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Paediatric Diagnosis: When Human Mind Meets Artificial Intelligence

It is hard to disagree, even in this technology-driven world in the twenty-first century, that the most revered components of the practice of clinical medicine remains to be a well-taken history followed by a carefully conducted physical examination. In children with heart conditions and prolonged fever, one is obliged to look for 'ephemeral spots of a painful nodular erythema, chiefly in the skin of the hands and feet', although young residents let alone medical students may know little of the 'Father of Modern Medicine' who lent his name to this cutaneous manifestation referred to as Osler's nodes. Just listen to your patient, he is telling you the diagnosis, unsurprisingly remarked by Dr Osler who placed his firm belief on the centrality of history taking and physical examination in each of the clinical encounters. By contrast, the fictional Dr McCoy, the iconic physician in Star Trek, begins his diagnosis almost without exception using the tricorder, the non-invasive medical scanner, among the numerous other medical gadgets on board Star Trek. To the people of the past, this fictional character and his gadgets belong to an unimaginable future. To us, perhaps, we are a step closer to seeing the realisation of Dr McCoy's tricorder. To us, we are facing a non-fictional new breed of digital physicians who is creeping into the consultation clinics and hospital wards and finding its way to potentially transform the future of medicine.

As vividly described by Obermeyer and Lee, 'In the good old days, clinicians thought in groups; "rounding", whether on the wards or in the radiology reading room, was a chance for colleagues to work together on problems too difficult for any single mind to solve.' This time-honoured approach remains central to our daily clinical practice and is illustrated in the diagnosis of the various paediatric conditions highlighted in the current issue of the Journal: enteroviral meningitis, childhood hydatid disease, syndromal disorders including 15q duplications syndrome, Reye's syndrome, and Denys Drash syndrome, and rare clinical presentations of paediatric surgical conditions including intestinal malrotation after neonatal period and an extramural duodenal ectopic pancreas.

Clinical diagnosis involves the connection of dots: dots of pieces of information in the history provided by patients, parents and caretakers, dots of physical signs obtained through physical examination, dots of past experience whether good or bad being imprinted over the years of practice, dots of intuition, and dots of the yet unknown to be unveiled through exchanges with colleagues and, in the present era, the use of search engines. It is inarguable, however, that medical knowledge and clinical data are expanding rapidly, expanding at a pace beyond the ability of the human brain to assimilate, to analyze and to apply in a timely manner. On the other hand, artificial intelligence, the mimicking of human cognition by computers, is becoming a reality in medicine. For some, the combination of big data and artificial
intelligence represents the next industrial revolution.11

The beating of the grandmaster of Go, an ancient Chinese abstract strategy board game, by AlphaGo Zero of Google DeepMind has made its way to the news headline. Its ability to master the game without human knowledge is discussed in a recent article in *Nature.*12 By their very nature, the two players of Go are competing against each other, one destined to become the winner, while the other would inevitably be called the loser. The AlphaGo Zero story that, to some, may implicate direct confrontation between artificial intelligence and the human mind is probably not the best example to illustrate the potentials of translating artificial intelligence to clinical care. Multidisciplinary input from different members of the healthcare profession is an important component in clinical diagnosis, decision making and management. The way to incorporate the protean of artificial intelligence technologies, including data mining, machine learning, case-based reasoning, Bayesian modeling, and artificial neural network into the clinical diagnostic and management pathways is becoming the crux of the question for the present and future generations of healthcare professionals.

In paediatrics, reports on the potential applications of artificial intelligence are emerging. Kruszka et al from the National Human Genome Research Institute, US, and their international collaborators recently reported on the successful use of facial recognition software to diagnose 22q11.2 deletion syndrome in diverse populations.13 Machine learning algorithm based on the face scanning patterns may be able to identify children with autistic spectrum disorders.14 The paediatric intensive care setting, with the wealth of data, may be the ideal interface between paediatric intensivist and artificial intelligence technologies.15 Big datasets coupled with machine learning has also been explored to determine brain maturation in preterm infants16 and to predict the relapse of acute lymphoblastic leukaemia in children.17

Would the rise of artificial intelligence herald the diminution of human touch in clinical medicine? In paediatrics, the touch is the touch of sympathy, empathy, and affection. Human touch is integral to the art of medicine. The late Stephen Hawking said, ‘In short, the rise of powerful artificial intelligence will be either the best, or the worst thing, ever to happen to humanity.’ When the mind of human physician meets artificial intelligence, who is to decide the outcome?

YF Cheung
Chief Editor

References

Diagnosing Enteroviral Meningitis Using Real-time RT-PCR with Cerebrospinal Fluid and Stool Specimens

JS Jeon, HS Song, JK Kim

Abstract

Enteroviral infections are common among children and are a main cause of meningitis. Cerebrospinal fluid (CSF) analysis is important for diagnosing meningitis, although CSF sampling is difficult and time-consuming. In contrast, stool testing provides simpler sampling and a higher positive rate. We performed polymerase chain reaction testing for paediatric patients (≤ 18 years old) who were admitted to Cheonan Dankook University Hospital during 2011-2015 for suspected meningitis (942 patients, 1,884 specimens). The stool specimens exhibited the highest positive rate, and 114 patients exhibited positive CSF and stool specimens. Fourteen patients had positive CSF specimens and negative stool specimens, while 101 patients had positive stool specimens and negative CSF specimens. CSF analysis combined with stool testing may provide a more efficient and accurate diagnosis of enteroviral meningitis, compared to only CSF or stool testing.

Key words

Enterovirus; Meningitis; Polymerase chain reaction

Introduction

Enteroviruses (EV) belong to the Picornaviridae family and exhibit >70 different serotypes, which include coxsackieviruses. In Korea, EV infections typically occur between early spring and summer. Large-scale EV infections have been reported worldwide, although EV infections occur more frequently in children, compared to adults. Once infected, the patient may exhibit various clinical symptoms that range from mild upper respiratory tract infection and Guillain-Barre syndrome to severe symptoms of paralysis that are associated with transverse myelitis. Furthermore, EV infections are a major source of central nervous system infections in children and infants. Moreover, 85% of aseptic meningitis cases are caused by EV. However, it is difficult to differentiate between bacterial meningitis and viral meningitis that is caused by the herpes simplex virus, and this difficulty can result in unnecessary hospitalisation, excess treatment costs, and antibiotic misuse. Thus, it is important to accurately diagnose the meningitis, in order to prevent unnecessary diagnostic testing and treatment.

The traditional method for confirming a diagnosis of aseptic meningitis is cerebrospinal fluid (CSF) analysis and culture to detect the virus. However, this procedure is invasive, can cause patients anxiety, requires a prolonged detection period, and can prevent early diagnosis and treatment based on the difficulty of obtaining CSF culture results. In addition, low virus titers are common in clinical specimens, which can create low sensitivities for many
serotypes, including the group A coxsackieviruses.\textsuperscript{14-16} Thus, polymerase chain reaction (PCR) testing has been developed as an accurate and rapid diagnostic test for aseptic meningitis.\textsuperscript{17} Both CSF and stool specimens are typically used for PCR testing, as a CSF specimen is essential for diagnosis,\textsuperscript{18} although it has a lower positive rate than PCR stool testing\textsuperscript{14-18} and has been associated with diagnostic issues that are related to the sampling period.\textsuperscript{18} Thus, it is difficult to confirm a diagnosis using PCR with only a CSF specimen. Moreover, very few studies have directly compared the efficacy of single or repeated testing. Therefore, the present study aimed to evaluate the usefulness of real-time reverse-transcription PCR (real-time RT-PCR) with CSF and stool specimens that were obtained from children at our center during the last 5 years. We believe that the results of this analysis may provide the basis for fast and accurate diagnosis of aseptic meningitis.

**Methods**

1. Patients

   This retrospective study analysed real-time RT-PCR results from CSF and stool specimens that were being tested for EV infection. The specimens were obtained from children (≤18 years old) who were admitted to Cheonan Dankook University Hospital for suspected aseptic meningitis between January 2011 and October 2015. This study received ethical approval from the Dankook University institutional ethics review board (2015-11-011).

2. Experimental Methods

   Specimens were collected from patients with symptoms of meningitis during a single hospital admission. CSF specimens were collected via lumbar puncture, and stool specimens were also collected at approximately the same time. The specimens were subjected to same-day nucleic acid extraction, or were stored at 4°C for next-day nucleic acid extraction. The CSF and stool nucleic acid extractions were performed using an automated QIAcube system with the QIAamp DNA Mini Kit (Qiagen, Hilden, Germany), according to the manufacturer’s protocol. The real-time RT-PCR was performed using 40 µL of the eluent from the QIAamp Spin column. The extracted RNA was dissolved in 50 µL of nuclease-free water and stored at -80°C until testing.

   The real-time RT-PCR assay was performed according to the manufacturer’s instructions using an AccuPower\textsuperscript{®} Enterovirus real-time RT-PCR Kit (Bioneer, Daejeon, Korea), which contains primers and probes for the highly-conserved 5’-nontranslated region of the human EV genome. Positive specimens were subjected to semi-nested RT-PCR in the VP1 coding region for molecular typing, as previously described,\textsuperscript{19} and the VP1 amplicons were sequenced using internal primer sets.

   All data were expressed as median and range. The chi-square test was used to analyse categorical data. A p-value of <0.05 was considered statistically significant.

**Results**

A total of 942 patients were included in this study, and both CSF and stool specimens were obtained from each patient (total: 1,884 specimens). Among the 942 patients, 229 patients (24.3%) tested positive for EV, 128 CSF specimens tested positive, and 215 stool specimens tested positive (Table 1). Male patients were most likely to exhibit positive CSF and stool results (Figure 1), although the difference was not statistically significant (p=0.23). The average age was 1.87 years, and children who were <1 year old accounted for 49.2% of the CSF specimens and 54.4% of the stool specimens; similar results were observed for patients who were <1 year old and ≥1 year old (Figure 2). During the 5-year study period, the lowest number of positive specimens was detected during 2012, and the highest numbers were detected during 2011 and 2015 (Figure 3). Monthly comparisons revealed that the positive rates were highest during June-August, and a gradual decline was observed during late fall.

A comparison of the CSF and stool specimen results revealed that 713 patients had negative results for both specimens, and 114 patients had positive results for both specimens. Fourteen patients had a positive CSF specimen and a negative stool specimen, and 101 patients had a

<table>
<thead>
<tr>
<th>Patients</th>
<th>CSF</th>
<th>Stool</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td>All patients</td>
<td>942</td>
<td>229 (24.3)</td>
</tr>
<tr>
<td>Male patients</td>
<td>549</td>
<td>138 (25.1)</td>
</tr>
<tr>
<td>Female patients</td>
<td>393</td>
<td>91 (23.2)</td>
</tr>
</tbody>
</table>

PCR: polymerase chain reaction; CSF: cerebrospinal fluid
negative CSF specimen and a positive stool specimen (Table 2). A higher positive rate was observed among stool specimens, compared to CSF specimens (Figure 4).

**Discussion**

In the present study, we analysed the use of CSF and stool specimens for real-time RT-PCR testing to diagnose aseptic meningitis that was secondary to EV infection. Both the CSF and stool results revealed that male patients had a higher positive rate, compared to female patients, although this difference was not statistically significant ($p=0.23$). Similarly, previous studies have reported higher positive rates among male patients (vs. female patients),$^{18,20,21}$ and some have even reported that the positive rate was two-fold higher among male patients.$^{21}$ This difference may be related to sex-based differences in immunity$^{22}$ that arise from differences in genetic and endocrine functions.$^{23}$

When we compared the annual positive rates for EV during the past 5 years, both the CSF and stool results exhibited similar increasing and decreasing trends. For example, the highest positive rates were observed in 2011 and 2015. Moreover, examination of the entire 5-year period revealed that the EV infection rate appeared to exhibit a significant quadrennial increase. This is similar to a previous study that found that a national EV pandemic occurred approximately every 3 years.$^{20}$

The monthly EV positive rates during the 5-year period revealed that positive CSF and stool specimens were most frequently detected during June-August, and that the number of positive specimens gradually decreased during the fall. This result is similar to the findings of a study regarding EV infection in Chungnam during 2005-2006,$^{24}$ and is also

**Table 2** Comparing the CSF and stool results

<table>
<thead>
<tr>
<th></th>
<th>Stool</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
</tr>
<tr>
<td>CSF</td>
<td>114</td>
</tr>
<tr>
<td></td>
<td>101</td>
</tr>
</tbody>
</table>

CSF: cerebrospinal fluid

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*Figure 1* Sex ratios for positive cerebrospinal fluid (CSF) and stool specimens.

*Figure 2* Positive specimen rates according to age group.

*Figure 3* Annual positive rates for cerebrospinal fluid (CSF) and stool specimens.

*Figure 4* Monthly numbers of positive specimens.
consistent with findings from other studies that reported higher frequencies of EV infection in the summer and fall.\textsuperscript{19,25,26} These findings are likely related to the high temperature and humidity during the summer, as previous studies have found that EV infection is common during the summer and fall in temperate regions, but occurs year-round in tropical regions.\textsuperscript{21} Moreover, this trend for EV infections was also observed during 2007-2009.\textsuperscript{8} Positive CSF and stool specimens were also most frequent among patients who were <1 year old, and this finding is similar to those of past studies,\textsuperscript{18,24} which suggests that EV infection is more likely among younger patients.

Stool specimens were more frequently positive for EV, compared to CSF specimens. Furthermore, there were a greater number of cases with negative CSF specimens and positive stool specimens, compared to cases with positive CSF specimens and negative stool specimens. These results suggest that stool testing was associated with a higher positive rate, compared to CSF testing. However, there is controversy regarding whether CSF and/or stool specimens should be used to diagnose aseptic meningitis, as varying positive rates are observed in clinical practice. For example, one study found a higher positive rate in stool specimens, compared to CSF specimens,\textsuperscript{18,27,28} and our findings validate that difference. This difference may be explained by the nature of EV, which is stable in an acidic environment and easily reaches the lower gastrointestinal tract.\textsuperscript{21} Thus, once an infection has developed, it may take 4-8 weeks (or even up to 11 weeks) for the virus to be cleared from the stool.\textsuperscript{28} Moreover, other studies have suggested that there is a high possibility of past EV infections causing aseptic meningitis, based on the prolonged clearance time, although it is difficult to evaluate this theory.\textsuperscript{18}

Kim et al have reported that there is a sharp decline in positive rates that is based on the sampling time.\textsuperscript{18} For example, positive RT-PCR results were observed in approximately 50% of their specimens that were obtained within 2 days, compared to 4.2% in specimens that were obtained after 2 days. In contrast, stool specimens provided an average positive rate of 90.5%, even after 7 days. This may be because EV meningitis is caused by viremia during the early EV infection period, and viral detection in CSF specimens may only be possible during a short period after the infection. Moreover, EV replication persists in the gastrointestinal tract after infection, which led those authors to conclude that sampling time was an important factor.\textsuperscript{18}

This study has several limitations that warrant consideration. First, we only analysed results from a single institution in the Cheonan area during 2011-2015. Second, we used a retrospective design, which is associated with several well-known risks of bias. Third, it is possible that we did not identify all cases of EV infection, based on potential procedural variations that may have introduced RNA denaturation during the specimen freezing and thawing.\textsuperscript{29}

In conclusion, our comparison of real-time RT-PCR results from CSF and stool specimens during the past 5 years revealed similar trends in the sex-specific, annual, and monthly positive rates. Furthermore, we did not observe any significant source-specific differences, unlike the differences in the age-specific positive rates (highest among patients who were <1 year old). Thus, we propose that the co-analysis of CSF and stool specimens during the early disease stage may provide a faster and more accurate diagnosis. This is especially important because differences in the source-specific positive rates and sampling times may complicate the diagnosis of EV infection. Therefore, our results may help to reduce the extended hospitalisation, medical costs, and antibiotic misuse that are related to incorrect diagnosis in cases of EV infection.

