Editorial
Real-World Clinical Evidence versus Randomised Controlled Trials in Paediatrics: The Competition has Begun
Cheung

Original Articles
A Report of Infant Urolithiasis in a Tertiary Hospital
Yel, Düsünsel, Dursun, Elmali, Yılmaz

Vitamin D and Nutritional Status of Children Evaluated via Bioelectric Impedance Analysis
Khalilova, Özetin, Kılıç, Baş, Yetim, Keskinodemir, Gür, Darendeliler

Depression and Eating Disorders in Children with Type 1 Diabetes
Sanlier, Ağagündüz, Erzaoztürk, Bozbülüt, Karaçıl Ermişmu

Antiemetics to Control Vomiting in Children: A Double-Blind Placebo-Controlled Trial in Children
Karakaşlı, Yılmaz, Divriklioglu, Yigit, Halhalli

Case Reports
Overcoming Perioperative Challenges in a Patient with Congenital Vascular Ring Undergoing Cardiac Surgery
Chong, Saedah, Rosdan, Mamat

Perianal Mercury Deposition from a Broken Thermometer in a Small Child
Lin, Chen, Zhao, Wang

Urticaria in Skin Care with Skin Cream Containing a Wheat Compound and Prompt Treatment at Home
Taniguchi, Ichiyama, Uemichi

The First Case of Cobalamin F Disorder in China: Report and Literature Review
Tong, Yang, Chen, Zhao

Letter to the Editor
Filicides in Hong Kong
Hon, Chan, Chan

Clinical Quiz
What is the Diagnosis?
Wong, Fung, Chung

Abstracts of Articles in Chinese

MCQs

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Real-World Clinical Evidence versus Randomised Controlled Trials in Paediatrics: The Competition has Begun

The amount of data created on a daily basis is estimated to be 2.5 quintillion bytes.\(^1\) With 17 zeros that follow '25', this number represents a quarter of the total number of all insects alive on this planet at any time.\(^2\) For data related to healthcare, industry analysts estimate their growth to about 2,300 quintillion bytes (exabytes) by 2020.\(^3\) Review of microfilms of scanned clinical records is a moment of analogue nostalgia. Those were the days. Health data currently stored in the hospital administrative database, electronic healthcare systems, clinical registry, laboratory and medical imaging database, insurance claim records, and biometric data are the digital realities. How to make sense of these big data for the generation of evidence to improve healthcare has become a focus of attention.

The clinical wisdom in the practice of paediatrics is based on knowledge acquired through real-world clinical encounters, dissemination and discussion of interesting case reports, sharing of collective experience by publication and analysis of prospectively or retrospectively collected clinical data, and conducting of randomised controlled trials, the latter being ranked the top of the hierarchical level of evidence generated for evidence-based clinical practice. In this issue of the *Journal*, Karakayali et al. performed a randomised double-blind placebo-controlled trial to determine to the efficacy of ondansetron and metoclopramide in managing children who presented to the emergency department with acute vomiting.\(^4\) Included in this issue are also two cross-sectional studies, one assessing the vitamin D and nutritional status of lean, normal weight and obese children,\(^5\) and the other is a questionnaire survey assessing depression and eating disorders in children with type 1 diabetes mellitus.\(^6\) Another original article explored the associations between infant feeding modalities and metabolic risk factors for urolithiasis in infants.\(^7\)

The 1989 United Nations General Assembly "Convention on the Rights of the Child" acknowledges the right of the child to the enjoyment of the highest attainable standard of care,\(^8\) which includes without doubt the right to benefit from the highest level of evidence generated from research for management of paediatric diseases. Nonetheless, the unique challenges in paediatric trials including the concern of testing new interventions in children, recruitment logistics and success, and consent seeking cannot be overemphasized. The inconvenient truth of a high probability of discontinuation and nonpublication of randomised clinical trial conducted in children is shown recently by the retrospective cross-sectional study of Pica and Bourgeois.\(^9\) They found that 19% of the 559 trials registered in ClinicalTrials.gov from 2008 to 2010 were discontinued early, with difficulty in patient accrual and conduct of the trial\(^5\) being the most common given reasons for trial discontinuation. Additionally, they found that 30% of the complete trials were not published.\(^9\) These findings inevitably translate to the disappointing fact that thousands of children have been exposed to behavioural, pharmacologic, device, procedural, dietary and other types of interventions, who had accepted certain degree of potential harm and may not directly benefit from the study findings, but without leading to findings to improve paediatric healthcare.
Even beyond the unique paediatric challenges, limitations of randomised controlled trials have been witnessed over the past seven decades since formalisation of the methodology in the 1940s. It is beyond the scope of this editorial to elaborate on the limitations and lessons learnt from the history of randomised controlled trials. Interested readers can refer to recent discussions on this topic. Some have argued that evidence-based medicine may already be in crisis for a number of reasons: the evidence-based quality mark has been misappropriated by interest, the volume of evidence has become unmanageable, statistically significant benefits may be marginal in clinical practice, inflexible rules and technology-driven prompts may produce care that is management driven rather than patient centred, and evidence based guidelines often map poorly to complex multimorbidity. Incorporation can be combined with clinical context and professional expertise for optimal care of individual patients. Incorporation of personalised clinical data, patient and physician-wise, for the generation of this type of evidence seems to be a logical move.

Increasingly, headlines in media and debates in meetings have hinted on the possibility of real-world clinical performance and medical big data eclipsing or replacing the role of randomised controlled trials. While sparking controversies and being met with skepticisms, the big data technology has found its way to the medical arena, albeit in its nascent stage. Rumsfeld et al have described for example eight potential areas of applications of big data analytics in cardiovascular care, including predictive modeling for risk and resource use, population management, drug and medical device safety surveillance, disease and treatment heterogeneity, precision medicine and clinical decision support, quality of care and performance measurement, public health, and research applications.

The use or reuse of health data for generation of research data are nonetheless met with challenges and controversies. Strong evidence of the benefits of big data analytics over traditional medical research methods is lacking at this moment. Issues on data quality, heterogeneity, and inconsistency are important obstacles. Peek and Rodrigues recently discussed the important controversial issues on whether: i) data shall be used only for the purpose for which they well collected, ii) big data can replace traditional medical research methods, and iii) to protect the privacy of patients, health data should not be reused for research without explicit consent of the patients concerned. These controversies remind us of the latest scandals related to data breach of the social media.

In this era of digital transformation, there is always special feeling of nostalgia on memorable analogue moments. Equally, the special moment of unleashing the potential of data analytics in paediatric healthcare is here and we have to stay ahead of the game of competition between the digital data of real-world clinical evidence and the analogue medical research methodologies.

YF Cheung
Chief Editor

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A Report of Infant Urolithiasis in a Tertiary Hospital

S YEL, R DÜŞÜNSEL, İ DURSUN, F ELMALI, K YILMAZ

Abstract

Aim: The aim of the present study was to evaluate the associations between infant feeding modalities and metabolic risk factors for urolithiasis in infants. Patients and Methods: A total of 70 infants (<12 months) with urolithiasis were included in the present study. Patients with chronic disease or anatomic abnormalities were excluded. A questionnaire was completed by the mothers. Dietary characteristics (breast and/or formula feeding, plus water supplementation) and family history of urolithiasis were determined. Patients underwent 24-h urine collection via an urethral catheter for analysis of metabolic risk factors for urolithiasis. Results: The mean age at diagnosis of stone disease was 4.47±2.41 months. The major clinical symptoms of the patients were restlessness (45.7%) and vomiting (14.3%); however, 24% of infants were asymptomatic. The majority of patients (64.2%) were solely breastfed and the remaining were given formula to supplement breastfeeding. Twenty-four of the 70 patients were supplied with water. Fifty patients (71.4%) had microlithiasis. At least one metabolic abnormality was found in 90% of the patients. Hypercalciuria and hyperuricosuria were detected in 40% and 47% of the patients, respectively. No effects of water supplementation on urinary metabolite excretion were found. Higher urinary phosphorus and uric acid excretion were detected in patients who were given formula to supplement breastfeeding. Conclusion: Urolithiasis in infancy remains a serious problem in Turkey. Infants with urolithiasis may present with non-specific symptoms. A positive family history of urolithiasis and formula feeding was associated with increased occurrence of urolithiasis in infants.

Key words Infant feeding; Metabolic risk factors; Urolithiasis

Introduction

Urolithiasis in infancy is an important medical problem with increasing frequency. Increased awareness and the routine use of ultrasonography (USG) may play a role in this situation.1,2 It is well known that childhood urolithiasis is related to certain risk factors including genetic inheritance, nutrition, metabolic abnormalities, environmental factors, and stone-inducing drugs.3

In the present study we aimed to investigate the associations between nutritional and metabolic risk factors for urolithiasis in infants. Infants sharing the same
environment and with no urological problems were selected so that we could focus on the association between nutritional status and the development of urolithiasis.

**Patients and Methods**

We prospectively analysed 70 term infants with urolithiasis referred to the Pediatric Nephrology Clinic of Erciyes University Hospital over 12 months. A questionnaire was completed by the mothers. Patients were evaluated for associated symptoms, a dietary history with emphasis on vitamin D supplementation, breast and/or formula feeding plus water supplementation, family history of stone disease, consanguinity, and past medical history. Family history of urolithiasis was accepted as positive when first- or second-degree relatives were found to have a past history of urolithiasis. Associated symptoms were defined as complaints or problems prior to the ultrasonographic examination on which the urolithiasis or microlithiasis were detected. Parents were asked whether their child's urine smelled different from usual (abnormal urine odour) or whether their child had recurrent vomiting or restlessness (different conditions to usual). Patients with chronic disease, anatomical abnormalities, history of hospitalisation during the neonatal period and medication use were excluded. Patients with urinary tract infection were examined following treatment when the urine culture was negative. Inadequate weight gain was defined as gaining weight at a slower rate according to standard growth charts published by the World Health Organisation.

Urolithiasis was diagnosed as echogenic foci that caused posterior acoustic shadowing; calculi <3 mm were defined as microlithiasis and those >3 mm as urolithiasis. Images of the calculi were verified by two independent radiologists. All 70 infants were hospitalised and underwent 24-h urine collection via a urethral catheter. Urine cultures were sent for bacteriological examination. Urinalysis of all patients was performed and the presence of haematuria, proteinuria, or pyuria was determined by dipstick and microscopic examination. Tests for metabolic risk factors, including hypercalciuria, hyperphosphaturia, hyperoxaluria, hypocitraturia, hyperuricosuria and hypomagnesuria, and an analysis of urinary amino acid profiles were carried out. Parathyroid hormone (PTH), 25-hydroxy vitamin D (25-OH vit D), calcium, magnesium, creatinine, uric acid, and phosphorus levels in the serum were measured in all patients.

Values above 60 ng/mL (150 nmol/L) for 25-OH vit D were accepted as hypervitaminosis D. Hypercalciuria was diagnosed when the amount of calcium in the urine exceeded 4 mg/kg/24 h. Cystinuria was diagnosed when the 24-h urinary excretion of cystine was >0.5 mmol/1.73 m². The normal value for urinal citrate was accepted as >1.6 mmol/1.73 m²/24 h. The normal value for tubular phosphate reabsorption was accepted as 4.1±0.6 mg/dL (1.32±0.19 mmol/L)/glomerular filtration rate. The normal daily value for oxalate excretion was <0.5 mmol/1.73 m²/24 h and the normal value for uric acid excretion was accepted as <0.56 mg/dL (<33.32 µmol)/glomerular filtration rate.

Patients were divided into groups according to 1) nutritional status; 2) water supplementation; and 3) size of the calculus on USG examination.

1) Nutritional status: Patients who received solely breastfeeding were named the breastfeeding group and patients who received breastfeeding and supplementary formula were named the formula+breastfeeding group. There were no patients who received solely formula.

2) Water supplementation: Patients who were given at least 10 mL/day water free from nutrition were named the water-supplemented group and the remaining were named the non water-supplemented group.

3) Size of the calculus on USG examination: Calculi <3 mm were defined as microlithiasis and those >3 mm as urolithiasis.

Hypercalciuria, hyperphosphaturia, hyperoxaluria, hyperuricosuria, hypocitraturia, and hypomagnesuria were defined as abnormal metabolite excretion. There was no control group in the present study since normal values of urinary metabolites have been previously studied. Moreover, we avoid the use of urethral catheters in healthy infants.

Descriptive statistics and a Chi-squared test were performed using the statistical software package SPSS version 16. The distributions of all parameters were determined using the Shapiro-Wilk test. Comparisons among the groups for the parameters with a normal distribution were carried out using a Student’s t-test, and for the parameters with an abnormal distribution, comparisons were carried out using the Mann-Whitney U test. A p-value of <0.05 was accepted as statistically significant.

**Results**

In the present study, the patients consisted of 37 female and 33 male infants (ratio 1.1:1). The mean age at diagnosis
was 4.47±2.41 months, with the majority of patients (80%) being diagnosed in the first six months of life. The most remarkable associated symptoms were defined for each patient as shown in Table 1. Irritability/restlessness was found in 32 patients (45.7%), and 17 were asymptomatic (24.3%).

Urinalysis revealed haematuria in 12 (17.1%) patients, pyuria in 6 (8.6%), haematuria+pyuria in 6 (8.6%), and normal findings in 46 (65.7%) patients. Urinary tract infection was not present at the time of examination. Failure to thrive or weight loss below the 3rd percentile were not detected in any patients. All blood pressure measurements, renal function tests, and PTH levels were within the normal range.

All patients were breastfeeding; 45 (64.3%) were solely breastfeeding and 25 (35.7%) were given formula to supplement breastfeeding. There were no patients who were solely formula fed. Water supplementation was detected in 24 (34.3%) of the 70 patients; 14 of the 45 breastfed patients and 10 of the 25 formula+breastfed infants were supplemented with water. There was no significant difference in the ratio of water supplemented to non-supplemented patients between the breastfeeding and the formula+breastfeeding groups.

Microlithiasis (<3 mm) was found in 50 patients, while 20 patients had urolithiasis (>3 mm). The number of patients with microlithiasis was highly independent of the feeding modality. In 32 (45.7%) of the 70 patients, the stones were bilateral; in patients with microlithiasis, 23 of the 50 were bilateral, 5 were on the right side, and 22 were on the left side, and in patients with urolithiasis, 9 of the 20 were bilateral, 3 were on the right side, and 8 were on the left side.

A positive family history of urolithiasis was determined in 44 patients (62.9%). The number of patients with microlithiasis was significantly higher in the positive family history group as compared with the negative family history group (Table 2; \( p=0.01 \)).

All patients underwent a metabolic evaluation. At least one abnormal metabolite excretion was detected in 63 (90%) patients. Hyperuricosuria was the most commonly detected abnormality, which was found in 33 (47%) of the 70 patients. Hypercalciuria was found in 28 (40%) of the 70 patients (Figure 1).

The levels of urinary excretion of phosphorus and uric acid were significantly higher in patients in the formula+breastfeeding group than in those in the breastfeeding group (Tables 3 and 4). There were no statistically significant differences in the levels of urinary metabolites between the water supplemented and non-water-supplemented groups. Similarly, no statistically significant differences were found in the levels of urinary metabolites between the microlithiasis and urolithiasis groups.

There was a history of vitamin D administration to all patients. Serum levels of 25-OH vit D, Ca\(^{2+}\), and PTH are shown in Table 5. Hyperparathyroidism D was identified in 7 of the 67 patients whose serum levels were measured. A significant correlation was detected between serum levels of 25-OH vit D levels and Ca\(^{2+}\) (correlation coefficient: 0.251; \( p<0.05 \); Figure 2); however, no significant correlation was demonstrated between serum levels of 25 OH vit D and urinary levels of Ca\(^{2+}\) (correlation coefficient: -0.1; \( p>0.05 \)). Urinary Ca\(^{2+}\)-excretions were similar in both the positive and negative family history groups and in both the microlithiasis and urolithiasis groups.

**Discussion**

Infantile urinary stone disease is an important medical problem in Turkey. The number of new patients referred to our clinics annually for infantile urolithiasis has increased in recent years. Delay in the diagnosis of stones or inadequate treatment may cause damage to the renal parenchyma and result in renal failure by obstruction. Studies carried out in

<table>
<thead>
<tr>
<th>Table 1</th>
<th>The associated symptoms of patients</th>
</tr>
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<tbody>
<tr>
<td>Associated symptoms</td>
<td>n</td>
</tr>
<tr>
<td>Irritability/restlessness</td>
<td>32</td>
</tr>
<tr>
<td>Vomiting/urinary tract infection</td>
<td>10</td>
</tr>
<tr>
<td>Abnormal urine odor</td>
<td>5</td>
</tr>
<tr>
<td>Inadequate weight gain</td>
<td>6</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td>70</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Relationship between family history and size of calculus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history for urolithiasis</td>
<td>Size of calculus</td>
</tr>
<tr>
<td></td>
<td>&lt;3 mm</td>
</tr>
<tr>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Positive</td>
<td>36 (81.8)</td>
</tr>
<tr>
<td>Negative</td>
<td>14 (57.7)</td>
</tr>
<tr>
<td>Total</td>
<td>50 (71.4)</td>
</tr>
</tbody>
</table>

\( p=0.01 \)
Turkish children have found that urinary stones are the aetiological factor in 3.8% of children with chronic renal failure. Recent reports from Turkey regarding childhood urolithiasis have shown that 34-41% of patients are infants, and in the global literature, 9-23% of reported child patients are infants. Infantile urolithiasis should be examined differently due to differences in nutrition, symptoms, aetiologies, and genitourinary tract maturation.

Many studies have reported a male predominance in childhood urolithiasis; however, in the present study, the male-to-female ratio was found to be 1:1.1. Recent reports from Turkey regarding infantile urolithiasis have shown similar ratios.

Renal calyceal microlithiasis is a renal echographic finding defined as the presence of hyperechogenic spots <3 mm in diameter in the renal calyces. Some studies have revealed that microlithiasis may be the first step in stone formation. Alpay et al. reported that 67% of children who had microlithiasis were younger than 12 months old,

<table>
<thead>
<tr>
<th>Number of patients with</th>
<th>Breasting</th>
<th>Breast feeding+Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>urinary metabolites</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Urinary oxalate</td>
<td>18/43 (41.9)</td>
<td>6/23 (26.1)</td>
</tr>
<tr>
<td>Urinary citrate</td>
<td>7/42 (16.7)</td>
<td>1/23 (4.3)</td>
</tr>
<tr>
<td>Urinary Ca</td>
<td>15/45 (33.3)</td>
<td>13/25 (52.0)</td>
</tr>
<tr>
<td>Urinary P</td>
<td>5/45 (11.1)</td>
<td>15/25* (60.0)</td>
</tr>
<tr>
<td>Urinary UA</td>
<td>16/45 (35.6)</td>
<td>17/25* (68.0)</td>
</tr>
<tr>
<td>Urinary Mg</td>
<td>11/45 (24.4)</td>
<td>7/25 (28.0)</td>
</tr>
</tbody>
</table>

Table 4 Urinary metabolite excretions according to feeding modality

<table>
<thead>
<tr>
<th>Urinary metabolites</th>
<th>Breasting</th>
<th>Breast feeding+Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR: Glomerular filtration rate</td>
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<table>
<thead>
<tr>
<th>Variables</th>
<th>Breasting</th>
<th>Breast feeding+Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Ca (mg/dL)</td>
<td>10.24±0.47</td>
<td>10.35±0.38</td>
</tr>
<tr>
<td>Serum 25-OH vit D (ng/mL)</td>
<td>(4.50-85.00)</td>
<td>(15.30-56.70)</td>
</tr>
<tr>
<td>Serum PTH (pg/mL)</td>
<td>15.20</td>
<td>24.10</td>
</tr>
<tr>
<td>x 0.249 for mmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>x 2.496 for nmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>x 0.106 for pmol/L</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The parameters with normal distribution were expressed as mean ± SD, and the parameters with abnormal distribution were expressed as median (minimum-maximum).
similarly, Alamzadeh-Ansari from Iran reported that 69.7% of children with microlithiasis were infants.\textsuperscript{15} Consistent with the literature, we found that 71.4% of the studied infants had microlithiasis.

Urolithiasis in childhood has a different pattern of presentation from that in adults, and symptoms can change with age. Non-specific symptoms such as vomiting and restlessness are frequently reported in infancy.\textsuperscript{1,3,13} Conversely, in the present study it was shown that 24.3% of patients were asymptomatic and 65.7% had no laboratory clues. These findings suggest that the probability of urolithiasis should be kept in mind and infant patients should undergo renal ultrasonography examination to exclude urolithiasis in endemic regions. Delay in the diagnosis of stones or inadequate treatment may result in damage to the renal parenchyma and renal failure by obstruction.

In contrast to that in adults, childhood urolithiasis is more often associated with underlying metabolic abnormalities; ranging from 33% to 93% in different reports. Younger patients are more likely to have an identifiable metabolic risk factors.\textsuperscript{16} Infant studies in Turkey have reported these factors to range from 46% to 82%.\textsuperscript{1,2,13} Consistent with the literature, we demonstrate at least one metabolic abnormality in 90% of patients. Hypercalciuria is the most commonly detected metabolic abnormality in both adult and child patients. Hyperuricosuria was the most commonly detected abnormality in the present study, similar to two other reports from the same centre.\textsuperscript{2,17} As a health policy in Turkey, water is not recommended for infants who are breastfed, since breast milk is considered sufficient to maintain a normal hydration status in the infant. A probable mild dehydration could be the cause of hyperuricosuria.

Urinary solute concentrations and urine volume are important parameters in the determination of metabolite excretions. Environmental factors such as climate or a long summer and urinary tract problems that lead to stasis may affect these parameters. Moreover, hydration and nutrition statuses are listed. In the present study, we aimed to evaluate patients sharing the same environment with no urological or systemic problems to allow focus on the effects of water supplementation and feeding modalities.

Increased fluid intake is a mainstay for the prevention of recurrent stone formation, with the aim of avoiding supersaturation through the dilution of urine. A plethora of level 1 evidence indicates that increased water intake can reduce the risk of stone recurrence by up to 50%.\textsuperscript{18,19} In the present study we found no effect of water supplementation on infants' urinary metabolite excretions. As an important limitation of the present study, we learned water supplementation information retrospectively from mothers, which is based on recall and could be misleading.

