that one of the patients had intussusception.

When the patients presented to the emergency department, the workup for the etiology of their problems was different. Table 2 summarises the results of the preoperative evaluation. For the most part, multiple imaging modalities were necessary to accurately diagnose the bezoar. Despite the lack of solid confirmation via endoscopy, the majority of patients had a correct preoperative diagnosis of a trichobezoar.

Table 2 Preoperative evaluation

	Patient population (n = 7)
Preoperative diagnosis of trichobezoar	5 (71%)
Abdominal radiograph	3 (43%)
Abdominal ultrasound	3 (43%)
Abdominal computed tomography scan	2 (29%)
Upper GIT endoscopy	4 (57%)

Table 1 Patient clinical data

	Patient population (n = 7)
Female	7 (100%)
Mean age	9.3 y
Clinical manifestations	
Abdominal pain and vomiting	5 (71%)
Abdominal distension	2 (29%)
Chronic GI symptoms	5 (71%)
Small bowel obstruction	2(29%)
Peritonitis	3 (43%)
Palpable abdominal mass	3 (43%)
Trichophagia	6 (86%)
Trichotillomania	3 (43%)



Figure 1 Abdominal CT scan abdomen showing intragastric bezoar.

Following is a summary of the patients' perioperative care. A diagnostic endoscopy was performed on one patient who had been diagnosed with small intestinal obstruction in order to ascertain the cause. After detecting two hard lumps in the jejunum that looked like trichobezoars, the treatment was changed to a laparotomy. History, examinations, or endoscopy were used to make a preoperative diagnosis of trichobezoar in 5 individuals (71%). The patients who remained were diagnosed during surgery. After clinical optimisation, all of the patients received open surgery, with the exception of six who were operated on as an emergency. Endoscopic retrieval was attempted in three individuals, however none of them were successful. During the operation, one patient developed jejuno-jejunal intussusception while swallowing magnetic beads (Figures 3). Our operational findings, surgical

techniques, and patient outcomes are detailed in Table 3. All of the patients had no complications. The average length of stay was 12 days, with a range of 10 to 18 days. Following surgery, the patients were discharged and referred to the psychiatric department. Five patients who were recently managed are being followed up on, with the rest of the patients being lost to follow-up.

Discussion

Rapunzel syndrome is an uncommon form of trichobezoar in which long hair loops from the stomach protrude into the small intestine.¹ It is especially common in young females who have trichotillomania, a concurrent psychological condition that is typically untreated.

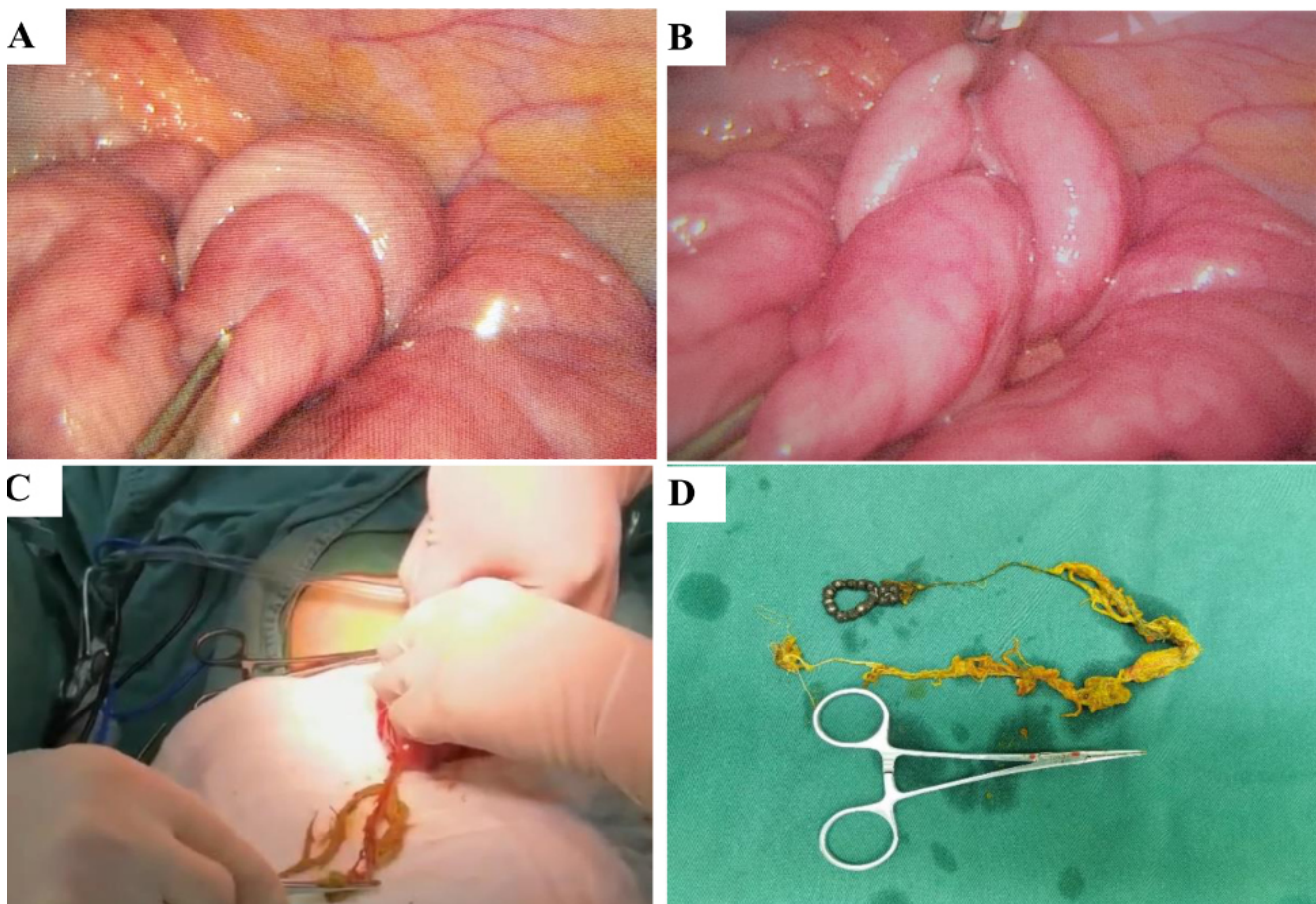


Figure 2 (A, B) Laparoscopy finding of a jejuno-jejunal intussusception, with attempted laparoscopic removal failed. (C) Enterotomy performed for removal of the intestinal trichobezoar concretion after reduction of jejuno-jejunal intussusception. (D) Complete trichobezoars and magnetic beads were removed, consisted of: (1) sixteen magnetic beads were found in the proximal jejunum, (2) a small intestinal trichobezoar.

Stomach trichobezoar can cause bleeding, perforation, and obstruction of the gastric outlet. Rapunzel syndrome commonly manifests later in life, after years of absorption of enormous volumes of hairs. Trichobezoar is most commonly found in the stomach, although it can also spread to the duodenum, resulting in the Rapunzel syndrome.

Rapunzel syndrome is frequently diagnosed late due to a low threshold of suspicion and the fact that individuals may go years without symptoms until the bezoar has grown large enough to cause intestinal obstruction. Depending on the degree of obstruction, the patient may have a palpable lump in the belly, abdominal discomfort, nausea, vomiting, weakness, and constipation. In the gastrointestinal tract, the bezoar can create an obstruction or a gastric ulcer. The telescoping of the proximal jejunum into the distal jejunum, which leads to intussusception, may have started with the extension and migration of the

trichobezoar tail into the jejunum.⁹ However, the lack of comorbidities and a complete medical history may make a preoperative diagnosis impossible. Furthermore, the majority of parents did not mention a history of hair consumption. Radiological examinations may confirm the preoperative diagnosis. In the context of a patient with trichophagia and a palpable mass, plain radiographs frequently show a stomach shaped partly opacified area. CT scan is a superior examination because it not only detects but also defines the extent of a heterogeneous bezoar.^{10,11} Upper GI endoscopy is the preferred diagnostic method, and it can also be used to treat minor bezoars.¹²

Endoscopic retrieval was attempted in four children in our study, but it was unsuccessful. To yet, the success rate of endoscopic retrieval is not encouraging. Laparotomy was used to successfully treat all of our patients. In a recent analysis of all case reports involving bezoars, 100 (92.5%) of 108 patients were treated with a laparotomy, with a