Sources of Funding

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Declaration of Interest

The authors have no conflicts of interest.

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Clinical Characteristics of Childhood Hydatid Disease: A Single Tertiary Centre Experience from Turkey


Abstract

Purpose: Hydatid disease is a parasitic infection and it is a major health problem in some areas. We aimed to evaluate the demographic and clinical findings of patients with hydatid disease in our hospital.

Methods: Between January 2009 and December 2015, patients with hydatid disease were included retrospectively in this study. Demographic characteristics, clinical findings, laboratory and imaging results, treatment modalities and complications were collected.

Findings: Twenty-eight patients were involved in our study. The median age of patients was 154 (55-197) months. Most frequently affected organs were liver (71.4%) and lungs (57.1%). In addition cysts were detected in atypical locations. Medical treatment was given in all patients.

Conclusions: Hydatid disease is an important problem in Turkey. Multiple organ involvement may occur at the same time. Therefore, advanced imaging methods should be used for the detection of localised atypical cysts. Long term outcomes are satisfactory with adequate treatment.

Key words: Children; Echinococcus granulosus; Hydatid disease; Treatment outcomes

Introduction

Hydatid disease (HD) is a zoonotic infection which is caused by larval forms of Echinococcus species. The adult form is located in intestinal lumen of dogs. Infected eggs are dispersed into the environment with animal feces. Intermediate host (sheep, goats, etc.) eats contaminated food and parasite eggs drop to the intestine of animals. It may cause cysts formation in organs by absorption into the bloodstream. Then carnivores eat the animals' organs which contain cysts, and the parasite becomes adult form by reaching the animal's intestine again. Humans may be infected by ingestion of parasitic eggs, occasionally may become an intermediate host.1

Hydatid disease is a major problem in large sheep raising areas like Mediterranean, South America, Asia, Europe and Kenya.2 The incidence is reported <1 to 220 per 100000 in endemic areas.3 Although it is seen in all regions of Turkey, most patients are reported from Eastern Anatolia, Southeastern Anatolia and Central Anatolia. The incidence is approximately 2-6/100000 in Turkey.4 Hydatid disease is more frequently reported in children compared to adults. Liver, lungs, spleen, kidney, heart, bones and central
nervous system may be affected.\textsuperscript{5}

We aimed to examine epidemiologic characteristics, clinical and laboratory findings of patients with HD and to compare our data with previous studies.

Methods

Patients admitted to our hospital between January 2009 and December 2015 with diagnosis of HD, were retrospectively included in this study. Patients who did not come to routine examinations were excluded. Hydatid disease was diagnosed with clinical, radiological and serological tests. Pathological examination was performed in all patients who underwent surgical procedures. Demographic characteristics like patients’ age, gender, contact with an animal, symptoms, clinical and laboratory findings, echinococcal indirect hemagglutination test (IHA) results, radiological imaging, treatment modalities and complications were collected from data system by using ICD-10 codes. Chest X-ray, abdominal ultrasonography, echocardiography and brain magnetic resonance imaging (MRI) were performed in all patients. Thorax and abdomen computed tomography (CT) was used in some cases that required advanced imaging. Echinococcal IHA result $\geq 1/32$ was accepted as positive. All patients received albendazole (15 mg/kg/day in two divided doses) treatment after diagnosis. Radiologic imaging was periodically performed to non-operated patients. Disappearance of cysts, calcified cysts and collapse were accepted as a complete healing and treatment was discontinued. Puncture-aspiration-injection-reaspiration (PAIR) was performed in some patients with hepatic hydatid cysts. While albendazole treatment was given to operated patients for one month after the surgery, non-operated patients received treatment at least 6 months.

Results

Thirty-one patients were diagnosed as a HD between January 2009 and December 2015. Three of them were excluded because they did not come to routine examination. Twenty (71.4%) patients were male. The median age of patients’ was 134 (55-197) months. A history of animal contact was found in 35% of boys (7/20) and in 25% of girls (2/8).

Most common complaints were cough, fever, abdominal pain, nausea and vomiting. In addition, 3 (10.7%) patients were asymptomatic and they were diagnosed incidentally. Two of these patients who were admitted to hospital because of chest pain, were diagnosed during transthoracic echocardiographic examination. Another patient was diagnosed with abdominal ultrasonography which was performed after trauma. Most common physical finding was decreased breath sounds. Pulmonary crackle, hepatomegaly, hepatosplenomegaly, convulsions and abdominal mass were detected as other findings. Physical examination was found completely normal in 9 (32.1%) patients. But history and radiographic images of these patient support HD. Patients’ clinical symptoms and physical examination findings are summarised in Table 1.

According to localisation; HD was found in as follows: 20 (71.4%) liver, 16 (57.1%) lungs, 2 (10.7%) spleen, 2 (7.1%) heart, 2 (10.7%) brain, 1 (3.6%) pancreas, 1 (3.6%) kidney and 1 (3.6%) pelvis. While 5 (17.9%) patients had only lung involvement; in 10 (35.7%) patients cysts were

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical symptoms and physical examination findings of patients</th>
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<tbody>
<tr>
<td>Symptoms</td>
<td>n (%)</td>
</tr>
<tr>
<td>Cough</td>
<td>11 (39.3)</td>
</tr>
<tr>
<td>Fever</td>
<td>10 (35.7)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>8 (28.6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (25.0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7 (25.0)</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>4 (14.3)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>3 (10.7)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>3 (10.7)</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>5 (17.9)</td>
</tr>
<tr>
<td>Purulent sputum</td>
<td>3 (10.7)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>2 (7.1)</td>
</tr>
<tr>
<td>Urticaria</td>
<td>2 (7.1)</td>
</tr>
</tbody>
</table>

Physical examination findings

<table>
<thead>
<tr>
<th></th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased breath sounds</td>
<td>11 (39.3)</td>
</tr>
<tr>
<td>Pulmonary crackle</td>
<td>4 (14.3)</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>2 (7.1)</td>
</tr>
<tr>
<td>Hepatosplenomegaly</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>Convulsions</td>
<td>2 (7.1)</td>
</tr>
<tr>
<td>Abdominal mass</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>Normal</td>
<td>9 (32.1)</td>
</tr>
</tbody>
</table>
seen in only liver. Hydatid disease was detected in 37.5% (6/16) right lobe, 37.5% (6/16) left lobe and 25% (4/16) both lobes of lungs. In addition it was found in 45% (9/20) right lobe, 40% (8/20) left lobe and 15% (3/20) both lobes of liver (Table 2). Some radiographic imaging of patients with hydatid cyst are presented in Figures 1-4.

Echinococcus IHA was not performed in 2 patients who were previously diagnosed at another hospital. This test was found positive in 69.2% (18/26) of the patients.

Treatment modalities were as follows: 60.7% (17/28) surgical treatment, 14.3% (4/28) interventional radiologic drainage, 21.4% (6/28) only medical treatment and 3.6% (1/28) interventional radiology drainage and surgery treatment together (Table 3). All patients received albendazole treatment in various times and any drug side effects were not observed.

Post-operative complications were seen in 4 (14.3%)%

Table 2  Localisation of cyst hydatid lesions

<table>
<thead>
<tr>
<th>Localisation</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>10 (35.7)</td>
</tr>
<tr>
<td>Lung</td>
<td>5 (17.9)</td>
</tr>
<tr>
<td>Liver+Lung</td>
<td>7 (25.0)</td>
</tr>
<tr>
<td>Liver+Lung+Spleen</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>Liver+Lung+Heart+Spleen</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>Lung+Renal</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>Liver+Lung+Pelvis</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>Heart+Brain+Pancreas</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>Brain</td>
<td>1 (3.6)</td>
</tr>
</tbody>
</table>

Figure 1  Contrast enhanced CT coronal reformatted image shows hepatic and splenic hydatid cysts (arrows).

Figure 2  A 9-year-old girl, coronal reformatted contrast-enhanced CT reveals a thick-walled right renal hydatid cyst (arrows).

Figure 3  Axial contrast-enhanced CT; liver hydatid cyst, wall calcifications are noted.
patients. While bile leakage and cholangitis occurred in 2 patients with hepatic hydatid cysts, pneumothorax and lung fistula were seen in 1 patient with pulmonary hydatid cysts. Post-operatively infected cyst was detected in 1 (3.6%) patient. Additionally during preoperative period, cyst was infected in 5 (17.9%) patients with lung hydatid cyst.

No mortality occurred, but recurrence was seen in 1 (3.6%) patient with brain hydatid cyst. This patient was operated and received albendazole treatment for 6 months. After the surgery, the cyst had completely disappeared. However, one year after operation, cyst occurred in the brain again. The patient was operated on a second time and received albendazole treatment for 6 months. The cyst disappeared at the end of therapy.

Treatment failure was detected in 1 patient with kidney hydatid cyst who received only medical treatment. Surgical features, postoperative complications and recurrence are summarised in Table 4.

**Discussion**

Hydatid disease is a parasitic infection which is caused by larval form of the genus *Echinococcus*. Most responsible species are *Echinococcus granulosus* and *Echinococcus multilocularis*. It is a major health problem in some areas where farming is widespread.3 This disease may be acquired in childhood, however diagnosis may be delayed due to long incubation period. In literature many centers report their experience of childhood HD.6-13 In this study, we aimed to evaluate our experience of childhood HD and to compare our results with previous studies.

Hydatid disease is more frequently reported in boys than girls. This difference was considered due to more contact with animals in boys.14 We reported a history of animal contact was found in 35% of boys and 25% of girls. Our study supports the hypothesis above.

Although HD may be seen in many organs; liver and lungs are commonly involved. Lungs are affected more often than liver in children.11,15 Hepatic involvement is most frequently seen in adults.3 In addition cysts may be detected atypical in locations such as heart, brain, spleen, pancreas, kidney, eye and pelvis. Çakır et al analysed 41 pediatric patients with HD which was detected in 37% lungs, 35% liver, 17% both lungs and liver, 5% spleen, 2% both spleen and heart, 2% brain, 2% both brain and heart. Hydatid cysts were identified in 29% right lobe, 15% left lobe and 10% both lobes of lungs. In addition 34% right lobe, 12% left lobe and 7% both lobes of liver involvement were seen in children.11 However there were some studies showing opposite results.6,9 In Tiryaki et al's study 101 children who were operated because of hydatid cysts were examined retrospectively. They found HD in 32% lungs, 48% liver, 16% both lungs and liver, 2% spleen, 1% retrovesical and 1% retroperitoneal region.6 Djuricic et al's study included 149 children with 272 hydatid cysts. They reported HD was detected in 60.7% liver, 30.1% lungs and 9.2% other localisations (omentum, peritoneum, intestine, spleen,}

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**Figure 4**  
CT of thorax axial images in soft tissue (A) and lung (B) window demonstrate ruptured lung hydatid cyst. Detached membranes (arrows) and fluid collections and right sided pneumothorax (asterisk) is visible.
kidney, abdomen, heart, pancreas and abdominal wall). Both lungs and liver involvement were identified in 9 (6.0%) patients. We found liver was more frequently affected than lungs and some cysts were detected in atypical localisation.

In our study cardiac involvement was found in 2 patients. In literature cardiac hydatid cysts are rare and it is reported 0.2-3% of all cases. The most common affected areas are the left (75%) and right ventricles (18%) and the interventricular septum. In our patients, left ventricle and interventricular septum involvement were detected. Both patients had also operated and they were completely recovered.

This disease may have different number of cyst. As single cyst may be detected in single organ, multiple cysts may occur in multiple organs. Djuricic et al identified single cyst in 59 patients, multiple organ involvement was seen in 18 children. Additionally in 24 patients, multiple cysts were detected in the same organ. In our study, 16 patients had one organ involvement and single cyst was found in single organ in 10 patients. Our study supports single cysts are more common in children.

Clinical manifestations of HD may be seen according to localisation, size, number and condition of cyst. While abdominal pain, vomiting, hepatomegaly, obstructive jaundice may occur in hepatic hydatid cysts; cough, fever, dyspnea, haemoptysis and chest pain may be seen in pulmonary hydatid cysts. Symptoms may appear early in lungs and brain tissue because of weak tissue support. Oral et al found abdominal pain, tenderness, abdominal mass and fever were common symptoms in hepatic hydatid cysts. Tiryaki et al detected abdominal pain and cough were the most prevalent clinical findings. In our study, patients were frequently admitted to hospital with abdominal pain, cough, and fever. Although liver was more often affected than lungs, patients were frequently admitted to hospital with pulmonary symptoms. It supports that clinical symptoms occur earlier in lungs. Brain hydatid cysts may cause headache, seizures, nausea, vomiting, increased intracranial pressure syndrome and cranial nerve palsy. Our patients with brain HD had headache and seizures.

Chest X-ray may show pulmonary hydatid cysts and gives information whether the cyst is intact, ruptured and rupturing of cysts indicates specific radiologic findings like "meniscus sign and snake sign". Ultrasonography is useful test for diagnosis and follow up. According to the WHO classification; cysts are seen in 5 stages. Type I cysts are unilocular and simple which may contain uniform anechoic content. Type II cysts are multivesicular and multiseptated. Daughter cysts may fill the unilocular mother cyst. Type III cysts are unilocular and they may contain daughter cysts and echoic areas. Type IV cysts show heterogeneous echo pattern; and type V cysts have a calcified wall. Other imaging techniques such as computed tomography (CT), echocardiography and MRI are used to identify detailed anatomical location and appearance of cysts (daughter cysts, ruptured or calcified cysts). In this study, tests above were sufficient for diagnosis.

There is no consensus about ideal serological test for HD. Echinococcus IHA, specific immunoglobulin (Ig)E,
IgM, and IgG enzyme-linked immunosorbent assay, latex agglutination or immunoelctrophoresis tests are used for supporting the diagnosis. Serologic titers may be increased due to antigen release within 3 months after surgery. Immunoelectrophoresis, specific IgE and IgM antibody titres reduce and become negative within the postoperative second year. If recurrence occurs, their levels rise again. Serum IgG titer remains positive for a long time after successful operation. Because of all these reasons, use of serological tests for diagnosis and evaluation the response of treatment may lead to false results. In this study, Echinococcus IHA was 78% positive. Specific IgE, IgM and IgG tests were not used routinely for diagnosis and follow-up.