Elucidation of the effect of feeding modalities was another goal of the present study. Breast milk contains 6.25 mmol/L calcium and 4.52 mmol/L phosphorus,\textsuperscript{20} and formula contains 11.5 mmol/L calcium and 8.40 mmol/L phosphorus.\textsuperscript{21} Thus, breast milk is low in phosphorus, and formula is high in both calcium and phosphorus to compensate for the reduced absorption of these minerals by formula feeding. Breast milk also has a lower citrate content than formula. Comparison of urinary metabolite excretions in the present study groups shows that urinary uric acid and phosphorus levels were higher in the formula+breastfeeding group than in the breastfeeding group. As another limitation of the present study, no patients were fed solely formula. Despite the lack of a comparison between solely breastfeeding and solely formula feeding, we demonstrated that certain urinary metabolite excretions were affected by the addition of formula to the diet.

An underlying metabolic abnormality was generally found in the majority of cases. We could not show any effect of water supplementation on urinary metabolite excretions; however, due to the demonstrated risk factors associated with formula feeding, we suggest that beneficial effects of water supplementation may be seen at a later date.

Certain subpopulations of children are at greater risk of developing stone disease; those with a family history of stone disease or metabolic abnormalities. It must be noted that family history data do not always distinguish between inherited and environmental factors.\textsuperscript{22} Stechman et al, reviewed the strong heritability of hypercalciuria in twin studies. Genetic predisposition and certain genes determine over 50% of urinary calcium excretion rates. Up to 65% of patients with hypercalciuric nephrolithiasis may have a family history of the disorder.\textsuperscript{23} Alpay et al, reported that the rate of hypercalciuria is higher in patients with microlithiasis.\textsuperscript{3} In the present study no difference was detected in urinary calcium levels between patients with a family history and those without. The number of patients with microlithiasis was significantly higher in the positive family history group as compared with the negative family history group, which appears to be a result of early detection in infants with a family history.

The present study has an important limitation: there was no control group, since we avoid using urethral catheters in healthy infants; thus, we decided to use literature data as a reference.

In conclusion, it is clear that the risk of developing urolithiasis begins in the first year of life. When there is a
family history of urolithiasis, any infant presenting with non-specific symptoms may have to undergo urinary ultrasonography examination to exclude urolithiasis. Further studies regarding the relationship between infantile urolithiasis and nutrition/water intake are warranted.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgement

Compliance with Ethical Standards: We had approval from our Local Ethics Committee and the study was performed in accordance with the Declaration of Helsinki. Informed consent was given by the parents for all patients prior to inclusion.

References

Original Article

Vitamin D and Nutritional Status of Children Evaluated via Bioelectric Impedance Analysis

F Khalilova, M Ozctin, A Kilic, F Bas, A Yetim, G Keskindemirci, E Gur, F Darendeliler

Abstract

Objective: Nutritional disorders affect growth in children. The present study aimed to assess the nutritional status and vitamin D levels in children by use of different nutritional assessment parameters via bioelectric impedance analysis. Methods: Two hundred and seventy-nine patients who applied to our general paediatrics outpatient clinic with various complaints, such as poor nutrition, obesity, weakness, fatigue, pain in the legs and a lack of adequate sunshine, were included in the study. Anthropometric measurements, body composition analysis data gathered with an In-Body 230 device, and bioelectric impedance analysis (BIA) data were assessed for all patients. The patients were grouped according to BMI SDS as lean, normal weight, overweight or obese. The subjects' 25(OH)D vitamin levels were obtained from laboratory recordings. Results: Of the patients, 44.1% (n=123) were female. The mean age was 10.0±3.6 (2-17) years. Of the patients, 18.6% (n=52) were lean, 47.3% (n=132) were normal weighted, 14.7% (n=41) were overweight, and 19.4% (n=54) were obese. The mean 25(OH)D levels of the lean, normal weighted, overweight and obese patients were 22.9±13.5 ng/mL, 25.8±11.8 ng/mL, 20.7±7.7 ng/mL and 17.9±9.7 ng/mL respectively. Levels of 25(OH)D were lower in the obese group than in the other groups, but this difference was not significant. The prevalence of obesity is increased in boys during adolescence, while 25(OH)D levels are decreased among girls. Conclusions: The evaluation of nutritional status and body fat composition via BIA may be a helpful and reliable method of preventing and treating childhood obesity and malnutrition.

Key words

Bioelectric impedance analysis; Body composition analysis; Malnutrition; Vitamin D

Introduction

Growth reflects a child's general health and nutritional status. Adequate nutrition in children is possible with the intake of the necessary calories, protein, vitamins, minerals and trace elements required to survive and to provide adequate growth. 1 Malnutrition refers to both inadequate nutrition and overnutrition. Both have become serious health problems worldwide. Nutritional deficiency has been defined as an alteration in the normal body composition that can be prevented or treated with nutritional replacement. 2,3 In recent years, bioelectrical impedance analysis (BIA) has been used with gradually increasing frequency because of easy application, noninvasiveness, high reproducibility and fast results in determining nutritional status, along with physical nutritional...
Recent studies have shown that BIA-derived body composition measurements are helpful in the evaluation of nutritional status and growth (to determine basic measures and follow-up for the progression of changes in nutritional status). Vitamin D, which has a key role in the maintenance of normal bone mineral balance, plays significant roles in many parts of the body. Studies have shown a correlation between low serum 25(OH)D vitamin levels and obesity, diabetes mellitus and metabolic syndrome. This is thought to be related with the expression of vitamin D receptor in adipose tissue, the solubility of vitamin D in fat and the deposition of vitamin D in adipose tissue.5,6

This study was conducted to determine the nutritional states of patients who presented to the Division of General Pediatrics between 2015 and 2016 and the correlation between their nutritional states and 25(OH)D vitamin levels.

**Methods**

Two hundred seventy-nine patients aged between 2 and 17 years who presented to the Istanbul Faculty of Medicine, Department of Pediatrics, Division of General Pediatrics between January 2015 and September 2016 were included in this study. After approval was obtained from the local ethics committee of the Istanbul Faculty of Medicine (ethics committee file number: 2016/831), the body compositions and nutritional states of the patients were evaluated using the bioelectrical impedance method. The demographic properties of all subjects were recorded by asking face-to-face questions. Body weights were measured using an InBody 230 bioelectrical impedance analyser (100 g sensitivity). Heights were measured using a stadiometer (1 mm sensitivity) with shoes and clothes off. Body mass index (BMI) values were calculated with a bioelectrical impedance analysis device. Standard deviation scores (SDS, z score) for body weight, height and BMI were calculated based on the normal age- and gender-appropriate values using the following formula:

\[ \text{SDS (z score)} = \frac{\text{Current height} - \text{Mean height}}{\text{Standard deviation (SD)}} \]

The subjects’ body weight (kg), body muscle mass (kg), body fat mass (kg) and %, body water mass (kg), body protein mass (kg), body mineral mass (kg), body mass index (kg/m²) and basal metabolism rate (kcal) values were analysed using an InBody 230 bioelectrical impedance analysis device. The subjects’ lean body weight values were calculated by adding the body mineral, protein and water ratios. In our study, the subjects’ 25(OH)D vitamin levels were obtained from laboratory recordings.

SPSS (Statistical Package for Social Sciences) Version 24.0 was used for the statistical analysis of the data obtained in the study. In the analyses in which groups and descriptive statistical methods (mean, standard deviation, median, minimum and maximum) were compared, a Student’s t-test was used for the mean values between two groups, and a chi-square test was used for the categorical variables. A one-way Anova test was used in comparisons of three or more groups that showed a normal distribution. Pearson’s correlation test (coefficient: r), which is a parametric test, was used to investigate correlations between the data. A p-value of <0.05 was considered statistically significant.

**Results**

A total of 279 subjects who presented to the Department of General Pediatrics between 2015 and 2016 were included in the study. One hundred and twenty-three (44.1%) of these subjects were female, and 156 (55.9%) were male. The mean age was 10.0±3.69 (2-17) years (Table 1). In our study, 25(OH)D vitamin levels were measured in a total of 106 patients, 62 (58.5%) of whom were male and 44 (41.5) of whom were female (mean age 9.89±3.75 years). No statistically significant differences were found between the genders in terms of height, body weight or BMI SDS (Table 1). According to the BMI SDS levels, 18.6% (n=52) of all subjects were lean, 47.3% (n=132) were normal, 14.7% (n=41) were overweight and 19.4% (n=54) were obese. No statistically significant difference was found between the genders in terms of BMI measurement.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age* (years)</th>
<th>Height† (cm)</th>
<th>Weight† (kg)</th>
<th>BMI† (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SDS</td>
<td>SDS</td>
<td>SDS</td>
<td>SDS</td>
</tr>
<tr>
<td>Female (n=123)</td>
<td>10.8±3.82</td>
<td>141±19.7</td>
<td>43.1±22.8</td>
<td>20.1±7.04</td>
</tr>
<tr>
<td></td>
<td>-0.09±1.63</td>
<td>0.09±1.63</td>
<td>0.17±2.1</td>
<td></td>
</tr>
<tr>
<td>Male (n=156)</td>
<td>9.33±3.45</td>
<td>134.9±21.2</td>
<td>35.8±19.5</td>
<td>18.3±5.41</td>
</tr>
<tr>
<td></td>
<td>0.01±1.38</td>
<td>-0.05±1.82</td>
<td>-0.06±1.84</td>
<td></td>
</tr>
<tr>
<td>Total (n=279)</td>
<td>10.0±3.69</td>
<td>137.6±20.8</td>
<td>39.0±21.3</td>
<td>19.1±6.24</td>
</tr>
<tr>
<td></td>
<td>0.05±1.48</td>
<td>0.04±1.98</td>
<td>0.04±1.96</td>
<td></td>
</tr>
</tbody>
</table>

* p<0.05; †p>0.05
When the BIA data were compared by gender, statistically significant differences were found in terms of body water mass, the amount of protein, muscle mass, mineral mass, lean body weight and body fat mass. The lean body mass obtained via BIA was found to be 72.5±12.4% in the girls and 77.6±12.1% in the boys (Table 2). No statistically significant difference was found when basal metabolism rates were compared by gender.

No statistically significant difference was found between the BMI SDS subgroups in terms of age distribution. When the BIA data were compared between the BMI SDS subgroups, statistically significant differences were found in terms of body water, minerals, protein, lean body weight, muscle mass, body fat mass or basal metabolism rate (Table 3). Also, 29.2% of subjects (n=31) whose 25(OH)D vitamin levels were examined were lean, 47.2% (n=50) were normal, 7.5% (n=8) were overweight and 16% (n=17) were obese.

Among the BMI SDS groups, no statistically significant differences were found between the age distributions of the subjects whose 25(OH)D vitamin levels were examined. Statistically significant differences were found in terms of body water mass, the amount of body protein, body muscle mass, lean body weight and body fat mass. No statistically significant differences were found in terms of the basal metabolism rate and serum 25(OH)D vitamin levels between the BMI SDS subgroups (Table 4).

When the relationships between 25(OH)D vitamin levels and anthropometric values were examined, a negative correlation was found between 25(OH)D vitamin levels and body fat mass (p:0.021, r:-0.223). A statistically significant positive correlation was found between 25(OH)D vitamin levels and body water, protein and lean body weight (p:0.23, r:0.014, p:0.020, r:0.227, p:0.013, r:0.241). No correlation was found between the 25(OH)D vitamin levels and the basal metabolism rate or mineral or muscle mass. A negative correlation was found between the height SDS

Table 2  Analysis of the bioelectrical impedance analysis (BIA) data by gender

<table>
<thead>
<tr>
<th>BIA data</th>
<th>Female (n=123)</th>
<th>Male (n=156)</th>
<th>Total</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body water mass (%)</td>
<td>55.3±9.51</td>
<td>53.2±9.22</td>
<td>57.0±9.44</td>
<td>0.001*</td>
</tr>
<tr>
<td>Amount of body protein (%)</td>
<td>14.7±2.41</td>
<td>14.1±2.45</td>
<td>12.2±2.28</td>
<td>0.000*</td>
</tr>
<tr>
<td>Mineral (%)</td>
<td>5.18±0.86</td>
<td>5.2±0.85</td>
<td>5.30±0.85</td>
<td>0.008*</td>
</tr>
<tr>
<td>Body fat mass (%)</td>
<td>24.4±12.3</td>
<td>27.4±12.4</td>
<td>22.0±11.6</td>
<td>0.000*</td>
</tr>
<tr>
<td>Body muscle mass (%)</td>
<td>37.6±6.00</td>
<td>36.4±5.81</td>
<td>38.6±5.97</td>
<td>0.001*</td>
</tr>
<tr>
<td>Lean body weight (%)</td>
<td>75.3±12.5</td>
<td>72.5±12.4</td>
<td>77.6±12.1</td>
<td>0.001*</td>
</tr>
<tr>
<td>Basal metabolism rate (kcal)</td>
<td>971.1±257.4</td>
<td>999.2±238.0</td>
<td>947.8±269.8</td>
<td>0.097</td>
</tr>
</tbody>
</table>

*p<0.05 (significant difference)

Table 3  Analysis of the bioelectrical impedance analysis (BIA) data by body mass index (BMI) for all subjects

<table>
<thead>
<tr>
<th>BMI</th>
<th>&lt;2 SDS (lean)</th>
<th>1 to -2 SDS (normal)</th>
<th>1 to 2 SDS (overweight)</th>
<th>&gt;2 SDS (obese)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>10.4±4.42</td>
<td>9.42±3.61</td>
<td>10.9±2.95</td>
<td>10.9±3.44</td>
<td>0.058</td>
</tr>
<tr>
<td>Height (SDS)</td>
<td>-0.77±1.51</td>
<td>-0.21±1.43</td>
<td>0.92±0.91</td>
<td>0.82±1.25</td>
<td>0.000*</td>
</tr>
<tr>
<td>Weight (SDS)</td>
<td>-2.47±0.81</td>
<td>-0.48±1.17</td>
<td>1.37±0.80</td>
<td>2.73±0.66</td>
<td>0.000*</td>
</tr>
<tr>
<td>BIA data</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body water mass (%)</td>
<td>63.6±8.70</td>
<td>58.9±5.33</td>
<td>49.8±5.44</td>
<td>42.7±4.76</td>
<td>0.000*</td>
</tr>
<tr>
<td>Amount of body protein (%)</td>
<td>17.1±1.05</td>
<td>15.6±1.48</td>
<td>13.3±1.55</td>
<td>11.4±1.34</td>
<td>0.000*</td>
</tr>
<tr>
<td>Mineral (%)</td>
<td>1.56±0.64</td>
<td>1.72±0.78</td>
<td>2.13±0.73</td>
<td>2.51±0.86</td>
<td>0.000*</td>
</tr>
<tr>
<td>Body fat mass (%)</td>
<td>11.9±4.85</td>
<td>19.8±7.06</td>
<td>32.3±7.56</td>
<td>41.9±6.46</td>
<td>0.000*</td>
</tr>
<tr>
<td>Body muscle mass (%)</td>
<td>41.8±5.42</td>
<td>39.5±4.85</td>
<td>35.1±4.03</td>
<td>30.9±3.57</td>
<td>0.000*</td>
</tr>
<tr>
<td>Lean body weight (%)</td>
<td>86.8±9.09</td>
<td>80.1±7.14</td>
<td>67.9±7.38</td>
<td>58.1±6.48</td>
<td>0.000*</td>
</tr>
<tr>
<td>Basal metabolism rate (kcal)</td>
<td>863±206.8</td>
<td>915±240.6</td>
<td>1027.5±219.5</td>
<td>1165.6±257.4</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

*p<0.05 (significant difference)
value and several of the BIA data, including the amount of body water, the amount of body protein, mineral weight and lean body weight, in the study group (p=0.008, r=-0.257; p=0.003, r=-0.289; p=0.000, r=-0.21; and p=0.004, r=-0.279, respectively). On the other hand, a positive correlation was found between height and body fat mass and basal metabolism rate (p<0.001, r=0.306 and p<0.003, r=0.284, respectively) (Table 5).

**Discussion**

Nutritional disorders affect growth in children and are among the first and most significant indicators of a disruption in the general health state. Rapid advancements in science and technology have led to a decrease in health problems related with inadequate nutrition. On the other hand, problems related with overnutrition and excess energy have increased. Malnutrition, which refers to both inadequate and excessive nutrition, has become a significant health problem worldwide. There are regional differences across Europe, obesity rates reaching up to 23% and 29% have been found in the 7-11 age group and 12-18 age group, respectively. The frequency of obesity is usually higher in girls than in boys. Studies conducted in our country show that the frequency of obesity in childhood has reached 6.5% and the frequency of being overweight has reached 14.3%. In our study, the frequency of obesity in the 2-17 year age group was found to be 19.4% (10.1% in boys and 9.3% in girls) and the frequency of being overweight was found to be 14.7% (7.5% in boys and 7.2% in girls). In conclusion, the frequency of obesity in our study was found to be higher than in other studies conducted in our country but lower than in studies conducted in Europe. The frequency of being overweight was found to be similar to the results of other studies conducted in our country.

Although body composition is being analysed extensively in adults, body composition analysis is a method that is still being developed, especially for use in children, and may be helpful in obtaining information regarding the health and nutritional states of patients. The main components of body composition are fat mass (FM), total body water (TBW) and fat free mass (FFM). Our information related with body composition in children is limited due to the large differences between children and adults. These differences cause additional difficulties in determining body composition in children. It has been shown that lean body weight and water and bone mineral content change during growth. Similarly, body water mass, mineral mass and lean body weight decreased and body muscle mass, fat mass and the basal metabolism rate increased as the age increased within the 2-17-year age group in our study.

In children, the impact of gender is minimal until the

| Table 4 | The bioelectrical impedance analysis (BIA) data by body mass index (BMI) for subjects whose serum 25(OH)D vitamin levels were examined |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                | <−2 SDS (lean)  | 1 to −2 SDS (normal) | 1 to 2 SDS (overweight) | >2 SDS (obese) | p               |
| Age (years)    | 10.6±4.15      | 9.00±3.48       | 11.2±4.24       | 10.5±3.61      | 0.317           |
| Height (SDS)   | -1.15±1.49     | -0.55±1.50      | 0.73±1.21       | 0.55±0.92      | 0.008*          |
| Weight (SDS)   | -2.44±0.82     | -0.71±1.25      | 1.30±1.03       | 2.63±0.72      | 0.000*          |
| 25(OH)D vitamin (ng/ml) | 22.9±13.5 | 25.8±11.8 | 20.7±7.76 | 17.9±6.69 | 0.106 |
| BIA data       |                |                |                |                |                 |
| Body water mass (%) | 62.8±10.86 | 59.1±5.93 | 49.9±7.60 | 42.3±5.60 | 0.000*          |
| Amount of body protein (%) | 17.0±1.10 | 15.7±1.67 | 13.3±2.03 | 11.3±2.04 | 0.000*          |
| Mineral (%)    | 6.10±0.41      | 5.48±0.57      | 4.88±0.74      | 3.86±0.54      | 0.000*          |
| Body fat mass (%) | 12.0±4.98 | 19.5±7.98 | 31.8±10.3 | 42.5±7.60 | 0.000*          |
| Body muscle mass (%) | 41.7±5.98 | 38.8±5.62 | 35.0±4.99 | 30.4±3.99 | 0.000*          |
| Lean body weight (%) | 85.9±11.1 | 80.4±7.97 | 68.2±10.3 | 57.4±7.65 | 0.000*          |
| Basal metabolism rate (kcal) | 866.6±206.8 | 863.7±206.8 | 1062.6±283.5 | 1147.1±288.8 | 0.059         |

*p<0.05 (significant difference)
age of 10 years, but this impact increases after the age of 10 years. At this time, changes in body composition occur in girls and boys due to increases in sex hormones. Body composition and the segmental distribution of fat and muscle mass begin to vary by gender as age increases. In our study, it was found that body water decreased as the age increased, and more body water was seen in boys than in girls. In 2009, Kaya and Özçelik evaluated 335 adolescent girls aged between 14 and 18 years and 409 adolescent boys aged between 14 and 18 years and found the body fat percentage obtained via BIA to be 23.6 ± 0.3 in the girls years and 21.2 ± 9.9 in the boys. In our study, the body fat percentage obtained via BIA was found to be 29.3 ± 12.8% in the girls and 23.0 ± 12.9% in the boys. In our study, these values were found to be slightly higher.

The basal metabolism rate is affected by many factors, including age, gender, amount of muscle tissue, lean body mass, growth and hormones. In our study, no significant difference was found between genders in terms of the basal metabolism rate. However, it was found that the basal metabolism rate increased as age increased in both female and male subjects. These results show that the basal metabolism rate increases as adolescence approaches.

As the fat mass in the body increases, the amounts of body water and muscle mass decrease. Similarly, it was found that body fat mass, the basal metabolism rate and the mineral rate were increased and the amount of body protein, water, muscle and lean body weight were decreased in obese subjects in our study. In a study conducted in Australia to investigate body compositions in obese children via DEXA and BIA, the body fat percentage obtained via BIA was found to be 41.4 ± 8.3%. In our study, the average body fat percentage in obese subjects was found to be similar (41.9 ± 6.46%).

Adequate nutrition is very important for the development of the bone structure and its ability to endure mechanical stress. Vitamin D levels may be low in lean subjects because of eating habits that lead to inadequate nutrition. Therefore, the correction of malnutrition and the administration of vitamin D is necessary in excessively lean subjects. In a study conducted in Uganda with 158 subjects aged between 6 and 24 months, 117 of whom had malnutrition and 41 of whom had normal weight, serum vitamin D levels were found to range between 32.5 mmol/l and 32.2 mmol/l (below 20 ng/ml) in subjects who had malnutrition. In our study, 25(OH)D vitamin levels were measured in a total of 106 (%38) patients with various medical conditions which may affect the nutritional or vitamin D status. For this reason, the results make it difficult to generalise to other children in the population. Vitamin D levels were found to be low in 40% of the subjects who had normal body weight, excluding subjects who had low body weight.