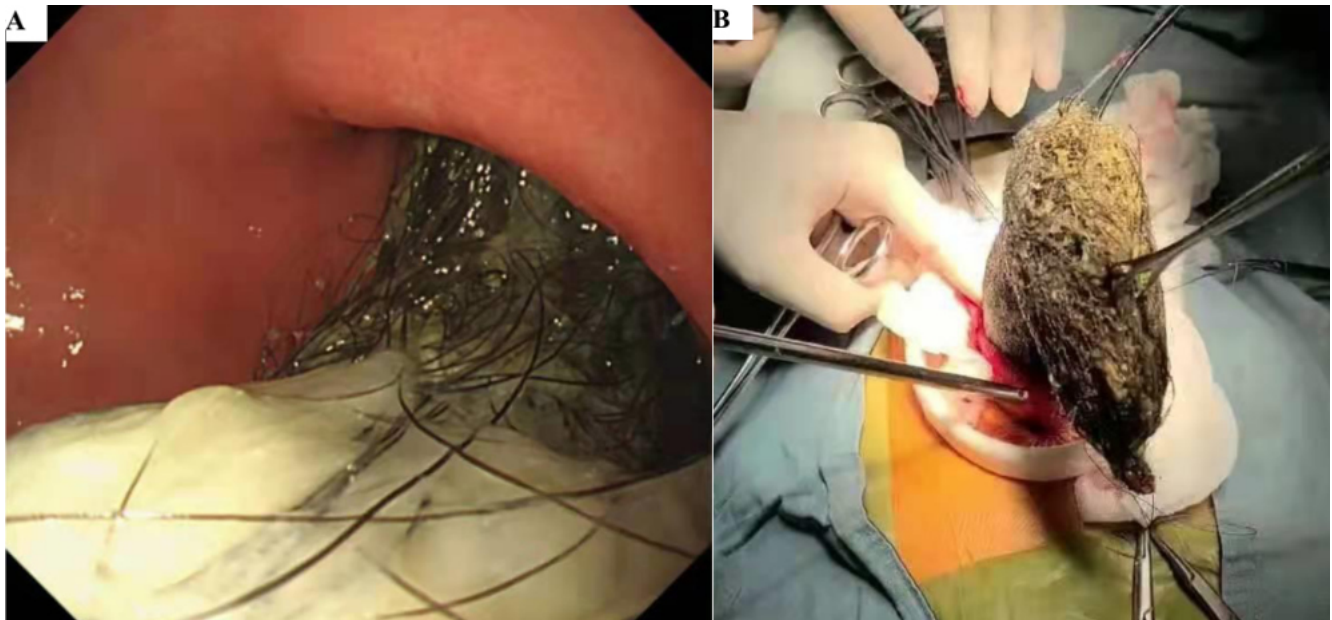


Figure 3 (A) Endoscopic finding of a trichobezoar extended beyond the pylorus, with attempted endoscopic removal failed. (B) A large gastric bezoar with duodenal extension measuring $10.5 \times 10.5 \times 8.5$ cm as it is delivered through the gastrotomy.

Table 3 Operative findings, surgical procedure and outcome

Patients	Surgery performed	Dimensions in bezoar	Outcome
Case 1	Gastrotomy and removal	15*8*6 cm	Alive
Case 2	Gastrotomy and removal	NR	Alive
Case 3	Enterotomy, Gastrotomy and removal	8*4*4 cm	Alive
Case 4	Gastrotomy and removal	17*13*10 cm	Alive
Case 5	Gastrotomy and removal	10*6*6 cm	Alive
Case 6	Enterotomy, Gastrotomy and removal	16*8*6 cm	Alive
Case 7	Enterotomy and removal	5*4*4 cm	Alive

success rate of 99 percent and a complication rate of 12 percent.¹³ Our findings are comparable, with a success rate of 100 percent and a complication rate of 0 percent. The average length of stay in the hospital was around one week, and all of the patients had good outcomes. One patient with a preoperative diagnosis of small bowel blockage was treated with laparoscopy at first, but when the jejuno-jejunal intussusception was discovered, the surgery was changed to an open procedure. Some authors were against the laparoscopic method because of the increased risk of bezoar contents spilling into the abdomen and the high conversion rates.¹³

Because the impulsive behaviour associated with trichophagia in these patients is difficult to manage, and the risk of recurrence is considerable, long-term mental treatment is essential, as well as follow-up endoscopic or contrast testing.¹⁴ Psychiatric care was sought by 71% of our patients. Every patient should get a psychiatric evaluation as part of their therapy.¹³ A randomised control trial investigated the efficacy of behavioural therapy compared with minimal attention control on patients with trichotillomania found that behavioural therapy was a superior treatment strategy for both management of symptoms and durability of treatment gains.¹⁵ Furthermore, A recent randomised control trial that compared habit reversal training (HRT) with treatment-as-usual (TAU) revealed that trichotillomania was largely improved with HRT compared to TAU.¹⁶ No one in our study experienced a recurrence. Recurrence that necessitated reoperation was uncommon, and it was largely owing to a lack of competent psychiatric follow-up.¹⁷

In conclusion, the diagnosis of Rapunzel syndrome requires a high index of clinical suspicion, which can be established with a thorough history combined with radiography. Early diagnosis and prompt surgical intervention after rapid clinical optimisation help ensure a good prognosis. Psychiatric evaluation and management are key to prevent further trichophagia and trichobezoars.

Statement of Ethics

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Hangzhou Children's Hospital ethical review committee and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's parents for publication of this article and any accompanying images.

Disclosure Statement

The authors declare no conflict of interests.

Funding Sources

The study was supported by grant from the Medical health Science and Technology project of Zhejiang Province (2022492938).

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Case Report

Infantile Gaucher Disease Due to a Novel Variant in the *PSAP* Gene

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Abstract

Prosaposin deficiency is a rapidly progressive fatal neurovisceral lysosomal storage disorder (LSD) caused by pathogenic variation in the *PSAP* gene. The phenotype overlaps with LSDs and the short lifespan of patients has led to misdiagnosis of these complex and rare diseases. A 2-month-old girl presented with encephalopathy, resistant tonic-clonic seizures, giant hepatosplenomegaly, hypotonia, and delay in head control with lack of sucking reflex. Due to persistent respiratory distress and resistant seizures, the child succumbed in the fourth month of her life. Although clinical findings suggest Gaucher disease, the diagnosis was rejected because of normal β -glucosidase activity. Whole exome sequencing identified a previously unidentified homozygous, frameshift, clearly pathogenic variant of p.Arg186Profs*9 (c.551dupG) in the *PSAP* gene. This frameshift variation has been classified as "likely pathogenic," according to the ACMG Guidelines. As a result of homozygous variation in *PSAP* gene our case was accepted as combined prosaposin deficiency with early infantile onset and severe neurological involvement. Detected frameshift variation that leading protein length changes has not been previously reported.

Key words

Encephalopathy; Hepatosplenomegaly; Hypotonia; Infant; Seizures

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Received March 31, 2022

Introduction

Prosaposin (pSap) deficiency is a rapidly progressive fatal neurovisceral lysosomal storage disorder caused by mutations in the *PSAP* gene.¹ It is characterised by the absence of pSap and pSap proteolytic processing products. These polypeptide products, called saposins (Saps, sphingolipidhydrolase activating proteins), are activators of a number of lysosomal sphingolipid hydrolases. In the absence of Saps, sphingolipid substrates remain intact. Substrates accumulating in visceral cells lead to swelling of lysosomes. It results in organ failure similar to classical lipid storage disorders.²

Inherited deficiency of the major Saps proteins Sap A, Sap B or Sap C causes sphingolipidoses, which are noted

as late-onset Krabbe disease, metachromatic leukodystrophy (MLD), and Gaucher disease (GD), respectively. A mutation in the Sap D domain of another pSap causes Farber's disease.³

Our patient is an ultra rare case in the literature with a homozygous variation in the *PSAP* gene that causes combined saposin deficiency. The detected variation has not been previously reported. Our patient provides new information concerning of combined saposin deficiency. With our case, we wanted to emphasize the importance of genetic diagnosis in rare diseases.

Case

A 2-month-old girl, the fourth child of consanguineous parents, presented with encephalopathy, resistant tonic-clonic seizures, giant hepatosplenomegaly, hypotonia, and failure to thrive (delay in head control with lack of sucking reflex). The child was born with normal delivery and the birth weight was 3 kg. At birth, the baby presented with respiratory distress. In the first month, tonic-clonic seizures, abdominal distension, hepatosplenomegaly, hypotonia in all extremities and deep tendon reflexes were evident. Response to antiepileptic drug was poor and the patient continued to be in encephalopathic condition. Ventilator support was given to the child due to recurrent

respiratory distress. Brain magnetic resonance imaging showed signal changes in hypointense myelin foci with corticomedullary enlargement in the hyperintense demyelinating area of the white matter on both sides suggesting MLD. Biochemically, the child had leukopenia, anaemia, thrombocytopenia, and abnormal liver transaminases. Acid sphingomyelinase and β -glucosidase activity were normal, plasma chitotriosidase level was elevated, and galactosylceramidase activity was low. Gaucher cells were not found in the bone marrow biopsy and smear. Liver biopsy was consistent with lysosomal storage disease (LSD) (Figure 1). Due to persistent respiratory distress and resistant seizures, the child succumbed in the fourth month of her life. Although clinical findings suggest Gaucher disease, the diagnosis was dismissed due to normal β -glucosidase activity and absence of Gaucher cells in the bone marrow. In whole-exome sequencing, a previously unidentified homozygous, clearly pathogenic p.Arg186Profs*9 (c.551dupG) variant was identified in the *PSAP* gene (Figure 2). This variation has been classified as "likely pathogenic" according to the ACMG.⁴ As a result of homozygous frameshift variation in the *PSAP* gene in genetic examination, our case was accepted as combined pSap deficiency with early infantile onset and severe neurological involvement. Written consent was obtained from the patient's parents for publication.