Medical, surgical treatment and PAIR are used for therapy. Surgery is the first choice treatment for cysts which have following criteria: large cysts with multiple daughter cysts, superficial location amenable to rupture, cyst compressing the neighboring organs and cysts in atypical locations such as brain, bones, spleen, kidneys, heart. In this study, surgery was the most preferred treatment modality. Antimicrobial treatment (albendazole or mebendazole) is given to prevent the spread of protoscolex into the abdominal cavity during surgery and it is started one week before the surgery and continued until at least postoperative four weeks.

While postoperative complications are reported in less than 1% of cases; recurrence is seen 2-25% in literature. In Ran et al's study 26 children who underwent radical surgery were compared with 86 pediatric patients with conservative surgery. They found that biliary complications and recurrence were more commonly seen in conservative surgery group than in radical surgery group. However, there was no significant difference between these groups. In our study post-operative complications after treatment were detected in 14.3% of the patients.

Recurrence was seen in 1 (3.6%) patient with brain HD. The patient was admitted with seizures and vomiting to our hospital. Brain CT showed cyst in the right parietal region of the brain and she was successfully operated. However five months after the operation, she was admitted again with seizures and headache. Radiologic imaging showed hydatid cyst in right occipital region of brain. The patient was operated again and on follow up hydatid cyst did not occur again. Although recurrence is seen very rarely in the literature, some cases with recurrent HD were reported at the postoperative period.

In one patient with kidney hydatid cyst who had received only medical treatment, the size of the cyst was increased and it was considered treatment failure. The patient was operated and there were no complications during follow-up. Mortality has also been reported rarely. Jordanova et al's study included 2005 children and 7366 adult patients with HD. They detected 3 patients died due to anaphylaxis which occurred after spontaneous rupture of cysts. In our study, there was no mortality.

In conclusion, HD should be considered in patients with suspicious clinical and radiological findings in endemic areas. According to affected organs, clinical signs may vary. Multi organ involvement should be considered. Advanced imaging methods such as abdominal ultrasonography, echocardiography and brain MRI should be performed in all patients for the detection of atypically located cyst. Serological tests may be used for supporting the diagnosis. Clinical results are satisfactory with adequate treatment.

References


Original Article

Overweight and Obesity in Children Under Phenylalanine Restricted Diet

Y Ozturk, P Gençpinar, B Erdur, Y Tokgoz, I Isik, SB Akin

Abstract

Introduction: The aim of this study is to determine the obesity and overweight frequency in children with phenylketonuria (PKU) and hyperphenylalaninaemia (HPA). Methods: From the patients' demographic data, diagnosis, type of diet, weight for height, body mass index, serum phenylalanine concentrations were obtained and recorded. Results: Four hundred and forty charts were evaluated and 288 of them were enrolled in the study. Two hundred and forty-six (85.4%) were under phenylalanine-restricted diet with protein support. Of those, 23 (9.3%) were obese and 16 (6.5%) were overweight. When we compared the obesity ratio of 246 patients with PKU and HPA to the obesity ratio in the Turkish population, the difference was statistically significant (p=0.025). Conclusion: The frequency of obesity was higher in PKU and HPA children who underwent phenylalanine-restricted diet treatment than in the normal population in Turkey. Detailed studies are needed to increase the understanding of the obesity risk factors in this special disorder group.

Key words

Hyperphenylalaninaemia; Obesity; Overweight; Phenylalanine restricted medical diet; Phenylketonuria

Introduction

Phenylalanine is an essential amino acid and most of it is converted into tyrosine by phenylalanine hydroxylase. For this chemical reaction, oxygen and tetrahydrobiopterine are needed, as well as the enzyme activity. If the enzyme or cofactor is deficient, phenylalanine levels are increased in the blood and clinical symptoms such as motor and mental retardation, convulsions, microcephaly and behavioural problems may develop. Phenylalanine-restricted diet is the most effective treatment. It is thought that, obesity or overweight is a potential risk in these cases, since the daily calorie is supplied by fats and carbohydrates and, related eating behavioural problems in this disorder may develop.

The purpose of this study is to determine the obesity and overweight frequency in children with phenylketonuria (PKU) and hyperphenylalaninaemia (HPA), who are also under phenylalanine-restricted diet treatment.
Methods

All patients with PKU and HPA, which were followed by Dokuz Eylul University Pediatric Metabolic Disease Department, were evaluated retrospectively. PKU defined as ‘phenylalanine level is 6-10 mg/dl despite 400-600 mg/day phenylalanine intake’, and HPA defined as ‘phenylalanine level is <10 mg/dl despite >600 mg/day phenylalanine intake’. There was no patient, who was diagnosed with BH4 (tetrahydrobiopterin) metabolism disorders. From the patients’ medical records, demographic data, diagnosis, type of medical diet, weight for height, body mass index (BMI), serum phenylalanine, T4, TSH, insulin and cortisol levels were obtained and recorded. Weight for height and BMI were evaluated by relevant percentiles of the gender. Weight for height was used for the patients 0-36 months old and BMI was used for the patients older than 36 months. According to these evaluations, lower than 85th percentile was considered as normal, 85-97th percentile was considered as overweight and higher than 97th percentile was considered as obese.

Statistical Analysis

Statistical evaluation was performed by using SPSS software (version 15.0, SPSS Inc, Chicago, IL). Mann-Whitney U test was used to compare average values of the groups, exact Chi-square test or Fisher’s exact test was used to compare rational values of the groups. Binominal test was used to compare obesity or overweight data with population data. p<0.05 values were regarded as statistically significant.

Results

Four hundred and forty charts were evaluated and 288 of them had complete records and were enrolled in the study. The follow-up duration was between 2.5-5 years. The rest of them were excluded because of missing information of patients such as anthropometric measurements and inadequate follow-up. All patients were referred from the newborn screening program. There was no responsive patient to 48-hour BH₄ loading test. The patients were under phenylalanine-restricted diet by using PKU-formula without support of BH₄.

Of the 288 patients, 141 (49%) were female and 147 (51%) were male. Two hundred and forty-six (85.4%) were under phenylalanine-restricted diet with protein support. Of those, 39 (15.9%) were obese (n=23) and overweight (n=16).

Mean age for obesity/overweight diagnosis was 7.50±5.10 years, and their PKU and HPA diagnosis age was 1.7±0.8 months. Of the 23 obese patients, 22 were PKU and one was a HPA patient.

When the obese/overweight and non-obese PKU children who underwent phenylalanine-restricted diet treatment groups were compared individually, no statistical significance was present on gender, recommended protein supplement doses, phenylalanine and protein amounts on diet (Table 1). When the obesity ratio of the 246 patients with PKU and HPA was compared to the overall Turkish population obesity ratio, the difference was statistically significant (p=0.025). Mean blood phenylalanine concentration in the obese/overweight group was 10.70±5.70 mg/dl, and this was 9.70±7.71 in the non-obese group. The difference was not statistically significant (p=0.156).

Table 1  Comparison of clinical, demographic features in obese and non-obese children with phenylketonuria (PKU)/hyperphenylalaninaemia (HPA) who underwent phenylalanine-restricted diet (n=246)

<table>
<thead>
<tr>
<th></th>
<th>Obese/overweight (n=39)</th>
<th>Non-obese (n=207)</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of the children at the time of diagnosis PKU/HPA (mean±SD; months)</td>
<td>1.7±0.8</td>
<td>1.9±1.5</td>
<td>0.41</td>
</tr>
<tr>
<td>Gender (F/M)</td>
<td>99/108</td>
<td>20/19</td>
<td>0.60</td>
</tr>
<tr>
<td>Recommended PA concentration in dietary (mg/kg/day)</td>
<td>28.1±20.2</td>
<td>26.3±13.2</td>
<td>0.782</td>
</tr>
<tr>
<td>Recommended natural protein in dietary (g/day)</td>
<td>1.2±0.3</td>
<td>1.5±0.4</td>
<td>0.437</td>
</tr>
<tr>
<td>Mean serum phenylalanine concentrations (mg/dl)</td>
<td>10.7±5.7</td>
<td>9.7±7.7</td>
<td>0.156</td>
</tr>
<tr>
<td>Age of the children at the time of diagnosis obesity/overweight (mean±SD;years)</td>
<td>7.5±5.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
There was a correlation between individual mean blood phenylalanine concentration and individual mean BMI value (r=0.362; p=0.023) in the obese/overweight group.

**Discussion**

Obesity is a very important health problem and its frequency is increasing worldwide. According to data provided by the Ministry of Health of the Republic of Turkey, the frequency of obesity among children has increased ten-fold compared with the frequency in the seventies. In a study named "The Pro Children", which was carried out in 9 countries in Europe in 2003, the frequency of overweight was found to be 17% in males and 14% in females. In the United States, prevalence of obesity among children 2-19 years old was reported to be 16.3-17%. There are few studies about obesity prevalence among children with PKU and on a phenylalanine-restricted diet. In a study of 236 adults with PKU, the percentages of participants reported having obesity or overweight, were 31% and 24%, respectively. Although those ratios are in accordance with their normal population values, they are two-fold the values that are obtained from previously mentioned larger studies. In a study carried out in Spain, 160 children with PKU were evaluated and, it was found that girls older than 13 years have significantly higher BMI. In a study that evaluates 87 PKU patients from United States, it is reported that girls have two-fold the frequency of obesity and overweight. In our study, we could not find difference between males and females.

In a study that was carried out in 0-18 year-old children, in our country in 2010, the frequency of obesity was 6.9%, and overweight was 14.4%. Subsequent to comparison of these results, we found that obesity frequency is increased in children with PKU. We speculate that, phenylalanine-restricted medical diet with protein supplements and eating disorders which are associated with PKU may be responsible for this increased obesity frequency. However, we currently have no direct evidence to support this thought. Among important limitations of this study, there is no assessment of dietary energy intake of subjects. However, we can say for now, it should be kept in mind that general risk factors for obesity are also relevant for the PKU patient group.

Regarding to blood phenylalanine level and increased obesity risk, conflicting results have been obtained in the literature. In Robertson et al’s study, a positive correlation was found between blood phenylalanine levels and BMI; however, no correlation was found in the study carried out on Spanish children with PKU. In our study, we also have found a correlation between blood phenylalanine concentrations and BMI values in obese/overweight children with PKU/HPA who underwent phenylalanine-restricted diet treatment.

The effect of phenylalanine-restricted diet on patients’ metabolism is not clear. One of the most popular explanations is increased carbohydrate intake. Robertson et al stated that they, especially adult patients, consume much more instant foods, prefer fatty food instead of fresh vegetables and fruits and were not willing to exercise. More interestingly, studies on patients on diet show that calorie intake were very close or lower than suggested calorie intake. But the latest data suggest patients’ declarations may not be trustworthy. Therefore, dietary compliance may be followed by growth charts, BMI and/or weight for height. Limitations of our study are the retrospective design, and limited data about dietary compliance and daily exercise levels.

The frequency of obesity, an important health problem, is increasing. In the literature, there are very few studies evaluating obesity and overweight frequencies in PKU patients. According to our results, children with PKU under phenylalanine-restricted diet are at risk for obesity.

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**Authors Contributions**

PG prepared the manuscript. BE, YT, İ, SBA collected the data. YO is co-corresponding author.
Declaration of Conflicting Interest

The authors declared no potential interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

The local ethics committee approved this study.

References

The Clinical and Molecular Spectrum of 15q Duplication Syndrome in Chinese

HM Luk, IFM Lo

Abstract

15q duplication syndrome (OMIM #608636) is a neurodevelopmental disease that characterised by hypotonia, developmental delay, intellectual disability, epilepsy and distinctive facial gestalt. A territory-wide study of 15q duplication syndrome is performed in Hong Kong with aim to examine its clinical and molecular features among Chinese patients. There are total of 12 cyogenetically and molecularly confirmed individuals between the period of January 2011 and December 2015. Four of them have interstitial duplication and 8 of them have isodicentric chromosome 15. The prevalence of 15q duplication syndrome in our Chinese cohort with intellectual disability and autistic spectrum disease is estimated to be 1.0% and 2.9%, respectively. As compared with western population, epilepsy is less common while squint is more prevalent in our Chinese patients. However, no genotype-phenotype correlation can be demonstrated in this study. Conclusion: The prevalence and clinical features of 15q duplication syndrome patients in Hong Kong Chinese are comparable with other western populations. It is hope that by having the better understanding of its underlying pathomechanism and their genotype-phenotype correlation would lead to better management and genetic counselling for patient with 15q duplication syndrome.

Key words

15q duplication syndrome; Chinese; Interstitial duplication 15q11-q13; Isodicentric chromosome 15

Introduction

The chromosome 15q11-q13 region is a complex imprinted region that prone to genomic rearrangement. Within this region, some genes are only expressed on the maternally inherited chromosome 15, like UBE3A and ATP10C; while other genes are only expressed on the paternally inherited chromosome 15, like MKRN3, MAGEL2, NDN, C15orf2, SNURF-SNRPN. Moreover, this region harbours five duplicons or breakpoints (BP) that consisted of large segment low copy repeats (LCR).1,2 Through non-allelic homologous recombination and U-type crossover mechanism,3 various forms of deletion, duplications, triplications, translocations, and supernumerary marker chromosomes (SMC) at proximal chromosome 15q region would result. Depend on the parent-of-origin and the size of rearrangement, such genomic rearrangement would lead to Angelman syndrome, Prader-Willi syndrome and 15q duplication syndrome.

15q duplication syndrome (OMIM #608636) is a clinically recognisable neurogenetic syndrome. It is caused by either interstitial duplication of chromosome 15q11.2 or extra isodicentric chromosome 15(idic(15)(p11.2-13.3)).3 The clinical features included hypotonia, developmental delay, intellectual disability, epilepsy and distinctive facial gestalt. Most affected individuals would meet the diagnostic criteria of autism or autism spectrum disease. Apart from that, some would also develop behavioural problems like anxiety disorder and attention deficit hyperactivity.
disorder.\textsuperscript{3,4} The prevalence of 15q duplication syndrome in autism cohort is estimated to be 1-3\% in early studies.\textsuperscript{5,6} However, the prevalence, comprehensive clinical spectrum and molecular study of 15q duplication syndrome have never been reported in Chinese.

The aim of this study is to summarise the clinical and genetic findings of all cytogenetically and molecularly confirmed 15q duplication syndrome patients in Hong Kong Chinese.

**Patients and Method**

The Clinical Genetic Service (CGS) of Department of Health is the only government funded tertiary genetic referral center that provides comprehensive genetic counselling, diagnostic and laboratory service for the whole of Hong Kong population. More than 95\% of population in Hong Kong is ethnic Chinese. Patients with suspected genetic or syndromic cause of intellectual disability and autism or autism spectrum disease (ASD) are referred for clinical assessment and genetic testing.

In this study, all records of patients with genetically confirmed 15q duplication syndrome between January 2011 and December 2015 under CGS are retrieved from the computer database system. The clinical and laboratory data of these patients are being analysed. The diagnosis of intellectual disability, autism and autistic spectrum disease are made by paediatricians, developmental paediatricians, clinical psychologists or child psychiatrists.