In our study, 29.2% of subjects whose vitamin D levels were measured were lean, and 16.1% were obese. The frequency of obesity was higher in the male subjects in our study than in the females (12.3% of the male subjects and 3.8% of the female subjects). Although vitamin D levels were investigated at a higher rate in the lean subjects, these levels were found to be higher in these subjects as compared to the obese subjects (the mean vitamin D level was found to be 22.9 ± 13.5 ng/ml in the lean subjects and 17.9 ± 9.6 ng/ml in the obese subjects). This result shows that vitamin D is deposited in the adipose tissue, as stated in other studies. In the study conducted by Wortsman et al, it was reported that there was no significant difference between obese and non-obese subjects in terms of vitamin D synthesis in the skin. In a study conducted by Reinehr et al, 133 obese and 23 non-obese children were examined in terms of

<table>
<thead>
<tr>
<th>Bioelectrical impedance analysis</th>
<th>Amount of body water (%)</th>
<th>Amount of body protein (%)</th>
<th>Mineral (%)</th>
<th>Body fat mass (%)</th>
<th>Body muscle mass (%)</th>
<th>Lean body weight (%)</th>
<th>Basal metabolic rate (kcal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>p</td>
<td>r</td>
<td>p</td>
<td>r</td>
<td>p</td>
<td>r</td>
<td>p</td>
<td>r</td>
</tr>
<tr>
<td>25(OH)D vitamin</td>
<td>0.014*</td>
<td>0.237</td>
<td>0.020*</td>
<td>0.227</td>
<td>0.064</td>
<td>0.180</td>
<td>0.021*</td>
</tr>
<tr>
<td>Height (SDS)</td>
<td>0.008*</td>
<td>-0.257</td>
<td>0.003</td>
<td>-0.289</td>
<td>0.000</td>
<td>-0.333</td>
<td>0.001*</td>
</tr>
<tr>
<td>Weight (SDS)</td>
<td>0.000*</td>
<td>-0.648</td>
<td>0.000</td>
<td>-0.741</td>
<td>0.000</td>
<td>-0.802</td>
<td>0.000*</td>
</tr>
<tr>
<td>BMI (SDS)</td>
<td>0.098</td>
<td>-0.686</td>
<td>0.000</td>
<td>-0.792</td>
<td>0.000</td>
<td>-0.842</td>
<td>0.000*</td>
</tr>
</tbody>
</table>

*p<0.05 (significant difference)
vitamin D levels, and vitamin D levels were found to be lower in the obese children than the non-obese children.\textsuperscript{20} Similar results were found in our study. In a retrospective study conducted by Smotkin-Tangorra et al with 217 obese children, vitamin D deficiency was found in 55.2\% of these children.\textsuperscript{21} In our study, vitamin D levels were found to be below 20 ng/mL in ten (58.8\%) of 17 subjects. It was found that the amount of body minerals also increased as the amount of body fat increased in the 279 subjects included in the study. In 106 subjects whose vitamin D levels were investigated, the amount of minerals was observed to decrease as the amount of body fat increased. However, no significant correlation was found between vitamin D and the amount of minerals in the correlation analysis.

The American Association of Clinical Endocrinologists considers a vitamin D level of 30 ng/mL or above to be adequate.\textsuperscript{22} We used the vitamin D classification of the American Association of Clinical Endocrinologists and considered a vitamin D level of 20 ng/mL or below to be deficient, a vitamin D level of 21-29 ng/mL to be insufficient and a vitamin D level of 30 ng/mL or above to be normal.\textsuperscript{22} In a study conducted by Absoud et al with 1,102 children and adolescents aged between 4 and 18 years in Great Britain, vitamin D deficiency (<20 ng/mL) was found in 35\% of the participants.\textsuperscript{23} Similarly, the vitamin D level was found to be below 20 ng/mL in 48.1\% of the subjects and between 21 and 29 ng/mL in 28.5\% of the subjects in our study. Vitamin D deficiency or insufficiency were found in 76.4\% of the subjects.

Adolescent girls have a lower intake of vitamin D via foods and lower serum 25(OH)D levels as compared to boys.\textsuperscript{24} The subjects in the adolescent group who participated in our study were not receiving vitamin D. Severe and prolonged vitamin D deficiency in adolescence may be asymptomatic and go unnoticed, in contrast to vitamin D deficiency in children. In a study conducted by Rockell et al with 1,585 children aged between 5 and 14 years in New Zealand, vitamin D levels were found to be below 15 ng/ml in 31\% of the participants and lower in the girls as compared to the boys.\textsuperscript{25} One meta-analysis emphasized that being an adolescent was a risk factor for vitamin D deficiency and that vitamin D deficiency was more frequent in girls than boys.\textsuperscript{24} In our study, serum 25(OH)D vitamin levels were found to be lower in adolescent girls as compared to boys in the same age group.

Our study is one of the few studies to examine the relationship between nutritional status, as determined via BIA, and 25(OH)D vitamin levels. As observed in this study, 25(OH)D deficiency is common in children. The improvement of vitamin D levels across all age groups is important because vitamin D plays a significant role in the lifecycle of the human body.

It is important to highlight that we cannot generalise our results, principally due to the small sample size. Therefore BIA data may not be sufficient to represent children’s nutritional status. When the results obtained in our study were evaluated, certain limitations were observed. These limitations include a lack of consideration of the nutritional information regarding the subjects, the low number of the subjects, the inability to fully evaluate clothing style, which is one of the factors that affects vitamin D level; and the failure to use questionnaires regarding eating frequency.

In conclusion, vitamin D deficiency is commonly observed in adolescents according to the results obtained in our study. Female adolescents and obese individuals are at risk in terms of vitamin D deficiency. Therefore, the regulation of nutrition and vitamin D supplementation are necessary in obese individuals. The body composition in children with malnutrition might make them susceptible to nutritional disorders; therefore, a health-oriented nutrition education is necessary in order to modify dietary habits. In addition, the evaluation of nutritional status and body fat composition via BIA may be a helpful and reliable method of preventing and treating childhood obesity.

Acknowledgments

We appreciate all the participants and all those who helped us in this study.

Declaration of Interest

The authors declare that there is no conflict of interest.

References

4. Lee SY, Gallagher D. Assessment methods in human body
**Abstract**

*Objective:* This study investigates depression and eating disorders in children with type 1 diabetes mellitus (DM) and aims to determine the associated factors. *Methods:* This cross-sectional study was conducted with 149 children with type 1 DM aged 10-17 years. The Children's Depression Inventory and Diabetes Eating Problem Survey-Revised were administered, anthropometric measurements were taken, and certain biochemical results were evaluated. *Results:* The mean age of the children was 13.42±2.31 years. The children who did not use carbohydrate counting had higher depression scores and lower eating disorder scores than those who did and depression and eating disorder scores were lower in children who used insulin pumps than in those who did not. A one unit increase in the children's HbA1c levels caused a three unit increase in eating disorder scores and 1.3 times greater risk of depression. *Conclusions:* Nutritional, biochemical and psychiatric evaluation, and monitoring are recommended when providing diabetes control among children.

**Key words**  Children;  Depression;  Eating disorder;  HbA1c;  Type 1 diabetes mellitus

**Introduction**

Type 1 diabetes mellitus (DM) is characterised by a deficiency in insulin production in the body. The causes of type 1 DM are unknown and there are no valid data concerning the prevention of this serious disease. The incidence of type 1 DM in children is increasing in Europe every day. It is predicted that the number of new cases will double in children younger than 5 years and will increase by 70% in children younger than 15 years by 2020.

Providing glycaemic control by means of exogenous administration of insulin is the prevalent treatment of this disease. As a result, certain factors, such as insulin dependence, especially at a young age, the maintenance/protection of body weight, fear of hypoglycaemia, and certain eating patterns to prevent hypoglycaemia lead to an increased risk of anxiety, depression, and disordered eating behaviour in individuals. Furthermore, according to a recent meta-analysis, disordered eating behaviour is more common in adolescents with type 1 DM compared with peers and is associated with poorer glycaemic control.

The prevalence of depressive symptoms in children and adolescents has been found to be 30.0%, and associated with elevated glycated haemoglobin (HbA1c) levels and poorer metabolic control. Furthermore, an increased incidence of depression in children with eating disorders...
has been reported.\textsuperscript{5} Some methods, such as the use of insulin pumps\textsuperscript{14,15} and carbohydrate counting,\textsuperscript{16} can be used to provide metabolic control. Studies have shown that carbohydrate counting and medical therapy together could reduce HbA1c and hypoglycaemia\textsuperscript{17,18} and improve quality of life.\textsuperscript{18} Likewise, insulin pump therapy has been found to have an effect on reducing HbA1c levels 3-6 months after starting treatment.\textsuperscript{19}

Although both carbohydrate counting and insulin pump therapy are associated with a reduction in HbA1C, there are limited data examining the psychosocial effects of the use of these methods and studies on the effect of carbohydrate counting on depression are contradictory.\textsuperscript{20} Consequently, in this study we aimed to assess disordered eating and depression scores according to carbohydrate counting and insulin pump usage, as well as to detect the prevalence of disordered eating behaviour and depression in our study group and determine associated factors.

\section*{Methods}

\subsection*{Sample and Procedure}

The sample of the study consisted of 149 children (81 male, 68 female) with type 1 DM, aged 10-17 years, who were admitted to the Department of Paediatric Endocrinology of a university hospital in Ankara, Turkey between February and May 2016. The participants were selected on the basis that they did not have another chronic disease (cardiovascular disease, polycystic ovary syndrome, thyroid dysfunction, asthma, etc.) and received no hormone treatment or medication.

\subsection*{Data Collection}

Data were collected using a questionnaire prepared by the researchers. The questionnaire was divided into six sections:

i. Demographic information (14 questions)
ii. Health information (carbohydrate counting, use of insulin pump, etc.) (5 questions)
iii. Children's depression inventory (27 items)
iv. Diabetes eating problem survey-revised (DEPS-R) (16 items)
v. Anthropometric measurements (5 items)
vi. Biochemical results (3 data)

Ethical approval for the study was obtained from the Istanbul Medipol University Non-Interventional Clinical Studies Ethics Board (number: 10840098-604.01.01-E. 2296). Oral and written informed consent was obtained from the children’s parents before they were included. The participants were informed that their information would be kept confidential and used only for scientific purposes. Each participant signed a voluntary participation form and completed the questionnaires. All procedures were in line with the Helsinki Declaration. The questionnaire, which took approximately 25 minutes to complete, was administered to the volunteering children's parents by the researchers.

\subsection*{Anthropometric Measurements}

Anthropometric measurements, including weight (kg), height (cm), and waist circumference (cm) were measured by well-trained investigators, using standard measurement protocols. Height was measured with a stadiometer to the nearest 0.1 cm. Waist circumference was measured at the mid-point, above the iliac crest, and below the lowest rib margin at minimum respiration, using a flexible tape to the nearest 0.1 cm.\textsuperscript{21,22} The children were weighed using a body composition analyser (TBF-300A, Body Composition Analyzer) to the nearest 0.1 kg. Body fat mass (kg) and body fat percentage (%) were also obtained using this analyser.\textsuperscript{23} Weight and height were used to calculate the body mass index (BMI), calculated as weight (kg) divided by height squared (m\textsuperscript{2}). BMI for age Z-scores (BMI z-score) were calculated using WHO AnthroPlus software.\textsuperscript{24}

\subsection*{Biochemical Results}

The fasting blood glucose, fasting insulin, and HbA1c parameters of the children, which are routinely analysed by the biochemistry service of hospital, were evaluated.

\section*{Instruments}

\subsection*{Children's Depression Inventory}

The Children's Depression Inventory (CDI) is used to detect depressive symptoms in children. This scale was developed by Kovacs\textsuperscript{25} and validated for Turkey in a study conducted by Öy.\textsuperscript{26} It consists of 27 items and the child is asked to choose the most appropriate of three statements describing their symptoms over the previous 2 weeks. Each statement was scored from 0 to 2 depending on the severity of the depressive symptom. The scores were added to give a final score (0-54). Higher scores indicate an increase in the severity of depression. Scores of 19 or above identify potentially clinically depressed children. The validity and
reliability value of the scale is 0.80. In this study, Cronbach’s alpha was found to be 0.898, which was considered acceptable.

**Diabetes Eating Problem Survey-Revised**

The Diabetes Eating Problem Survey-Revised (DEPS-R) is a DM-specific self-report scale for eating disorders. The original instrument consists of 28 items and is used to determine DM-specific eating disorders in adults. It has recently been revised to create an instrument for the paediatric population, comprising a brief 16-item version, used by Markowitz et al in 2010. The DEPS-R can be completed in less than 10 min and has demonstrated good psychometric properties. Items are scored on a Likert scale from 0 (never) to 5 (always) and the score range is 0-80. A higher score indicates more disturbed eating behaviour and greater pathology. The validity and reliability value of the scale is 0.86. The DEPS-R was used to evaluate eating disorders in the children with type 1 DM in this study, with an acceptable Cronbach’s alpha of 0.85.

**Statistical Analyses**

The Statistical Package for the Social Sciences (version 15.0) software was used for all analyses. Quantitative data were analysed using visual (histogram and probability plots) and analytical methods (Kolmogorov-Smirnov and Shapiro-Wilk tests) to determine whether the data were normally distributed. The mean and standard deviation values of age, anthropometric measurements, body composition, biochemical findings, and CDI and DEPS-R scores of the children were obtained using t-tests for parametric data and the Mann-Whitney U test for nonparametric data. Correlations were calculated using the Spearman or Pearson test. Independent effects of the different factors on the eating disorder score were evaluated using a multivariate linear regression model. The goodness of fit of the multiple logistic regression models was assessed using the Hosmer-Lemeshow test. Odds ratios and 95% confidence intervals were presented. A p-value of less than 0.05 was considered to be statistically significant.

**Results**

**General Characteristics**

The mean age of the children was 13.42±2.31 years and they were diagnosed with DM at a mean age of 8.52±2.96 years; 30.2% of the children had DM in their family history. In terms of treatment, 65.1% of the children had been using carbohydrate counting for an average of 26.87±25.62 months and 16.1% of the children had been using an insulin pump for an average of 18.38±20.74 months.

**Evaluation of Health and Biochemical Status**

The means of fasting blood glucose and HbA1c of participants were 191.09±87.36 mg/dL and 9.03±2.00%, respectively (Table 1). Fasting blood glucose (mg/dL), serum insulin, and HbA1c (%) levels were statistically similar in both genders. There was no statistically significant difference in the use of carbohydrate counting and insulin pump duration according to gender (p>0.05) (Table 1).

In all, 11.9% of the participants skipped insulin pump usage. More than half of the children (68.4%) thought that their daily life was inhibited because of DM. Some of the children had difficulty using the insulin pump (39.0%), following up blood glucose (28.0%), adhering to the recommended nutrition programme (27.1%), and exercising regularly (5.9%). In terms of adherence to the recommended nutrition programme, the children could not eat meals when they wanted (51.7%), or as they wished (33.9%), and they

**Table 1** Evaluation of general characteristics and biochemical findings of the children by gender

<table>
<thead>
<tr>
<th>Variables</th>
<th>Boys (n:81)</th>
<th>Girls (n:68)</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>13.56±2.17</td>
<td>13.26±2.47</td>
<td>0.795</td>
<td>0.428</td>
</tr>
<tr>
<td>Age diagnosed with diabetes (year)</td>
<td>8.72±3.03</td>
<td>8.28±2.88</td>
<td>0.892</td>
<td>0.374</td>
</tr>
<tr>
<td>Carbohydrate counting duration (month)</td>
<td>26.56±26.81</td>
<td>27.19±24.61</td>
<td>-0.119</td>
<td>0.905</td>
</tr>
<tr>
<td>Insulin pump usage duration (month)</td>
<td>22.40±16.88</td>
<td>14.72±23.94</td>
<td>0.840</td>
<td>0.411</td>
</tr>
<tr>
<td>zBMI (SDS)</td>
<td>0.31±1.05</td>
<td>0.52±0.98</td>
<td>-1.223</td>
<td>0.223</td>
</tr>
</tbody>
</table>

**Biochemical Findings**

| Fasting blood glucose (mg/dL)          | 193.25±94.35| 188.43±78.57 | 0.332| 0.741|
| Serum insulin (µIU/mL)                 | 2.93±1.80    | 2.97±2.11    | -0.500| 0.961|
| HbA1c (%)                              | 9.07±1.97    | 8.98±2.04    | 0.282| 0.778|
failed to use carbohydrate counting (10.2%), or to wait for a while after using the insulin pump (4.2%).

The eating disorder and depression scores of the children are given in Table 2. There was no statistically significant difference between the eating disorder scores of boys and girls (11.19±6.75 and 11.76±6.97, respectively) (p>0.05). However, there was a statistically significant difference between the eating disorder scores of the children using (18.94±11.84) or not (26.34±10.27) carbohydrate counting and using (16.16±13.76) or not (22.56±11.19) an insulin pump (p<0.05) (Table 2).

In all, 11.4% of the children had a depression score <19. There was no statistically significant difference between the depression scores of boys and girls (21.49±11.49 and 21.57±12.30, respectively) (p>0.05). The children who did not use carbohydrate counting (13.63±7.14) had higher depression scores than who did (10.28±6.40) (p<0.05). Similarly, depression scores were lower in those using insulin pumps than not (8.58±5.59 and 12.00±6.93, respectively) (p<0.05) (Table 2).

The results of the multiple linear regression analysis between demographic characteristics, DM treatment methods, diagnostic criteria, and associated factors for DM of the participants and eating disorder scores are shown in Table 3. The HbA1c levels and waist circumference of the children had significant effects on their eating disorder scores. HbA1c levels had the greatest effect: a one unit increase in the children’s HbA1c levels caused a three unit increase in the eating disorder score.

The effects of some risk factors on the depression status of the children are given in Table 4. A one unit increase in the children’s HbA1c levels increased the risk of depression 1.3 times (p<0.05). The age at which the children were diagnosed with DM (year) and body fat mass (kg) did not

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**Table 2** Eating disorder and depression scores of the children according to use carbohydrate counting and insulin pump

<table>
<thead>
<tr>
<th></th>
<th>Eating disorder</th>
<th>Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>t</td>
<td>p</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys (n:81)</td>
<td>11.19±6.75</td>
<td>-0.041</td>
</tr>
<tr>
<td>Girls (n:68)</td>
<td>11.76±6.97</td>
<td>0.795</td>
</tr>
<tr>
<td>Using Carbohydrate Counting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n:97)</td>
<td>18.94±11.84</td>
<td>-3.799</td>
</tr>
<tr>
<td>No (n:52)</td>
<td>26.34±10.27</td>
<td>1.645</td>
</tr>
<tr>
<td>Using Insulin Pump</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n:24)</td>
<td>16.16±13.76</td>
<td>-2.466</td>
</tr>
<tr>
<td>No (n:125)</td>
<td>22.56±11.19</td>
<td>1.620</td>
</tr>
</tbody>
</table>

*p<0.05

**Table 3** Effects of some properties on DEPS-R scores

<table>
<thead>
<tr>
<th>Variables</th>
<th>B</th>
<th>SE</th>
<th>Beta</th>
<th>t</th>
<th>p</th>
<th>95 % CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>-0.049</td>
<td>0.432</td>
<td>-0.010</td>
<td>-0.113</td>
<td>0.910</td>
<td>-0.903</td>
</tr>
<tr>
<td>Gender</td>
<td>1.388</td>
<td>1.542</td>
<td>0.060</td>
<td>0.900</td>
<td>0.370</td>
<td>-1.661</td>
</tr>
<tr>
<td>Age diagnosed with diabetes (year)</td>
<td>-0.104</td>
<td>0.297</td>
<td>-0.027</td>
<td>-0.351</td>
<td>0.726</td>
<td>-0.691</td>
</tr>
<tr>
<td>Using carbohydrate counting</td>
<td>0.613</td>
<td>1.885</td>
<td>0.025</td>
<td>0.325</td>
<td>0.746</td>
<td>-3.115</td>
</tr>
<tr>
<td>Using insulin pump</td>
<td>3.853</td>
<td>2.207</td>
<td>0.121</td>
<td>1.746</td>
<td>0.083</td>
<td>-0.510</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>3.103</td>
<td>0.534</td>
<td>0.054</td>
<td>6.923</td>
<td>0.000*</td>
<td>3.899</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>0.345</td>
<td>0.108</td>
<td>0.286</td>
<td>3.178</td>
<td>0.002*</td>
<td>0.130</td>
</tr>
<tr>
<td>Body fat mass (kg)</td>
<td>0.029</td>
<td>0.021</td>
<td>0.270</td>
<td>0.788</td>
<td>-0.182</td>
<td>0.240</td>
</tr>
</tbody>
</table>

R² = 0.451, (*p<0.05), β: Coefficient of regression, SE: Standart error of mean
correlate with depression risk. However, a one unit increase in the weight of the children increased depression prevalence risk 1.04 times. This result was found to be borderline significant (p=0.056) (Table 4).

Table 4  Effects of some risk factors on depression status of the children

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR</th>
<th>95 % CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age diagnosed with diabetes (year)</td>
<td>1.066</td>
<td>0.891 1.276</td>
<td>0.486</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>1.045</td>
<td>0.999 1.094</td>
<td>0.056</td>
</tr>
<tr>
<td>Body fat mass (kg)</td>
<td>0.994</td>
<td>0.929 1.065</td>
<td>0.874</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>1.300</td>
<td>1.005 1.681</td>
<td>0.045*</td>
</tr>
</tbody>
</table>

*p<0.05

The correlation of the DEPS-R and depression scores with HbA1c (%) levels is shown in Figure 1. Positive correlations were found between DEPS-R scores and HbA1c (%) (r=0.605, p=0.000) (Figure 1A), depression scores and HbA1c (%) (r=0.597, p=0.000) (Figure 1B), and DEPS-R scores and depression scores (r=0.714, p=0.000) (Figure 1C).

Discussion

Diabetic individuals are an important risk group in terms of psychological problems, such as depression, anxiety, and eating disorders.11,26 In this study, we aimed to investigate depression and eating disorder scores in children with type
1 DM and the effect of associated factors on depression and eating disorders. As a result of the study, we obtained the following results. First, 1 in 10 children had depression (depression score >19) according to the CDI. There is a close significant relationship between the physiological and physical health of individuals with type 1 DM. Moreover, children and adults with type 1 DM have at least double the risk of depression compared with the general population. Our results support the existing evidence. The possible reasons for this may be the risk of psychological difficulties is known to increase with age in diabetic children, especially during adolescence. However, our results fail to support the current evidence. The possible reasons for this may be the age of diagnosis in our sample and the nascent gender awareness of these children.