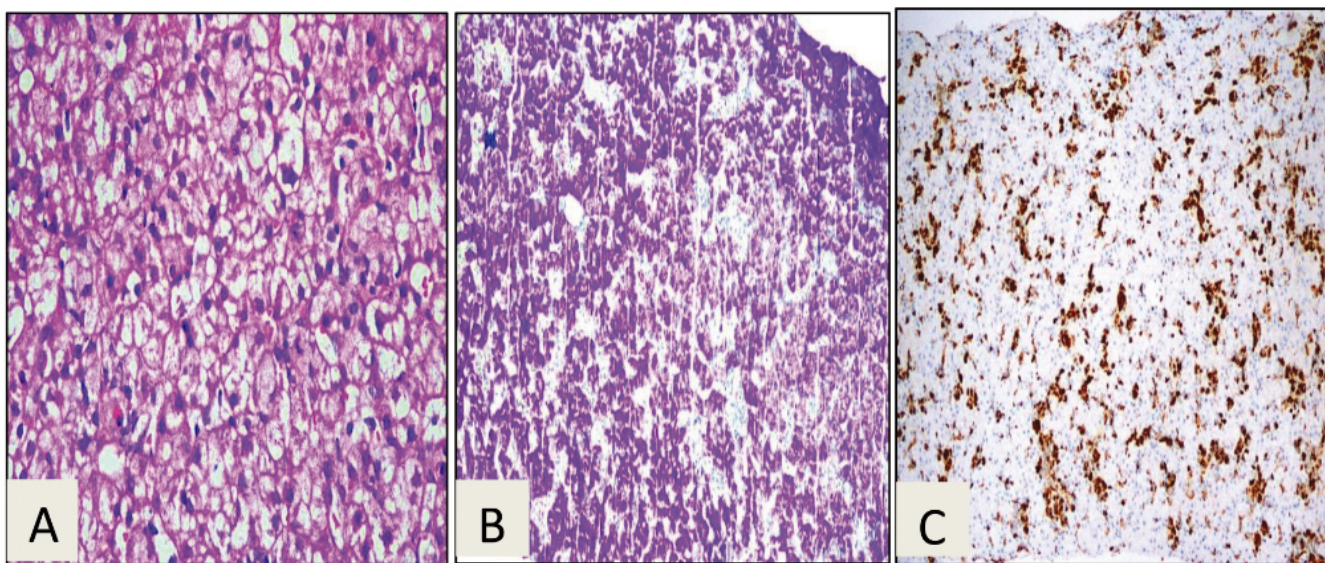


Figure 1 Liver biopsy. A. Swelling and vacuolar-foamy appearance in hepatocytes (H&E 400x), B. No staining with histochemical PAS-Ab (PAS-Ab 100x), C. Staining in foamy histiocytes with CD68 (CD68, DAB 100x).

Discussion

LSDs are congenital metabolic diseases characterised by excessive accumulation of substrates in cells of various organs due to defective functioning of lysosomes. They cause dysfunction in the organs where they accumulate and as a result, morbidity and mortality.⁵ GD is one of the most common lysosomal storage diseases. GD type 2 (also called acute neuronopathic GD) has an estimated incidence of 1 in 150,000.⁶

The phenotypic overlap with LSDs and the short life span of patients has led to misdiagnosis of this complex and rare disease. The initial clinical of our patient suggested GD. It included dismyelination of cerebral white matter with a very rapid neurological deterioration that resulted in death at four months. This diagnosis was abandoned because the glucocerebrosidase enzyme was normal in our patient and Gaucher cells were not observed in the bone marrow. Krabbe disease was also considered in the diagnosis due to the low level of galactoseramidase enzyme, but it was excluded because the clinical findings were not compatible. In order to find out the final diagnosis, whole exome sequencing was performed. A homozygous variation in the *PSAP* gene, p.Arg186Profs*9

(c.551dupG) was discovered. Apart from genetic examination, a specific and rapid method is needed for rapid diagnosis. Molecular analysis and plasma lysoSL profiling resulting in increased amounts of LysoGb3 and GLSph can be performed for early diagnosis of pSap deficiency.⁷ Motta et al⁸ screened plasma lysoSLs and the diagnosis of pSap deficiency was confirmed by molecular analysis. They showed that the quantitative analysis of plasma lysoSLs is a very informative tool in the early diagnosis of pSap deficiency and can be used to screen for different sphingolipids such as GD, Fabry disease, Niemann-Pick type A/B and type.⁸ Because the clinical course of our patient was rapidly progressive and resulted in death in the early period, these examinations could not be performed.

In summary, plasma lysoSL profiling can be used as a rapid and informative pre-test that can be used to guide diagnostic genetic analysis in metabolic disorders with complex phenotypes lacking pathognomonic features. We also wanted to draw attention to the necessity of genetic examination to clarify the diagnosis of pSap deficiency in infants with early-onset severe neurological involvement, hepatosplenomegaly, and failure to thrive.

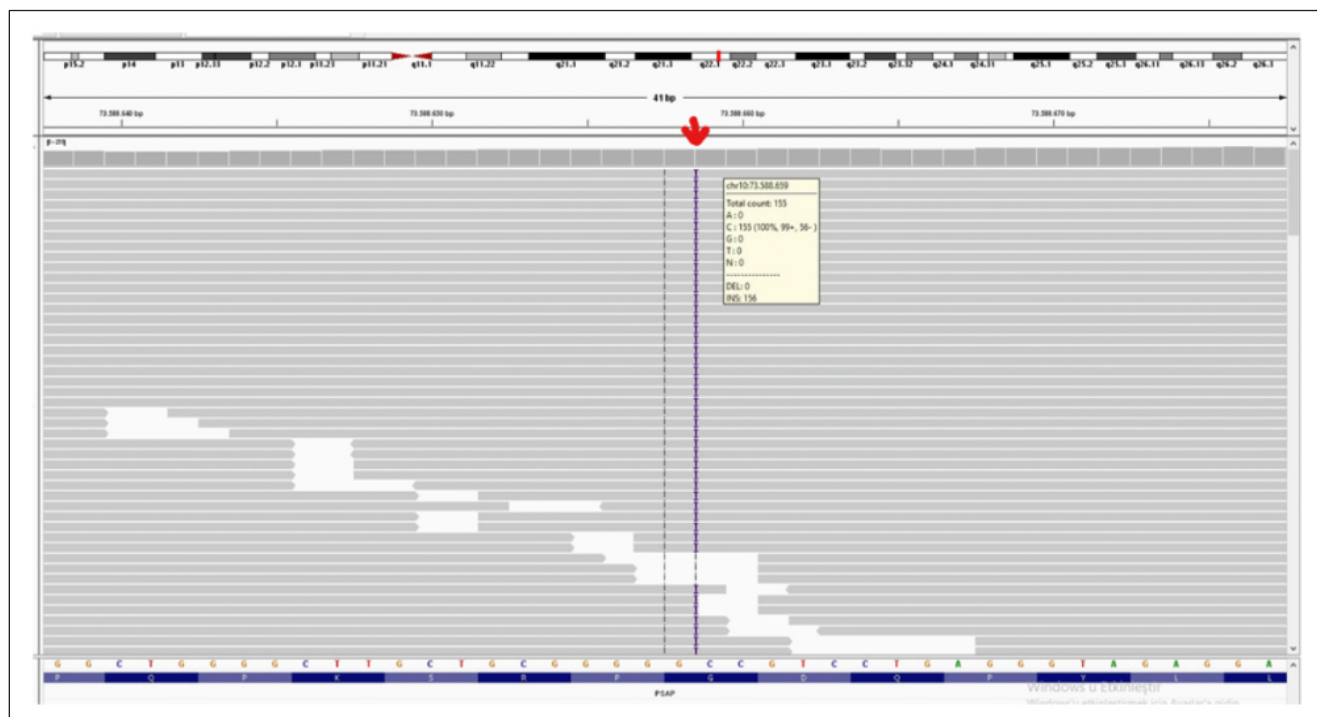


Figure 2 The homozygous p.Arg186Profs*9 (c.551dupG) variation discovered in the patient.

Declaration of Interest

The author(s) indicated no potential conflicts of interest. No financial or nonfinancial benefits have been received or will be received from any party related directly or indirectly to the subject of this article.

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Case Report

Atypical Mouth/Lip Asymmetry Affecting a Newborn with Bilateral Cleft Lip and Palate: A Case Report

PMY TANG, EKW CHAN, NSY CHAO, KH LEE

Abstract

Introduction: Congenital hypoplasia of depressor angularis oris muscle (CHDAOM) is a rare cause of asymmetric crying facies in newborn. The association of CHDAOM with bilateral cleft lip and palate has not been reported. **Aims:** We report a case of a neonate with bilateral cleft lip and palate and CHDAOM. **Methods:** A full term baby girl with bilateral cleft lip and palate was transferred to our hospital for centralised care of cleft anomalies. She was born by spontaneous vaginal delivery with a birth weight of 2.4 kg and no history of birth trauma. Clinical examination showed complete bilateral cleft lip and palate. Upon further evaluation, while her facial features remained symmetrical at rest, there was drooping (downward and lateral movement) of the left sided lower corner of the mouth on crying, with preserved upper face symmetry. Magnetic resonance imaging brain confirmed normal brainstem structure. Genetic test did not reveal any microdeletion of the chromosome 22q11. Echocardiogram showed no significant cardiac structural anomalies. As the baby was unable to tolerate oral feeding with significant choking and recurrent aspiration, endoscopy was performed and it showed right partial vocal cord paralysis. Ultrasound of the lips showed thinner and smaller right depressor angularis oris muscle, confirming the diagnosis of CHDAOM on the right. **Results:** As the baby remained tube - feeding dependent, elective laparoscopic gastrostomy and surgical repair of the bilateral cleft lip were performed at 4 months of age. Post-op recovery was uneventful. **Conclusions:** While surgeons might be well familiar with the pre-operative management of baby with cleft lip anomalies, it is important to observe the baby for other unusual facial anomalies which in this case only become apparent at crying while manifesting a contralateral pathology. Timely documentation, appropriate investigations and anomalies screening, counselling on expectations on surgical outcomes are important when managing patient with cleft lip/palate anomalies and CHDAOM.