**Cytogenetic and Molecular Study**

The diagnosis of 15q duplication syndrome is confirmed either by standard cytogenetic G banding technique with fluorescence in situ hybridization (FISH) method or array Comparative Genomic Hybridization (aCGH) study. Further molecular studies like microsatellite analysis with parental DNA or methylation-specific multiplex ligation dependent probe amplification (MS-MLPA) is used to delineate the parent-of-origin of the 15q duplication.

**MLPA**

Patients are screened for rearrangements involving the 15q11-q13 region with the ME028 PWS/AS (MRC-Holland, Amsterdam, The Netherlands). The copy number change and methylation status is detected by methylation-sensitive restriction enzyme. Analysis of the MS-MLPA PCR products is performed on an ABI3500 Genetic Analyser using the GeneMapper software (Applied Biosystems, Foster City, Calif., USA). For copy number analysis, the data generated are being intra-normalised by dividing the peak area of each amplification product by the total area of the reference probes. The ratios are then obtained by dividing the intra-normalised probe ratio in a sample by the average intra-normalised probe ratio of all reference runs. For methylation analysis, the intra-normalised peak area of each MS-MLPA probe from the digested sample is divided by the value obtained for the undigested sample.

**Fluorescence In Situ Hybridization (FISH)**

FISH is performed on metaphase chromosome spreads preparations from peripheral blood. Three commercial DNA probes that hybridize to the SNRPN locus at 15q11q13 region, PML locus at 15q22 region and centromere of chromosome 15 at 15p11.2 region from Vysis (Abbott) are being used. Ten metaphase cells are being examined to detect cells with loss or gain of specific signals.

**Microsatellite Analysis**

The microsatellite analysis is studied by using standard protocol. Haplotype analysis is being performed by using eleven polymorphic markers in 15q regions (D15S219, Gabrb3, SC2, 14150, D15S217, M37, SC3, AFM262, AFM323, AFM291 and AFM164). PCR products are visualised with a DNA sequencer and allele sizes are determined by using Genescan and Genotyper software (Applied Biosystems). A positive diagnosis required evidence of unique parental inheritance at ≥informative 2 markers.

![Figure 1](image) The diagnostic algorithm of 15q duplication syndrome in this study.
Array-CGH

High-resolution whole genome analysis is performed by using PerkinElmer CGXTM 8x60K Human Genome microarrays (Agilent Technologies, Santa Clara, CA). This contains approximately 60 000 sixty-mer probes with resolution of 190Kb in the backbone and 28kb average probe spacing. Labelling is performed by using Agilent Genomic DNA enzymatic labelling kit (Agilent Technologies, Santa Clara, CA, USA) and clean-up of labelled genomic DNA is performed by using Amicon ultra 0.5 ml centrifugal filters according to manufacturers' instructions (Millipore, Billerica, MA, USA). Slides are scanned on an Agilent scanner and processed with Feature Extraction software (v10.7). Each patient DNA is labelled in Cy5 and sex matched reference DNA is labelled in Cy3, which then co-hybridized against the array chip. Results are analysed by using Agilent Genomic Workbench (v6.0 and v6.5) software with the following settings: ADM2 as aberration algorithm, threshold of 6.0, moving average 2 Mb. The results are according to Human Genome build 19 and include imbalances with at least three consecutive probes with abnormal log2 ratios. All the imbalances are interpreted by consulting the UCSC genome browser (http://genome.ucsc.edu), Decipher (Database of Chromosomal Imbalance and Phenotype in Humans Using Ensembl Resources - http://decipher.sanger.ac.uk/), ClinGen (Clinical Genome Resource - https://www.clinicalgenome.org/), OMIM (Online Mendelian Inheritance in Man - http://www.ncbi.nlm.nih.gov).

Data Analysis and Statistical Calculation

Epidemiological data, physical characteristics, growth records and molecular findings are then collected for analysis. Clinical photographs are taken during consultation with written consent. For statistical calculation, Fisher's exact test is used for categorical variables. Two-tailed p-values are being computed. Differences are considered to be statistically significant when the p-value is ≤0.05.

Results

During this 5 years’ study period, a total of 1,116 patients with intellectual disability and 313 patients with autism or ASD are being referred to our genetic clinic for assessment. Twelve individuals among 10 families with 15q duplication syndrome are diagnosed. All are ethnic Chinese. Their current age in year 2016 are ranged from 3 years 6 months to 34 years old, with a median of 8 years 2 months old. The male to female ratio was 1:2.

Among them, 11 of them have intellectual disability and 9 of them have autism or ASD. Therefore the prevalence of 15q duplication syndrome in our Chinese cohort with intellectual disability and autism or ASD is 1.0% and 2.9%, respectively.

Concerning the underlying genetic mechanism, 4 of them have interstitial duplication and 8 have isodicentric chromosome 15. Two out of these 8 isodicentric cases are in mosaic pattern with abnormal cell lineage ranged from 50% to 93%. The genomic aberration for all symptomatic cases are maternal inherited in origin, that mean the duplication occur in the maternal allele of chromosome 15. Two families with interstitial duplication are identified in this study and the rest of the cases with genomic aberration that arise de novo. The clinical features of our 15q duplication cohort are summarised in Table 1. The facial profiles of patients in this study are shown in Figure 2.

The clinical features of our Chinese patients are compared with western populations in Table 2. It showed that most of clinical features in our Chinese cohort included dysmorphism, joint laxity, hypotonia, intellectual disability and autism are comparable with Caucasian. However, epilepsy is less common while squint is more prevalent in Chinese patients with 15q duplication syndrome.

Discussion

15q duplication syndrome is a neurogenetic syndrome that frequently associated with neurodevelopmental disease. The prevalence of 15q11-q13 duplication in patients with autism is widely assumed to be 1-3% based on two early studies.5,6 With the advancement of genomic technology like aCGH and better understanding in the association of copy number variation (CNV) with human disease. It is now known that approximately 10-20% of patients with intellectual disability and 10% of autism or ASD patients have clinical significant CNVs.18,19 In the latest reviews and meta-analysis, it has found that 15q11-q13 duplication happened in 1% of patients with autism or ASD and 3% of patient with intellectual disability.20,21 The prevalence of 15q duplication in our Chinese cohort with intellectual disability and autism or ASD is 1.0% and 2.9%, respectively.

Concerning on the clinical phenotype, the most consistent features in our study are hypotonia and intellectual disability. About two third of them have facial
dysmorphism and autism. All these are comparable with other studies in the literatures.\textsuperscript{7-17} Epilepsy occurs in 60% of 15q duplication syndrome in the latest survey by Dup 15 alliance with 80% has multiple seizure types and 40% has infantile spasm.\textsuperscript{22} In our cohort, only 33.3% (4/12) of them have epilepsy with tonic-clonic and focal seizure as the most common seizure semiology. Only one of our patients has infantile spasm with the onset at 3 months of age. Despite multiple anticonvulsant, his epilepsy is refractory that currently evolving into Lennox-Gastaut syndrome. For the rest of the patients, the epilepsy is well controlled by one anticonvulsant. Despite pseudosquint are common among Chinese, true squint happen in more than 90% of our patients that is statistically significant different from other ethnic groups.

Chromosome 15q11-q13 region imprinting patterns and its long range gene expression are mediated by imprinting control region (ICR) that located upstream of paternal transcription unit SNRPN gene through the UBE3A gene interaction.\textsuperscript{23} The imprinting and parent-of-origin effect has been well demonstrated by our 2 families with interstitial duplication. By methylation specific-MLPA and microsatellite study, the interstitial 15q 11.2 duplication in the mothers of family 6 and family 10 in our study have confirmed to locate at paternal and maternal allele of chromosome 15, respectively. The mother in family 6 with interstitial 15q11.2 duplication in the paternal allele has normal phenotype, while the mother in family 10 with

<table>
<thead>
<tr>
<th>Family</th>
<th>Sex/age</th>
<th>Rearrangement</th>
<th>Origin</th>
<th>Autism</th>
<th>Hypotonia</th>
<th>Intellectual disability</th>
<th>Epilepsy</th>
<th>Dysmorphism</th>
<th>Joint laxity</th>
<th>Squint</th>
<th>Others</th>
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<tbody>
<tr>
<td>1</td>
<td>F/5yr 4m</td>
<td>idic(15) (p11.2-13.3)</td>
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<td>Yes</td>
<td>Yes</td>
<td>Moderate</td>
<td>No</td>
<td>No</td>
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<td></td>
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<tr>
<td>2</td>
<td>F/22yr 5m</td>
<td>idic(15) (p11.2-13.3)</td>
<td>M</td>
<td>Yes</td>
<td>Yes</td>
<td>Mild</td>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Behavioural Problems on SSRI</td>
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<td>3</td>
<td>F/17yr 1m</td>
<td>mos. idic(15) (p11.2-13.3)(93%)</td>
<td>M</td>
<td>No</td>
<td>Yes</td>
<td>Mild</td>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>4</td>
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<td>M</td>
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<td>Yes</td>
<td>Moderate</td>
<td>Tonic-clonic, focal seizure since 5 yr</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>5</td>
<td>F/27yr 4m</td>
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<td>Yes</td>
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<td>interstitial duplication 15q11.2q11.2</td>
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<td>7</td>
<td>F/4yr 9m</td>
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<td>Yes</td>
<td>Moderate</td>
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<td>Yes</td>
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<td>8</td>
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<td>9</td>
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<td>idic(15) (p11.2-13.3)</td>
<td>M</td>
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<td>yes</td>
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<td>No</td>
<td>Yes</td>
<td>No</td>
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</tbody>
</table>

M: maternal; P: paternal; mos: mosaic; SSRI: selective serotonin reuptake inhibitors
inherited interstitial 15q11.2 duplication in the maternal allele has hypotonia and mild intellectual disability. Maternal duplication of the UBE3A gene is the proposed mechanism for such imprinting effect.24,25

For the genotype-phenotype correlation, a dosage effect on 15q11-q13 copies to clinical severity has been demonstrated in previous studies.13,16,26 The clinical presentation for isodicentric chromosome 15 with 4 copies of SNRPN gene is more severe than interstitial duplication with 3 copies of SNRPN gene. The mitigating effect of mosaic 15q duplication has also been reported which depend on the percentage and type of cell line involved. However, such correlation cannot be shown in our Chinese cohort due to small sample size. The phenotypic spectrum and severity among those isodicentric chromosome 15, interstitial duplication and mosaic isodicentric chromosome 15 are similar in this study.

Concerning on recurrence risk and genetic counselling, for isodicentric chromosome 15, it usually arise denovo that recurrence risk in family is negligible. For interstitial duplication, the inheritance risk to offspring from affected proband is 50%. Due to genomic imprinting, the phenotypic effect depends on the parent-of-origin. Duplication in the maternal allele of chromosome 15 has high risk of developing neurodevelopmental disease and epilepsy, while duplication in the paternal allele usually phenotypically normal.15,18

Table 2 The prevalence of clinical features in our Chinese cohort and comparison with other studies in the literature2-17

<table>
<thead>
<tr>
<th>Feature</th>
<th>Our study (total 12)</th>
<th>Literatures</th>
<th>P value</th>
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<tr>
<td>Autism</td>
<td>9 (75%)</td>
<td>84% (25-100%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypotonia</td>
<td>11 (91.7%)</td>
<td>82% (72-100%)</td>
<td>NS</td>
</tr>
<tr>
<td>Intellectual delay</td>
<td>11 (91.7%)</td>
<td>100%</td>
<td>NS</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>4 (33.3%)</td>
<td>79% (50-100%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Dysmorphism</td>
<td>8 (66.7%)</td>
<td>73% (20-100%)</td>
<td>NS</td>
</tr>
<tr>
<td>Joint laxity</td>
<td>7 (58.3%)</td>
<td>50% (12.5-64%)</td>
<td>NS</td>
</tr>
<tr>
<td>Squint</td>
<td>11 (91.7%)</td>
<td>41% (25-44%)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

NS: not statistically significant

Figure 2 The facial profile of patients with 15q duplication syndrome in our study. Patients 6, 8 and 10 have interstitial 15q duplication while the rest have isodicentric chromosome 15. The dysmorphic features included high forehead, epicanthic folds, squint, short nose and depressed nasal bridge (Consents have been obtained for publication).
Conclusion

This 5 years' review is the first territory-wide study of 15q duplication syndrome in Chinese. It showed that the incidence and clinical features of Chinese 15q duplication are comparable with other western populations. The prevalence of 15q duplication in our Chinese cohort with intellectual disability and autism or autistic spectrum disease is 1.0% and 2.9%, respectively. Early diagnosis is important for managing 15q duplication patients as they have high risk of developing epilepsy and neurodevelopmental disorder that anticipatory guidance from different specialties is essential. Genetic confirmation on the underlying mechanism for 15q duplication is also important for reproductive risk assessment.

Acknowledgement

We thank all the paediatricians and physicians who have referred their 15q duplication syndrome patients to our service. We are also grateful to all the laboratory staff in CGS for their technical support.

Conflict of interest

We have no conflict of interest to declare.

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13. Battaglia A. The inv dup (15) or idic (15) syndrome (Tetrasomy 15q). Orphanet J Rare Dis 2008;3:30.
Case Report

Rare Clinical Presentation of Intestinal Malrotation After Neonatal Period: Protein-losing Enteropathy Symptoms Due to Chronic Midgut Malrotation

YH Fang, SQ Shang, J Chen

Abstract

Protein-losing enteropathy is caused by a variety of diseases. However, it is rarely caused by chronic intestinal malrotation. A 1-year-11-month old male baby and a 12-year-old female presented with chronic diarrhoea and hypoproteinaemia. Both of the patients underwent an exploratory laparotomy, in which a midgut malrotation was discovered. Intestinal malrotation should be considered as one of the differentials when diagnosing protein-losing enteropathy.

Key words

Diarrhoea; Hypoproteinaemia; Intestinal malrotation; Laparotomy

Introduction

Intestinal malrotation is a congenital anomaly, which is mainly diagnosed during infancy. The presenting malrotation symptoms are mainly bilious vomiting, abdominal distention, and incomplete or complete intestinal obstruction. Protein-losing enteropathy (PLE) is rarely caused by chronic intestinal malrotation. Here, we present two cases, a 1-year-11-month old male baby and a 12-year-old female, who presented with chronic diarrhoea and hypoproteinaemia. Both of the patients underwent an exploratory laparotomy, which confirmed midgut malrotation.

Case Report

Case one was a 1-year-11-month old male baby with a chief complaint of recurrent diarrhoea for six months and a decreased level of serum albumin for five months. The patient had watery diarrhoea for six months, with 5-6 bowel movements per day, which was accompanied by a mild fever. After being admitted into the ward, the laboratory examinations revealed a decreased level of serum albumin (17.6 g/L), while the complete blood count was normal. The faecal tests for pathogens were all negative, and the liver and renal functions were normal. There was no significant finding during gastroendoscopy or colonoscopy. A gastrointestinal contrast indicated intestinal malrotation. An abdominal computed tomography (CT) scan confirmed that the mesenteric vessels presenting as a "whirl sign" (Figure 1). During the physical examination, his vital signs were stable, the weight of the patient was 12.4 kg, and the height was 89 cm. Lung and cardiac auscultation were normal. No abdominal tenderness was present during abdominal palpation, nor was there evidence of hepatosplenomegaly or oedema of the lower limbs. And then he underwent an exploratory laparotomy, in which a midgut malrotation with mesenteric swelling and narrowing was discovered. He underwent the Ladd procedure and recovered.