The second finding is that the depression scores showed no variation for gender or age (Table 2). However, women with type 1 DM have been found to be more depressed than men with type 1 DM. Mood has also been found to be an important reason for diagnosis with DM among women in adulthood. Furthermore, age is thought to be important for the depression status of patients with DM. The risk of psychological difficulties is known to increase with age in diabetic children, especially during adolescence. However, our results fail to support the current evidence. The possible reasons for this may be the age of diagnosis in our sample and the nascent gender awareness of these children.

The third result is that an increase in the children’s HbA1c levels resulted in an increase in the risk of depression (Table 4). In addition, a positive correlation was found between depression scores and HbA1c levels (Figure 1B). Mental health comorbidities cause adverse effects on disease management in adolescents with chronic diseases. Depression has been associated with increased HbA1c. Psychological (mood) problems are considered to worsen metabolic control through the neuroendocrine pathway, which is associated with stress and inflammation in these patients. Anxiety increased nearly two-fold in individuals with poor glycaemic control in a cross-sectional study. Moreover, HbA1c levels are the central mediator of long-term metabolic outcomes and depression and worsening of glycaemic control may cause an increased risk of psychological problems. These findings are consistent with our study.

We also found that the children using carbohydrate counting had lower depression scores than those who were not (Table 2). The diabetic diet and certain dietary restrictions may complicate living with DM and dietary advice can often be rejected. Carbohydrate counting increases flexibility in food choice and is considered a tool that makes the lives of those with DM more manageable. However, the positive effects of carbohydrate counting on HbA1c and psychological status are still debatable.

The children using insulin pumps (continuous subcutaneous insulin administration) showed lower depression scores than those who did not (Table 2). The psychological and metabolic effects of the use of insulin pumps are contradictory and there is insufficient evidence concerning diabetic children and adolescents. Treatment with insulin pumps has previously been shown to cause negative results in children and adolescents due to the self-administration of insulin, lower overall parental involvement, and greater self-consciousness about the disease. However, in recent years, research on children who use insulin pumps has found positive psychological outcomes, similar to our findings. Using an insulin pump rather than undergoing multiple doses of insulin administration yields positive developments in terms of self-efficacy, depression, and the quality of life of adolescents with type 1 DM. In addition, it is easier to cope with DM using an insulin pump than multiple doses of insulin administration. Using an insulin pump results in fewer physical complaints and restrictions than the injection method, but it also results in more self-reported fear and stress when problem solving and leads to people being less social. However, these results may be due to the use of less objective and more open-ended scales. Moreover, with the development of technology, the emergence of new pumps will give rise to differences between the old and new literature.

This study also shows a positive correlation between depression scores and eating disorder scores in children (Figure 1C). In particular, 75.0% of girls with depression have an eating disorder and girls with high depression scores have higher eating disorder scores. Furthermore, the risk of depression symptoms are greater in girls with eating disorders and 69.2% of girls with eating disorders have symptoms of depression. This relationship is expected because depression and eating disorders are involved in the aetiology of one another.

Eating disorders adversely affect health and physiological functions and cause repetitive negative episodes in eating behaviour. Eating disorders are more common in individuals with type 1 DM than in the general population. These conditions significantly affect the physical and emotional health and nutritional status of individuals with DM and are associated with impaired metabolic control and a higher risk of medical complications, including higher mortality rates. Brief self-report screening measures are available for the detection of eating disorders.
and skipping insulin doses are more common behaviours related to weight loss in patients with type 1 DM. In this study, 11.9% of children and adolescents skipped their insulin (data not shown). Restricting or skipping insulin doses increases the risk of eating disorders tenfold, so it is thought to be beneficial to follow patients in this respect.

This study found no difference in terms of eating scores between genders (Table 1). However, the prevalence of eating disorders among adolescents with type 1 DM is 8-30% and is more common in girls than boys. Increases in body weight, body dissatisfaction, and a history of dieting and depression contribute to eating disorders in female patients with both type 1 and type 2 DM. Body dissatisfaction especially occurs more commonly among girls with type 1 DM and it is important to pay attention to the potential of developing eating disorders in the age range of 13-14 years. Puberty is an important period in the development of eating disorders, so it will be important to consider this issue in future studies.

In this study, eating disorder scores were lower in children with type 1 DM using insulin pumps and carbohydrate counting (Table 2). In addition, the use of an insulin pump and carbohydrate counting are not risk factors for disordered eating behaviour (Table 3). Using an insulin pump provides normalisation of eating behaviour rather than giving more importance to food intake through carbohydrate counting. Eating disorder scores decreased over time and the use of an insulin pump was associated with a reduction in eating disorder behaviour in a study conducted among children with type 1 DM aged 10-17 years who used an insulin pump for 6 months. Our results support this. However, the results for the effect of carbohydrate counting on disordered eating behaviour risk are inconsistent. In addition to rigid controls, carbohydrate counting may contribute to the development of eating disorders and the risk of eating disorders may be lower in patients using carbohydrate counting.

We also identified a positive correlation between eating disorder scores and HbA1c levels (Figure 1A). Parallel with this result, a one unit increase in HbA1c levels resulted in a three unit increase in eating disorder scores (Table 3). The presence of DM and eating disorders together causes poor glycaemic control and an increased risk of complications over the long term. Retinopathy has been shown to develop in 86.0% women with high-level eating disorders and only 24.0% of women with normal eating behaviour after 5 years. In another study, consciously skipping insulin to lose weight caused deterioration in all psychological variables and higher BMI. More impaired metabolic control was observed in patients missing insulin than not. A comorbidity of eating disorders is low glycaemic control, which may increase the risk of eating disorders in children with type 1 DM. However, the comorbidity of eating disorders over the long term cannot be determined in this study. In this context, longitudinal and large sample size studies would be useful.

In conclusion, our study shows that children with type 1 DM are at risk of depression. The depression and eating disorder scores were higher in children who did not use carbohydrate counting and insulin pumps. In particular, depression and eating disorders can be seen more often in children with type 1 DM, whose metabolic outcomes are more impaired than those of other children. For this reason, nutritional, biochemical and psychiatric evaluation, and monitoring are important for providing DM control in children. A DM management team, including a physician, dietician, nurse, and mental health professional, is recommended for DM management.

**Limitations**

Undertaking a similar study with a large sample of patients of all ages, as well as comparison with a control group, would be useful. Further research should examine the early indicators of eating disturbances in pre-teen and early male and female teenagers, as well as the longer-term impact on adults as they progress beyond adolescence and into early adulthood. We expect that innovations leading to the replacement of traditional insulin injection, blood monitoring, carbohydrate counting, and dietary compliance will have a major impact on the development of eating disturbances in children with type 1 DM.

**Acknowledgements**

We would like to thank all the parents who devoted their time to participating in this study for their children. They are warmly acknowledged for their helpful and whole-hearted cooperation.

**Declaration of Interest**

The authors declare that they have no conflict of interests.
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Original Article

Antiemetics to Control Vomiting in Children: A Double-Blind Placebo-Controlled Trial

O KARAKAYALI, S YILMAZ, YS DIVRIKLIOGLU, Y YIGIT, HC HALHALLI

Abstract

Aim: The goal of this investigation was to prospectively compare the efficacy of ondansetron, metoclopramide and a placebo in children presenting to the emergency department with acute vomiting. 

Materials and Methods: In this randomised double-blind trial, the participants, who were younger than 18 years of age, were randomly assigned to receive treatment with (a) 0.15 mg/kg intravenous ondansetron, (b) 0.2 mg/kg intravenous metoclopramide in 100 mL normal saline, and (c) 100 mL normal saline as a placebo. The primary outcome was measured as recurrence of vomiting after 60 minutes subsequent to antiemetic therapy. 

Results: A total of 234 patients were randomised into the three treatment groups with (a) ondansetron (n=77), (b) metoclopramide (n=79) and (c) placebo (n=78). The median age was 68.27±39.97 months, and 49.1% were male. The results showed the occurrence of vomiting within the first 60 minutes was significantly different in the three groups (p=0.001), but there was no difference between the ondansetron and metoclopramide groups (p=0.557). The 30th, 120th, and the 240th minute results were statistically significant among the treatment groups (p=0.002, p=0.000, p=0.000 respectively), but there were no difference between ondansetron and metoclopramide (p=0.357, p=0.188, p=0.126, respectively). Extrapyramidal symptoms were found in 1 patient in the metoclopramide group (1.3%). There was no difference among the 3 treatment groups in terms of vomiting during the 24-hour follow-up (p=0.200). Conclusion: Intravenous single-dose slow infusion of antiemetics is effective in controlling vomiting compared to placebo.

Key words Antiemetics; Emergency Medicine; Paediatrics; Vomiting

Introduction

Vomiting is a non-specific sign of a number of childhood diseases, and it constitutes a significant portion of emergency paediatric cases. The most common cause of vomiting in older infants and children is infectious gastroenteritis, many non-gastro-intestinal infections may generate vomiting as a symptom, as well. Stimulation of either the vomiting centre, a central "control centre" in the medulla near the respiratory centre, or the chemoreceptor trigger zone (CTZ) in the area postrema on the floor of the fourth ventricle can generate
vomiting. Afferent impulses from other areas of the brain, such as the vestibular system, the amygdala (as with emotion or fear), or from certain organs outside the GI tract can stimulate vomiting in a similar mechanism. In children with dehydration from gastro-enteritis, oral rehydration is recommended as the first line therapy by the American Academy of Paediatrics. Parenteral therapy is considered to be useful in reducing vomiting symptoms in cases in which oral rehydration fluids are not adequate to correct the dehydration.

In the guidelines recorded before 2008, antiemetic therapy was not recommended, particularly as first-line treatments for children with gastroenteritis; nevertheless, it has been emphasized in subsequent guidelines that antiemetic treatment is effective in selected cases. Despite all these suggestions, it has been noted that 79.2% of emergency physicians and only 52.2% of paediatricians in the United States prefer to use antiemetic agents in order to control vomiting and their side-effect.

Antiemetics such as prochlorperazine, ondansetron and metoclopramide are recommended in the paediatric oncology guideline for the control of paediatric vomiting cases. Studies on ondansetron and metoclopramide have mostly been performed for the control of post-operative vomiting and on hospitalised oncological patients receiving chemotherapy, but studies on single intravenous (IV) dose for rapid and effective vomiting control in the emergency department are limited. Although prochlorperazine and metoclopramide have been compared in a limited number of emergency department studies, they have not been found to be superior to normal saline infusion; however, the number of cases studied has been small. In a limited number of studies, symptom control for patients during follow-ups in the emergency department was taken into consideration; the rates of post-discharge vomiting and re-admissions due to resistant vomiting were not specified.

Ondansetron, a selective serotonin antagonist, is the most commonly used antiemetic agent for the control of paediatric vomiting due to its effects on the central and peripheral nervous system. Placebo-controlled randomised trials have shown that ondansetron reduces the rate of hospitalisation, especially in the control of vomiting secondary to gastroenteritis, and it decreases the need for IV fluids and the frequency of vomiting. However, there are controversies related to the use of ondansetron in many other studies besides the high cost of the drug.

Metoclopramide, a dopamine and serotonin antagonist, controls vomiting by affecting the chemoreceptor trigger zone in the central nervous system. Many adverse effects have been reported when using metoclopramide as an antiemetic, the most common being extrapyramidal symptoms is dystonia. Defined extrapyramidal symptoms have been noted in the case-control series; but randomised double-blind placebo controlled studies on the safety of antiemetics are limited. It was demonstrated that these side effects occurred most frequently during rapid infusions of less than 15 minutes and in cases of chronic use. The frequency of extrapyramidal symptoms with single doses and slow infusions in the emergency department were not clearly defined. Studies on the control of vomiting and the frequency of re-admissions to the hospital after discharge are predominantly related to the oral use of antiemetics. The meta-analysis of these studies showed that oral antiemetics were superior to placebos, but many of the studies were found to be limited since they included high-risk bias criteria.

**AIM:** The goal of this investigation was to prospectively compare the efficacy of ondansetron, metoclopramide and a placebo in children presenting to the emergency department with acute vomiting.

**Methods**

**Study Design**

A randomised, double-blind, placebo-controlled prospective study was carried out on paediatric patients presenting with the complaint of vomiting to the emergency department of Derince Training and Research Hospital, Kocaeli, Turkey between 01.01.2016 and 01.06.2016. Ethics committee approval of the study was provided by Kocaeli University, Faculty of Medicine, Kocaeli, Turkey (Number: 13/23, protocol: KOU KAEK 2014/180). The study was conducted in accordance with the principles of the World Medical Association Declaration of Helsinki and the current guideline on effective clinical procedures. All patients were informed about the study before inclusion, and the consents of both patients and their relatives were obtained.

**Participants**

The study included patients of 1-18 years of age, who had presented to the Paediatric Emergency Department of the Derince Training and Research Hospital with the complaint of vomiting without the presence of blood and bile at least 3 times in the preceding 24 hours. At the time of admission, the patients were questioned about their history of drug use, drug allergy status and antiemetic use within the last 24 hours. The study excluded patients those weighing...
less than 8 kg, those with a history of allergic reactions to any group of antiemetics, those who had taken oral antiemetic drugs within 24 hours before admission, who were suffering from severe dehydration or an underlying disease which would affect the assessment of volume (such as renal failure or known hypoalbuminaemia), those with a history of extrapyramidal side effects due to the use of any kind of drugs, and those with a history of previous abdominal surgery and with a complaint of vomiting after trauma and those with suffering from gastrointestinal haemorrhage (haematemesis, melena).

**Randomisation**

The participants were divided into 3 groups according to the type of treatment by a computer generated randomisation. All groups were equally distributed. The patients were to assigned respective groups as ondansetron group 1, metoclopramide group 2 and placebo group 3, according to the type of treatment. The types of treatment were numbered in closed envelopes according to the order of application. The randomisation codes were kept secret until all data were completed.

**Procedures**

**Study Protocol**

The patients included in the study were evaluated at the time of admission by a senior resident having at least 2 years' of experience. Their clinical features including those in the preceding 24 hours were recorded. Five etiologic sub-groups such as infection of the upper respiratory tract, the thorax, the abdominal or the genitourinary tract and other causes identified. Haemogram, blood urea, creatinine, sodium, potassium and c-reactive peptide levels were routinely requested from all patients at the time of admission. Complete urinalysis and stool analysis were determined as additional tests according to the patients' histories and physical examinations.

All of the patients were transferred to the standard short-stay units, and a different researcher who was not involved in the diagnosis and treatment processes, was informed and was given information only about the weight of the patients for determination of the drug dose. The researcher opened the closed envelopes according to the order of randomisation, and the treatment was administered according to the number in the envelope. The patients marked with the number 1 in their envelopes were injected with 0.15 mg/kg IV ondansetron (Zofran 10 mg/mL vial, Polifarma) in 100 cc normal saline; the patients marked with the number 2 were given 0.2 mg IV metoclopramide (Methpamid 1 g/2 mL, Onfarma) in 100 cc normal saline, the patients in group 3 were given 100 cc normal saline IV infusion for 30 minutes. All patients in the three groups were infused with 20 cc/kg/h normal saline after the loading treatment. All drugs and fluids given in the treatment were prepared at standard room temperature. No information about the treatment was given to the physician taking care of the patients, the health practitioners and the relatives of the patients.

All patients were followed for at least 240 minutes in the emergency room. Oral rehydration fluids, which were prepared beforehand, were given to the patients after 30 minutes, 1 hour, 2 hours and 4 hours. Vomiting episodes were recorded after each administration of the oral rehydration fluids. The patients in whom adverse effects such as extrapyramidal symptoms, allergies and pruritus were observed during the follow-ups were excluded from treatment by break-up of the randomisation, and the drug group in which the adverse effects were observed was recorded.

The patients who did not complain of vomiting and who had no evidence of dehydration within 4 hours were discharged from the hospital after the follow-up. Patients in whom persistent vomiting after 4 hours of follow-up continued received only normal saline infusion. No additional medical treatment was given in either study group. Unstable patients still complaining of vomiting and having dehydration findings were transferred to the paediatric department. After the evaluation, the patients were classified according to the discharge status, hospitalisation in the paediatric department and transfer to the intensive care unit. Oral antiemetic treatment was not prescribed for the patients after the discharge.

The researchers called the patients after 24 hours using their contact information in order to inquire about possible adverse effects and continuation of vomiting after discharge, and the patients were questioned about the re-admission to any emergency department due to vomiting, side effects and continuation of the existing complaints. The patients who could not be contacted through their phone numbers after 24 hours were excluded from the study.

**Outcome**

Primary Outcome: Recurrence of vomiting after 60 minutes subsequent to antiemetic therapy.

Secondary Outcome: Recurrence of vomiting after 30th, 120th, and 240th minutes, adverse effects, length of stay in
the emergency department, proportion of patients in all study group discharged within 4 hours, hospitalisation rates, readmissions rates after 24 hours.

**Sample Size**
Sample size calculation was carried out the G power program with an assumption of $\alpha$: 0.05 and $\beta$: 0.80 and an effect size of 0.20 was used. The requisite sample size was calculated as 269.12.

**Statistical Analysis**
Statistical analyses were carried out using the SPSS software version 21. The conformity of the variables with the normal distribution was examined using visual histograms, probability diagrams and analytical methods (Kolmogorov-Smirnov and Shapiro-Wilk tests). Descriptive analyses were performed using the mean and standard deviations for normally distributed variables, and median and interquartile ranges for non-normal distributed variables. The One-way analysis of variance (ANOVA) or the Kruskal-Wallis analysis was utilised according to the compliance with the normal distribution for the comparison of demographic data among the treatment groups. While the effects of the different treatments on the patients’ vomiting frequency, the two-way ANOVA and ANCOVA tests were performed in terms of the effects of sex and age. Repeated measurement analysis of variance was used for evaluation of the effects of the different treatments on the changes observed in patients’ vomiting incidence over time. The analyses were not intention-to-treat analyses and only patients with outcome data available were analysed for each outcome. The Greenhouse-Geisser correction was used in cases when the assumption of sphericity could not be achieved. The total type-1 error level was determined as 5% for statistical significance.

**Results**
During the study period, 342 patients complaining of vomiting more than 3 times in the last 24 hours had presented to the emergency department. Of these patients, 27 were not included in the study because they did not qualify for inclusion, and 45 patients were also excluded since they did not give their consent to participate in the research. A total of 270 patients were included in the study and randomised into treatment groups (Figure 1). After treatment randomisations, 2 patients, who developed adverse reactions (allergic reaction in 1 patient in the ondansetron group, extrapyramidal reaction in 1 patient in the metoclopramide group), 22 patients, who could not be reached at the 24th hour on the contact number (9 patients in the ondansetron, 6 patients in the metoclopramide, 7 patients in the placebo groups), and 14 patients who withdrew from the study due to the individual factors such as long follow-up time (3 patients in ondansetron, 4 patients in metoclopramide, 7 patients in placebo group), were excluded from study. Finally, patients participating in the study were divided into groups to receive IV ondansetron (n=77), IV metoclopramide (n=79) and IV placebo (n=78) according to treatment groups.

The median age of the patients was 68.27±39.97 months, and 49.1% of the patients were male (n=115). The focus of infection, laboratory results and the demographic data of the patients have been presented in Table 1. The demographic data, focus of infection and laboratory results obtained at the time of application were similar in all treatment groups. At the baseline laboratory findings, there was no patient in either group with elevated urea, elevated creatinine, hypoatraemia or hypernatraemia. The baseline C-reactive peptide levels were elevated in 38 patients (49.3%) in the ondansetron, in 46 patients (58.2%) in the metoclopramide, and in 30 patients (38.4%) in the placebo groups. Although not statistically significant, the average CRP in the placebo group appeared to be much lower than the treatment groups and this may confound the results (p=0.39). The vomiting conditions of the treatment groups depending on the duration have been summarised in Table 2.

Vomiting persisted in 13 patients (16.9%) in the ondansetron group, in 13 patients (16.5%) in the metoclopramide group, and in 31 patients (39.7%) in the placebo group after 60 minutes, and the difference among the treatment groups was statistically significant (p=0.001). This difference was observed to have resulted from the placebo group subsequent to the binary cross-analysis carried out between each of the groups. At 30th minutes, there was no significant difference between the ondansetron and metoclopramide groups (p=0.557). Vomiting was still observed in 11 patients (14.3%) in the ondansetron group, in 14 patients (17.7%) in the metoclopramide group and in 28 patients (35.9%) in the placebo group at the 30th minute. The continuation of vomiting at the 30th minute was statistically significant among the treatment groups (p=0.002). This difference was observed to have resulted from the placebo group and there was no significant difference between the ondansetron and the metoclopramide groups (p=0.557). The vomiting conditions of the treatment groups depending on the duration have been summarised in Table 2.
minutes when measurements were made (p=0.000, p=0.000, respectively). No significant difference was found between the metoclopramide and the ondansetron groups in these periods (p=0.188, p=0.126, respectively).

The average emergency follow-up time for the patients was 250.26±26.1 minutes in the ondansetron group, 270.51±54.89 minutes in the metoclopramide group, and 287.18±62.15 minutes in the placebo group. There was a significant difference among the three groups (p=0.000). The difference resulted from the placebo group in the post-hoc analysis, and there was no significant difference between the metoclopramide and the ondansetron groups (p=0.039).

When the current status of the patients was examined, 2 patients in the ondansetron group (2.6%), 6 patients in the metoclopramide group (7.6%) and 7 patients in the placebo group (9%) had been hospitalised, and 97.4% of the patients in ondansetron, 92.4% of patients in metoclopramide group, and 91% of patients in placebo group had been discharged after the follow-up period. Although hospitalisation cases were less commonly observed in the ondansetron group, the difference was not significant (p=0.234).

In terms of treatment complications, an allergic reaction was detected in 1 patient (1.3%) in the ondansetron group, and extrapyramidal symptoms were found in 1 patient in the metoclopramide group (1.3%). The symptoms of the patient determined to have extrapyramidal symptoms had regressed through treatment. Adverse effects were not observed in the placebo group. There was no significant difference among the groups in terms of adverse effects (p=0.405).