Key words

Cleft lip; Depressor angularis oris

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Received January 14, 2022

Introduction

Bilateral cleft lip anomalies are often diagnosed antenatally nowadays, with the increasing use of routine antenatal screening ultrasound, giving parents the opportunities to learn more about the condition. However, a dynamic facial disorder, such as the asymmetric crying facies would be almost impossible to be detected antenatally. There is currently scanty literature describing patients suffering from these two conditions

simultaneously. We report a full term newborn girl who is suffering from bilateral cleft lip and palate and congenital hypoplasia of the depressor angularis oris muscle (CHDAOM).

Case Report

A female neonate was born by spontaneous vaginal delivery at term. There was known antenatal diagnosis of bilateral cleft lip and unremarkable family history. The delivery was smooth with no apparent birth trauma. The birth weight was 2.4 kg. The baby was then transferred to our hospital for the centralised care of babies with cleft anomalies. At physical examination, apart from bilateral cleft lip and palate, there was no other obvious facial dysmorphism. Echo-cardiogram did not reveal any significant structural anomaly. Pre-op lip taping was applied and oral motor training was commenced, as per our hospital protocol for all patients with cleft anomalies. However, upon swallowing assessment by the speech therapist, it was found that the baby had very poor swallowing effort. Desaturation was often observed during oral feeding and there were also multiple episodes of aspiration pneumonia. In view of suspected anatomical anomalies that might be impairing her swallowing, examination under anaesthesia was performed by the Ear, Nose & Throat surgeon, showing partial paralysis of the right vocal cord. Clinical examination showed no cranial nerve palsy. With time, we started to notice an increasing obvious asymmetry of the lower face when the baby was

crying, with the left sided corner of the mouth moving downwards and laterally when the right sided corner of the mouth remained unmoved (Figure 1). The upper face musculature including the frontalis, orbicularis, oculi and the zygomaticus remained symmetrical at rest and when crying. Clinical evaluation of the symmetry of the nasolabial fold was difficult given the baby's bilateral cleft lip. Magnetic resonance imaging brain was performed to exclude neurological cause for the asymmetric facies and it confirmed no structural anomaly in the brain and along the course of the facial nerve. Ultrasound of the lips showed thinner and smaller right depressor angularis oris muscle, confirming the clinical diagnosis of CHDAOM on the right (Figure 2). The diagnosis of congenital hypoplasia of depressor angularis oris muscle was made, the natural course of the disease and management options were explained to the parents. With the mother's consent, genetic testing was performed and it did not reveal any micro-deletion of the chromosome 22q11. Elective laparoscopic gastrostomy and repair of the bilateral cleft lip was performed at 4 months of age and the post op recovery was uneventful. The drooping of the left sided corner of the mouth when crying remained similar after the cleft lip repair (Figure 3).

Discussion

CHDAOM had been reported to have an incidence of 6 per 1000 live birth and it was often confused with facial nerve palsy.¹ It attaches to the skin and the mucous membrane of the lower lip, drawing the lower corner of mouth downward and everts the lower lip.² Hence, when the baby is crying, the angle of mouth would be pulled down on normal side due to unopposed action of depressor angularis oris muscle while no movement on the hypoplastic side. The lower lip on the affected side would usually appear thinner and smaller due to lack of eversion and muscle agenesis. According to the literature, although the cause of hypoplastic development of the depressor angularis oris muscles remained idiopathic, intra-uterine subclinical viral infection and familial heredity have been speculated to have some causative influence.³ CHDAOM is often characterised by the isolated involvement of the corner of the mouth, sparing the upper face, resulting in symmetrical forehead wrinkling, eyes closure and nasolabial fold depth. Although CHDAOM was usually a clinical diagnosis, such diagnosis in a patient with underlying bilateral cleft anomaly would be difficult, especially with early pre-op surgical adjuncts such as lip



Figure 1 Pre-operative photo showing bilateral cleft lip and left sided drooping of the mouth when crying, with the pre-op lip taping and oral gastric feeding tube.

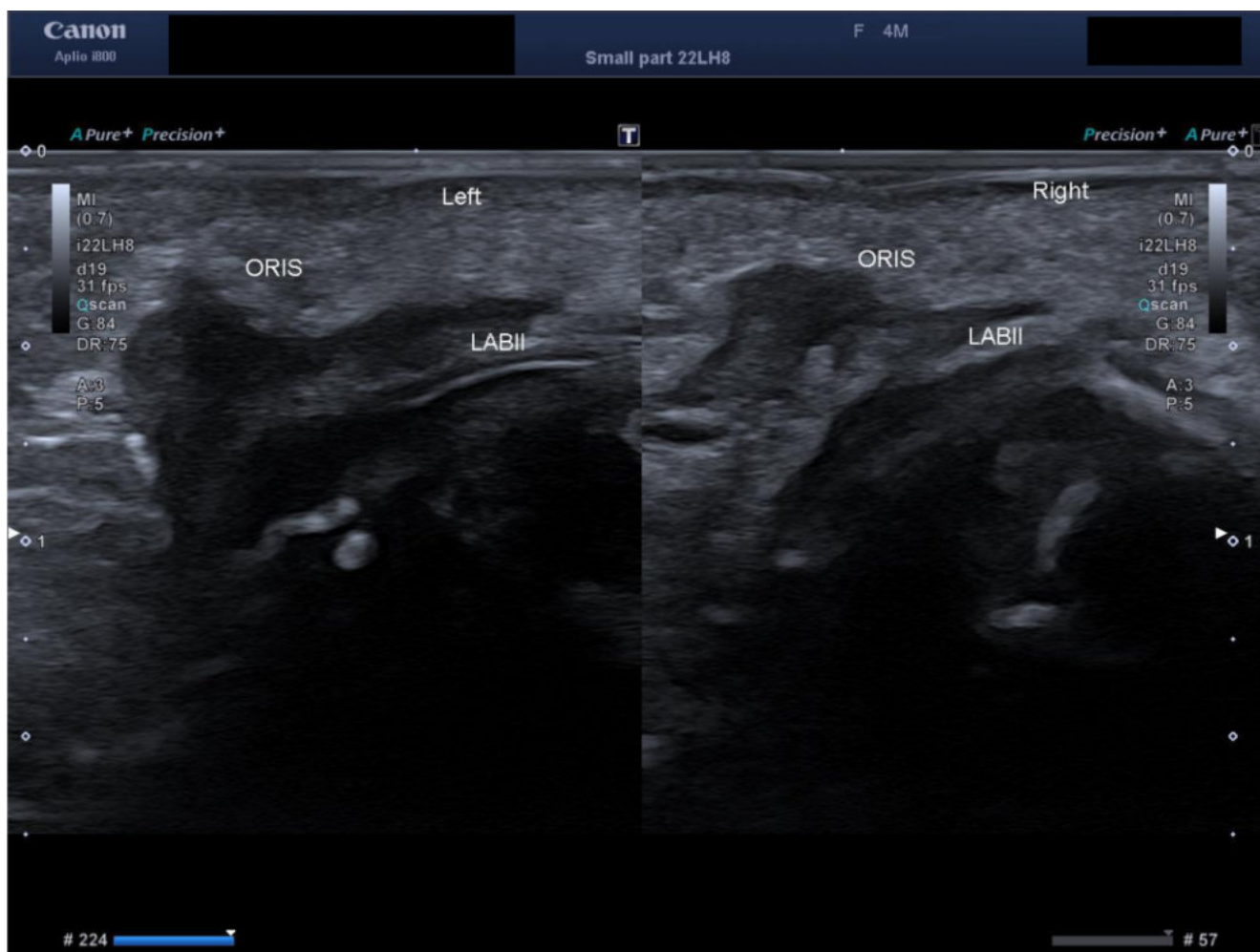


Figure 2 Ultrasound finding of thinner and smaller right depressor angularis oris muscle (2.4 mm) compared to the normal left depressor angularis oris muscle (3.2 mm).



Figure 3 Post-operative photo showing persistent left sided drooping of the mouth when crying.

taping or naso-alveolar molding, which might physically interfere with the interpretation of facial dynamic movement. In addition, in our case, as the patient was dependent on oral-gastric tube feeding, the presence of the feeding tube would further complicate the clinical picture. The partial unilateral vocal cord palsy could potentially explain the choking and aspiration, and since the baby has improved oral feeding clinically, no follow up endoscopic assessment was arranged. While facial nerve pathologies such as nerve compression in utero, trauma to the facial nerve during delivery, or congenital facial nerve palsy may give rise to similar clinical presentation, the facial asymmetry in these cases would usually be present both at rest and while crying. Electro-diagnostic testing of the facial nerve has been advocated in some centers to rule out facial nerve pathology,⁴ however, it was not done in our

case due to limited resource. Instead, ultrasound was utilised to demonstrate the thinning of the muscle at the affected side, confirming the diagnosis of CHDAOM.² Fortunately, we were able to make the diagnosis of CHDAOM prior to the surgical repair of the bilateral cleft lip, and timely appropriate counseling could be given. CHDAOM is a benign condition and it does not affect speaking or eating in the long term follow up, while botulinium-A toxin injection to the unaffected side of the depressor angularis oris muscles to obtain temporary facial symmetry had been described in the literature, the parents opted for conservative management for the time being. The prognosis of the return of muscle function has not been well documented, some mentioned that the dynamic facial asymmetry would become less noticeable after the child becomes older as the adjacent muscles may develop some compensatory movement. Intervention is usually considered when there is presence of social inhibition or psychological difficulties. While CHDAOM usually occurs as an isolated clinical finding, 45%-70% of cases could occur with other congenital malformations. Thorough physical examination and comprehensive newborn screening should be performed to rule out potential associated syndromes and to facilitate prompt treatment of the more serious co-existing abnormalities.³

Declaration of Interest

There are no conflicts of interests.