Case two was a 12-year-old female who presented with a primary complaint of an intermittent fever and diarrhoea occurring for six months and lower limbs oedema over a
period of 12 days. The patient had intermittent fever accompanied with diarrhoea for six months, 2-3 mushy stools per day, and mild abdominal pain. The laboratory test showed decreased serum albumin level 20 days ago, and she presented with lower limbs oedema 12 days ago. During the physical examination, her vital signs were stable at the time of admission, the weight of the patient was 33 kg. The lung and heart sounds were normal. The patient had abdominal distension with a positive shifting dullness. Her face, abdominal skin, and lower limbs had pitting oedema. The albumin level was 8.5 g/L, while the complete blood count was normal. The electrolyte analysis revealed mild hypokalaemia and hyponatraemia. There were no significant findings during the gastroendoscopy and the colonoscopy. She underwent surgery, which confirmed a midgut rotation with volvulus; the duodenum and ascending colon were compressed by Ladd's bands.

Discussion

PLE is caused by a variety of diseases, such as primary and secondary lymphangiectasia, intestinal inflammation, vasculitic disorders, and tumour. Intestinal malrotation is a congenital anomaly that results from an abnormal or incomplete rotation and fixation of the midgut during embryonic development. Approximately 75% to 85% of these patients are diagnosed during infancy. The symptoms of malrotation include bilious vomiting, abdominal distention, and incomplete or complete intestinal obstruction. About one-third of intestinal malrotation cases are diagnosed beyond the period of infancy. The chronic presentation is a diagnostic challenge. The chronic intestinal malrotation symptoms in older patients usually include either atypical symptoms, such as abdominal pain, nonbillious vomiting, failure to thrive, malabsorption, anaemia, chylous diarrhoea or a lack of any clinical symptoms, and is only discovered during surgery for other diseases. The pathophysiology of these chronic symptoms may relate to the compressive effects of the peritoneal bands running from cecum and ascending colon to the right lateral wall. In the study of Nilesh G, recurrent colicky abdominal pain (61.9%), nonbillious vomiting (38.1%), and failure to thrive/weight loss (33.3%) were the most common presentations of the older patients. Other older patients in this study presented with early satiety, abdominal bloating, acute pancreatitis or acute small intestinal obstruction, and some were diagnosed with malrotation intraperatively.

The diagnosis of intestinal malrotation is mainly based on the typical clinical manifestations. An upper gastrointestinal contrast study is diagnostic for malrotation in most patients. Ultrasonography can reveal either an abnormal relationship of the superior mesenteric artery (SMA) and vein or a classic whirlpool sign of the midgut volvulus for some patients. Contrast CT scan is needed to confirm or differentiate a diagnosis, and sometimes is helpful in assessing mesenteric ischaemia. The characteristic appearance of a twisted mesentery, collapsed small bowel loops, and mesenteric fat wrapped around the SMA is pathognomonic for malrotation and is commonly referred to as the "whirl sign" or "clockwise whirlpool sign". Intestinal malrotation with chronic symptoms usually need surgery as soon as possible in case of intestinal volvulus. Emergence surgery would be more complicate than elective operation, including life-threatening bowel necrosis requiring an extensive small intestinal resection.

It is rare that intestinal malrotation presents with protein losing enteropathy symptoms. Protein losing enteropathy can be caused secondary to either lymphatic obstruction or intestinal lymphangiectasia as a result of malrotation. To our knowledge, there are only two case reports documenting a malrotation-induced protein-losing enteropathy. One case was a 17-month-old boy presenting with hypoalbuminaemia, peripheral oedema, diarrhoea, and failure to thrive since 9 months of age. His laboratory analyses revealed a low serum level of albumin and a lymphopenia without sings of lymphangiectasia. A CT of the abdomen revealed a whirlpool sign and suggested an incomplete vascular volvulus. During the laparotomy, chronic midgut volvulus was discovered.
with a 180° twisting of the jejunum and the superior mesenteric vessels causing a lymphatic obstruction and leakage of milky white lymph into the cut surfaces of the mesentery.  

Morozov et al reported a young Russian male patient with protein-losing enteropathy, who was diagnosed a malrotation of the duodenum with recurrent midgut volvulus causing secondary intestinal lymphangiectasia.  

The two cases reported identified either lymphatic obstruction or lymphangiectasia. However, in our cases, we did not find any evidence of lymphangiectasia or lymphatic obstruction. Although intestinal malrotation is rare beyond the age of infancy, it should be considered as an atypical manifestation. For protein losing enteropathy, intestinal malrotation should be added as one of the causes of the disease.

Conclusion

To conclude, an intestinal malrotation should be suspected in all patients presenting with varied acute or chronic abdominal symptoms. Intestinal malrotation should be considered as one of the differentials when diagnosing protein losing enteropathy.

Acknowledgements

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Conflicts of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

Case Report

An Extramural Duodenal Ectopic Pancreas Mimicking an Exophytic Pancreatic Tumour in an Adolescent

YH Wu, CW Chen, YT Chang

Abstract

Ectopic pancreatic tissues are rare anomalies and are usually submucosal lesions most commonly located in the stomach and proximal small intestine. The authors herein describe an uncommon case of an extramural duodenal ectopic pancreatic tissue, which was misinterpreted as an exophytic pancreatic tumour on imaging examination. Laparoscopy was undertaken because of unresolved symptoms, and the ectopic pancreatic tissue was located beyond the duodenal submucosal and muscular layer on pathologic examination.

Key words
Adolescent; Duodenal ectopic pancreatic tissue; Laparoscopy

Introduction

Ectopic duodenal pancreatic tissues account for approximately 17%-36.3% of all ectopic pancreatic tissues, and usually appear as intraluminal protrusions with normal overlying mucosa. The description of an extramural location has been rarely reported in the literature. Herein we present such a case, of a female adolescent, successfully managed by laparoscopic excision of an extramural duodenal pancreatic tissue.

Case Report

A 15-year-old female had suffered from recurrent episodes of moderate to severe epigastralgia and feeding intolerance for the past two years. She was admitted with the complaint of these symptoms increasing in intensity over the recent week. Physical examination of the abdomen noted marked tenderness localised to the upper abdomen without pain radiation to the back. There was neither distention nor any palpable masses observed. The haemoglobin level was 14.4 g/dL, and total white blood cell count was $6.70 \times 10^9$/L. The platelet count was $221 \times 10^9$/L, and C-reactive protein was undetectable. Serum amylase was 136 U/L, and lipase was 22 IU/L. The upper gastrointestinal X-ray series showed normal filling and gastric and duodenal mucosal folds. Endoscopic ultrasound disclosed a narrowing of the first portion of the duodenum. A nodular lesion with calcified change was noted at the head of the pancreas close to the portal vein. Abdominal computed tomography showed a soft tissue lesion below duodenal bulb which similar enhancement pattern as the pancreas (Figure 1). Magnetic resonance image showed that there was an exophytic pancreatic tissue at pancreas head with compression to adjacent gastrointestinal tract.

Because of persistent symptoms and the abnormal image findings, it was decided that a surgical intervention should be performed; and a laparoscopic approach was elected. The patient was placed in a supine modified lithotomy...
position with the surgeon standing between the legs. Laparoscopy was performed with a 5-mm Hasson port at the umbilicus, and video laparoscopy was performed with a 5-mm 30-degree laparoscope (Karl Storz GmbH, Tuttlingen, Germany). Two additional 5-mm working ports at the right and left middle subcostal regions were placed. Initially, Harmonic scalpel (Ethicon Endosurgery, Cincinnati, Ohio, USA) was used for the division of the gastrocolic ligament to expose the lesion. However, the mass was found to be located over the first portion of the duodenum (Figure 2). Therefore, resection of the tumour and wedge resection of the duodenum were performed. The anastomosis of the duodenum was performed intracorporeally. Operative time was 80 minutes, and blood loss was estimated as 10 mL without blood transfusion. The patient was discharged 10 days after operation and continued to remain free of epigastric pain on two-year follow-up at our outpatient clinic.

Histology confirmed the diagnosis of heterotopic pancreas. Macroscopically, the specimen consisted of one tissue fragment measuring 4 cm × 2 cm × 0.7 cm in diameter. Cut sections of the specimen displayed a normal pancreas with lobular arrangement. On microscopic examination, it showed an ectopic pancreatic tissue beyond the duodenal submucosal and muscular layers, composed of typical islets of Langerhans scattered in the exocrine pancreas (Figure 2).

Discussion

Heterotopic pancreatic tissue, first described by Jean Schultz in 1727, is a relatively uncommon tumour, accounting for 1% to 2% in an autopsy series. It usually remains asymptomatic throughout life and is found incidentally during gastroendoscopy or other imaging modalities in patients between 40 and 70 years of age, and sometimes has nonspecific clinical manifestations. According to Heinrich classification system, ectopic pancreas can be classified into three types under microscopy: type 1 (endocrine and exocrine element: acini, ducts, and islet cells), type 2 (exocrine element: acini and ducts) and type 3 (only ducts). Our case was considered to be the type 1 heterotopic pancreas which contains all components
Duodenal Ectopic Pancreas

... of pancreas. Although previously considered benign, reports of ductal adenocarcinoma arising in ectopic pancreas have been published.7

The most common sites of the ectopic pancreas include the stomach (25%-38.2%), duodenum (17%-36.3%) and jejunum (15%-21.7%).1,2 However, it has also been reported in the lungs, gallbladder, mediastinum, mesentery, oesophagus, bile ducts and umbilical cord.1 Of the alimentary tract, ectopic pancreas is typically a submucosal mass covered by normal mucosa.1 Endoscopic ultrasonography is the mainstay of imaging modalities in the detection the neoplasm located in the stomach and first and second portions of the duodenum.1 Unlike submucosal localisation of other reported ectopic pancreatic tissues, the lesion at our present case originated from the submucosal layer and extended extramurally.

Some papers have mentioned that the operation technique and patient selection might be made on the basis of location and size of lesion and the patient's comorbidities. The optimal treatment for asymptomatic lesions of ectopic pancreatic tissue is not well defined. Also, laparotomy should be considered if there are emergency complications secondary to ectopic pancreas such as intussusception or peritonitis.8 However, these reports relate mostly to gastric ectopic pancreas. Currently, there is still no clear consensus guideline for the treatment of duodenal ectopic pancreas. With refinements in minimally invasive surgery, laparoscopy in the treatment of ectopic pancreas was first reported in 2002.5 This, however, appears to be the first report of complete laparoscopic excision of a duodenal ectopic pancreas in an adolescent.

The detailed pre-operative examination including imaging survey and video magnification of the endoscopy can offer surgeons better exposure of the extramural duodenal mass and its surrounding vessels and nerves. Therefore, delicate manoeuvres can be performed to protect nearby important structures during surgery. Despite the present case representing experience within the learning curve and was a time-consuming operation, the laparoscopic approach holds promise for providing advantages seen with minimally invasive approaches in other procedures, such as postoperative recovery and cosmetic considerations.10

Conclusions

This case presents a relatively uncommon clinical problem and is the first case report of successful laparoscopic management in an adolescent with an extramural duodenal ectopic pancreas. Laparoscopic wedge resection for duodenal ectopic pancreas appears to be safe and feasible.

Declaration of Interest

The authors have no conflicts of interest.

References

Reye's Syndrome Arising from the Treatment of Kawasaki Disease

EJ Su, JH Hsieh, CC Hsu, KT Chen

Abstract
We report on a 20-month-old girl who presented with vomiting and lethargy after being discharged from the ward following treatment for Kawasaki disease. The symptoms occurred after five days of aspirin therapy. The clinical features and laboratory tests proved the presence of Reye's syndrome and she recovered after intensive treatment. In addition, we collected three similar reported cases. All the patients came from East Asia and the mortality rate reached 50%. Since salicylate is an effective and imperative treatment for Kawasaki disease, paediatricians and emergency physicians can consider using a low dose of aspirin (3-5 mg/kg) as maintenance therapy, discontinuing aspirin for a short period or replace it with dipyridamole during influenza or varicella epidemics, and having a high index of suspicion of Reye's syndrome in patients with Kawasaki disease.

Key words Aspirin; Complication; Kawasaki disease; Reye's syndrome; Salicylate

Introduction
Reye's syndrome is an acute failure of mitochondria and occurs mainly in childhood. The cause of this severe disease is still uncertain; however, the affected child usually presents with a prodrome of acute viral infection and the use of salicylate during the prodromal illness, followed by an acute encephalopathy, fatty degeneration of the liver, and metabolic decompensation.1-4 In addition, salicylate consumption is correlated with severity of Reye's syndrome.2 After warnings had been issued about the use of salicylates in children with those viral infections, the incidence of Reye's syndrome in the United States declined dramatically.2

However, some children still require long-term use of salicylate, such as those with connective tissue disorders, and these patients run a greater risk of developing Reye's syndrome.2 We report on a 20-month-old girl who developed Reye's syndrome after treatment for Kawasaki disease and review three case reports to demonstrate the unique features of the involved children.

Case
This 20-month-old girl, who was previously well, had suffered from high fever for 5 days and was admitted to Chi-Mei Medical Center. She had a normal birth history (birth weight: 3070 gm, gestation age: full term, via normal
spontaneous delivery), regular vaccinations, negative results of newborn screening for metabolic diseases, and normal growth and development. She was the second child in the family (G2P2A0) with no family history of sudden infant death or inborn errors of metabolism. After admission, she was diagnosed as having Kawasaki disease due to the presence of wheal-like exanthema on the palms and buttocks, erythematous fissured lips and bilateral conjunctivitis as well as leukocytosis (white cell count: 16000/µL) and elevation of C-reactive protein (62.6 mg/dL) in laboratory tests.5 The paediatricians initiated intravenous immunoglobulin at a dose of 2 g/kg and a high dose of oral aspirin of 88/mg/kg per day. The patient's fever subsided after the initiation of treatment and her appetite and activity improved. Echocardiography showed normal coronary arterioles without dilatation. Subsequently, the aspirin dose was reduced to 55 mg/kg per day and she was discharged after 15 days of hospitalisation.