There was no significant difference among the 3 treatment groups in terms of vomiting in the 24-hour follow-up (p=0.200). When the re-admission cases due to resistant vomiting after discharge were analysed, 11 patients (14.6%) in the ondansetron group, 14 patients (19.1%) in the metoclopramide group and 12 patients (16.9%) in the placebo group had been re-admitted to the hospital due to recurrent vomiting. There were no statistically significant differences in the demographic characteristics such as age and sex at re-admitted to hospital group (p=0.835, p=0.135, respectively). It was observed that antiemetic agents were not superior to placebo (p=0.835).

Figure 1   Consort diagram of enrolled patients.
### Table 1  Baseline characteristics of enrolled patients

<table>
<thead>
<tr>
<th></th>
<th>Ondansetron</th>
<th>Metoclopramide</th>
<th>Placebo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (Months, Mean, CI)</td>
<td>65.57 ([57.09)-(74.06])</td>
<td>67.67 ([58.68)-(76.66])</td>
<td>71.56 ([61.99)-(81.13])</td>
<td>0.64</td>
</tr>
<tr>
<td>Sex (male, %)</td>
<td>35 (48.5%)</td>
<td>44 (55.7%)</td>
<td>36 (46.2%)</td>
<td>0.36</td>
</tr>
<tr>
<td>Vomiting frequency (n, CI)</td>
<td>5.96 ([5.34)-(6.59])</td>
<td>6.35 ([5.81)-(6.9])</td>
<td>6.31 ([5.71)-(6.9])</td>
<td>0.59</td>
</tr>
<tr>
<td><strong>Vital sign</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature(°C) (Median)</td>
<td>36.54</td>
<td>36.68</td>
<td>36.9</td>
<td>0.3</td>
</tr>
<tr>
<td>Fever (n, %)</td>
<td>11 (14.6%)</td>
<td>14 (19.1%)</td>
<td>12 (16.9%)</td>
<td>0.51</td>
</tr>
<tr>
<td><strong>Infection</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>URT (n, %)</td>
<td>20 (26%)</td>
<td>24 (30.4%)</td>
<td>19 (24.4%)</td>
<td></td>
</tr>
<tr>
<td>LRT (n, %)</td>
<td>5 (6.5%)</td>
<td>5 (6.3%)</td>
<td>6 (7.7%)</td>
<td></td>
</tr>
<tr>
<td>Abdominal (n, %)</td>
<td>32 (41.6%)</td>
<td>35 (44.3%)</td>
<td>33 (42.3%)</td>
<td>0.76</td>
</tr>
<tr>
<td>Genitourinary (n, %)</td>
<td>10 (13%)</td>
<td>3 (3.8%)</td>
<td>7 (9%)</td>
<td></td>
</tr>
<tr>
<td>Other (n, %)</td>
<td>10 (13%)</td>
<td>12 (15.2%)</td>
<td>13 (16.7%)</td>
<td></td>
</tr>
<tr>
<td><strong>Laboratory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemoglobin (g/dl) (CI %)</td>
<td>12.58 ([12.33)-(12.83])</td>
<td>12.49 ([12.24)-(12.73])</td>
<td>12.79 ([12.53)-(13.04])</td>
<td>0.23</td>
</tr>
<tr>
<td>WBC (10^3/µgL) (CI %)</td>
<td>13411.69</td>
<td>12579.11</td>
<td>15700</td>
<td>0.43</td>
</tr>
<tr>
<td>Platelet (10^3/µgL) (CI %)</td>
<td>286493.5</td>
<td>272278.49</td>
<td>294465.56</td>
<td>0.26</td>
</tr>
<tr>
<td>Urea (mg/dl) (CI %)</td>
<td>28.22 ([26.56)-(29.88)]</td>
<td>30.42 ([28.26)-(32.58])</td>
<td>27.95 ([26.28)-(29.62])</td>
<td>0.12</td>
</tr>
<tr>
<td>Creatinin (mg/dl) (CI %)</td>
<td>0.52 ([0.5)-(0.54)]</td>
<td>0.54 ([0.51)-(0.56])</td>
<td>0.5 ([0.48)-(0.52)]</td>
<td>0.49</td>
</tr>
<tr>
<td>Sodium (mEq/l) (CI %)</td>
<td>137.22 ([136.71)-(137)]</td>
<td>137.04 ([136.45)-(137.62)]</td>
<td>135.41 ([132.26)-(138.57)]</td>
<td>0.33</td>
</tr>
<tr>
<td>Potassium (mEq/l) (CI %)</td>
<td>4.19 ([4.11)-(4.26])</td>
<td>4.15 ([4.04)-(4.26])</td>
<td>4.27 ([4.19)-(4.36])</td>
<td>0.18</td>
</tr>
<tr>
<td>C-reactive protein (mg/l) (CI %)</td>
<td>12.65 ([6.26)-(19.04)]</td>
<td>12.1 ([7.68)-(16.51)]</td>
<td>9.56 ([4.84)-(14.29)]</td>
<td>0.39</td>
</tr>
</tbody>
</table>

CI: Confidence Interval, n: Number; URT: Upper Respiratory Track, LRT: Lower Respiratory Track; WBC: White Blood Cells

### Table 2  Primary and secondary outcomes for total and by treatment arm

<table>
<thead>
<tr>
<th></th>
<th>Ondansetron</th>
<th>Metoclopramide</th>
<th>Placebo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 minutes</td>
<td>Vomiting (+) n,%</td>
<td>11 (14.3%)</td>
<td>14 (17.7%)</td>
<td>28 (35.9%)</td>
</tr>
<tr>
<td>60 minutes</td>
<td>Vomiting (+) n,%</td>
<td>13 (16.9%)</td>
<td>13 (16.5%)</td>
<td>31 (39.7%)</td>
</tr>
<tr>
<td>120 minutes</td>
<td>Vomiting (+) n,%</td>
<td>8 (10.4%)</td>
<td>14 (17.7%)</td>
<td>29 (37.2%)</td>
</tr>
<tr>
<td>240 minutes</td>
<td>Vomiting (+) n,%</td>
<td>5 (6.5%)</td>
<td>11 (13.9%)</td>
<td>23 (29.5%)</td>
</tr>
<tr>
<td>24 hours</td>
<td>Vomiting (+) n,%</td>
<td>17 (22.1%)</td>
<td>18 (22.8%)</td>
<td>26 (33.3%)</td>
</tr>
<tr>
<td>Length of stay</td>
<td>Minute (±SD)</td>
<td>250.26 (±26.1)</td>
<td>270.51 (±54.89)</td>
<td>287.18 (±62.15)</td>
</tr>
<tr>
<td>Discharged</td>
<td>n, %</td>
<td>75 (97.4%)</td>
<td>73 (92.4%)</td>
<td>71 (91%)</td>
</tr>
<tr>
<td>Hospitalisation</td>
<td>n, %</td>
<td>2 (2.6%)</td>
<td>6 (7.6%)</td>
<td>7 (8.9%)</td>
</tr>
<tr>
<td>Readmission</td>
<td>n, %</td>
<td>11 (14.6%)</td>
<td>14 (19.1%)</td>
<td>12 (16.9%)</td>
</tr>
</tbody>
</table>

n=number
Discussion

In a randomised, double-blind, placebo-controlled study, it was observed that ondansetron and metoclopramide were more effective than the placebo at the 60-minute vomiting control, and that neither of the two antiemetic agents were superior to each other at the target measurement and other measurement times. In our study, it was seen that there was no significant difference between antiemetic agents and placebo in terms of side effect profiles, and the rate of extrapyramidal symptoms related to metoclopramide after slow infusion was found to be 1.3%. Antiemetics were not superior to the placebo in terms of vomiting control after discharge and reducing the rate of re-admission.

Although it has been stated in the guidelines of the American Academy of Pediatrics and NICE that there is no need for using antiemetics in eliminating the symptoms of vomiting after diarrhoea, in the meta-analysis of the studies carried out in contrast to the above-mentioned guidelines, antiemetics were found to be effective, and this contradiction has necessitated the emerging of new studies in the field. The current contradiction has limited the use of these agents in emergency departments. In a limited number of studies comparing antiemetics with placebo, demonstrated that ondansetron was not superior to metoclopramide (p=0.14) in controlling vomiting, but the efficacy of both groups against a placebo was not compared. In the study carried out on paediatric patients receiving chemotherapy, it was stated that antiemetics were superior to placebo; however, the superiority of antiemetics among themselves was not examined, and it was emphasized that ondansetron was effective in patients receiving oral rehydration. Contrary to all these studies, it was demonstrated in another study conducted on adult patients that antiemetics were not superior to placebo; nevertheless, the low number of patients constitutes the basic limitation of the study. In our study, antiemetics were shown to be effective in controlling vomiting compared to placebo, and our results are important due to the limitations of other studies.

In the American Academy of Pediatrics guideline, the use of antiemetics for control of vomiting cases, especially those resulting from gastroenteritis, has been restricted due to the adverse-effect profiles; however, the safety and efficacy of antiemetic agents have been described in the compilation of 7 studies carried out on 1020 patients. The use of metoclopramide in daily practice is particularly limited by clinicians due to the side effects of defined extrapyramidal symptoms related to metoclopramide. Extrapyramidal symptoms have been predominantly described in case-control series, and their frequency has been defined to be contradictory, because they are lower than 1% in certain studies and 9% in some case-control series. It has been shown that this extrapyramidal side effect is more frequently observed after a rapid infusion of less than 2 minutes, and that this adverse effect decreases in slow infusions. The reliability of these studies is limited, since they are not randomised and double-blinded. Our study is important, because it is randomised and double-blinded, and the adverse effect profile in the slow infusion is as low as 1.3% and not life-threatening. At the same time, priority is given to the cost-effective use of metoclopramide, since ondansetron costs $26 and it is difficult to access.

Limitations

The present study has several limitations. First, our study was conducted in a single centre with a relatively small sample size, which limits the generalisability of our findings. All patients also received an IV isotonic sodium chloride solution infusion after bolus first-line treatment, which may also have affected their vomiting. The presence of vomiting at the 30th minute after the initial treatment is likely to have been caused by ‘IV drip’. For this reason, in our study, the presence of vomiting was determined as the primary outcome at 60 minutes rather than 30 minutes. Although vomiting was not significant at 30 minutes, the effectiveness of antiemetics in the early period was taken into account statistically. In our study, in order to keep the sample size high, different etiologies that cause vomiting were included in our study, so that our study group was heterogeneous. Despite the heterogeneous distribution of the patient groups, there was no statistically significant difference between the patient groups in terms of the source of infection. We also think that antiemetic agents will not cause any significant limitation, since they affect the same aetiology frequently with the same mechanism. There are patients who withdrew from treatment in each treatment group after the patient had been treated after randomisation and we could not reach 18 patients after they were discharged from hospital; therefore, the adverse-effect profiles of the patients and the presence of vomiting could not be defined, since they did not participate in the check-up sessions. The analyses were not intention-to-treat analyses and only patients with outcome data available had been analysed for each outcome.
Conclusion

IV single-dose slow infusion of antiemetics is effective in controlling vomiting compared to placebo, and they reduce the length of hospital stays, but there is no evidence that they are effective in reducing the hospitalisation rate or the readmission rate. Although the slow infusion of metoclopramide has been shown to reduce extrapyramidal symptoms compared to rapid infusion in a small proportion of patients, the clinician should be careful that metoclopramide may cause extrapyramidal side effects.

Declaration of Interest

The authors declare that there is no conflict of interest.

References

Case Report

Overcoming Perioperative Challenges in a Patient with Congenital Vascular Ring Undergoing Cardiac Surgery

SE CHONG, A SAEDAH, S ROSDAN, AZ MAMAT

Abstract

Children with double aortic arch are often associated with other congenital heart problems which require intervention. We report a case of congenital vascular ring due to double aortic arch in an infant with ventricular septal defect, heart failure, pulmonary hypertension and tracheomalacia undergoing pulmonary artery banding and double aortic arch repair. The perioperative challenges of a concomitant stenosed trachea and cardiopulmonary disease, in particularly smooth induction and safe weaning is discussed and reviewed.

Key words

Airway management; Anaesthesia; Double aortic arch; Vascular ring

Introduction

Double aortic arch is an abnormal formation of aorta, in which two aortic arches was formed instead of one. These aortic arches may form a vascular ring which can compress the trachea and oesophagus. This condition is associated with heart defects such as ventricular septal defect (VSD).1 As the vascular ring leads to narrowing and stenosis of the airway, cardiac surgery on such patient poses a challenge to the anaesthetists. Induction of anaesthesia put the patient at risk of complete airway obstruction and trauma caused by severe narrowing of the trachea. Intraoperatively, there are risk of massive haemorrhage and complications from cardiopulmonary bypass. In addition, weaning from mechanical ventilation may be difficult due to tracheomalacia or tracheal stenosis.2,3 Failure of extubation, severe respiratory distress after surgery and prolonged ventilation requiring tracheostomy have been reported.4,5 We report our experience of anaesthetic management during cardiac surgery for an infant with a double aortic arch and underlying heart failure. Postoperative weaning was facilitated by a modified nasopharyngeal continuous positive airway pressure (CPAP) device.

Case Report

A six-month old girl presented to us in heart failure. She was found to have large perimembranous ventricular septal defect (PMVSD) three months ago. She had been admitted since then, and suffered from uncontrolled heart failure as well as pulmonary hypertension despite receiving multiple anti-failure medications. She was noticed to have persistent stridor. However, airway study was unable to be conducted because the patient was unfit due to the recurrent episodes of heart failure.
Echocardiography showed a patent foramen ovale (PFO), a large PMVSD (10 mm) with muscular extension, with left to right shunt. Double aortic arch was also noticed by echocardiography and was confirmed by computed tomography angiography (CTA) (Figure 1a). Three-dimensional reconstruction thoracic CTA showed that she had a right-dominant double aortic arch. It encased the trachea and oesophagus forming a complete ring causing narrowing of the trachea (Figure 1b). The narrowest part of the trachea was located 14.5 mm above the carina, measuring 2.5 mm in diameter (Figure 1a). Normal trachea diameter for her age should be 4.7-5.8 mm.6

She was scheduled for pulmonary artery banding and double aortic arch repair through left thoracotomy. In the operating theatre, gas induction of general anaesthesia with sevoflurane 1-3% was performed, under fractional inspired oxygen (FiO₂) of 50%. SpO₂ was maintained near the baseline of 92% to avoid the deleterious effect of over-circulated lung perfusion due to exaggerated left to right shunt and pulmonary congestion. After mask ventilation was confirmed to be adequate, a 3.5 mm internal diameter uncuffed endotracheal tube (ETT) (SoftVent® Pro, HVLP-Cuff, Murphy, Unomedical, Malaysia) was inserted and anchored at 9.5 cm without bypassing the narrowest part of the trachea. The ETT was placed with the designated black mark located at the level of vocal cords. Mechanical ventilation was adequate for both lungs by the evidence of adequate tidal volume (6-8 ml/kg), peak airway pressure of 20 cm H₂O, equal and clear lung fields on auscultation, as well as an adequate oxygen saturation. Arterial blood gas showed pH 7.5, pCO₂ 30 mmHg (4.0 kPa), pO₂ 249 mmHg (33.2 kPa), HCO₃⁻ 29 mmol/L and BE of 5 mEq.

The ETT was not advanced beyond the tracheal stenosis area to reduce the risk of bronchospasm as well as trauma to the airway and the surrounding major vessels. Intravenous (IV) rocuronium 0.6 mg/kg was administered just before the start of thoracotomy. Anaesthesia was maintained with sevoflurane 2-3% and FiO₂ of 50%. Surgery was uneventful and she was put on adrenaline 0.1 mcg/kg/min, dobutamine 10 mcg/kg/min upon completion.

After the surgery, the patient was admitted to intensive care unit (ICU) for close monitoring. Ventilation was maintained at a higher positive end expiratory pressure (PEEP) of 12 cmH₂O via CPAP with the pressure support (Ps) of 4 cmH₂O above PEEP. She received continuous morphine infusion 10 mcg/kg/hour as analgesic which was tapered down slowly. On the third postoperative day, she was extubated to a modified nasopharyngeal CPAP device, and pressure support was slowly tapered down. Five days later, she was successfully weaned off from the non-invasive ventilation and was discharged back to ward. She had occasional stridor. However it improved subsequently and she was able to be discharged home well.

Discussion

Patients with vascular ring may present with minimal symptoms such as cough or may just be asymptomatic.7 If a patient with suspected cardiac abnormality is having persistent respiratory symptoms such as stridor, that should raise the suspicion of vascular ring during
echocardiography. For further confirmation, multiple detector computed tomography / angiography and magnetic resonance imaging (MRI) should be done because of the high accuracy.8

Difficulty with ventilation has been reported in a case of undiagnosed vascular ring during ventriculo-peritoneal (VP) shunt surgery.3 In that particular case, difficulty in ventilation was encountered after patient was paralysed with muscle relaxant, and fibrotic bronchoscopy revealed a tracheomalacia. Adequate ventilation was achieved only when the tip of the ETT was pushed in between the stenotic part and the carina.

The recommended technique of intubating a patient with vascular ring is by preoperative or intraoperative bronchoscopy.9 This is because a bronchoscopic evaluation is accurate to assess proper endotracheal tube position. However, in our patient who was suffering from recurrent chronic heart failure and pulmonary hypertension, forcing the ETT through the stenotic site may pose a risk of overstimulating the airway leading to complications such as bronchospasm or even trauma and bleeding. Therefore, we opted for gentle handling of the airway. In the present case, muscle relaxant was not given during induction and intubation. It was given much later i.e. just before skin incision of the thoracotomy. If ventilation problem encounters, the plan was to push in the ETT gently down towards the carina, or may consider a rescue dose of sugammadex. In case airway obstruction does not improve with the above method, measures including endobronchial intubation by surgeon after thoracotomy or immediate release of compression had been considered.

Using an FiO₂ of 0.5 during the induction of anaesthesia, intubation without rocuronium and the placement of ETT above trachea stenosis site may have a potential to make the patient deteriorate. However, we opted for more physiologically friendly methods custom tailored to the patient after considering the risk and benefits. The strategy had nicely worked and the patient turned out well.

A vascular ring may also cause tracheomalacia leading to prolonged ventilation post-surgery.5 Prolonged tracheal intubation may increase the risk of subglottic stenosis and ventilated associated pneumonia. Therefore, vigilant and careful management is necessary during the postoperative period. In view of presence of tracheomalacia due to the longstanding vascular ring, we maintained a higher PEEP via CPAP during the immediate postoperative period, then extubated the patient to a modified nasopharyngeal CPAP device (Figure 2a). There are several ways of delivering CPAP non-invasively, including the use of nasopharyngeal prongs or nasal masks.10 However, securing the nasal prongs in place is a problem as the child tends to move about. We therefore modified the ETT by shortening it, inserting the tip into the nasopharynx, turning it into a nasopharyngeal CPAP device (Figure 2b). This had helped to maintain a patent airway for weaning after extubation. To the best of our knowledge, there has been no report describing in detail about such technique.

In conclusion, the main anaesthetic strategy in this complicated case was to prevent life-threatening events caused by the difficult management of the airway, heart problem as well as difficulty in weaning off ventilatory support. A modified nasopharyngeal CPAP with shortened ETT may also be researched in future studies to improve the effectiveness of non-invasive ventilation.

Figure 2   (a) Modified nasopharyngeal CPAP ensures a more secured CPAP; (b) Shortened Endotracheal tube functioning as modified nasopharyngeal CPAP. CPAP: continuous positive airway pressure.
Acknowledgments

We sincerely thank the team from Healing Little Hearts Foundation which is based in United Kingdom to provide paediatric cardiothoracic services as a charity programme in Hospital Universiti Sains Malaysia (HUSM), Malaysia. We would also like to thank Dr. Mohd Rizal Mohd Zain for his excellent care to the patient before and after the surgery, Dr. Jo Anne Lim and Mdm Lee Jong Koh for critical reading and useful comments on this manuscript.

Conflict of Interest Statement

The authors declare that there is no conflict of interest regarding the publication of this paper.

References

Case Report
Perianal Mercury Deposition from a Broken Thermometer in a Small Child

X Lin, C Chen, Y Zhao, Y Wang

Abstract
Deposition of mercury in the intraperitoneal and extraperitoneal compartments from a broken thermometer is quite rare. Neither the outcome nor the management for such a situation is certain. We report here a case in a 28-month-old boy who was exposed to elemental mercury from a broken mercury thermometer. Radiographic imaging data showed the mercury was scattered in the intraperitoneal and extraperitoneal pelvic cavity. Laparoscopic surgical procedure was performed, but it failed to remove the mercury deposits. Fortunately, clinical follow-up at 3+ years did not reveal any clinical or biochemical features of mercury toxicity.

Key words
Child; Elemental mercury; Laparoscopy; Thermometer

Introduction
There are a few risks when mercury thermometers are used rectally to measure core body temperature. These risks not only include possible perforation,1 but also mercury exposure.2 Nowadays most paediatric hospitals have replaced mercury thermometers with the use of digital thermometers. Moreover, western centres have even discontinued the use of mercury manometers for measuring blood pressure, although the digital measurements are notorious for being accurate. However, traditional mercury thermometers are still widely used at home, especially in China. In this article, we present and discuss an unusual paediatric case of intraperitoneal and extraperitoneal exposure to elemental mercury from a broken thermometer. We describe the treatment process and the results of long-term follow-up in detail, which have not been reported in the English medical literature yet.

Case Presentation
A 28-month-old boy was admitted to our hospital because of a broken mercury thermometer. The patient showed no obvious signs and symptoms. Blood biochemical features were normal. Abdominal radiograph revealed the existence of a foreign body, which like the bulb of a thermometer, as well as multiple small radiopaque densities scattered in the small pelvis (Figure 1a). Computed tomography (CT) scan, on the fourth day, suggested the possibility that the mercury particles were outside the lumen of the bowel and some of them were inside the abdomen (Figure 1b). Surgical intervention was performed on the 11th day after injury. Laparoscopy revealed no traumatic change in the wall of rectum and the sigmoid colon. During the operation we were unable to remove the mercury deposits since we were unable to locate the mercury or the glass fragments, pertaining to the thermometer, within the intraperitoneal cavity. The child remained stable throughout the operation, and was ultimately discharged three days later.
One month after the injury an abdominal radiography showed persistence presence of mercury. The serum mercury was 4.8 μg/L (ref <10 μg/L) and corresponding random urine mercury was 3.6 μg/L. The child did not receive chelation therapy before or after the operation. Further abdominal radiography performed on two separate dates, six months and eleven months after the injury, also showed similar findings. Magnetic resonance examination of the brain was normal eleven month after the injury. One year after the injury, the serum mercury concentration increased to 6.5 μg/L. Two years after the injury, the serum mercury level was 8.3 μg/L, while three years after injury, the serum mercury concentration decreased to 7.8 μg/L. Fortunately, clinical follow-up at 3+ years did not reveal any clinical or biochemical features of mercury toxicity.