Financial Support and Sponsorship

Nil.

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Case Report

MOG-IgG Associated Brainstem Encephalitis in a Chinese Boy: Complication of *Mycoplasma pneumoniae* Infection

HT LEUNG, KH MA, KW TSUI

Abstract

MOG-IgG associated disorder is uncommon in children. It has a wide range of presentation which may make diagnosis difficult. The triggering factor for the disease is not well reported. We reported a 5-year-old Chinese boy with slurred speech and unsteady gait, presented ten days after *Mycoplasma pneumoniae* infection, and he was later diagnosed to have MOG-IgG associated brainstem encephalitis.

Key words

Brainstem encephalitis; MOG-IgG associated disorder; *Mycoplasma pneumoniae*

Introduction

MOG-IgG associated disorder (MOGAD) is an uncommon acquired immune mediated demyelinating disease, and is recently recognised as a distinct clinical entity. Myelin oligodendrocyte glycoprotein antibody (MOG-Ab) targets the myelin oligodendrocyte glycoprotein (MOG) on the outer surface of the myelin sheath and plasma membrane of oligodendrocyte, leading to a spectrum of demyelinating syndromes, such as acute disseminated encephalomyelitis (ADEM), optic neuritis (ON) and transverse myelitis.¹ While demyelinating disease was well-known to be triggered by viral infection or immunisation, to our knowledge, only one case of MOG-associated ADEM was reported following *Mycoplasma pneumoniae* infection in paediatric population.² Our case demonstrated different clinical features and treatment strategy that was worth reporting.

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Received August 13, 2022

We described a 5-year-old Chinese boy, who developed slurred speech and unsteady gait following *Mycoplasma pneumoniae* infection was finally diagnosed to have MOG-IgG associated brainstem encephalitis.

Case Report

In June 2019, a 5-year-old locally born Chinese boy with good past health was first admitted to our hospital with 5-day history of fever and dry cough. On examination, his temperature was 38.5°C, blood pressure 94/59 mmHg, pulse rate 109 beats per minute and respiratory rate of 32 per minute. Examination of chest revealed bilateral basal crepitation with no respiratory distress. Cardiovascular, abdomen and neurological examinations were unremarkable.

Complete blood count, liver function test and renal function tests were normal. C-reactive protein (CRP) was elevated at 17.3 mg/L (<9.9 mg/L). Nasopharyngeal swab for *Mycoplasma pneumoniae* DNA polymerase chain reaction (PCR) was positive. It was negative for influenza A, influenza B, adenovirus, parainfluenza virus and enterovirus/rhinovirus. Chest X-ray showed no consolidation and pleural effusion. Patient was treated as *Mycoplasma pneumoniae* with Azithromycin. Fever settled and cough improved, hence he was discharged three days after admission.

Ten days after fever onset, patient was readmitted to

our department for slurred speech and unsteady gait. There was no drowsiness, focal weakness, headache and seizure. Physical examination revealed that he was afebrile. The blood pressure was elevated, up to 150/75 mmHg. The patient was fully conscious and showed mild slurred speech with associated gurgling sound. Examination showed mild truncal ataxia with wide-based gait. Other cerebellar signs were negative. Otherwise, examination of the cranial nerves was unremarkable and the gag reflex was present. He had normal motor tone, full muscle power and normal deep tendon reflexes with bilateral down going plantar response. Chest, cardiovascular and abdominal examinations were unremarkable.

Repeated blood tests showed thrombocytosis with platelet count of $576 \times 10^9/L$ ($150-384 \times 10^9/L$). The white cell count and haemoglobin were normal. The previously elevated CRP was normalised. Previous *Mycoplasma pneumoniae* came back to be 23S rRNA Gene positive. Chest X-ray showed no interval change. Magnetic resonance imaging (MRI) brain showed fluffy T2 hyper-intense signals over the medulla oblongata, central and posterior portion of pons, substantia nigra and periaqueductal region (Figure 1). There was neither associated restricted diffusion nor abnormal contrast enhancement.

Lumbar puncture was performed and cerebral spinal fluid (CSF) yielded normal white cell count and no red

blood cell. The protein and glucose levels were normal. There was no bacterial growth. Latex agglutination showed negative for *Escherichia coli* K1, *Streptococcus* group B, *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Haemophilus influenzae* type B, *Cryptococcus antigen*. PCR was negative for herpes simplex virus DNA, enterovirus RNA, varicella zoster virus DNA, human herpesvirus 6 DNA and Japanese encephalitis. CSF for *Mycoplasma pneumoniae* PCR was not performed as validated test was not available locally.

Patient was empirically started on IV Cefotaxime and IV Levofloxacin on admission. He was also put on intravenous immunoglobulin (IVIG) of total 2 gram/kg for 2 days for suspected post infectious immune mediated encephalitis. Patient responded well to the treatment. He was given a dose of hydralazine for elevated blood pressure, which was subsequently normalised. The patient was also assessed by speech therapist and confirmed to have dysphagia. Feeding was gradually stepped up from soft diet under the guidance of speech therapist. He then tolerated normal diet 3 days after completion of IVIG. Slurred speech and unsteady gait gradually improved after IVIG and fully resolved 3 days afterwards.

Pre-IVIG sample later came back showing the serum anti-MOG was positive. Serum anti-aquaporin-4, anti-NMDA-receptor, anti-GQ1b, anti-GM1, anti-GD1b, anti-CASPR2, anti-LGI1, anti-AMPA1/2, anti-DPPX, anti-

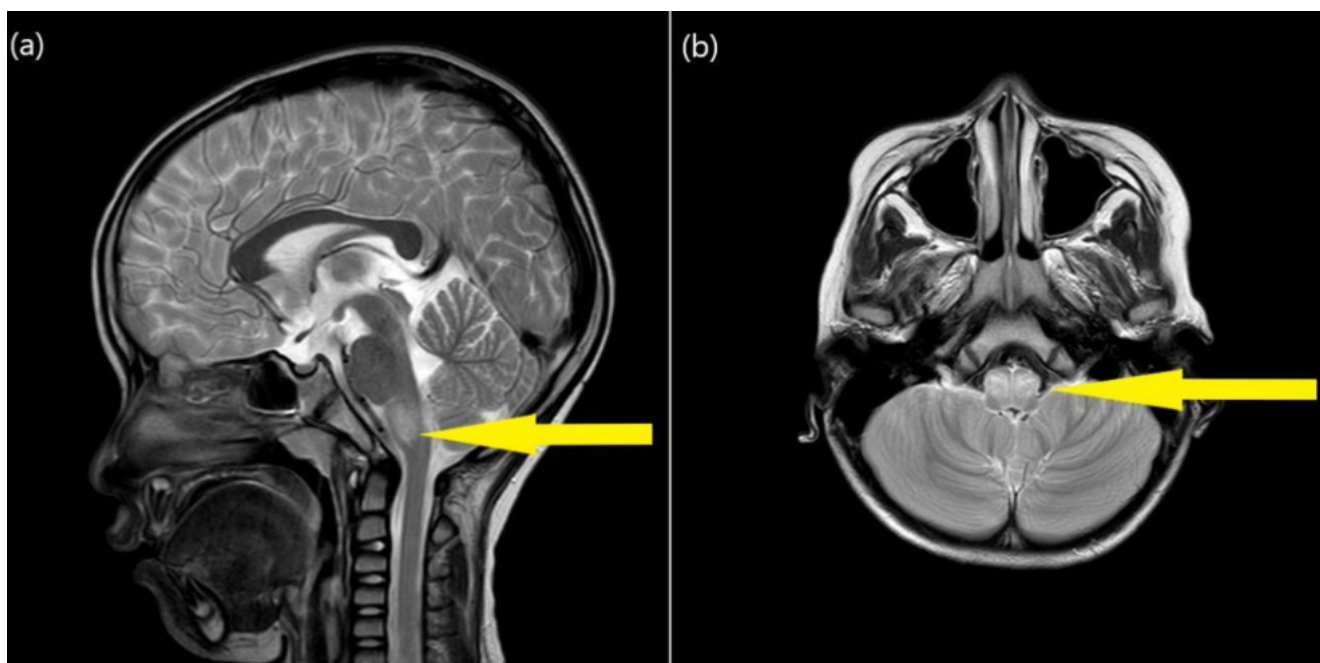


Figure 1 Magnetic resonance imaging brain showing fluffy T2 hyper-intense signals over the brainstem. (a) Sagittal plane (b) Axial plane.