On the next day after discharge, about the fifteenth day after administering the first dose of aspirin, the patient was found with persistent vomiting, drowsiness and fever and was admitted to Chi-Mei Medical Center again. Physical examination of the patient revealed fever, tachycardia, lethargy, decreased muscle tone, and decreased urine output. A computed tomographic scan of the head demonstrated bilateral basal ganglia lesions and cortical swelling. Serum tests revealed hyperammonaemia (214 µg/dL), and elevations of aspartate aminotransferase and alanine aminotransferase (AST: 461 IU/L, ALT: 255 IU/L). Initial differential diagnosis included aspirin intoxication and Reye's syndrome, and therefore aspirin was discontinued immediately. The patient was transferred to National Cheng Kung University Hospital because of progression to coma status. A subsequent lumbar puncture found increased intracranial pressure (35 cm H 2O) and the analysis of cerebral spinal fluid showed negative results for bacterial or viral infection. A hepatic biopsy demonstrated typical manifestations of Reye's syndrome. The patient underwent tracheal intubation and mechanical ventilation for coma, supportive treatment for metabolic derangement, intravenous mannitol for cerebral oedema, and continuous veno-venous haemofiltration to eliminate aspirin. After intensive care, the patient recovered and was discharged after two weeks of hospitalisation without permanent sequelae.

Discussion

Nowadays, high-dose aspirin (80 to 100 mg/kg per day) and intravenous immunoglobulin are recommended as the initial treatment for Kawasaki disease, followed by a reduction of the aspirin dose after the child has been afebrile for 48 to 72 hours. The therapy effectively reduces the rate of subsequent ischaemic heart disease and sudden death.5 However, children who undergo aspirin treatment carry additional risk of Reye's syndrome. Except this presented case, we discovered another three patients with Reye's syndrome arising from the treatment of Kawasaki disease. All the reported patients were found in East Asia, three in Taiwan and one in Japan6-8 All the affected children were under two years of age, and included three females and one male. The symptoms of Reye's syndrome appeared within 15 days after the initiation of salicylate therapy. The presented symptoms included vomiting, poor appetite, decreased activity, hepatomegaly, and lethargy. Two of the four reported cases died (50% mortality rate) (Table 1).

Takahashi and Mason indicated that the subset of children most susceptible to Kawasaki disease (Asians younger than four years of age) and the subset most susceptible to Reye's syndrome (white children older than six years of age) do not overlap.9 The lack of overlap in the two groups of affected children might explain the low incidence of Reye's syndrome occurring in Kawasaki disease. With regard to the benefit of cardiovascular effects, children with Kawasaki disease should still undergo salicylate treatment. Though the absence of evidence concerning the correlation between incidence of Reye's syndrome and dosage of aspirin, the authors proposed that the dosage of salicylate should be kept as low as possible. In addition, the study by Saulsbury et al showed that low-dose aspirin (3-5 mg/kg) is as effective

Table 1 The clinical manifestations among three reported cases (Nejihashi 1980, Lee 1991 and Wei 2005) and our presented patient (Su 2012)

<table>
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<td>Age (month)</td>
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<tr>
<td>Gender</td>
<td>F</td>
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<td>F</td>
</tr>
<tr>
<td>Aspirin administration (day)*</td>
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<td>4</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>Dose of aspirin (mg/kg/day)†</td>
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<td>10</td>
<td>3-5</td>
<td>55</td>
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<tr>
<td>Mortality</td>
<td>Expired</td>
<td>Expired</td>
<td>Alive</td>
<td>Alive</td>
</tr>
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*symptoms of Reye's syndrome after the initiation of aspirin therapy
†maintenance dose of aspirin
as high-dose aspirin therapy. Because most Reye's syndrome children have a prodrome of viral infection, those who undergo long-term salicylate treatment can discontinue aspirin for a short period or replace it with dipyridamole during influenza or varicella epidemics. In addition, those children who undergo salicylate therapy should be observing closely for symptoms of Reye's syndrome within 15 days after initiation treatment.

Though rare, Reye's syndrome arising from the treatment of Kawasaki disease does occur. Since salicylate is an effective and imperative treatment for Kawasaki disease, paediatricians and emergency physicians can consider using low doses of aspirin (3-5 mg/kg) as maintenance therapy, discontinuing aspirin for a short period or replace it with dipyridamole during influenza or varicella epidemics, and having a high index of suspicion of Reye's syndrome in patients with Kawasaki disease.

**Declaration of Interest**

The authors have no conflicts of interest.

**References**

Case Report

Denys Drash Syndrome, What Paediatrician Should Know About?

AKH Kwok, SMY Wong, MT Leung, WKY Chan

Abstract

We report on a boy with known bilateral undescended testes who was incidentally detected to have proteinuria on a routine pre-operative assessment. Further investigations confirmed childhood nephrotic syndrome. Because of atypical features, an early ultrasound kidney was arranged and it showed bilateral nephroblastomatosis. His karyotype was 46XY. Further DNA analysis showed a heterozygous mutation in Wilms tumour suppressor gene 1 (WT1 gene). A diagnosis of Denys Drash syndrome was made and he underwent treatment for Wilm's tumour.

Key words

Denys-Drash syndrome; Genes, Nephrotic syndrome; Pseudohermaphroditism; Wilms tumour; WT1 proteins

Case Report

LCY, an 18-month-old boy, was born full term with normal spontaneous delivery. His neonatal history was uneventful except he was noted to have bilateral undescended testes. His scrotum was well formed and penile length was normal. Both testes were high in the inguinal canals. He was well until 14 months of age. He was admitted for bilateral orchidopexy. Pre-operative assessment showed puffy eyelids with blood pressure 130/90 mmHg and urine albumin 3+ for protein. His body weight was above 97th percentile and body height was 75th percentile. Subsequent work up showed serum albumin 18 gram/L (normal range: 38-54 gram/L). 24-hour urine protein was 3.49 gram/day (normal range: <0.1 gram/day). Cholesterol was 4.9 mmol/L. Serum urea was 6.0 mmol/L (normal range: 1.8-6.4 mmol/L), serum creatinine was 36 umol/L (normal range: 21-36 umol/L). Anti-nuclear antibody, anti-neutrophil cytoplasmic antibody and anti-dsDNA were negative. C3 and C4 levels were normal. Ultrasound of kidneys showed multiple hypoechoic nodules on bilateral kidneys suggestive of nephroblastomatosis. CT abdomen showed multiple hypodense hypoenhancing mass lesions in both kidneys, the largest hypodense lesion measures 3.8 cm in right lower pole. The findings were consistent with bilateral nephroblastomatosis. In view of early onset nephrotic syndrome with bilateral renal tumour and undescended testes, karyotype study and genetic work up for WT1 mutation were performed. It showed heterozygous mutation in WT1 gene (NM_024426.3(WT1):c.1384C>T; changing codon 462 from arginine to tryptophan, i.e. p.Arg462Trp) (Figure 1). Karyotyping of patient was 46XY. WT1 mutation screenings for parents were negative. Our patient was started on angiotensin-converting enzyme inhibitor, calcium channel blocker and vasodilator for hypertension and heavy proteinuria. Options of prophylactic bilateral nephrectomy,
versus renal salvage approach for nephroblastomatosis with adjuvant chemotherapy were discussed with parents.

In view of the rapid growth in renal mass, LCY underwent 4 cycles of neo-adjuvant chemotherapy with intravenous Actinomycin D 550 microgram and intravenous Vincristine 0.75 mg once per week. MRI abdomen afterwards showed resolved lesions over left kidney but mild enlargement in right lower pole lesion. Right total nephrectomy was done 2 months after presentation, an 8x7 cm right renal tumour with multiple lymph nodes on the inferior vena cava (IVC) excised. Pathology showed triphasic nephroblastoma with clear margins. There were no malignant cells in the lymph nodes. Renal histology confirmed diffuse mesangial sclerosis with mild global glomerulosclerosis and mild chronic tubulointerstitial injury (Figure 2).

Patient was put on chemotherapy according to the SIOP (International Society of Pediatric Oncology) nephroblastoma clinical trial 2001 protocol, intermediate risk arm. His chemotherapy comprises of weekly injection of intravenous actinomycin D and/or vincristine. He suffered from several infective complications. His nephrotic syndrome was treated with regular albumin transfusion and ACEI. Renal function however, was noted to be gradually deteriorating over a few months. His creatinine rose from baseline of 25-35 umol/L to 100-110 umol/L over 5 months. His latest estimated glomerular filtration rate by Schwartz formula is 28 ml/min/1.73 m². His condition remained stable initially but progressive renal failure is anticipated and he is having his scheduled chemotherapy with close monitoring of renal function.

Discussion

Denys-Drash syndrome (OMIM 194080) was first described in 1967 as a triad of 46XY pseudohermaphroditism, nephrotic syndrome due to diffuse mesangial sclerosis and predisposition to unilateral or bilateral Wilms tumour and gonadoblastomas. Denys-Drash syndrome (DDS) is caused by inactivating mutations in the WT1 gene, which is located on chromosome 11p13 and encodes a zinc-finger DNA-binding protein that acts as a transcriptional activator or repressor. The gene is expressed in a wide variety of embryonic tissue including the mesenchymal cells of the foetal kidney, and the stromal cells of the gonads and spleen. It is thus essential in normal formation of the kidney and genital/urinary system. Different mutations in WT1 gene lead to a spectrum of different phenotypes including DDS, Frasier syndrome (FS) or isolated steroid-resistant nephrotic syndrome.

Classically, DDS and FS are two separate entities with different clinical features. DDS patients have early onset nephrotic syndrome during infancy due to diffuse mesangial sclerosis, with rapid progression to renal failure. In contrast, FS patients have nephrotic syndrome due to focal segmental glomerulosclerosis in the second to third decade of life. DDS patients are prone to Wilms' tumour whilst FS patients are prone to gonadoblastoma. DDS and FS are both known to be related to gonadal dysgenesis. DDS patients have 46XY
partial gonadal dysgenesis, with variable external phenotype depending on the degree of testicular function. The phenotype can range from ambiguous genitalia, under-virilized male to normal male phenotype with reduced sperm production. In contrast, FS patients have 46XY complete gonadal dysgenesis. They have normal Mullerian structures with bilateral streak gonads due to the lack of gonadal steroid production.6,7 Our DDS patient is genetically XY and he had bilateral undescended testes. In a local case report by Chan et al,8 a post-renal transplant patient presented with delayed pubertal development at the age of 15 years. She had a normal female phenotype but karyotype was 46XY. DNA analysis confirmed diagnosis of Frasier syndrome.

Since the 1990s, more than 80 mutations have been reported in DDS patients. Missense mutations in exons 8 and 9 are the commonest identified mutations, with truncating mutations also described. There is significant evidence to suggest genotype/phenotype correlation in DDS mutation patients. Patients with missense mutations in exons have onset of proteinuria at median age of 6 months, which is much earlier than those with truncating mutations and intron mutations. They also progress more rapidly toward end stage renal disease (ESRD), with need for renal replacement therapy (RRT) at median age of 1.1 years.5

Our patient has the classical genotype and phenotype described in DDS. However, he presented to us with undescended testes which is a common paediatric problem which could hardly be linked to this rare disorder at the beginning. His nephrotic syndrome was subtle too as he was asymptomatic and was only picked up by a careful physical

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**Figure 2**  (a) The pale looking circumscribed tumour was seen in the lower pole of right bivalved kidney. (b) H&E 4x view showed the intralobar nephroblastomatosis which was a feature of nephroblastoma seen in patients with WT1 mutation. (c) H&E 10x view showed the immature glomeruli which were of smaller size as compared with “normally developed glomeruli” and had parietal epithelial cells with high nuclei-cytoplasm ratio in the periphery of the glomeruli. (d) H&E 20x view showed the diffuse mesangial sclerosis in this glomerulus with parietal epithelial cells proliferation and these cells composed of podocytes with vacuolated nuclei.
examination and laboratory test. DDS only came to our mind when he was detected to have early onset of nephrotic syndrome. The presentation was subtle and an early ultrasound helped to pick up the renal tumour which pointed to the rare diagnosis of DDS.

Genetic test was arranged after detection of nephrotic syndrome and bilateral nephroblastomatosis. Within a few days' time, DDS was confirmed by detection of the missense mutation c.1384C>T, which is one of the most described mutations amongst DDS patients. The genetic test result sufficed to imaging findings suggestive of Wilm's tumour. It also provides a realistic expectation towards management goal and parent counselling during the gradual deterioration of renal disease.

The management of renal condition in DDS patients is challenging. Diffuse mesangial sclerosis is reported to be resistant to steroids and immunosuppressive drugs. Careful monitoring of disease, adequate nutrition, medical treatment for hypertension and proteinuria are all important to slow the declining renal function.

Nephrectomy with adjuvant chemotherapy is the mainstay of treatment for DDS patients with Wilms' tumour. Bilateral nephrectomy is recommended for DDS patients with ESRD. For those without Wilm's tumour or ESRD upon diagnosis, timing for nephrectomy is debatable. Some authors prefer "early" bilateral nephrectomy in view of the high risk for Wilms' tumour. Other authors suggest delaying nephrectomy until onset of ESRD, with careful monitoring of patients every 4 to 6 months by abdominal ultrasonography.

Both diffuse mesangial sclerosis and Wilms' tumour contribute to an inevitable progression to ESRD in DDS patients. Renal replacement therapy is eventually needed. Outcomes of children with Wilms' tumour and DDS who proceeded to renal transplantation are comparable with children with other diagnoses, with no graft failures because of recurrence. It is generally recommended to wait 1 to 2 years after completion of chemotherapy for Wilms' tumour. However, studies have shown a high early mortality before renal transplant. Questions have thus been raised upon the optimal timing of renal transplant.

DDS is a complex disease which requires good collaboration amongst various disciplines, including paediatrician, nephrologist, oncologist, endocrinologist, geneticist, and vast nursing and social support. Thorough counseling with the family on management options is mandatory.

Conclusion

DDS is a rare but important entity that should not be missed. Our patient illustrates that, while nephrotic syndrome is common in children, clinicians should be particularly aware of the possibility of rare causes like DDS, especially in those with early onset nephrotic syndrome and ambiguous external genitalia. DNA analysis is a useful means of confirming the diagnosis.

Declaration of Interest

All authors do not have any financial and personal relationships with other people or organisations that could inappropriately influence their work.

References

Commentary

Integrative, Integrated Medicine But No Integration: Tarnishing Steroid and Chinese Medicine is Vanity

KL Hon, AKC Leung

On June 21, 2017, the Department of Health (DH) of the Hong Kong Government urged clients who consulted a registered Chinese medicine practitioner (CMP) not to use creams prescribed by that CMP as the creams were suspected to contain undeclared Western medicine (WM) ingredients. The investigation followed complaints of skin hypopigmentation of two 6-month-old male infants whose parents had applied on their infants unlabeled bottles of brownish grey cream prescribed by the CMP for the treatment of eczema. Part 1 poisons clobetasol propionate and miconazole were detected in the cream. The DH's officers conducted investigations in the premises concerned for the possible source of the ingredients. Compared with adults, children are at higher risk of both local and systemic effects. According to the Pharmacy and Poisons Ordinance (Cap 138), illegal sale or possession of Part I poisons are criminal offences. The maximum penalty for each offence is a fine of HK$100,000 and two years' imprisonment. The DH has set up a hotline and has referred the case to the Chinese Medicine Council of Hong Kong for possible disciplinary actions. The CMP responded to reporters that the cream would not have been prescribed if he knew that it contained corticosteroid (CS), indirect implying that CS is an evil product and he was also a victim. Within the same period, another CMP in the same district was reported to prescribe CS to young children with eczema. A mini-outbreak of CS phobia occurred involving over two hundred anxious parents phoning DH for consultation. The DH issued letters to all CMPs and Chinese medicine associations to alert them to these recent cases. They were again reminded that CMPs must not prescribe Chinese medicines (CM) which contain WM to their patients as such act violates the laws and endangers public safety and health.