Discussion

Rectal thermometers have been used for recording temperature in infants and small children for many years, especially in the developing country. Although it is uncommon, there is still a risk of perforating the rectum if thermometers are broken.

When perforation occurs, some elemental mercury from a broken thermometer may quickly be excreted outside of the body. However, some elemental mercury may penetrate the rectal wall into the intraperitoneal and extraperitoneal cavity. Small amount of ingested mercury may be harmless, because it is not readily absorbed, mercury that remains in the body for a long period time can be harmful. Firstly, Mercury contamination of the peritoneum has been associated with granuloma formation and intestinal obstruction. Secondly, systemic toxicity following peritoneal contamination with mercury and methylmercury, methylated by gut flora, may occur. Mercury is toxic not only to central nervous system, but also to peripheral nerves and kidneys.

We observed the persistent presence of mercury on consecutive abdominal plain films and CT scan, which was why we consequently performed laparoscopy. Unfortunately, we could not find that the mercury was free in the intraperitoneal cavity during the operation. C-arm fluoroscopy during the operation showed some mercury were located in the extraperitoneal pelvic cavity (mainly in the rectovesical pouch) and others were wrapped in the intraperitoneal cavity. It has been reported that the majority of mercury deposits can be removed by incising the peritoneal reflection in the rectovesical pouch. However, considering that we had no experience to perform this surgical maneuver, we decided to end the operation.

The remaining mercury still posed the potential risks of chronic absorption. In some cases, the mercury became encapsulated in fibrous tissue and didn't induce systemic toxicity. Luckily, the serum mercury and corresponding random urine mercury of this child was measured to be in the normal range, probably due to the small amount of retained mercury. The position of mercury had been relatively fixed on postoperative abdominal plain films. Fortunately, clinical follow-up at 3+ years did not reveal any clinical or biochemical features of mercury toxicity.

This is the first report in the English medical literature

Figure 1  (a) Radiography on the 1st day. (b) CT scan on the 4th day.
concerning the treatment process and the results of long-term follow-up for intraperitoneal and extraperitoneal elemental mercury exposure from a broken thermometer. From this, some problems are still to be addressed which hadn't been described in detail in the previous literature. Firstly, whether it's necessary for digital rectal examination to be used in early stage. Inappropriate digital rectal examination may lead to injury of rectal mucosa and rectal perforation. Secondly, whether it is necessary for colonoscopy to be used. Colonoscopy maybe helpful when observing traumatic changes to the mucosa of the rectum and the sigmoid colon, but it also can induce damage to the mucosa. Furthermore, and the most important issue to address, whether or not surgical intervention is appropriate? It should be noted that it is difficult to remove mercury completely, even when performing open surgery. When and how to perform the operation is also a problem. If the first operation is a failure, whether the second operation is necessary when the position of mercury had been relatively fixed on abdominal plain films. Finally, the significance of using chelation therapy. Chelation therapy with dimercaptosuccinate has been used to treat patients with peritoneal mercury exposure, but with limited success rate because of residual mercury deposits. If blood mercury levels exceed 10 µg/L or urinary mercury levels exceed 50 µg/L, active chelation therapy will be administered.

Conclusion

Intraperitoneal and extraperitoneal elemental mercury exposure from a broken thermometer is a rare but challenging situation to manage. A complete removal by surgical intervention is difficult and nearly impossible, therefore we should carefully balance the advantages against disadvantages of surgery. The standard therapeutic protocol can only be determined by long-term follow-up and symptomatic treatment.

Acknowledgement

We would like to thank our colleagues from the Department of Pediatric Surgery, for their assistance with the data collection.

Conflict of Interest

We declare that we have no conflicts of interest.

References

Case Report

Urticaria in Skin Care with Skin Cream Containing a Wheat Compound and Prompt Treatment at Home

K TANIGUCHI, Y ICHIYAMA, K UEMICHI

Abstract

Skin care is a basic treatment for children suffering from eczema. However, almost all individuals are not adequately aware of the pitfalls hidden in skin care. We herein report that a skin cream containing a wheat compound induced acute urticaria. An 8-year-old boy with no history of a wheat food allergy used a skin cream containing a wheat compound. Acute urticaria appeared on all parts applied with the skin cream immediately after application. The acute urticaria disappeared after treatment at home involving removal of the skin cream (taking a bath), an oral anti-histamine drug, and a steroid ointment. Skin creams that contain a wheat compound can induce acute urticaria. Prompt treatment, which can be performed at home, can prevent the allergic reaction from progressing. We should be aware of the pitfalls in skin care. We should also learn prompt treatments for unexpected allergic reactions as prehospital care.

Key words

Skin cream; Urticaria; Wheat allergy

Introduction

Skin care is a basic treatment for children suffering from eczema.1 There are various kinds of skin creams, and some contain compounds derived from nature.2,3 Although skin care is common, almost all individuals are not adequately aware of the pitfalls hidden in skin care. We herein report that acute urticaria was induced by a skin cream containing a wheat compound. Furthermore, we describe that prompt treatment at home involving removal of the wheat compound (taking a bath), an oral anti-histamine drug, and a steroid ointment prevented the allergic response from progressing.

Case Report

An 8-year-old boy had occasionally suffered from eczema since he was 6 months of age. He had no history of immediate hypersensitivity in a food allergy, food-dependent exercise-induced anaphylaxis, or bronchial asthma. The boy had often been treated with various skin creams obtained from pharmacies.

He applied a skin cream containing a wheat compound. Within a few minutes after application, acute urticaria with terrible itching appeared on all parts applied with the skin cream (Figure 1A & 1B). His father, a paediatrician, diagnosed as immediate hypersensitivity and instructed him to take a bath to wash off the skin cream. After removal of the skin cream, the boy took medicine. Specifically, he took diphenhydramine (single dose, 0.15 mg/kg), an oral anti-histamine drug, and applied alclometasone dipropionate ointment, a steroid ointment. All of the urticaria disappeared within 30 minutes of treatment and did not recur (Figure 1C & 1D). The allergic reaction was thus prevented from progressing into erythroderma, anaphylaxis, and stridor.

We raised two possibilities as causes of the immediate hypersensitivity. The first was a wheat allergy.
because skin creams that contained the same ingredients except for the wheat compound did not cause such immediate hypersensitivity on his body. The second was contamination with mites, *Staphylococcus aureus*, or molds. These microbes are often considered to be causes of contamination in skin creams.\(^4\) To evaluate the possibility of a wheat allergy, we investigated serum allergen-specific immunoglobulin E (IgE) antibodies by a fluorescence enzyme immunoassay. The results showed that the boy had multiple allergies (Table 1). Anti-wheat, *Dermatophagoides pteronyssinus* (*Der p*), aspergillus, and alternaria-specific IgE were 1.38 UA/mL (class 2), 165 UA/mL (class 6), 0.37 UA/mL (class 1), and 1.76 UA/mL (class 2), respectively. *Der p* is a type of mite, and aspergillus and alternaria are species of molds. These results suggested that wheat, mites, or molds caused the immediate hypersensitivity. To evaluate contamination by mites, molds, and *S. aureus*, we performed some experiments. Mitey Checker (Sumika Environmental Science, Osaka, Japan), an immunochromatography method,\(^5\) did not detect any mite antigens. Use of Sanita-kun Yeasts and Molds and Sanita-kun *Staphylococcus aureus* (both from JNC, Yokohama, Japan), as sheet culture media,\(^6\) did not detect the corresponding microbes. In the microscopic examination, we did not detect any live mites and microbes as well as dead ones. These findings suggested that mites, molds, and *S. aureus* were not involved. Thus, we suggested that the cause of acute urticaria in the patient was the wheat compound.

**Discussion**

The present case highlights two important clinical issues. First, skin creams containing a wheat compound can induce acute urticaria in a patient with no history of a wheat food allergy. Second, prompt removal of the wheat compound and medication with an oral anti-histamine drug and a steroid ointment can prevent the allergic response from progressing.

Regarding the first issue, we found that a skin cream containing a wheat compound induced acute urticaria in a patient with no history of a wheat food allergy. In previous reports, hydrolysed wheat caused severe contact dermatitis when individuals used cosmetics containing this component.\(^7\) Some patients with hydrolysed wheat-induced contact dermatitis showed symptoms of a wheat food allergy before or after using such cosmetics.\(^8\) However, the present patient did not show any symptoms of a wheat food allergy either before or after this episode. The patient includes wheat in his regular diet. These findings suggest that having no history of a wheat food allergy is insufficient to predict the risk of allergy to skin creams containing a wheat compound. Although we considered a skin prick test to investigate direct evidence for IgE reaction, the patient

### Table 1 Results of the fluorescence enzyme immunoassay

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Category</th>
<th>Value (UA/mL)</th>
<th>Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wheat</td>
<td>Grains</td>
<td>1.38</td>
<td>2</td>
</tr>
<tr>
<td><em>Der p</em></td>
<td>Mites</td>
<td>165</td>
<td>6</td>
</tr>
<tr>
<td>Aspergillus</td>
<td>Molds</td>
<td>0.37</td>
<td>1</td>
</tr>
<tr>
<td>Alternaria</td>
<td>Molds</td>
<td>1.76</td>
<td>2</td>
</tr>
</tbody>
</table>

*Der p: Dermatophagoides pteronyssinus*
did not agree to undergo the test. Still we regarded the contact reaction in the present case as IgE reaction because the symptom showed the characteristics of IgE reaction. First, the symptom appeared immediately after application. Second, acute urticaria with itching was the typical symptom of IgE reaction. Furthermore, treatment using an anti-histamine drug and a steroid ointment was effective.

For the second issue, we report that prompt removal of the wheat compound and medication with an oral anti-histamine drug and a steroid ointment prevented the allergic response from progressing in our patient. We recommend that patients should proceed in this manner as prehospital care if they notice symptoms following application of a skin cream that produces acute urticaria at home. We also suggest that clinicians should transmit this information to their patients as prehospital care. An acute allergic response often progresses from immediate hypersensitivity including acute urticaria with itching to life-threatening stages such as erythroderma, anaphylaxis, and stridor. Once anaphylaxis occurs, intramuscular administration of epinephrine (adrenaline) followed by volume support, nebulised bronchodilator use, intravenous administration of glucocorticoid, anti-histamine drugs, and steroid ointments is required to save the lives of patients. Some patients with previous experience of an anaphylactic episode possess epinephrine (adrenaline) for self-administration as prehospital care. However, individuals who have never experienced anaphylaxis are not equipped with epinephrine (adrenaline). There is no equipment for volume support, nebulised bronchodilator use, and intravenous administration in regular homes. In our patient, the allergic response was prevented from progressing by prompt treatment involving removal of the wheat compound (taking a bath), an oral anti-histamine drug, and a steroid ointment. This treatment is a quick and easy method that can be performed at home.

Skin care is such a basic treatment for repeated eczema episodes that many individuals who suffer from eczema regularly use skin creams. However, almost all individuals are not aware of the pitfalls hidden in this common treatment. Indeed, the acute urticaria in this case was an unexpected phenomenon for the boy and his parents. Based on this case report, we propose that people who use skin creams containing certain compounds for the first time should initially try a small amount to check whether immediate hypersensitivity such as acute urticaria occurs.

In conclusion, skin creams containing a wheat compound can induce acute urticaria in a patient with no history of a wheat food allergy, and prompt removal of the wheat compound and medication with an oral anti-histamine drug and a steroid ointment can prevent the allergic response from progressing. We must be aware that pitfalls can be hidden even in usual skin care. In addition, we should learn and transmit information for adequate treatment for unexpected symptoms as prehospital care.

**Declaration of Interest**

None

**References**


Case Report

The First Case of Cobalamin F Disorder in China: Report and Literature Review

F Tong, RL Yang, R Chen, ZY Zhao

Abstract

Objectives: To investigate the phenotype, genotype and prognosis of cblF disorder (CblF). Methodology: Data including newborn screening and clinical features, LMBRD1 mutations, treatment and prognosis of the first CblF case in China and 17 reported CblF cases were collected and analysed. Results: This case was picked up by newborn screening (NBS) due to elevated blood propionylcarnitine (C3) (5.50 μmol/L), propionylcarnitine / acetylcarnitine (C3/C2) ratio (0.47), propionylcarnitine / free carnitine C3/C0 ratio (0.25) and decreased methionine (Met) (5.27 μmol/L) identified by tandem mass spectrometry (MS-MS), then decreased serum Vitamin B12 (cobalamin; Vit B12) (116 pmol/L), elevated homocysteine (tHCY) (82.9 μmol/L), macrocytic anaemia and atrial septal defect, and patent ductus arteriosus were confirmed. This is similar to what has been reported in the literature. Besides, two novel truncated LMBRD1 mutations of p.R277* and p.C29* were confirmed. The data of all the 18 cases show that the common clinical features are macrocytic anaemia, failure to thrive, developmental delay, congenital heart disease, and small for gestational age. Similar biochemical characters were identified in all 3 cases from NBS, and a total of 35 LMBRD1 mutations in 10 different sites including frame-shift mutations (30/35), splice site mutations (2/35), nonsense mutations (2/35), and large fragment deletions (1/35) were observed, among which c.1056delG mutation was reported the most frequently (24/35). After Vit B12 injection and supportive treatment, all of the biochemical abnormalities and most of the clinical presentations have been significantly improved within 3 months in all cases. Conclusion: The biochemical characters of CblF are similar to the combined methylmalonic acid (MMA), except for decreased serum Vit B12, which should be distinguished from Vit B12 deficiency. Typical phenotype includes macrocytic anaemia, growth and development problems, and congenital malformations, all of which are nonspecific. The c.1056delG mutation is the common mutation. The concentrations of C3, C3/C2, C3/C0 and Met by MS-MS and the target genetic panel of MMA should be chosen for suspected MMA cases. CblF is a treatable disease, and injection of Vit B12 is effective, but the appropriate dosage remains unclear.

Key words Cobalamin; Genotype; Phenotype; Prognosis; Treatment

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Introduction

Methylmalonic acid (MMA) is a heterogeneous disease caused by different genes of complementation groups including cblA-G, cblJ, cblX, and mut, which is divided as isolated MMA (cblA, cblB, cblD, mut) and combined MMA with hyperhomocysteinaemia (cblC, cblD, cblF, cblJ).

First reported by Rosenblatt in 1985, CblF (OMIM 277380) is an autosomal recessive disorder, and the LMBRD1 has been identified as the cause of the disease.
The number of people suffering from CblF is scarce, to the best of our knowledge, there are only 17 reported patients worldwide and no reported case from Chinese population so far.

We summarised all information of the first CblF case in China and other 17 cases published in journals that can be obtained reviewed the phenotype, genotype, treatment and prognosis.

**Case Report**

The patient was a girl born at 41 weeks of gestation with a birth weight of 3.6 kg. She is the first child of her parents, from a non-consanguninity Han Chinese family without genetic disease history. Newborn screening (NBS) by MS-MS was undertaken on Day 3 after her birth. Her abnormal metabolic profile included elevated blood C3 (5.50 µmol/L), C3/C2 ratio (0.47), C3/C0 ratio (0.25) and decreased Met (5.27 µmol/L). Besides, decreased serum Vit B₁₂, elevated tHCY, and macrocytic anaemia were identified (Table 1). At the same time, serum folic acid, blood ammonia, blood lactate, fasting blood glucose and liver/kidney function were tested and proven to be normal. Her mother’s serum levels of Vit B₁₂ were normal, and atrial septal defect (ASD), patent ductus arteriosus (PDA) were confirmed by cardiac ultrasonography.

Thus, the infant was highly suspected to be Vit B₁₂ deficiency or MMA. Daily intramuscular injection of 1 mg of cyanocobalamin (CNCbl), oral 100 mg/kg levocarnitine, and 250 mg/kg betaine was performed, then C3 and tHCY values were rapidly dropped within the normal reference interval after 5 days of medication (Table 1). Hence, the levocarnitine and betaine were terminated.

Molecular testing was performed after informed consent from the parents was gained on Day 15 after birth. Genetic panel of MMA (including cblA, cblB, cblC, cblD, cblE, cblF, cblG, cblJ, and mut), were tested by next generation sequencing (Beijing Gold Gene Technology Co., Ltd, Beijing, China), and compound heterozygous novel mutations of LMBRD1 were found in the infant. Sanger sequencing confirmed these two nonsense mutations, i.e. a heterozygous c.829C> T from her mother and a heterozygous c.87C> A from her father (Figure 1). There was no report about c.87C> A and c.829C> T mutations in the ExAC database, both of which result in truncated LMBD1 proteins. SIFT, LRT and MutationTaster softwares demonstrated that the both mutations were located in the conserved region of LMBD1 protein, and it is presumed that they have a great, destructive effect on the structure and function of LMBD1 protein. As a result, the infant was diagnosed as CblF finally.

Subsequently, the medication was adjusted to 1 mg of hydroxocobalamin (OHCbl) through intramuscular injection twice a week. Ten days later, anaemia parameters were significantly improved and recovered on the 75-day-old infant after continuing treatment with OHCbl (Table 1). The case has been followed up for 23 months until now, all

<table>
<thead>
<tr>
<th>Age</th>
<th>Measurements</th>
<th>Patient values</th>
<th>Reference interval</th>
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<tr>
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<td>C3/C0</td>
<td>0.02</td>
<td>0.02-0.15</td>
<td></td>
</tr>
<tr>
<td>Met</td>
<td>19.25 µmol/L</td>
<td>7.18-41.35 µmol/L</td>
<td></td>
</tr>
<tr>
<td>Vit B₁₂</td>
<td>1867 pmol/L</td>
<td>156-672 pmol/L</td>
<td></td>
</tr>
<tr>
<td>tHCY</td>
<td>8.3 µmol/L</td>
<td>5.0-15.0 µmol/L</td>
<td></td>
</tr>
<tr>
<td>Hb</td>
<td>94 g/L</td>
<td>110-155 g/L</td>
<td></td>
</tr>
<tr>
<td>MCV</td>
<td>97 fL</td>
<td>75.0-92.0 fL</td>
<td></td>
</tr>
<tr>
<td>MCH</td>
<td>30.7 pg</td>
<td>26.0-31.0 pg</td>
<td></td>
</tr>
<tr>
<td>MCHC</td>
<td>317 g/L</td>
<td>315-365 g/L</td>
<td></td>
</tr>
<tr>
<td>75d</td>
<td>C3</td>
<td>1.12 µmol/L</td>
<td>0.43-3.8 µmol/L</td>
</tr>
<tr>
<td>C3/C2</td>
<td>0.02</td>
<td>0.03-0.27</td>
<td></td>
</tr>
<tr>
<td>C3/C0</td>
<td>0.02</td>
<td>0.02-0.15</td>
<td></td>
</tr>
<tr>
<td>Met</td>
<td>24 µmol/L</td>
<td>7.18-41.35 µmol/L</td>
<td></td>
</tr>
<tr>
<td>Vit B₁₂</td>
<td>924 pmol/L</td>
<td>156-672 pmol/L</td>
<td></td>
</tr>
<tr>
<td>tHCY</td>
<td>5.6 µmol/L</td>
<td>5.0-15.0 µmol/L</td>
<td></td>
</tr>
<tr>
<td>Hb</td>
<td>109 g/L</td>
<td>110-155 g/L</td>
<td></td>
</tr>
<tr>
<td>MCV</td>
<td>83 fL</td>
<td>75.0-92.0 fL</td>
<td></td>
</tr>
<tr>
<td>MCH</td>
<td>26.7 pg</td>
<td>26.0-31.0 pg</td>
<td></td>
</tr>
<tr>
<td>MCHC</td>
<td>322 g/L</td>
<td>315-365 g/L</td>
<td></td>
</tr>
</tbody>
</table>

Hb: haemoglobin; MCV: mean corpuscular volume; MCH: mean corpuscular haemoglobin; MCHC: mean corpuscular haemoglobin concentration
biochemical measurements and milestone are normal. The results of cardiac ultrasonography indicated that both the ASD and PDA recovered, and the assessment of Bayley Scales of Infant Development was normal when the patient was 8 months old.

**Literature Review**

A keyword-based retrieval of "LMBRD1" and "cblF" was performed in PubMed (http://www.ncbi.nlm.nih.gov/pubmed), Ovid (http://ovidsp.ovid.com/autologin.cgi), Medline (http://apps.webofknowledge.com/MEDLINE_GeneralSearch_input.do?product=MEDLINE&search_mode), Wanfang Data (http://g.Wanfangdata.com.cn), Weibu periodicals (http://lib.cqvip.com/), and China National Knowledge Infrastructure (http://epub.cnki.net/KNS/brief/result.aspx?dbprefix=CJFQ). A total of 18 cases with cblF disorder were selected in our study, among which, 17 cases came from the research previously reported.

All clinical presentations were displayed in Table 2. A total of 35 LMBRD1 mutations in 10 different sites were found (Table 3).

All cases have received continuing injection of Vit B12 (OHChbl or CNChbl), with or without levocarnitine, betaine, and other supportive treatment. The dosage of Vit B12 ranged from 1 mg per day to 1 mg every 2 months. All of the abnormal biochemical changes and most of the clinical features have been significantly improved after medication.