GABAR B1/B2 were all negative. CSF anti-NMDA-receptor was also negative. Patient was diagnosed as MOG-associated brainstem encephalitis, as sequelae of *Mycoplasma pneumoniae* infection.

Visual evoked potential three months later was normal. MRI brain showed resolution of brainstem encephalitic change. Repeated serum test for anti-MOG 6 months later was negative. Patient had no relapse but he defaulted follow up after six months.

Discussion

MOGAD is a rare disease entity in paediatric population, with a higher incidence compared to adults (0.31 versus 0.16 per 100,000 populations).³ The development of highly specific cell-based assay allowed the detection of MOG-Ab in one third of the paediatric patients with acquired demyelinating syndrome.¹ MOG-Ab was found to be encephalitogenic and a wide variety of clinical manifestations have been described in these patients. Hence, MOGAD is now emerged as a new neuroinflammatory disease distinct from other acquired demyelinating syndromes of the central nervous system like neuromyelitis optica spectrum disorder and multiple sclerosis. MOGAD can present as different clinical phenotypes initially, which changes with age from ADEM in children to optic neuritis and myelitis in adults. Brainstem manifestation was quite infrequent at any age.⁴ Isolated attack of brainstem was reported down to 1.8% in a cohort. Although up to one third of patient can be asymptomatic, they can develop hypoventilation, dysarthria, dysphagia, balance difficulties, limbs weakness and ataxia.⁵ In our patient, he was tested positive for MOG-IgG, and the MRI brain showed involvement of the midbrain (periaqueductal region, substantia nigra), pons and medulla oblongata that could account for the unsteady gait, elevated blood pressure, slurred speech and dysphagia. We hence diagnosed our patient suffered from an exceedingly rare complication following *Mycoplasma pneumoniae* infection in paediatric population, which is MOG-IgG associated brainstem encephalitis.

Mycoplasma pneumoniae infection is a common cause of community-acquired pneumonia. It was well known that infection can be complicated by encephalitis, which can either caused by direct invasion or immune-mediated mechanism. These mechanisms are not mutually exclusive. Despite CSF *M. pneumoniae* DNA was not performed in our patient, the utility of the test in

identifying the true pathogenic mechanism might be limited as *M. pneumoniae* DNA was usually not detectable in either of the cases.⁶ Instead, our patient's symptoms arose after fever settled, together with the presence of anti-MOG, this would favour a greater contribution of the indirect type of nervous system damage by autoantibodies. It was hypothesized that molecular mimicry between some *M. pneumoniae* component and host myelin glycolipids contribute to auto-antibodies formation, which causes damage to splenium of corpus callosum or adjacent white matter, leading to encephalitis.⁶ An example of autoantibodies would include anti-MOG, which was reported to cause neuroinflammatory disease like ADEM.² In looking back to our case, brainstem encephalitis could have been caused by indirect type of nervous system damage secondary to MOG-Ab formation following *M. pneumoniae* infection. However, further study is required to accurately delineate the relationship between *M. pneumoniae* infection and anti-MOG associated disorder.

The optimal acute treatment for both MOGAD and neurological complications of *M. pneumoniae* infection are debated. Antibiotic treatment is the cornerstone of all *M. pneumoniae* related neurological disease. Studies reported antibiotics help prevent direct central nervous system damage and interrupt autoimmunity. However, the effectiveness of corticosteroids, IVIG and immunosuppressive drugs are still unclear but they can be considered in selective cases.⁶ As for MOGAD, there is lack of controlled trials in paediatric population. Intravenous high dose corticosteroid was considered as first line treatment. For patients with poor response to corticosteroid, IVIG or therapeutic plasma exchange was considered as second line therapy.⁷ For our patient, he was started on antibiotics with subsequent IVIG and showed good response. Interestingly, animal study showed that IVIG reduced autoantibodies associated demyelination by interfering with the complement cascade instead of blocking of the anti-MOG antibodies.⁸ The effectiveness of IVIG in our case would serve as a reference for future study on treatment of MOGAD, particularly after *M. pneumoniae* infection.

Serial testing of MOG-Ab might be useful in patients with MOGAD. 70-80 percent of children with MOGAD develop monophasic disease and hence their antibodies likely to disappear over time, with a median of 12 months.⁹ Children with persistent MOG-Ab are at risk of developing relapsing acquired demyelinating disease like multiphasic ADEM. Testing patient for conversion to seronegative

might have prognostic implication, hence, it was recommended to recheck MOG-Ab 6-12 months after acute attack.¹⁰ Our patient with good recovery showed negative MOG-Ab at 6 months after initial attack. However, the lack of long term data in children warrants continuous follow up for relapse of the disease.

In conclusion, MOGAD can be a complication of *Mycoplasma pneumoniae* infection. Physician should be alert of this disease entity, especially for patients presenting with neurological symptoms following *Mycoplasma pneumoniae* infection. Once diagnosis is made, appropriate treatment can be offered and our case also highlighted the potential use of IVIG as first line treatment.

Declaration of Interest

There are no conflicts of interests.

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Letter to the Editor

The Diversity of Paediatric Problems – Suggestions to Keep up the Learning Curve

Dear Editor,

I read with interest your recent editorial.¹ You raised the difficulty in defining the core in general paediatrics amidst the rapid development in paediatric knowledge. You mentioned that these is nothing to replace the exposure to sharing of experiences in problems in both hospital and general paediatric practice. The Department of Paediatrics of Queen Elizabeth Hospital have worked diligently publishing 2 books on past interesting patients: *Clinical Paediatrics 101* and *202*.^{2,3} The editors wish to use these to put into action their endeavour in medical education, specialist training and safeguarding quality patient care. Now there are regular case presentation meetings in various hospitals, community paediatric service units and private study groups. In the near future, would it not be possible for our fellows and members of the Hong Kong College of Paediatricians, both local and overseas, to gain easy access to regularly held clinical case discussions, either in person or via the internet? The Hong Kong Children's Hospital can be one of the venues supported by the various training units and study groups as in the hub and spoke model. Moreover, these can be recorded, archived and stored for a cycle of, say, 3 years so that fellows and members can watch them, complete the assessment and gain CME marks at convenient times and places.

The medical knowledge explosion is happening too quickly for anyone doctor to catch up easily. The College may think of organizing conferences on "Recent Advances in Paediatrics" in the form of multiple short lucid presentations, maybe cooperating with other tertiary educational institutions, once every 3 years coinciding with the CME cycles. Useful new knowledge, technologies, safety issues and practice changes may be disseminated directly, timely and regularly in these meetings hoping to attract a large audience among the College members, fellows and other interested health care professionals. A certificate may be awarded after an MCQ

or other forms of assessment.

Regarding the issue of the scope of post-fellowship level General Paediatrics, there would be diversity. Surely one has one's own way of keeping up one's learning curve. Besides adding on the various subspecialty interests to the mainstream general paediatricians' training, the College may consider establishing two sidestreams, namely, hospital paediatrics and community paediatrics so as to tailor the relevant training experiences to suit real practicing clinicians better. For the scope of hospital paediatrics, one may use the contents in the updated edition of the *Oxford Handbook of Paediatrics*⁴ as reference; for community paediatrics: the *Oxford Specialist Handbook of Community Paediatrics*.⁵ Another useful reference for the scope of hospital paediatrics is the *The Hospital for Sick Children Handbook of Pediatrics*,⁶ inside which there are many useful tables, charts and algorithms.

Learning medicine is just like sailing through the sea with no shore, one can only stay diligent and move forward, and do not forget to enjoy the beautiful sceneries.

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Clinical Quiz

What is the diagnosis?

PWC **Lo**, SLK **LEE**, TTW **CHOW**, JYL **TUNG**

History

A 15-year-old boy presented with symptoms of superior vena cava and airway obstruction was diagnosed of T-lymphoblastic leukaemia. Chemotherapy was commenced according to Chinese Children's Cancer Group Acute Lymphoblastic Leukaemia 2015 protocol. He developed severe necrotising enterocolitis requiring bowel resection and was supported with total parenteral nutrition (TPN) for one month. The lipid profile was normal when he was on TPN. His condition was stabilised and he proceeded to interim maintenance chemotherapy, which included Dexamethasone 12 mg per metre square per day from day one to five and Peg-asparaginase 2000 units per metre square on day three every three weeks for five doses. In the eighth week, he complained of abdominal pain and vomiting for one day. Milky serum was noted upon blood taking (Figure 1). The serum sodium level was 124-128 mmol/L.

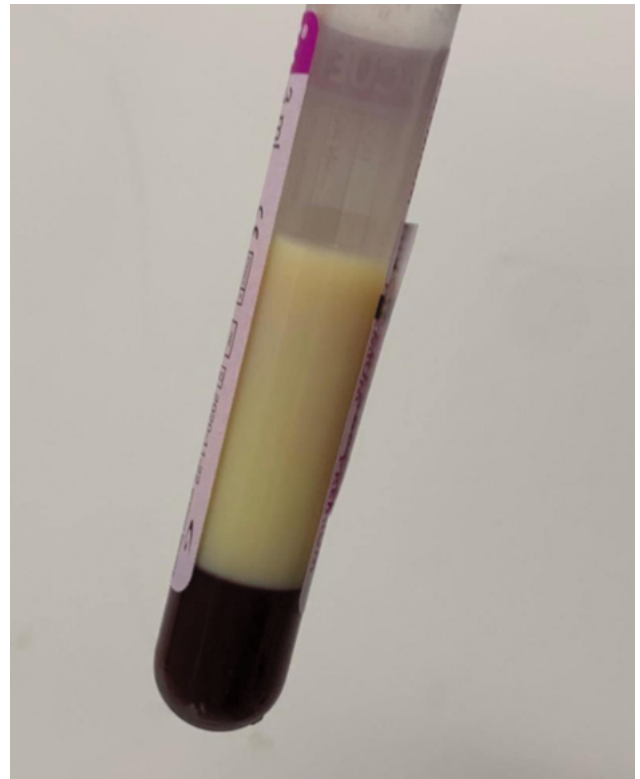


Figure 1 Milky serum of our patient taken 1 day after onset of gastrointestinal symptoms.