The incidents reflect the ongoing dilemma of non-integration of medical disciplines.

From time to time, the local media report cases of illegal prescription of CS to children with eczema by CMPs, some of them were depicted figuratively as "divine doctor for childbirth", "holy hand for eczema" and "father of naturopathy" etc. Physicians should be aware that unregistered CM can contain potent drugs such as CS. Like asthma and allergic rhinitis, childhood eczema is a common atopic disease which is associated with chronicity and impaired quality of life of the patients and their families. Management includes patient education, avoidance of triggers, optimal skin care through the regular use of emollient, appropriate use of topical CS, antihistamines, and even immunotherapy. Nevertheless, fears and non-adherence on various therapeutic aspects of WM prevail and management of this disease remains suboptimal. CS is the cornerstone of treatment during disease flare. Steroid phobia, however, has overwhelmingly counter-benefited the therapeutic efficacy of CS. In Hong Kong, many parents would seek alternative and folklore treatment of unproven efficacy, possibly because of their dissatisfaction with current WM treatment. Paradoxically, some of these alternative treatments may knowingly or unknowingly contain potent CS, and definitely unknowingly used by steroid-phobic parents. Many steroid-phobic parents are very skeptical about WM. In parallel to this
skepticism and non-trust, many citizens idolize complementary and alternative medicine (CAM) and believe that traditional Chinese medicine (TCM) and herbs are without much side effects. Many parents would purchase proprietary topical and oral preparations without knowing what they are, and use them liberally and indiscriminately on their children. Pressed by public's quest for efficacious and safe treatment and lucrative profits, CAM practitioners may risk prescribing CS and "WM" in the name of TCM. Hence, despite the prevalence of "steroid phobia" which may lead to the suboptimal use of prescribed topical CS, parents might unknowingly use over-the-counter potent CS and TCM which contains CS.

Eminent CMPs are especially tempted to prescribe CS to preserve their reputation that CM is efficacious as panacea treatment of any disease. It is difficult to convince anxious steroid-phobic parents to be vigilant in the use of often adulterated proprietary CM. Nevertheless, government and the media play important roles not to disgrace CM and tarnish CS usage. Scientifically, CM is an important branch of medicine, and topical or systemic CS is a very important class of immunomodulating and anti-inflammatory medication. The authors believe that in Hong Kong, both CM and CS have complementary roles in disease management and that the important and fashionable concept of integrative medicine (IM) is worth promoting. Tarnishing CS or CM usage certainly does not help with the already evil image of CS among steroid phobic parents. As a matter of fact, combining treatment with WM and CM has benefits in the treatment of atopic dermatitis because such treatment may prevent the adverse reactions induced by WM, while improving the efficacy of WM. WM and CM practitioners and the media should therefore work together to promote correct public health education on this important class of medicine. Western medicine practitioners should be more knowledgeable about CM and vice versa for CMPs. Both Western medicine practitioners and CMPs should pay attention to the interactions between WMs and CMs because CMs can affect the pharmacokinetic properties of WMs. Our common enemy is the naive belief by the naive parents that exclusive CM is the ultimate and safe solution for eczema. Money is not evil but the love of money is the root of all evil. In this regard, CS is definitely not an evil.

Notorious Examples of Non-integration

Attention of Hong Kong physicians was aroused when news broke out on December 17, 2015 that a 23-year-old man with eczema jumped off his apartment window and found dead whilst his mother was preparing herbal medicine decoction for him in the sitting room. There is no lack of dermatologists, allergists, internists, family medicine practitioners, CAM practitioners, and CMPs in Hong Kong for this common childhood condition. It is unacceptable that the patient should suffer and die of this miserable condition where treatment is readily available.

In Australia, an infant with eczema was denied WM and the parents exclusively used CAM. The homeopathy couple was jailed over their daughter's death. The daughter died of malnutrition and sepsis after the parents chose to use homeopathic remedies rather than conventional medicine to treat their daughter's severe skin disorder. Similarly, a tragic case was reported of an infant with eczema who died of group B streptococcus septicemia and malnutrition despite expensive dietary supplements. These tragic cases of "status eczematicus", defined arbitrarily as eczema exacerbation that does not respond adequately to ordinary therapeutic measures and usually requires hospitalisation, serve to remind us the grave consequences of inappropriately managed cases of eczema.

If either CM or WM is not "efficacious" in certain diseases, notably chronic and terminal illnesses, the ideal treatment will be integrative or combined CM and WM. In principle, integrative medicine will minimise side effects and maximise efficacy. CM and WM disciplines share a lot of similarities. Indeed, perhaps disagreed by some practitioners, the two branches of medicine are very similar in that both have long history of tradition, and both therapeutic processes involve detailed history taking and physical examination to arrive at a diagnosis and treatment discussed with patients based on the diagnosis. However, there is often no detail on clinical pharmacology on CM. IM may offer some benefits but well-designed scientific studies are lacking. Despite its advocacy, genuine IM is seldom practiced in the city of Hong Kong. CM and WM often go in parallel or exclusive rather than integrative. Local Hospital Authority and the two medical schools in Hong Kong have established certificate and diploma courses of CM for medical practitioners and allied health. This is a way in bridging the knowledge for WMPs. CMPs claim to treat pre-disease (i.e. preventive medicine) primarily. Contrary to common fallacies, CM can be potent and efficacious, but may not cure many diseases. In modern CM training, practitioners are more receptive to WM. Non-herbal medicines are commonly used too, such as insect exo-skeleton, animal body parts, minerals, and a rsenic.
The authors consider eczema a mental or psycho-social disease, rendering WM, CM, TCM, traditional Chinese herbal medicine, food avoidance, food supplementation, acupuncture and any CAM alone sub-optimal in efficacy. We need to be unified and join hands to create a holistic psycho-educational approach for this disease. The only chance for a successful management of complex psychosocial disease is to complement the strength and weakness of the two medical disciplines to make this truly integrative. The real problem often lies within the patient. Parents/patients generally do not want combined or IM. Many of them believe that CM has to be used alone. Even with an integrative approach, many parents/patients would demand to remove the WM component and request pure herbal ingredients (pure Han formula, purely herbal). Hence, our common "enemies" are the myths ("mind devils"), fallacies, fake or pseudo-CM, and the parent(s).

References

Dear Editor,

**Ethical Issue in Use of Expensive Drugs for Treatment of Rare Metabolic Diseases in Hong Kong**

In the past forty years, we have witnessed the dramatic change in the clinical management of rare metabolic diseases in Hong Kong. Before specific drug treatment was available, families with children with rare metabolic diseases had under great difficulty and experienced the inevitable downhill course and death of these children. With the advent of specific and new drug treatment, the prognosis of these unfortunate children has changed but an ethical issue arises as to who should pay for the cost of the treatment. Most if not all of these families cannot afford to pay for the huge cost involved and should public resource be used to treat just a small number of patients. It is known that public resource is used to treat these patients in Taiwan and Japan and Parents' Support Group in Hong Kong has urged the local Government to do likewise. I think there should be more public and open discussion on the issue before a concensus is reached and as a child advocate, our College might consider whether it should be involved in this hot subject.

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Our patient is a 28-year-old female who was referred to the Genetics Clinic for pre-marital counselling. The patient has generally good past health except she was always commented by her family doctor to have lax joints and loose skin. Upon examination, patient was noted to have hyper-extensibility, laxed skin, easy bruising, poor wound healing and a history of contusion of knee. Apart from the above characteristics, her physical health is unremarkable. Her cervical smear is negative and family history is uncertain. She is planning to have an IVF and Preimplantation Genetic Diagnosis in the future.

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

The clinical quiz was prepared by:
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Answer to "Clinical Quiz" on Pages 204-205
N.B. The Editors invite contributions of illustrative clinical cases or materials to this section of the journal.
Abstracts of Articles in Chinese

使用腦脊液和糞便樣本的實時熒光定量逆轉錄多聚酶鏈反應檢查診斷腸病毒腦膜炎


腸病毒感染是兒童常見感染和腦膜炎的主要病因。雖然腦脊液（CSF）取樣困難而且耗時，但是CSF分析對於診斷腦膜炎是十分重要的。相比之下，糞便測試取樣簡單，陽性率更高。我們對2011-2015年Cheonan Dankook大學醫院入院的疑似腦膜炎的病童（≤18歲）進行PCR檢查（942例病人，1,884標本），糞便標本陽性率最高，114例病人的CSF和糞便樣本呈現陽性，14例患者的腦脊液標本呈現陽性和糞便樣本呈現陰性，而101名患者糞便標本呈陽性和腦脊液標本呈現陰性。腦脊液分析結合糞便檢查相對單純的腦脊液分析或糞便檢查來說，可以更準確地診斷腸病毒性腦膜炎。

關鍵詞：腸病毒、腦膜炎、聚合酶鏈反應

兒童包蟲病的臨床特徵：來自土耳其一家醫學中心的經驗


目的：包蟲病是一種寄生蟲感染，是某些地區的主要健康問題。我們的目標是評價我院包蟲病患者的人口學和臨床特徵。方法：對2009年1月～2015年12月包蟲病患者進行回顧性分析。收集人口學特徵、臨床表現、實驗室和影像學結果、治療方法和併發症等資料。結果：二十八名患者參與我們的研究。患者的中位數年齡為134（55-197）個月。最常受累器官為肝（71.4%）和肺（57.1%）。此外，在非典型部位亦發現囊腫。所有患者均接受內科治療。結論：包蟲病是土耳其的一個重要健康問題。多器官可同時受累。因此，應採用先進的影像學方法來檢測局限性非典型囊腫。經過適當治療，遠期療效令人滿意。

關鍵詞：兒童、細粒棘球蚴病、包蟲病、治療結果
兒童接受苯丙氨酸限制性飲食的超重與肥胖情況


介紹：本研究旨在確定在苯丙酮尿症（PKU）和高苯丙氨酸血症（HPA）兒童中肥胖和超重的發生率。方法：收集和記錄病人的人口資料、診斷、飲食類型，體重身高，體重指數（BMI），血清苯丙氨酸濃度。結果：評估480例，其中288例納入這項研究。246例（85.4%）接受蛋白質支持的苯丙氨酸限制性飲食。其中23例（9.3%）肥胖和16例（6.5%）超重。當我們把246例PKU和HPA病人的肥胖發生率和土耳其人口肥胖比率作比較時，統計上的數據差異具研究價值（p=0.025）。結論：在土耳其，接受苯丙氨酸限制性飲食的兒童肥胖發生率比正常兒童為高。有關方面需要進行詳細的研究，以瞭解這個特殊群為組因的肥胖所引致的健康風險因素。

關鍵詞：高苯丙氨酸血症、肥胖、超重、苯丙氨酸限制醫療飲食、苯丙酮尿症

中國人15q重疊綜合徵的臨床和分子特徵


15q重疊綜合徵（OMIM # 608636）是一種神經發育性疾病，特點包括肌張力低下、發育遲緩、智力障礙、癲癇和獨特的面部特徵。香港開展了一項針對中國人15q重疊綜合徵的全港性研究，探討其在中國患者的臨床和分子特徵。從2011年1月至2015年12月期間收集到12個細胞遺傳學和分子學不同的個體。其中4個有間質重疊，8個有15號等臂雙著絲粒染色體。智障和自閉症在我國的15q重疊綜合徵人群的患病率估計分別為1%和2.9%。與西方人群相比，癲癇在中國患者中較少見，而斜視更為普遍。然而，在這項研究中沒有基因型-表型的相關性可以證明這一點。結論：通過香港的15q重疊綜合徵的中國患者的發病率，以及臨床特點與其他西方人群的患者比較，希望可以進一步理解其潛在的病理機制及其基因型-表型的相關性，為15q重疊綜合征患者提供更好的管理和遺傳諮詢。

關鍵詞：15q重疊綜合徵、中國人、15q11-q13重疊、15號等臂雙著絲粒染色體

新生兒期後的罕見腸道轉異不良：慢性腸道轉異不良導致蛋白質丟失的腸道症狀

YH Fang, SQ Shang, J Chen. Rare Clinical Presentation of Intestinal Malrotation After Neonatal Period: Protein-losing Enteropathy Symptoms Due to Chronic Midgut Malrotation. HK J Paediatr (new series) 2018;23:179-181

蛋白質丟失性腸病（PLE）是由多種疾病引起的。然而，此病症很少由慢性腸旋轉不良引起。一例1歲11月的男童和一例12歲的女性出現慢性腹瀉和低蛋白血症。兩例病人接受剖腹探查術，發現腸旋轉不良。腸旋轉不良在診斷蛋白質丟失性腸病應被視為鑑別診斷之一。

關鍵詞：腹瀉、低蛋白血症、腸旋轉不良、剖腹探查
一個患有類似外生性胰腺腫瘤的十二指腸異位胰腺的青少年


異位胰腺組織是一種罕見的異常，最常見異位於胃和鄰近小腸的粘膜下層。本文描述了一個罕見的十二指腸異位胰腺組織的病例，影像學檢查誤認為是一個外生性胰腺腫瘤。因症狀不緩解故進行了腹腔鏡檢查，病理結果證實是異位胰腺組織位於十二指腸粘膜下層和肌層。

關鍵詞：青少年、十二指腸異位胰腺組織、腹腔鏡

治療川崎病所引起的瑞氏綜合症

EJ Su, JH Hsieh, CC Hsu, KT Chen. Reye’s Syndrome Arising from the Treatment of Kawasaki Disease. HK J Paediatr (new series) 2018;23:185-187

我們報告一例20個月大的川崎病女童出院後出現嘔吐和嗜睡症狀。症狀發生在服用阿士匹靈5天後。臨床特徵和實驗室檢查證明為瑞氏綜合症，她在深切治療後好轉。此外，我們收集三個類似的病例報告。所有的病人來自東亞，死亡率達到50%。對川崎病而言，水楊酸是一種有效和必要的治療，兒科醫生和急診醫師可以考慮使用低劑量的阿士匹靈（3-5毫克／公斤）作為維持治療，在流感和水痘病程中，或是高度懷疑川崎病患者有瑞氏綜合症風險時，可短時間中斷阿士匹靈治療，並換用雙嘧達莫。

關鍵詞：阿士匹靈，併發症，川崎病，瑞氏症候群，水楊酸

Denys-Drash綜合症，兒科醫生應該知道什麼？


我們報導了一個雙側隱睾的男孩在常規術前評估時偶然發現有蛋白尿。進一步調查證實其患有腎病綜合症。因症狀不典型，故安排了腎臟超聲檢查，結果顯示他患有雙側腎細胞瘤病。他的染色體組型為46,XY。進一步DNA分析顯示，他的腎母細胞腫瘤抑制基因1（WT1基因）雜合突變。診斷Denys-Drash綜合症，並對他的腎母細胞瘤進行了治療。