<table>
<thead>
<tr>
<th>Clinical presentations</th>
<th>Patients number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematological features</td>
<td>9/18</td>
</tr>
<tr>
<td>Developmental delay</td>
<td>8/18</td>
</tr>
<tr>
<td>Failure to thrive</td>
<td>8/18</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>8/18</td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>7/18</td>
</tr>
<tr>
<td>Stomatitis +/- glossitis</td>
<td>5/18</td>
</tr>
<tr>
<td>Feeding difficulties</td>
<td>4/18</td>
</tr>
<tr>
<td>Gastric upset</td>
<td>3/18</td>
</tr>
<tr>
<td>Dental anomalies</td>
<td>3/18</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>3/18</td>
</tr>
<tr>
<td>Facial dysmorphism</td>
<td>2/18</td>
</tr>
<tr>
<td>Hepatic involvement</td>
<td>2/18</td>
</tr>
<tr>
<td>Rash</td>
<td>2/18</td>
</tr>
<tr>
<td>Seizures</td>
<td>2/18</td>
</tr>
<tr>
<td>Hypotonia</td>
<td>2/18</td>
</tr>
<tr>
<td>Torticollis</td>
<td>1/18</td>
</tr>
<tr>
<td>Pesequinovarus</td>
<td>1/18</td>
</tr>
<tr>
<td>Tracheoesophageal fistula</td>
<td>1/18</td>
</tr>
<tr>
<td>Arthritis</td>
<td>1/18</td>
</tr>
<tr>
<td>Recurrent infection</td>
<td>1/18</td>
</tr>
<tr>
<td>Recurrent apnoea</td>
<td>1/18</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>1/18</td>
</tr>
<tr>
<td>Cleft palate</td>
<td>1/18</td>
</tr>
<tr>
<td>Unilateral renal agenesis</td>
<td>1/18</td>
</tr>
</tbody>
</table>

**Figure 1** Mutations of LMBRD1 gene of the infant and parents. Red circle represents the mutation loci. Figure 1a shows the mutation c.87C>A of the infant, Figure 1b shows the mutation c.87C>A of the father, Figure 1c shows the mutation c.829C>T of the infant, and Figure 1d shows the mutation c.829C>T of the mother. Sanger sequencing results demonstrated that both mutations c.87C>A and C.829C>T of the infant were inherited from the father and the mother, respectively.
except for congenital malformations.

Among all cases, three were picked from NBS and treated with early Vit B\textsubscript{12} injection, their C3 (5.73-15 µmol/L) and tHCY (39-82.9 µmol/L) were increased, and their serum Vit B\textsubscript{12} (62-148 pmol/L) was decreased before treatment. A total of 6 LMBRD1 mutations were detected in these infants, including c.1339-G>T (2/6), c.1056delG, c.246+3476G>T, c.829C>T, and c.87C>A.

**Discussion**

CblF disturbs lysosomal release of cobalamin into the cytoplasm, causing cobalamin unavailable for the synthesis of adenosylcobalamin (AdoCbl) and methylcobalamin (MeCbl), and leading to combined MMA. This typical biochemistry was confirmed by our study. In addition, we discovered another interesting biochemical feature, decreased serum Vit B\textsubscript{12} concentration, which could be easily misdiagnosed as Vit B\textsubscript{12} deficiency. These two diseases should be carefully identified due to different treatment regimens: the former requires life-long treatment, while nutritional Vit B\textsubscript{12} deficiency could terminate Vit B\textsubscript{12} after serum Vit B\textsubscript{12} level returns to normal.

There are considerable wide clinical spectrum in CblF, whose common clinical features include macrocytic anaemia, failure to thrive and developmental delay, and congenital heart disease (CHD) and small for gestational age (SGA), all of which are nonspecific. Compared with type cblC, CHD and SGA are two more frequent-occurring diseases in CblF. Hence MS-MS and genetic testing are recommended for patients with unexplained macrocytic anaemia, growth and development delay, repeated infection, and feeding difficulty.

**LMBRD1**, which is located in the chromosome 6q12-13, contains 16 exons, and encoding LMBRD1 membrane protein consisting of 9 transmembrane domain sites. In our study, the frameshift mutation is the most frequent type, accounting for 85.7% of the total LMBRD1 mutations, and c.1056delG mutation is the most common type, with a frequency of 68.6%. Up to now, there is no report related to missense mutation, indicating that the missense mutation may be neglected due to its slight effect on the structure and function of LMBD1 protein. Compound heterozygous

<table>
<thead>
<tr>
<th>Patient</th>
<th>Mutation 1</th>
<th>Amino acid change</th>
<th>Mutation 2</th>
<th>Amino acid change</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (This study)</td>
<td>c.829C&gt;T</td>
<td>p.R277*</td>
<td>c.87C&gt;A</td>
<td>p.C29*</td>
</tr>
<tr>
<td>5\textsuperscript{*}</td>
<td>c.848_851delAGAG</td>
<td>p.E283Gfs*3</td>
<td>c.1056delG</td>
<td>p.N353Ifs*18</td>
</tr>
<tr>
<td>7\textsuperscript{*}</td>
<td>c.515-516delAC</td>
<td>p.T172Rfs*10</td>
<td>c.515-516delAC</td>
<td>p.T172Rfs*10</td>
</tr>
<tr>
<td>11\textsuperscript{*}</td>
<td>c.1056delG</td>
<td>p.N353Ifs*18</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>12\textsuperscript{*}</td>
<td>c.1405delG</td>
<td>p.D469Mfs*38</td>
<td>c.1405delG</td>
<td>p.D469Mfs*38</td>
</tr>
<tr>
<td>13\textsuperscript{*}</td>
<td>c.246+3476G&gt;T</td>
<td>/</td>
<td>c.1056delG</td>
<td>p.N353Ifs*18</td>
</tr>
<tr>
<td>14\textsuperscript{*}</td>
<td>c.916-1G&gt;T</td>
<td>/</td>
<td>c.1056delG</td>
<td>p.N353Ifs*18</td>
</tr>
<tr>
<td>15\textsuperscript{*}</td>
<td>c.1339-1G&gt;T</td>
<td>/</td>
<td>c.1056delG</td>
<td>p.N353Ifs*18</td>
</tr>
<tr>
<td>16\textsuperscript{*}</td>
<td>c.404delC</td>
<td>p.T135Ifs*15</td>
<td>c.1056delG</td>
<td>p.N353Ifs*18</td>
</tr>
</tbody>
</table>

novel mutations of c.87C>A and c.829C>T were detected in the Chinese case, it expands the genotype spectrum of CblF. In addition, digenic mutations have been reported for cobalamin deficiency in one study, which showed that the affected patient was identified that he carried mutations of LMBRD1 and MTR by exome sequencing. This study highlighted that the mutations in CblF may be more complicated, and different pathogenic genes may be involved in it. Due to the similar biochemistry among different types of combined MMA and Vit B₁₂ deficiency and complicated genotype of MMA, genetic panel including cblC, cblD, cblF, and cblJ is recommended instead of single gene sequence for timely and accurate diagnosis.

The genotype-phenotype correlations of CblF are not clear so far due to limited cases.

According to the data, all abnormal biochemical changes and most of clinical presentations in these cases have been significantly improved after Vit B₁₂ treatment, proving that Vit B₁₂ injection is an effective treatment for CblF. The dosage of Vit B₁₂ ranged from 1mg per day to 1 mg every 2 months, and the appropriate dosage remains to be explored.

Acknowledgement

This work was supported by Fund (2017YFC1001704/2017YFC1001703) from the Science and Technology Department of China.

Conflict of Interest

The authors declare that they have no competing interest.

References

Letter to the Editor

Dear editor,

Filicides in Hong Kong

Filicide is an intentional act of murdering one's own child.¹ There are very few medical reports on this tragic crime in Hong Kong and no accurate and up-to-date local statistics on filicide. It appears that cases may appear in clusters from time to time. According to the reports of social media, limited information about the physical and psychosocial well-being of the children involved was found (Table 1).

We have summarised cases involving filicide and possible risk factors pertinent to the city of Hong Kong in 2017-2018. These cases involved children of parents of both sexes and mostly under the age of 12. It is believed that these cases would be attributed to multi-dimensional factors; nevertheless, psychosocial risk factors are often described in social media and may be clues for interventions.¹⁻⁷ According to the media record in 2017-2018, psychosocial factors such as psychiatric morbidity of parents, postpartum depression and adverse life situation such as marital discord, single parenthood, unwanted pregnancy or financial strain appear to be the presenting issues for filicide in Hong Kong (Table 1).

Filicide is not rare in developed countries. Indeed, it is the third leading cause of death amongst American children 5 to 14 years old; and parents were responsible for 61% of children murders under the age of 5 years.³ There have been scanty Hong Kong data on filicide in the literature. Modes of filicide included predominantly jumping from height, charcoal burning, poisoning, dumping the baby corpus into rubbish bins and occasionally stabbing or strangulation. Unlike overseas, none of these cases involve firearms in Hong Kong.

Nationwide systematic collection of data on filicide with suicide may bring new insights to the problem. There have been escalating numbers of PubMed publications on the subject matter. Depression in terms of loneliness, helplessness or hopelessness might be one of the psychological conditions that the parents or caregivers who committed filicides, as they might perceive that nobody would be able or trustworthy enough to take care for the children if they committed suicide.¹,³ In a densely populated city, people are physically close but emotional distant. Mental health support remains thin in Hong Kong and is no substitute for a strong social support network.

Meanwhile, most of the people in Hong Kong are not highly aware of their own and others' mental health, especially for parents and primary caregivers. Further, it is uncertain if they may be concerned about social stigmatisation of help-seeking in times of need. In general, many choose to deal with emotional disturbances through suppression, distraction and avoidance. It is advisable for the medical professionals to work hand in hand with the social workers and psychological counselors for the best interest of the children and families by adopting a systemic perspective in healthcare settings.

An official registry can be set up to understand local factors and changing patterns pertinent to filicide, and to enable and implement preventive measures. A multi-dimensional and systemic screening tool for filicide risks is called for to better characterize cases for preventive purposes.⁶,⁷ It would be helpful if health care providers could be vigilant of the emotional state of parents or caregivers and address their psychosocial needs in order to prevent future tragic incidents.
Table 1  Cases of filicides reported in social media in Hong Kong in 2017-2018

<table>
<thead>
<tr>
<th>Date</th>
<th>Case</th>
<th>Link</th>
</tr>
</thead>
<tbody>
<tr>
<td>August 7, 2017</td>
<td>A 34-year-old Hong Kong father jumped from the balcony of a flat high in a Macau residential block with his two-year-old daughter in a suicide-murder case. The man is suspected to have stabbed his partner, the 30-year-old mother of the young girl, before he jumped holding the child.</td>
<td><a href="http://www.thestandard.com.hk/section-news.php?id=185953&amp;sid=4">http://www.thestandard.com.hk/section-news.php?id=185953&amp;sid=4</a></td>
</tr>
<tr>
<td>October 18, 2017</td>
<td>A corpse of new born baby girl was found inside of a garbage can in Wanchai. On November 6, 2017, a corpse of a new born baby in a public restroom of North Point Java Road Market.</td>
<td><a href="http://www.info.gov.hk/gia/general/201710/18/P2017101800973.htm">http://www.info.gov.hk/gia/general/201710/18/P2017101800973.htm</a></td>
</tr>
<tr>
<td>December 18, 2017</td>
<td>On, a 37-year-old mother was arrested after murdering and dismembering her 12-year-old daughter in a Hong Kong flat. The mother was found mentally confused, and suspected to be under the influence of drug.</td>
<td><a href="http://www.wikiwand.com/zh-sg/%E9%A6%99%E6%B8%AF%E5%91%BD%E6%A1%88%E5%88%97%E8%A1%A8#/E5.8F.82.E8.80.83.E6.96.87.E7.8C.AE">http://www.wikiwand.com/zh-sg/%E9%A6%99%E6%B8%AF%E5%91%BD%E6%A1%88%E5%88%97%E8%A1%A8#/E5.8F.82.E8.80.83.E6.96.87.E7.8C.AE</a></td>
</tr>
<tr>
<td>January 12, 2018</td>
<td>On, an Indonesian domestic helper gave birth to a baby girl secretly. She killed the baby and put her into a bin of rubbish collection station.</td>
<td><a href="http://www.wikiwand.com/zh-sg/%E9%A6%99%E6%B8%AF%E5%91%BD%E6%A1%88%E5%88%97%E8%A1%A8#/.E5.8F.82.E8.80.83.E6.96.87.E7.8C.AE">http://www.wikiwand.com/zh-sg/%E9%A6%99%E6%B8%AF%E5%91%BD%E6%A1%88%E5%88%97%E8%A1%A8#/.E5.8F.82.E8.80.83.E6.96.87.E7.8C.AE</a></td>
</tr>
<tr>
<td>January 14, 2018</td>
<td>A 42-year-old Korean woman and her 6-year-old son were cut in the throat by knife and found dead on a bed in a hotel room of Austin Road. Her husband was a businessman and failed in his business. He was found drunk and arrested at the hotel room.</td>
<td><a href="http://hk.on.cc/hk/bkn/cnt/news/20180115/bkn-20180115033016013-0115_00822_001.html">http://hk.on.cc/hk/bkn/cnt/news/20180115/bkn-20180115033016013-0115_00822_001.html</a></td>
</tr>
<tr>
<td>June 29, 2018</td>
<td>A corpse of new born baby girl was found out the rubbish collection station of Yau Oi Estate.</td>
<td><a href="http://www.scmp.com/news/hong-kong/law-crime/article/2124706/mother-arrested-after-12-year-old-daughter-found">http://www.scmp.com/news/hong-kong/law-crime/article/2124706/mother-arrested-after-12-year-old-daughter-found</a></td>
</tr>
<tr>
<td>July 24, 2018</td>
<td>A two-year-old boy was thrown out of a window by his 35-year-old mother who was found on the ground next to the toddler on a public housing estate. The single mother was later certified dead. Police found a suicide note, blood and three knives in the only bedroom in the fourth-floor flat.</td>
<td><a href="http://www.scmp.com/news/hong-kong/hong-kong-law-and-crime/article/2156630/mother-dies-toddler-unconscious-after-fall">http://www.scmp.com/news/hong-kong/hong-kong-law-and-crime/article/2156630/mother-dies-toddler-unconscious-after-fall</a></td>
</tr>
<tr>
<td>August 7, 2018</td>
<td>A 44-year-old clinic nurse was found dead together with her 7-year-old daughter at her home in Tai Kok Tsui. She left a letter and stating that she was disturbed by love affair issues and did not want to continue her life.</td>
<td><a href="https://hk.news.appledaily.com/breaking/realtme/article/20180807/58535487/">https://hk.news.appledaily.com/breaking/realtme/article/20180807/58535487/</a></td>
</tr>
</tbody>
</table>
References


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Clinical Quiz

What is the Diagnosis?

Case History

Our propositus is a 15-year-old young gentleman who has ADHD and Asperger’s syndrome. He has normal IQ with satisfactory school performance. Upon physical examination, he was found to have café-au-lait spots all over the body and some freckles in axilla and inguinal areas. He also has some cutaneous and subcutaneous skin modules and the clinical diagnosis by dermatology is neurofibroma. MRI brain reveals two focal T1W isointense T2W hyperintense lesions up to 5 mm in size at bilateral basal ganglia. He is born from a non-consanguineous family with negative family history.

Figure 1  Clinical photos of the patient. (Consent for publication has been obtained)
Abstracts of Articles in Chinese

來自一所高水平（第三層）醫院的嬰兒尿石症報告


目的：本研究目的為評估嬰兒餵養方式與嬰兒尿石症代謝風險因素的關係。病人與方法：本研究總共有尿石症嬰兒（<12月齡）70例。慢性疾病或剖開異常的病人除外。由母親完成一份問卷。飲食特徵（母乳和／或配方乳餵養，加水份補充）和尿石症家族史要確定。用導尿管收集病人24小時尿液，進行尿石症代謝風險因素分析。結果：結石病發病的平均月齡為4.47±2.41月。病人的主要臨床症狀為煩躁不安（45.7%）和嘔吐（14.3%）；然而，24%嬰兒沒有症狀。大部份病人（64.2%）為單一母乳餵養，其餘的是配方乳作為補充餵養。70例病人中24例有喝水。微小結石症有50例（71.4%）。90%病人有至少1項代謝異常。病人中高鈣尿和高尿酸尿檢出率分別為40%和47%。未發現水分補充對尿路代謝排出有影響。在接受配方乳補充母乳餵養病人中，可檢出高尿磷和尿酸排出。結論：嬰兒尿石症在土耳其仍然是一個嚴重問題。尿石症嬰兒可無特異性症狀。尿石症陽性家族史和配方乳餵養可能增加嬰兒尿石症的發生。

關鍵詞：嬰兒餵養、代謝風險因素、尿石症

生物電阻抗分析法評估兒童維生素D和營養狀態


目的：營養障礙影響兒童生長。本研究目的為通過生物電阻抗分析使用不同的營養評估參數評估兒童的營養狀況及維生素D水平。方法：研究包含了279例多種症狀的普通兒科門診病人，如營養不良、肥胖、虛弱、乏力、腿疼，以及光照不足。所有病人評估了人體測量資料，使用In-Body 230設備收集人體成份分析資料，以及生物電阻抗分析（BIA）數據。病人通過體重指數標準差評分分組為體重過輕、正常體重、超重或肥胖組。25 羅維生素D水平通過實驗室記錄獲得。結果：病人中44.1%（n=123）是女性，平均年齡為10.0±3.6（2-17）歲。所有病人中，18.6%（n=52）為體重過輕，47.3%（n=132）為正常體重，14.7%（n=41）為肥胖，19.4%（n=54）為超重。25 羅維生素 D水平在體重過輕、正常體重、超重及肥胖組的平均水平分別是 22.9±13.5 ng/mL，25.8±11.8 ng/mL，20.7±7.7 ng/mL 及 17.9±9.7 ng/mL。肥胖組中25 羅維生素 D水平低於其他組，但是差別不顯著。青春期男孩肥胖的發病率上升，女孩25 羅維生素 D水平下降。結論：通過BIA評估營養狀況和人體脂肪成份對於預防和處理兒童肥胖及營養不良，可能是一種妥善和可靠的方法。

關鍵詞：生物電阻抗分析、人體成份分析、營養不良、羅生素D
1 型糖尿病兒童的抑鬱情況和進食障礙

N Sanlier, D Ağagündüz, Y Ertaş Öztürk, R Bozbunul, M Ş Karaçil Emumcu. Depression and Eating Disorders in Children with Type 1 Diabetes. HK J Paediatr (new series) 2019;24:16-24

目的：本研究旨在探討 1 型糖尿病兒童的抑鬱和進食障礙和確定相關性因素。兒童 1 型糖尿病。方法：以橫斷式研究 149 名 10-17 歲 1 型糖尿病病童。對這些病童執行抑鬱徵狀和糖尿病飲食問題的問卷調查，體位測量並評估生化結果。結果：兒童平均年齡為 13.42±2.31 年。沒有使用碳水化合物的兒童抑鬱分數更高，進食障礙得分低於那些使用碳水化合物的孩子。使用胰島素泵的兒童進食障礙，抑鬱分數低於那些不使用的。兒童糖化血紅蛋白升高一個單位造成進食障礙得分升高三個單位和抑鬱風險增加 1.3 倍。結論：控制兒童糖尿病時，建議提供營養、生化和精神評估和監測。

關鍵詞：孩子、抑鬱症、進食障礙、糖化血紅蛋白、1 型糖尿病

止吐藥治療兒童嘔吐：一項雙盲隨機安慰劑對照臨床研究


目的：本研究目的在於評估昂丹司瓊、甲氧氯普胺和安慰劑對於急診部門出現急性嘔吐兒童的療效進行前瞻性對比。方法：本隨機雙盲臨床研究中，研究對象為 18 歲以下病人，被隨機分組接受以下治療：（a）0.15 mg/kg 昂丹司瓊靜脈注射；（b）0.2 mg/kg 甲氧氯普胺加入 100 mL 生理鹽水中靜脈注射；（c）100 mL 生理鹽水，作為安慰劑。以止吐治療 60 分鐘後再次嘔吐出現為初步療效測定。結果：總共 234 人隨機性進入 3 個治療組：（a）昂丹司瓊（n=77）；（b）甲氧氯普胺（n=79）；（c）安慰劑（n=78）。中位年齡為 68.27±39.97 月，男性佔 49.1%。結果顯示 3 個治療組的第一個 60 分鐘內嘔吐情況有顯著差異（p=0.001），但昂丹司瓊組與甲氧氯普胺組之間無出現差異（p=0.557）。各治療組的第 30 分鐘、120 分鐘和 240 分鐘的結果差異在療效上有顯著性意義（分別為 p=0.002 , p=0.000 , p=0.000），但昂丹司瓊組與甲氧氯普胺組結果之間無差異（分別為 p=0.357 , p=0.188 , p=0.126）。甲氧氯普胺組中一例出現錐體外系統症狀（1.3%）。3 個的 24 小時嘔吐情況追蹤無差異（p=0.200）。結論：與安慰劑對比，單劑緩慢靜脈注射止吐藥可有效治療嘔吐。

關鍵詞：止吐藥、急診醫學、兒科、嘔吐
在－例接受心臟手術的先天性血管環患兒上治療圍術期出現臨床的問題


患有雙主動脈繫兒童常常有其他的先天性心臟問題需要干預。我們報告－例患兒因雙主動脈繫導致的先天性血管環並伴有室間隔缺損，心力衰竭，肺動脈高壓及氣管軟化，接受了肺動脈環縮術及雙主動脈繫矯正術。在此討論和回顧了這名患病患兒，特別是在術後導引及安全脫離儀器方面，因氣道狹窄及心肺疾病帶來的圍術期各種臨床問題。

關鍵詞：氣道管理、麻醉、雙主動脈繫、血管環

陳健良醫師

一例小兒因破損溫度計致肛周汞散落


因破損溫度計致汞散落在肛周內，外部，情況相當罕見。該狀況的結局和處理仍無定論。作者在此報告－例28月大男孩，因水銀溫度計破損致的元素汞暴露。放射影像顯示汞在肛周內部，外部的盆腔散落分佈。雖然進行了腹腔鏡手術，但未能清除汞散落。慶幸3年的臨床追蹤，並未顯示男童出現任何與汞中毒相關的臨床或生化表現。

關鍵詞：兒童，元素汞，腹腔鏡，溫度計

陳健良醫師

含有小麥成分皮膚霜進行皮膚護理致蕁麻疹和家中的及時治療

K Taniguchi, Y Ichiyama, K Uemichi. Urticaria in Skin Care with Skin Cream Containing a Wheat Compound and Prompt Treatment at Home. HK J Paediatr (new series) 2019;24:40-42