The clinical quiz was prepared by:

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Answer to "Clinical Quiz" on Pages 195-198

N.B. The Editors invite contributions of illustrative clinical cases or materials to this section of the journal.

Instruction:

1. Please use pencil to shade the box for the best and correct answer (only one answer for each question).
2. Send back the answer sheet (see loose leaf page) to the Hong Kong College of Paediatricians. One point will be awarded to each article if ≥ 3 of the 5 answers are correct. The total score of the 4 articles will be 4 CME points.

(A) The Effects of Education Program Applied to the Families of Moderate and Late Premature Infants on Breastfeeding, Parental-infant Attachment and Parents' Anxiety Levels in the First Year: A Randomised Controlled Trial

1. Moderate and late premature infants are born at;
 - a. 32^{0/7}-36^{6/7} gestational week
 - b. 34^{0/7}-36^{6/7} gestational week
 - c. 32^{0/7}-34^{6/7} gestational week
 - d. 28^{0/7}-32^{6/7} gestational week
 - e. 30^{0/7}-36^{6/7} gestational week
2. Moderate and late premature infants constitute how much percentage of the premature babies.
 - a. 42
 - b. 55
 - c. 67
 - d. 75
 - e. 84
3. When were the home educational visits made to the participating groups in the current study?
 - a. at one week after discharge than at 1 and 3 months corrected age (CA) of the infant.
 - b. at one week after discharge than at 1, 2, and 3 months CA of the infant.
 - c. at two weeks after discharge than at 1, 2, and 3 months CA of the infant.
 - d. at 1, 2, 3 and 4 months CA of the infant.
 - e. at two weeks after discharge than at 1 and 3 months CA of the infant.
4. In this study, the appropriate time of starting complementary feeding was recommended at which months of corrected age.
 - a. 3
 - b. 4
 - c. 5
 - d. 6
 - e. 8

5. Which one of the following assessment tools was not used in the current study?
 - a. The Maternal Attachment Inventory
 - b. Infant Character Perception Scale
 - c. Trait Anxiety Inventory
 - d. The Edinburgh Postnatal Depression Scale
 - e. The Paternal Postnatal Attachment Questionnaire

(B) Comparison of Three Critical Illness Scoring Systems for Assessing Septic Acute Kidney Injury

1. The best mortality assessment system for paediatric patients with stage 1 acute kidney injury (AKI) was?
 - a. PRISM III
 - b. PCIS
 - c. P-MODS
 - d. SOFA
 - e. A and B
2. The best mortality assessment system for paediatric patients with stage 2 AKI was?
 - a. P-MODS
 - b. PRISM III
 - c. PCIS
 - d. SOFA
 - e. None of the above
3. The best mortality assessment system for paediatric patients with stage 3 AKI was?
 - a. PRISM III
 - b. PCIS
 - c. P-MODS
 - d. SOFA
 - e. All the above

4. P-MODS is primarily used to assess the degree of organ dysfunction in children by evaluating parameters such as?
 - a. Bilirubin
 - b. Lactic acid
 - c. Fibrinogen and urea
 - d. Oxygenation index
 - e. All the above
5. Which system the P-MODS score does not include for assessment?
 - a. Circulation
 - b. Breathing
 - c. Liver function
 - d. Nervous system
 - e. Blood coagulation

(C) Paediatric Deep Neck Space Abscesses: Experience of a Tertiary Care Hospital

1. Which antibiotic is most preferred as the first choice for deep neck space abscesses?
 - a. Ceftriaxone
 - b. Ampicillin sulbactam
 - c. Clindamycin
 - d. Ampicillin
 - e. Piperacillin tazobactam
 2. Which symptoms can be seen in patients with deep neck space abscesses?
 - i. neck pain
 - ii. swelling of the cervical lymph nodes
 - iii. trismus
 - iv. hoarseness
 - a. i, ii, iv
 - b. i, ii, iii
 - c. ii, iii, iv
 - d. i, iii, iv
 - e. All the above
 3. In what age range is retropharyngeal abscess more common?
 - a. 1-2 years
 - b. 2-5 years
 - c. 5-10 years
 - d. 10-15 years
 - e. <1 year
4. Which complications can be seen secondary to deep neck space abscesses?
 - i. airway obstruction
 - ii. mediastinitis
 - iii. jugular vein thrombosis
 - iv. cranial nerve dysfunction
 - v. sepsis/septic shock
 - a. i, ii, iii
 - b. ii, iii, iv, v
 - c. i, iii, iv, v
 - d. i, iii, iv
 - e. All the above
 5. In this study, which time interval to surgery is considered for defining delayed surgical drainage from the start of first intravenous antibiotic treatment?
 - a. 12 hours
 - b. 24 hours
 - c. 48 hours
 - d. 72 hours
 - e. 96 hours

(D) Surgical Management of Rapunzel Syndrome: A Retrospective Report from Two Children's Medical Centres

1. The clinical manifestation(s) of Rapunzel syndrome include:
 - a. Abdominal pain, bloating
 - b. Nausea, vomiting
 - c. Early satiety
 - d. Diarrhoea, constipation
 - e. All of above
2. Rapunzel syndrome commonly appear as a result of:
 - a. Crapulent
 - b. Vegetarian diet
 - c. Absorption of enormous volumes of hairs
 - d. Moderate in eating
 - e. None of above
3. The complication(s) of Rapunzel syndrome include:
 - a. Anaemia
 - b. Haematemesis
 - c. Intestinal obstruction
 - d. Intestinal perforation
 - e. All of above

4. Why should psychiatric evaluation be part of the therapy for patients with Rapunzel syndrome?
- a. Because the impulsive behaviour associated with trichophagia in these patients is difficult to manage.
 - b. Because there are risks of recurrence should be considered
 - c. Because the patients may continue to overeat
 - d. Because the patients like vegetarian food and don't like meat
 - e. None of above
5. Which of the following examination is the preferred investigation to distinguish Trichobezoars from other probable epigastric mass aetiologies?
- a. Plain radiograph
 - b. Ultrasonography
 - c. Upper gastrointestinal contrast
 - d. Computed tomographic (CT)
 - e. None of above

Answers of April issue 2023

- (A) 1. e; 2. c; 3. a; 4. b
(B) 1. c; 2. e; 3. c; 4. a
(C) 1. e; 2. a; 3. b; 4. c

- (D) 1. c; 2. d; 3. c; 4. e
(E) 1. e; 2. e; 3. d; 4. b

CLINICAL QUIZ (p191) ANSWER

What is the cause of the milky serum and hyponatraemia?

The milky serum is as a result of hypertriglyceridaemia, in relation to combined steroid and asparaginase use. In our patient, the triglyceride level was >50 mmol/L (Reference range: acceptable <1.0 mmol/L, borderline high 1.0-1.5 mmol/L, High >1.5 mmol/L, Very High >5.6 mmol/L, Severely High >11.6 mmol/L). The severe hyponatraemia is due to pseudo hyponatraemia secondary to hypertriglyceridaemia which displaces water from plasma and when serum sodium level is measured by the indirect laboratory method. The triglyceride level was controlled to below 10mmol/l with use of insulin infusion and 10% dextrose based intravenous fluid at 120% maintenance rate to maintain adequate hydration, thus reduce chance of hyperviscosity related thrombosis. The serum sodium level rose to above 132 mmol/l on the next day with triglyceride level improved to around 30 mmol/l, which fully normalised on day 5 when triglyceride level was back down to 7.5 mmol/l.

How does the combined use of steroid and asparaginase cause hypertriglyceridaemia?

Asparaginase results in decreased enzymatic activity of lipoprotein lipase, resulting in decreased clearance of triglyceride-rich lipoproteins.¹ In addition, asparaginase also increases endogenous synthesis of very low density lipoprotein (VLDL).¹ On the other hand, systemic corticosteroid therapy increases endogenous production of VLDLs and hepatic cholesterol synthesis.¹ The two drugs work synergistically to cause severe hypertriglyceridaemia.

How common is asparaginase and steroid induced hypertriglyceridaemia and the potential complications?

Mild lipidemic alterations are commonly seen in paediatric patients with acute lymphoblastic leukaemia (ALL) treated with corticosteroids and L-asparaginase. Salvador et al reported 34.5% (41/119) children and adolescents developed hypertriglyceridaemia at two to three weeks of ALL induction therapy.¹ With the recent protocol utilising PEG-asparaginase instead of *E.coli* asparaginase (L-asparaginase), an increased proportion of severe hypertriglyceridaemia has been reported.² Severe hypertriglyceridaemia (defined as triglycerides >1000 mg/dL, i.e. 11.3 mmol/L) and very severe hypertriglyceridaemia (defined as triglycerides >2500 mg/dL, i.e. 28.2 mmol/L) were reported in 6.7% patients.¹ In addition to the commonly known acute pancreatitis, other potential complications of persistent severe hypertriglyceridaemia include peripheral neuropathy, central venous thrombosis due to increased blood viscosity, osteonecrosis and thromboembolism.^{1,2} However, in the context of transient but severe hypertriglyceridaemia induced by asparaginase and steroid, the chance of developing complications of hypertriglyceridaemia remains to be elucidated.