關鍵詞：Denys-Drash綜合症，基因／腎母細胞瘤，假兩性畸形，腎病綜合症，WT1蛋白
**MCQs**

**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) Diagnosing Enteroviral Meningitis Using Real-time RT-PCR with Cerebrospinal Fluid and Stool Specimens

1. What kinds of viruses belongs to Picornaviridae family and has more than 70 different serotypes and contain coxsackieviruses?
   a. Papillomavirus
   b. Norovirus
   c. Enterovirus
   d. Poxvirus
   e. Rhinovirus

2. Which of the following is NOT a clinical symptom of Enterovirus infection disease?
   a. Guillain-Barre syndrome
   b. central nervous system infections
   c. heart failure
   d. meningitis
   e. transverse myelitis

3. What is the traditional way to detect aseptic meningitis?
   a. Cerebrospinal fluid analysis
   b. Respiratory specimen culture
   c. Sputum culture
   d. Urine culture
   e. Blood culture

4. What are the most relevant viruses causing Aseptic meningitis?
   a. Poxvirus
   b. Enterovirus
   c. Paramyxovirus
   d. Papillomavirus
   e. Coronavirus

5. How old is the age group most vulnerable to enterovirus infection?
   a. 40 ~ 50 year old
   b. 30 ~ 40 year old
   c. 20 ~ 30 year old
   d. 10 ~ 20 year old
   e. 0 ~ 10 year old

(B) Clinical Characteristics of Childhood Hydatid Disease: A Single Tertiary Centre Experience from Turkey

1. The patient was admitted to hospital with cough, shortness of breath and pain in the chest. Radiologic examination of thorax showed "meniscus sign and snake sign". Which of the following is the most likely diagnosis?
   a. Tuberculosis
   b. Hydatid cyst
   c. Pulmonary embolism
   d. Hodgkin's lymphoma
   e. Metastatic cancer

2. Which of the following may be symptoms of pulmonary hydatid disease?
   a. Cough
   b. Chest pain
   c. Dyspnoea
   d. Haemoptysis
   e. All of them

3. Which of the following is the most common organ that hydatid cysts localised in humans?
   a. Lung
   b. Liver
   c. Bone marrow
   d. Spleen
   e. Kidneys
4. Which of the following drug is used to first choice treatment of Echinococcus granulosus induced hydatid cysts?
   a. Albendazole  
   b. Metronidazole  
   c. Ornidazole  
   d. Dehydroemetine  
   e. Pyrimethamine

5. Which of the following parasite is used to human as an intermediate host?
   a. Taenia saginata  
   b. Echinococcus granulosus  
   c. Fasciola hepatica  
   d. Enterobius vermicularis  
   e. Ascaris lumbricoides

(C) Overweight and Obesity in Children under Phenylalanine Restricted Diet

1. Phenylketonuria:
   a. Is an inborn error of amino acid metabolism disorder  
   b. Is a genetic autosomal dominant disorder  
   c. Is presented by elevated tyrosine levels  
   d. Can not be treated  
   e. Is an X-linked disorder

2. What is the molecular defect that produces classic phenylketonuria?
   a. Decreased activity of Tyrosine Aminotransferase enzyme  
   b. Decreased activity of Phenylalanine Hydroxylase enzyme  
   c. Defect of metabolism in neutral amino acid pathway  
   d. Decreased activity of Dihydropteridine Reductase enzyme  
   e. Decreased activity of Hystidine Decarboxylase enzyme

3. Gold standard therapy for phenylketonuria includes:
   a. A life-long diet with limited intake of phenylalanine  
   b. Enzyme replacement treatment  
   c. Liver transplantation  
   d. Bone-marrow transplantation  
   e. None

4. Obesity,
   a. is an important health problem  
   b. its frequency is increasing worldwide  
   c. may be related to increased carbohydrate intake in phenylketonuria (PKU) patients  
   d. is a potential risk in PKU patients  
   e. All

5. How can Phenylketonuria clinically present?
   a. Mental retardation  
   b. Macrocephaly  
   c. Status epilepticus in the newborn period  
   d. Metabolic crisis with lactic acidosis  
   e. Short Stature

(D) The Clinical and Molecular Spectrum of 15q Duplication Syndrome in Chinese

1. Which of the following is not a common feature of 15q duplication syndrome?
   a. Hypotonia  
   b. Intellectual disability  
   c. Epilepsy  
   d. Distinctive facial gestalt  
   e. Diaphragmatic hernia

2. What are the molecular mechanism(s) for 15q duplication syndrome?
   a. Interstitial duplication of chromosome 15q11.2  
   b. Extra isodicentric chromosome 15(idic(15)(p11.2-13.3))  
   c. UBE3A mutation  
   d. a and b  
   e. a, b and c

3. Which of the following molecular test(s) can be useful for diagnosis of 15q duplication syndrome?
   a. Karyotype  
   b. FISH study  
   c. Chromosomal microarray  
   d. Microsatellite study  
   e. All of above
4. Which of the following clinical features is more common in our Chinese cohort of 15q duplication when compared with western populations?
   a. Squint
   b. Autism
   c. Intellectual disability
   d. Epilepsy
   e. Joint laxity

5. Concerning the outcome and prognosis of 15q duplication syndrome, which of following statements is false?
   a. Duplication in maternal allele of chromosome 15 has better neurological outcome
   b. Interstitial duplication of chromosome 15q11.2 is better than extra isodicentric chromosome 15(idic(15)(p11.2-13.3))
   c. The recurrence risk for isodicentric chromosome 15 in subsequent siblings of proband is low.
   d. a and b
   e. All of above

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**Answers of January issue 2018**

(A) 1. c; 2. a; 3. d; 4. e; 5. b
(B) 1. c; 2. a; 3. e; 4. c; 5. a
(C) 1. e; 2. e; 3. e; 4. a; 5. a
(D) 1. a; 2. a; 3. e; 4. c; 5. c
Announcements from the Hong Kong Paediatric Society
56th Annual General Meeting & 11th Oration on Child Health

56th Annual General Meeting
The 56th annual general meeting of the Hong Kong Paediatric Society (HKPS) will be held on at 7:00PM on 17th May 2018 (Thursday) at The Ballroom, One -Three, 18/F, The Mira Hong Kong, 118 Nathan Road, Tsimshatsui, Kowloon. Members will receive agenda and related documents for the meeting by post.

The 11th Oration on Child Health
The Council of HKPS endorsed the setting up of the HKPS Medal on Child Health in 2007. The Medal is awarded to a notable person who has contributed significantly to the advancement of knowledge, betterment of services, health education, and advocacy on child health (including medical, social and educational sectors) in Hong Kong. The Awardee will be the orator to deliver a keynote lecture at the time of annual general meeting.

The Council of the HKPS resolved in the 4th council meeting held on 21st December 2017 that we would award Mrs. Priscilla Lui Tsang Sun Kai, B.B.S. (雷張愷佳) the HKPS Medal on Child Health 2018. Mrs. Lui is the chairperson of the Hong Kong Committee on Children's Rights (2016- present) and the former director of the Against Child Abuse (1979, 1983-2011). She is one of the founders of the Hong Kong Committee on Children's Rights in 1995 and the Macau Against Child Abuse in 2006.

Mrs. Lui has been invited as keynote speaker in international conferences including the 17th ISPCAN International Conference on Child Abuse in Hong Kong. She also served as trainer in Taiwan, Singapore, Macau and China. The awards she received include the Ten Outstanding Young Persons Award (1990), Bronze Bauhinia Star Award (2000), the Outstanding Community Services Leaders Award from the Lions Club (2001), the Outstanding Services Award from International Society of the Prevention of Child Abuse & Neglect (2006), The Hong Kong Humanity Award from the Red Cross (2009).

She contributed numerous articles to different journals and has published two books: Listen to the Voice of the Wounded Children 聽受傷的孩子在說話 in 2011, and the Child at Heart 說童心 in 2017.

We are pleased to announce that Mrs. Lui would receive the award and deliver the oration titled "From Child Welfare to Child Rights: the Importance of a Child Perspective" on 17th May 2018 after our Annual General Meeting.
What is the Diagnosis?

With indication in hyper-extensibility, laxed skin, easy bruising and poor wound healing, genetic testing on Ehlers-Danlos syndrome is immediately performed. Genetic panel test on Ehlers-Danlos syndrome reveals a c.1502delC change in exon 12 of the COL5A1 gene, which led to frameshift of the DNA and resulted in abnormal mRNA production. The genetic test also reveals that the patient is heterozygous for COL5A1 gene. Inheritance of Ehlers-Danlos Syndrome is autosomal dominant, the recurrence risk for offspring is 50% with a COL5A1 mutation.1

What is Ehlers-Danlos Syndrome?

Ehlers-Danlos syndrome (EDS), classic type (also known as EDS type I or II) is an autosomal dominant disease that affects connective tissues that support skin, bones, blood vessels and many other organs. The classic type of EDS is characterised by skin hyper-extensibility, abnormal wound healing and joint hyper-extensibility.

The skin of EDS patient is hyper-elastic and fragile. Its hyper-elastic features are demonstrated in both easy extension of skin and immediate snapping back after release. For area that is prone to minor trauma (e.g. forehead or chin) and joints (e.g. knees and elbows), splitting of dermis will be resulted. Continuous stretching of scars after primary wound healing and the lack of Type V collagen, therefore, lead to abnormal wound healing. Joint hyper-extensibility can be assessed using the below Beighton score (Table 1).2 Dislocations of shoulder, patellar digits hips, radius, and clavicle are usually observed. Apart from the above phenotype, patients suffer from hypotonia, muscle cramps and fatigue, and easy bruising.

Table 1  Beighton score for joint hyper-mobility

<table>
<thead>
<tr>
<th>Joint</th>
<th>Negative</th>
<th>Unilateral</th>
<th>Bilateral</th>
<th>Patient’s score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Passive dorsiflexion of the 5th finger &gt;90°</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Passive flexion of thumbs to the forearm</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Hyperextension of the elbows beyond 10°</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Hyperextension of the knees beyond 10°</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Forward flexion of the trunk with knees fully extended and palms resting on the floor</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

# Total Score ≥5 defines joint hyper-mobility  9

The following diagnostic criteria could be used when there is suspicion on individual suffering from classical EDS. The combination of the first three major diagnostic criteria should have a high specificity for classic type EDS. The presence of one or more minor criteria contributes to the diagnosis of classic type EDS but is not sufficient to establish the diagnosis. The patient satisfied 3 of the major and 1 of the minor diagnostic criteria: skin hyper-extensibility, widened atrophic scars, joint hyper-mobility and easy bruising.
Major Diagnostic Criteria
- Skin Hyper-extensibility
- Widened Atrophic Scars
- Joint Hyper-mobility
- Positive Family History

Minor Diagnostic Criteria
- Smooth, Velvety Skin
- Molluscoid pseudotumours
- Subcutaneous spheroids
- Complications of Joint Hyper-mobility
- Muscle Hypotonia
- Easy Bruising
- Manifestations of tissue extensibility and fragility
- Surgical complications

Traditionally, Ehlers-Danlos syndrome is tested by taking skin biopsy for electron microscopy and biochemical testing, but the diagnostics is sometimes not definite. Molecular genetic diagnosis by sequencing and deletion/duplication analysis is now a less invasive option that could account of \( \geq 50\% \) affected individuals.

What is the Molecular Genetics behind Elhers-Danlos Syndrome?

Mutations in a numerous of genes are found to be corresponded to EDS. Currently, it is estimated that around 50% of EDS classic type patients have mutations in \( \text{COL5A1} \) and/or \( \text{COL5A2} \) gene. A large proportion of them are characterised by a mutation leading to a non-functional \( \text{COL5A1} \) gene, while the others have a mutation that lead to production of functionally defective \( \text{COL5A1} \) allele. The severity of phenotype among patients could vary greatly. \( \text{COL5A1} \) and \( \text{COL5A2} \) code for Type V collagen alpha 1 or alpha 2 respectively. The production of collagen involves a complicated 6-step synthesis. Defects in formation of one of the intermediates: tropocollagen will lead to Ehlers-Danlos syndrome.

What is the Management of Ehlers-Danlos Syndrome?

Clinical examination should be given immediately after diagnosis of Ehlers-Danlos syndrome to assess skin hyper-extensibility, presence of atrophic scars and bruises, and other manifestations of classic type EDS.

Physiotherapeutic program and non-weight-bearing muscular exercise should be given to classic EDS children who are suffering from delayed motor developed and hypotonia. For individuals with muscle hypotonia and joint instability with chronic pain, advice should be given to adjust their lifestyles, which behaviour and psychological therapy will also be practical. Anti-inflammatory drugs may also help in relieving joint pain. Since EDS patients demonstrate abnormal wound healing, dermal wounds should be closed without tension, in two layers and with application of deep stitches.

As aforementioned, the patient in the clinical quiz aimed to carry a child. Therefore, management measures for pregnancy were also given. Ehler-Danlos syndrome has an autosomal dominant inheritance. There is a 50% chance for the patient to pass the pathogenic mutation down to her offspring in each pregnancy. The availability of prenatal diagnosis or preimplantation genetic diagnosis should be discussed with the care physician and obstetrician before pregnancy.
Moreover, Ehlers-Danlos mothers are more vulnerable to premature rupture of membranes, which results in prematurity. Since EDS patients are affected by hypotonia, probability of breech presentation will be more frequent. Dislocation of hips or shoulder of the newborn will result if the newborn is also affected by EDS. While and after delivery, tearing of perineal skin by forceps, extension of episiotomy incisions and prolapse of uterus and/or bladder may also occur. Therefore, pregnant women should be closely monitored throughout pregnancy and in the postpartum period. Vitamin C (Ascorbic acid) should also be given to relieve easy bruising.

Acknowledgments

We would like to express our gratitude to the patient and his family for their contribution. Informed consent was obtained for publication.

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 of preliminary findings 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 be not 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.
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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:

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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.

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**Discussion**

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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".

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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.

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Hong Kong Journal of Paediatrics
April Issue 2018
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Please fill in your Name: ___________________________ CME No. ___________________________
Contact Phone No. ___________________________ Email: ___________________________

MCQ can also be done at Hong Kong Academy of Medicine's iCMECPD website http://www.icmecpd.hk

(A) 1. a. [ ]  b. [ ]  c. [ ]  d. [ ]  e. [ ]
   (B) 1. a. [ ]  b. [ ]  c. [ ]  d. [ ]  e. [ ]
   (C) 1. a. [ ]  b. [ ]  c. [ ]  d. [ ]  e. [ ]
   (D) 1. a. [ ]  b. [ ]  c. [ ]  d. [ ]  e. [ ]

   2. a. [ ]  b. [ ]  c. [ ]  d. [ ]  e. [ ]
   3. a. [ ]  b. [ ]  c. [ ]  d. [ ]  e. [ ]
   4. a. [ ]  b. [ ]  c. [ ]  d. [ ]  e. [ ]
   5. a. [ ]  b. [ ]  c. [ ]  d. [ ]  e. [ ]
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