對於患有溼疹的兒童，皮膚護理是一基礎治療。然而，幾乎所有人都沒有意識到皮膚護理中的隱患。作者在此報告－種含有小麥成分的皮膚霜，導致急性蕁麻疹。－例8歲男孩，沒有小麥食物過敏史，使用了一種含有小麥成分的皮膚霜。使用皮膚霜後立即使全身出現急性蕁麻疹。經在家中洗澡清除皮膚霜、口服抗組胺藥、使用皮質激素膏後，急性蕁麻疹消退。含有小麥成分的皮膚霜可導致急性蕁麻疹。及時治療可預防過敏反應的進展，這些治療可以在家中進行。皮膚護理要意識到可能出現的隱患。作為醫院前治療，我們應學習對意外過敏反應的及時治療。

關鍵詞：皮膚霜、蕁麻疹、小麥過敏
中國首例鈷胺素（維生素 B12）F 障礙：報告和文獻綜述

F Tong, RL Yang, R Chen, ZY Zhao. The First Case of Cobalamin F Disorder in China: Report and Literature Review. HK J Paediatr (new series) 2019;24:43-47

目的：探討鈷胺素 F 障礙（CblF）表型、基因型和預後。方法：資料包括中國首例 CblF 障礙的新生兒篩查和臨床特徵，LMBRD1突變，在治療和預後和 17 CblF 病例收集和分析報告。結果：本例由新生兒篩查（NBS）發現，因血生化異常（MS-MS）検查出丙酰肉鹼（C3）（5.50 µmol / L），丙酰肉鹼／乙酰肉鹼（C3／C2）比（0.47），丙酰肉鹼／肉鹼自由基 C3／C0 比（0.25）和蛋氨酸（Met）減低（5.27 µmol / L），血清維生素 B12（氰鈷胺素；維生素 B12）減少（116 pmol / L），同型半胱氨酸升高（血漿總高半胱氨酸水準）（82.9 µmol / L），並證實合併大細胞性貧血，心房間隔缺損，動脈導管未閉。與文獻已報導相類似。此外，兩個新的 LMBRD1 基因的 p.R277* 和 p.C29 * 截斷突變獲證實。所有 18 例的資料表明，常見的臨床特徵是大細胞性貧血，生長遲滯，發育遲緩，先天性心臟病和小胎齡。NBS 的 3 個病例均有相似的生化特徵，在 10 個不同的位點共觀察到 35 個 LMBRD1 突變，包括框移突變（0/35）、剪切位點突變（2/35）、無意義突變（2/35）和大片段缺失（1/35），其中 c.1056delG 突變是最常報導（24/35）。維生素 B12 注射和支持治療 3 個月後，所有的病例的生化異常和大多數臨床表現均顯著改善。結論：CblF 生化特點與甲基丙二酸（MMA）類似，除了降低血清維生素 B12 之外，應區別於維生素 B12 缺乏症。典型的表型包括大細胞性貧血，生長和發育問題和先天畸形，這些都是非特異性的。c.1056delG 突變是常見的突變。疑似 MMA 病例可選擇 MS-MS 檢查 C3，C3 / C2，C3 / C0，Met 濃度和 MMA 基因檢測。CblF 是一種可以治癒的疾病和注射維生素 B12 是有效的，但合適的劑量仍有待確定。

關鍵詞：鈷胺素，基因型，表型，預後，治療
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) A Report of Infant Urolithiasis in a Tertiary Hospital

1. Which of the following is related with childhood urolithiasis?
   a. Genetic inheritance
   b. Nutrition
   c. Metabolic abnormalities
   d. Environmental factors
   e. All of the above

2. Which of the following metabolic risk factor is not related with urolithiasis?
   a. Hypercalciuria
   b. Hyperoxaluria
   c. Hypermagnesuria
   d. Hyperuricosuria
   e. Hypocitraturia

3. Which is the most common metabolic abnormality in both adult and child urolithiasis?
   a. Hypocitraturia
   b. Hypercalciuria
   c. Hypomagnesuria
   d. Hyperuricosuria
   e. Hyperoxaluria

4. What is wrong about comparison of breast milk and formulas?
   a. Calcium content of breast milk is higher than formulas.
   b. Phosphorus is low in breast milk.
   c. Phosphorus is high in formulas.
   d. Absorption of calcium in breast milk is higher than formula
   e. Absorption of calcium and phosphorus in formula is lower

5. Which of the following can be related with infant urolithiasis?
   a. Irritability/restlessness
   b. Urinary tract infection
   c. Abnormal urine odour or colour
   d. Asymptomatic infant
   e. All of the above

(B) Vitamin D and Nutritional Status of Children Evaluated via Bioelectric Impedance Analysis

1. According to the American Association of Clinical Endocrinologists, which level is sufficient for vitamin D?
   a. 30 ng/mL or above
   b. 20 ng/mL or above
   c. 10 ng/mL or above
   d. 50 ng/mL or above
   e. 100 ng/mL or above

2. How many years after children do the impact of gender appear more pronounced in their body composition?
   a. After age 1
   b. After age 5
   c. After age 10
   d. After age 15
   e. After age 18

3. Which vitamin supplement is important in obese individuals with nutritional regulation?
   a. Vitamin A
   b. Vitamin B
   c. Vitamin C
   d. Vitamin D
   e. Vitamin K

4. Which of the following is not one of the methods used to evaluate body composition?
   a. Bioelectrical impedance analysis (BIA)
   b. Dual-Enerji X-Ray absorptiometry (DEXA)
   c. Skin fold thickness measurement
   d. Calculation of body mass index
   e. Vitamin D level

5. Which of the following is more likely to have a deficiency of vitamin D than the others?
   a. Preschool girls
   b. Adolescent girls
   c. Preschool boys
   d. Adolescent boys
   e. No difference risks between them
**C** Depression and Eating Disorders in Children with Type 1 Diabetes

1. Type 1 diabetes mellitus is characterised by?
   a. Deficiency in insulin production
   b. Deficiency in leptin production
   c. Increasing in obesity
   d. Deficiency in glucagon production
   e. Impaired adiponectin control

2. Which one is a factor that lead to increased risk of depression in Type 1 diabetes mellitus?
   a. Insulin dependency
   b. Fear of hypoglycemia
   c. Desire of maintenance the ideal body weight
   d. Certain eating patterns
   e. All above of them

3. Diabetic individuals are an important risk group in terms of psychological problems. Which psychological problem is not associated with this disease according to article?
   a. Depression
   b. Agoraphobia
   c. Eating disorders
   d. Anxiety
   e. Mood disorders

4. Which one is not a symptom of Type 1 diabetes mellitus?
   a. Impaired glucose levels
   b. Increased HbA1C levels
   c. Decreased serum glucose levels
   d. Deficiency in insulin production
   e. Destruction in pancreatic beta cells

5. Which methods are used to provide metabolic control in Type 1 diabetes mellitus?
   a. Insulin resistance/glucose tolerance test
   b. Insulin resistance/carbohydrate counting
   c. Insulin pump/glucose tolerance test
   d. Insulin pump/carbohydrate counting
   e. None above of them

**D** Antiemetics to Control Vomiting in Children: A Double-Blind Placebo-Controlled Trial

1. In children with dehydration from gastroenteritis, which of the following is the first line therapy recommended by the American Academy of Pediatrics?
   a. Intravenous fluid
   b. Oral rehydration therapy
   c. Intravenous antiemetics
   d. Oral antiemetics
   e. None

2. Which of the following is the most common reason why antiemetic agents are not preferred by paediatricians in the treatment of dehydration?
   a. Difficult to reach
   b. High cost
   c. Adverse effect
   d. Not taking part in primary care
   e. Lack of experience

3. Which of the following metoclopramide treatments is most often associated with extrapyramidal symptoms?
   a. High dosage
   b. Orally given
   c. Rapid infusions less than 15 minutes
   d. Combined with ondansetron
   e. None

4. Which of the following is the reason why paediatricians do not prefer to select ondansetron as the first line therapy for dehydrated children?
   a. Difficult to reach
   b. High cost
   c. Lack of experience
   d. Limited randomised controlled studies
   e. a and b

5. Which of the following is wrong about the treatment of vomiting in children?
   a. Antiemetics were superior to the placebo in terms of vomiting control after discharge and which reduced the rate of re-admission
   b. The incidence of extrapyramidal symptoms due to metoclopramide depends on the rate of drug infusion
   c. The most common cause of vomiting in older infants and children is infectious gastroenteritis
   d. In the guidelines published before 2008, antiemetic therapy was not recommended as the first line therapy for dehydration
   e. Dystonia is the most common extrapyramidal symptom associated with the use of metoclopramide

**Answers of October issue 2018**

(A)  1. e; 2. a; 3. b; 4. c; 5. a  
(B)  1. d; 2. e; 3. c; 4. b; 5. c  
(C)  1. e; 2. d; 3. e; 4. e; 5. c  
(D)  1. c; 2. e; 3. a; 4. d; 5. b
CLINICAL QUIZ (p51) ANSWER

What is the Diagnosis?

Our patient is diagnosed with Neurofibromatosis type 1 (NF1). He fulfils three of the seven NIH criteria for NF1.
1. He has 18 café au lait spots (CAL) >15 mm in size and some smaller CAL spots of ~1 cm over trunk, buttocks, posterior thigh and extremities. The largest CAL is of 6 cm over the back of the left leg, and another similar one over the front of the left leg.
2. He has mild freckling in the right axillary region and over the inguinal areas.
3. He has more than two neurofibromas.

Regarding the genetic diagnosis, a variant (c.4267A>G, p.(Lys1423Glu)) is identified in the \textit{NF1} gene. He is therefore both clinically and genetically diagnosed to have NF1.

An interesting point to note is that the MRI finding revealed two focal T1W isointense and T2W hyperintense lesions up to 5 mm in size at bilateral basal ganglia. These unidentified bright objects (UBO) were at first a great concern to the clinicians. Upon discovering the UBO on MRI, clinicians were at first worried it could be a malignant or inflammatory lesion in the brain, which they suggested further investigations and frequent monitoring for our patient. Upon the genetic confirmation of NF1, clinicians were less worried about the UBO, as UBOs has well known association with NF1. Hyperintense lesions on T2-weighted MRI images of the brain, predominantly located in the basal ganglia, the brainstem and cerebellum, are frequent findings in patients with NF1. A study analysed MRI scans of 31 children with definite diagnosis of NF1 according to the NIH criteria, high-intensity lesions on T2-weighted images were present in 86% of the patients.\textsuperscript{1} These lesions typically appear at around 3 years old, with increasing number and size until 10-12 years old, and then decrease or even disappear at later years. Common locations include basal ganglia, thalami, dentate nucleus of cerebellum and brainstem. Generally, these lesions do not cause neurological symptoms, but they have been correlated with learning disabilities.\textsuperscript{2}

The genetic diagnosis helped ease the clinicians’ and the family's anxiety as UBO in the context of NF1 has a much better prognosis compared to a UBO in other health context. Thus, the confirmation of NF1 by genetic analysis helped bring great relief to the patient and his family.

What is Neurofibromatosis?

Neurofibromatosis has two recognised types: NF1 (previously known as von Recklinghausen disease on generalised neurofibromatosis) and NF2 (previously known as either central or bilateral acoustic neurofibromatosis).

Neurofibromatosis 1 is an autosomal dominant disease that affects multiple systems, primarily involving the skin and the nervous system. It affects 1 in 3500 individuals and is usually recognised at birth when cutaneous manifestations are apparent.\textsuperscript{3} Some features may be age-related thus may not present until later in life. Despite the marked clinical variability of NF1, most children with NF1 do well in their growth and development.

To establish the diagnosis of NF1 according to the National Institute of Health (NIH) Consensus Development Conference, at least 2 features out of the following 7 are required:\textsuperscript{4}
1. Six or more café-au-lait spots (CLSs) equal to or greater than 5 mm in longest diameter in prepubertal patients and 15 mm in longest diameter in postpubertal patients;
2. Two or more neurofibromas of any type or 1 plexiform neurofibroma;
3. Freckling in the axillary or inguinal regions;
4. Optic glioma (optic pathway glioma);
5. Two or more Lisch nodules (iris hamartomas);
6. A distinctive osseous lesion, such as sphenoid wing dysplasia or cortical thinning of the cortex of long bones, with or without pseudoarthrosis; and
7. A first-degree relative (parent, sibling, or child) with NF1 according to the aforementioned criteria.

Café-au-lait spots are usually the initial clinical manifestations of NF1, and tend to increase in number and size during early childhood. Skin folds freckling and dermal neurofibromas, which may grow in puberty. Plexiform neurofibromas, which are found in 25% of individuals, may result in disfigurement if on the face, trunk or extremities. Orthopaedics conditions such as tibial dysplasia and pseudoarthrosis also affect 2-3% of NF1 children. Optic gliomas may be present in up to 15%, one third of them may be symptomatic resulting in visual loss, proptosis, hydrocephalus or precocious puberty. Due to the variable multi-system involvement of NF1, periodic multidisciplinary monitoring is needed to minimise risk of complications.

Although NF1 is mostly clinically diagnosed, molecular technology can detect 95% of the mutations. With the increasing readiness of genetic testing, it is very useful in uncertain cases such as those with some features but not fulfilling the clinical diagnostic criteria.

What is the Molecular Genetics behind NF1?

The \textit{NF1} gene encodes for the protein neurofibromin, a tumour suppressor. Pathogenic mutations in \textit{NF1} cause reduced neurofibromin function, thus resulting in excess cell proliferation.

50\% of the NF1 patients have de novo mutation, which means the mutation is not inherited from either parent. It is an autosomal dominant condition. An individual with known pathogenic NF1 mutation has 50\% chance passing down the variant to his/her offspring in each pregnancy. Prenatal diagnosis is possible, but it cannot predict the clinical outcome of offspring who inherited the variant due to marked variability.

Due to the high penetrance of NF1, clinical manifestations will be expected in individuals who carry the mutation. In individuals who are mosaic for an NF1 mutation, they may have localised signs, or "segmental neurofibromatosis". The mutant gene may be transmitted to their offspring if the germ cells are affected.

What is the Management of NF1?

NF1 patients are usually mildly affected, but the presence of plexiform neurofibromas may result in serious complications. The lifelong risk of malignancy may be increased, with malignant peripheral nerve sheath tumours representing the most common neoplasm (5-10\%). Other malignancies include pheochromocytoma, rhabdomyosarcoma, leukaemia, and brain tumours such as optic gliomas. Short stature and macrocephaly may also be related to NF1. Neurofibromas in the gastrointestinal tract may cause obstruction or bleeding. Seizure may occur in 6-7\% of cases. Non-ossifying fibromas of long bones may cause fractures. Scoliosis is also present in 10-30\% of NF1 cases, which may lead to decrease pulmonary functions. Hypertension occurs in 4\% of NF1 cases due to essential hypertension, pheochromocytoma, renal artery stenosis, or aortic stenosis. NF1 is also associated with intellectual disability and ADHD, speech problems may occur due to velopharyngeal insufficiency. Approximately one-third of NF1 develop serious complications. Due to the marked variability, it is impossible to determine the prognosis after establishing a diagnosis of NF1.

Therefore, the management of NF1 requires a multidisciplinary approach due to its multi-organ involvement. The aim of management is both early detection and treatment of complications as they occur. Regular clinical evaluation is needed and should include: examining the skin for new neurofibromas and progression of lesions and plexiform neurofibromas; checking the child's blood pressure yearly for hypertension secondary to renal artery stenosis, aortic
stenosis, and pheochromocytoma; evaluating neurodevelopment progress - MRI may be needed to detect optic gliomas; ophthalmology testing yearly; evaluating for any skeletal changes such as scoliosis, tibial dysplasia, limb deformities; checking for signs of learning disabilities and attention-deficit/hyperactivity disorder, and also reviewing the effects of puberty on the disease.

To conclude, the management of NF1 is not limited to multi-disciplinary care by paediatricians, clinical psychologists, psychiatrists, orthopaedics and surgeons; it also requires life-long regular monitoring and care.

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**References**

Instructions to Authors

The Hong Kong Journal of Paediatrics (HKJP) is a joint quarterly publication of the Hong Kong College of Paediatricians (HKCPaed) and The Hong Kong Paediatric Society (HKPS). The HKJP publishes original research papers, review articles, case reports, editorials, commentaries, letters to the editor and conference proceedings. Topics of interest will include all subjects that relate to clinical practice and research in paediatrics and child health.

Manuscripts are accepted on the condition that they are submitted solely to the HKJP and have not been published elsewhere previously and are not under consideration by another journal. A complete report following presentation or publication elsewhere previously and are not under consideration by another journal. A complete report following presentation or publication elsewhere can be considered.

Categories of articles include the following:

**Original Articles** The text should not usually exceed 5,000 words excluding references; the number of tables, figures, or both should normally not be more than six, and references not more than 50.

**Review Articles** Reviews are usually invited systematic critical assessments of literature.

**Case Reports** Length should not exceed 1,500 words; the number of tables or figures used should not be more than two, and references should not be more than 10. **Limit the number of authors to 4.**

**Commentaries** Commentary on current topics is welcome. Length should not exceed 1,200 words; no tables or figures allowed, and references should not be more than 20.

**Clinical Quiz** The clinical quiz should be educational. It should i) include the description of a case in no more than 250 words and 3 clinical photos or figures, and ii) provide answers on the diagnosis, clinical features and findings, and management of the condition in no more than 1,000 words, 10 references, and 3 photos, figures or tables.

**Letters to the Editor** Letters discussing a recent article in the HKJP are welcome. Original letters that do not refer to an HKJP article may also be considered. Letters should not exceed 500 words and have no more than five references. Published letters may be edited.

Manuscript Preparation

1. Use Arabic numerals for numbers above nine, for designators (e.g. case 5, day 2, etc.) and for units of measure; numbers should be spelled out if below 10, at the beginning and end of sentences, and for fractions below one.
2. Manuscripts should be submitted as a Word document in British English in the following format: Typed doublespaced, page size 22 cm. x 29 cm. (8 1/2 in. x 11 in.), page margins 2.54 cm (1 in), font size 12 pt.
3. Do not use abbreviations in the title or abstract and limit their use in the text. Standard abbreviations may be used and should be defined on first mention in the text unless it is a standard unit of measurement.
4. SI units should be used or included in parentheses.

Ethical Consideration

For original clinical study, authors must state that the protocol for the research project has been approved by the Ethics Committee of the institution within which the work was undertaken. All investigations on human subjects must include a statement that informed consents have been obtained. Patient anonymity must be preserved. Photographs and video clippings need to be prepared to prevent human subjects being recognized unless prior written permission has been obtained. When reporting experiments on animals, authors should indicate whether the institutional and national guide for the care and use of laboratory animals was followed.

The manuscript should usually be arranged as follows:

**Title page**

This page should include the full names, and affiliations of all authors. A short title of no more than 40 characters should also be given. Up to three academic degrees for each author are allowed. If an author’s affiliation has changed since the work was done, list the new affiliations as well. Limit the number of authors to 4 for case reports and clinical quiz.

**Abstract and Key words**

The abstract should be no more than 150 words summarising the purpose, methods, findings and conclusions. Authors should provide no more than five key words to assist with cross-indexing of the paper. Key words should be taken from Index Medicus.

**Introduction**

**Methods**

**Results**

**Discussion**

**References**

Number references in the order they appear in the text. References should follow the Vancouver style and should appear in the text, tables and legends as Arabic numerals in superscript. Journal titles should be abbreviated in accordance with Index Medicus. List all authors and/or editors up to six; if more than six, list the first three and "et al".

Examples of References:

**Articles in Journals**


**Books and Other Monographs**


**Unpublished Material**


13. A reference to unpublished work which has not yet been accepted for publication should not appear in the reference list but should be cited in the text as unpublished data or personal communication.

**Tables**

Each table should begin on a separate page. Number tables consecutively in the order of their first citation in the text and supply a brief title for each. Give each column a short or abbreviated heading. Place explanatory matter in footnotes, not in the heading. Vertical rules and horizontal rules should be omitted.

**Illustrations (Figures)**

Each illustration must be submitted as a separate figure file. The file name should be the same as the figure number. Preferred formats for digital artwork submission include Encapsulated PostScript (EPS), Portable Document Format (PDF), and Tagged Image Format (TIFF). Letters, numbers and symbols should be clear and of sufficient size to retain legibility when reduced. Photographs of persons must be retouched to make the subject unidentifiable, or be accompanied by written permission from the subject to use the photograph.

Number illustrations consecutively according to the order in which they have been first cited in the text. Titles and detailed explanations should be confined to legends and not included in illustrations. The legends should be numbered and provided on a separate double-spaced page.

**Supplementary Video Clips**

Video clips can be submitted with your manuscript in MP4 file format with H264 codec. The size of the video should not exceed 5 MB. Patient anonymity must be preserved unless prior written permission has been obtained. If accepted, the video will appear online on the Journal's website, http://www.hkjpaed.org.

**Declaration of Interest**

All sources of funding for research are to be explicitly stated. All authors must disclose any financial and personal relationships with other people or organisations that could inappropriately influence their work. It is the sole responsibility of authors to disclose any affiliation with any organisation with a financial interest, direct or indirect, in the subject matter or materials discussed in the manuscript that may affect the conduct or reporting of the work submitted.

If there are no declarations, authors should explicitly state that there are none. This must be stated at the point of submission (within the manuscript, after the main text, under a subheading “Declaration of Interest”). Manuscript submission cannot be completed unless a declaration of interest statement (either stating the disclosures or reporting that there are none) is included. This will be made available to reviewers and will appear in the published article.

The intent of this policy is not to prevent authors with any particular relationship or interest from publishing their work, but rather to adopt transparency such that reviewers, editors, the publisher, and most importantly, readers can make objective judgments concerning the work product.

**Correspondence**

All manuscripts, correspondence and subscription should be addressed to Chief Editor, Hong Kong Journal of Paediatrics Limited, c/o Hong Kong College of Paediatricians, Room 801, HK Academy of Medicine Jockey Club Building, 99 Wong Chuk Hang Road, Aberdeen, Hong Kong, e-mail: hkjpaed@paediatrician.org.hk.

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