What are the other common causes of hypertriglyceridaemia?

Cholesterol and triglycerides are 2 main types of lipids in our body. Triglycerides form the basis of our energy stores of fatty acids and may provide fuel for beta-oxidation to generate adenosine triphosphate (energy). Lipids are insoluble and need lipoproteins to transport through the blood vessels to target organs such as skeletal muscle, fat and the liver. There are 5 types of lipoproteins, namely chylomicrons, VLDL, intermediate density lipoprotein, low density lipoprotein and high density lipoprotein.

Triglycerides in the lipoprotein carriers are hydrolysed by lipoprotein lipase into free-fatty acids that are either oxidized by the muscle cells to generate energy, stored in adipose tissue, oxidized in the liver, or used in hepatic VLDL synthesis. Hypertriglyceridaemia occurs when there is accumulation of triglyceride-rich lipoproteins, which is determined by excessive dietary fat uptake from the intestine or hepatic production, with or without reduced clearance of triglyceride-rich lipoproteins, and is classified as primary or secondary (Figure 2 and Table 1).³⁻⁵ Primary hypertriglyceridaemia is of genetic basis.^{3,4} Secondary hypertriglyceridaemia is believed to occur when minor genetic variants are exacerbated by conditions or drugs that increase triglyceride levels beyond the saturation point of triglyceride removal system, e.g., high fat diet, uncontrolled diabetes mellitus or insulin resistance, obesity, metabolic syndrome, hypothyroidism, hypercortisolism, renal disease, acute hepatitis, excessive alcohol intake, pregnancy or medications.^{3,5}

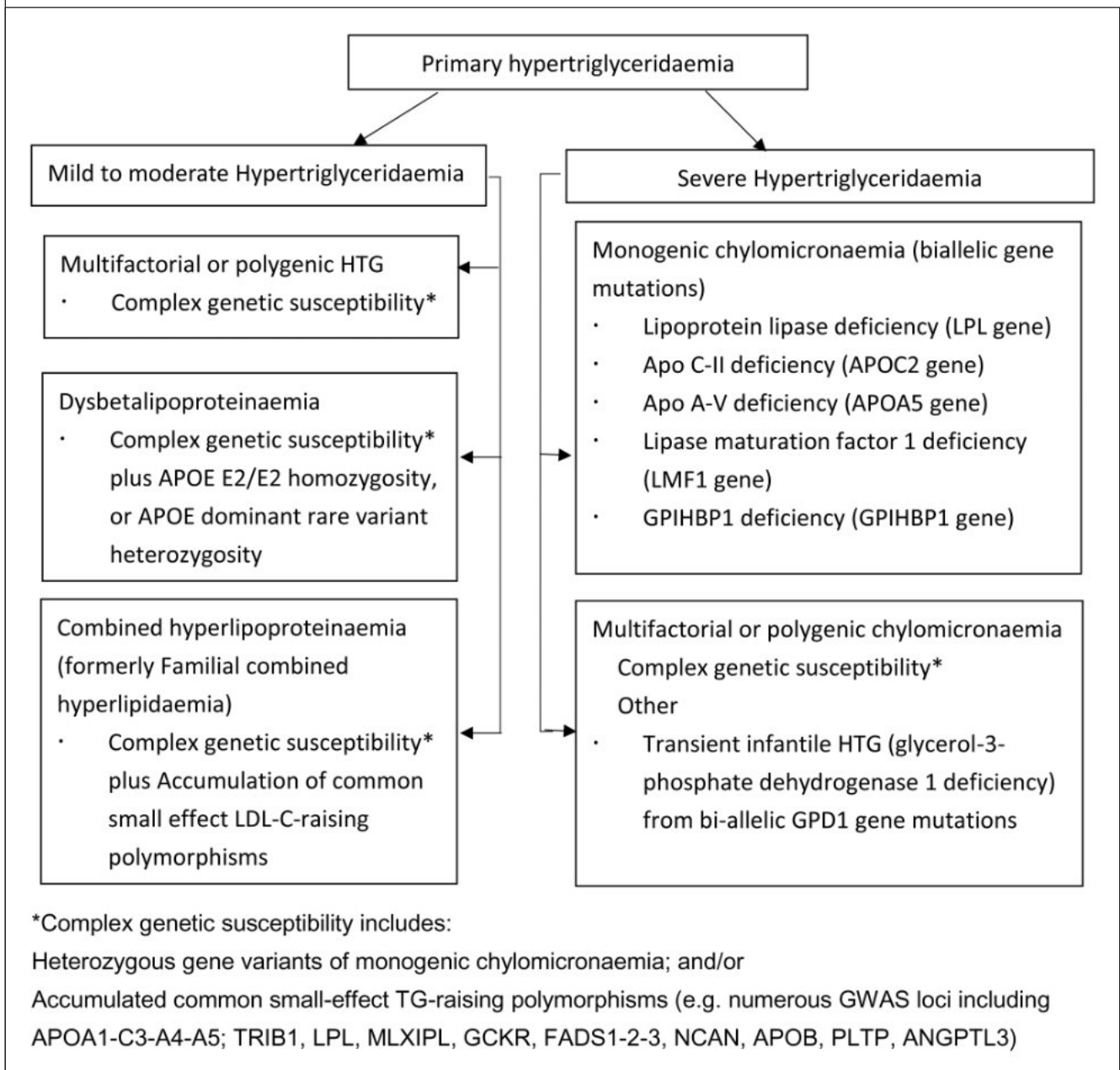


Figure 2 Causes of primary hypertriglyceridaemia.^{3,4}

What are the management options of hypertriglyceridaemia induced by asparaginase and steroid?

There is no consensus on the acute treatment of hypertriglyceridaemia secondary to ALL treatment. Majority of patients had normalisation of hypertriglyceridaemia with low fat diet (78%).¹ For mild hypertriglyceridaemia, fish oil (omega-3-fatty acids (>2 g/day)) could be considered as an effective option for treatment^{3,6} especially in the presence of deranged liver function for which fibrates or niacin are contraindicated. Long chain omega 3 (including eicosapentaenoic acid and docosahexaenoic acid) had been shown to reduce serum triglycerides in a dose-dependent manner.⁶ For severe hypertriglyceridaemia not responding to low fat diet or fish oil, insulin infusion has been shown to be effective.^{3,7} Insulin works by stimulating the synthesis of lipoprotein lipase by adipocytes and myocytes, which increase the clearance of triglyceride levels within two to three days after initiating insulin therapy. The other options include heparin and plasmapheresis. Heparin works by displacing the lipoprotein lipase into circulation and is a good add-on therapy in cases where hypertriglyceridaemia does not respond well to insulin infusion alone, though after an hour, the lipoprotein lipase is exhausted. Plasmapheresis was effective in treating severe hypertriglyceridaemia but was invasive, costly and with side effects reported as deep venous thrombosis due to a central venous catheter, anaphylaxis, hypocalcaemia and hypokalaemia.⁷

Rebound of hypertriglyceridaemia post plasmapheresis may also be rapid if underlying cause is not managed.³

Erwinase was reported to be associated with lower risk of severe hypertriglyceridaemia.² However, due to cost and the need for intramuscular injection for Erwinase, its use has been limited to selected patients. This could be considered for those with known pre-existing hypertriglyceridaemia or those with recurrent episodes of severe hypertriglyceridaemia during ALL treatment.

Conclusion

Severe hypertriglyceridaemia can occur in patients receiving asparaginase and steroid during treatment of ALL. Close monitoring of the triglyceride level is important to allow for early intervention to avoid potential complications. Pseudohyponatraemia could be a potential presentation of hypertriglyceridaemia. Since electrolytes are frequently

Table 1 Causes of secondary hypertriglyceridaemia^{3,5}

Causes	
High fat diet	
Uncontrolled diabetes mellitus	
Metabolic syndrome	Insulin resistance, obesity
Endocrine disease	Hypothyroidism, Hypercortisolism / Cushing's disease, Growth hormone deficiency, etc.
Renal disease	Proteinuria, Uraemia, Glomerulonephritis, Nephrotic syndrome, etc.
Liver disease	Acute hepatitis, bile duct obstruction, non-alcoholic fatty liver disease, etc.
Rheumatological disorder	Systemic Lupus Erythematosus, Rheumatoid arthritis, etc.
Metabolic disease	Glycogen storage disorder, etc.
Excessive alcohol intake	
Pregnancy	
Medications	Corticosteroids, thiazides, loop diuretics, beta-blockers, oral oestrogen, tamoxifen, retinoids, tacrolimus, cyclosporine, cyclophosphamide, asparaginase, protease inhibitors, antiretroviral therapy, second-generation antipsychotic agents, antidepressants, etc.

measured during the course of ALL treatment, triglyceride level should be checked when hyponatraemia occurs during use of asparaginase and/or steroid.

Declaration of Interest

The authors state that there are no conflicts of interest to disclose.

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