Editorial
A Crossroad between Paediatricians and Paediatric Surgeons
Leung

Original Articles
Clinical Analysis of 220 Infants Less Than 12 Months Old with Measles
Wu, Ning, Wang

Comparison of Conversion Reasons in Paediatric Laparoscopic Surgery to Adult Literature
Ates, Gollu, Ergun, Turedi, Mammadov, Bingol-Kaloglu, Yagmurlu, Aktug, Dindar, Cakmak

Developmentally-induced Hypothyroidism Alters mRNA Expression of Cerebral Angiotensin II Type 1 and Type 2 Receptors of Offspring in a Mouse Model
Wu, Zhang, Zou, Zhu, Zhao

Update on Clinical Practice
Update on Helicobacter pylori Infection in Children
Sham

Case Reports
Café Au Lait Spots: What is the Diagnosis If It Is Not Neurofibromatosis Type 1?
Yu, Luk, Lo

Long-term Extraterine Survival in a Triploid Infant: A Review of the Clinical Features of Live-born Infants with Triploidy
Hashimoto, Igarashi, Kobayashi, Tsutsumi

Neonate with Congenital Myotonic Dystrophy Conceived via In Vitro Fertilisation by an Asymptomatic Mother
Kim, Lee, Lee, Han

Epiploic Appendagitis with Chronic Abdominal Pain in an Obese Adolescent
Kim

Letter to the Editor
Interpreting Neonatal Serum Triglyceride Levels Against Reference Intervals
Poon

Clinical Quiz
What is the Diagnosis?
Ho, Wong

Abstracts of Articles in Chinese

MCQs

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A Crossroad between Paediatricians and Paediatric Surgeons

Prompt recognition and treatment of infectious diseases are the cornerstone of daily clinical paediatric practice, and effective vaccinations are available to prevent many of such microbes such as poliomyelitis, varicella-zoster virus, rotavirus, Corynebacterium diphtheriae and Streptococcus pneumoniae. The availability of immunoprophylaxis against hepatitis B virus and human papillomavirus can also substantially reduce the healthcare burden of highly prevalent cancers. Nonetheless, the success of this preventive strategy in the public health setting depends not only on efficacy and safety of the vaccines but also their availability, acceptability and uptake as well as the epidemiology and herd immunity of respective vaccine-preventable diseases in a defined population.1

Measles is a prototype of vaccine-preventable disease where different places develop different immunisation programmes in light of their epidemiological profiles. Whereas Hong Kong children are vaccinated against measles at 12 months and at primary one, the schedule of measles immunisation in the Mainland consists of two doses at 8 months and 18 months respectively. The two-dose vaccination coverage in Hong Kong has consistently been maintained at over 95 per cent since 2008, which effectively eliminated measles from our region as verified by the Western Pacific of the World Health Organization in September 2016 (https://www.info.gov.hk/gia/general/201609/21/P2016091900657.htm). On the other hand, measles remains a leading vaccine-preventable cause of child mortality in China. According to the Chinese Health Statistics Yearbook, the incidence of measles was 0.46/100,000 Chinese citizens in 2013. A recent report of a measles outbreak in China estimated the measles-containing vaccine coverage to be 90% or lower.2 In the first original article of this issue, Wu et al reported a case series of 220 infants with measles from the prefecture-level city of Jinhua in central Zhejiang province in eastern China.3 These cases were diagnosed serologically by anti-measles IgM between January 2008 and August 2015. Four-fifths of these cases were younger than eight months, and complications were more common in this younger than the older group. Complications were more prevalent in this patient group than among older infants. Sadly, seven patients had residual complications, two patients whose parents gave up treatment and one infant died. This study highlighted the need for good coverage for measles in the national immunisation programme, as well as the possible benefit of re-vaccination of women of childbearing age against measles.

In contrast to measles, Helicobacter pylori is a common worldwide infection that is an important cause for both peptic ulcer disease and gastric cancer. Children with H. pylori infection may also present with recurrent or chronic abdominal pain. A number of recent systematic reviews and meta-analyses indicated that the lowest prevalence rates of H. pylori infection were found in Oceania (24.4%) and the highest in Africa (79.1%). Studies in Europe suggested a declining trend.4 The recurrence rates were found to be directly related to the human development index and prevalence of infection. Thus, the disease burden of H. pylori remains substantial in many parts of the world. In this issue, Sham provided a literature update about the therapeutic strategy for this infection in children based on the recommendations from two major international guidelines.5 The materials were initiated as an Update on Clinical Practice document under the Hong Kong College of Paediatricians, which was reviewed and endorsed by the Hong Kong Society of Paediatric Gastroenterology, Hepatology and Nutrition. Both paediatricians and paediatric surgeons will find the updated diagnostic and prescribing information for H. pylori infection in this article useful in their daily practice on children with relevant gastrointestinal diseases.

The widespread use of endoscopy has advanced the care of paediatric surgical patients. In fact, paediatric surgeons were among the pioneers of laparoscopic surgery in the early 1970s.1 However, interest in laparoscopic surgery in children remained confined to a few enthusiasts until the recent availability of miniaturised instrumentation. More recent survey in USA suggested that 82% of paediatric surgeons perform laparoscopic surgery.4 In this issue, Ates et al evaluated the reasons for conversion to open surgery in 2068 laparoscopic cases in Turkish children between 2003-2015.9 They reported that 1848 (97.9%) of the 1887 cases intended to be performed by laparoscopy were successfully completed. High conversion rates to open surgeries were found for Nissen fundoplication and splenectomy. Whereas the success of laparoscopic surgery depends
The editors like to acknowledge with gratitude the major contributions of the reviewers who have rendered their valuable service in reviewing the articles submitted to our Journal in 2018.

### List of Reviewers

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12. Haspula D, Clark MA. Molecular basis of the brain renin angiotensin system in cardiovascular and neurologic disorders: Uncovering a key role for the astroglial angiotensin type 1 receptor AT1R. J Pharmacol Exp Ther 2018;366:251-64.
15. Haspula D, Clark MA. Molecular basis of the brain renin angiotensin system in cardiovascular and neurologic disorders: Uncovering a key role for the astroglial angiotensin type 1 receptor AT1R. J Pharmacol Exp Ther 2018;366:251-64.
Clinical Analysis of 220 Infants Less Than 12 Months Old with Measles

L Wu, B Ning, Y Wang

Abstract

Aims: To observe the clinical characteristics of infant measles and strengthen its prophylactic methods.

Materials and Methods: 220 cases diagnosed as infant measles were enrolled in the Central Hospital of Jinhua City in China from January 2005 to August 2012. Enzyme-linked immunosorbent assay (ELISA) kit was used to test specific immunoglobulin (Ig)M against measles. Routine blood tests, blood biochemistry and myocardial enzymes using venous blood were done for the 220 measles patients.

Results: All cases had fever fluctuating between 37.5°C to 41°C and mucosal plaques (Koplik's spots) on the oral mucosa. In all cases, measles IgM antibodies were found to be positive after eruption. 80.46% of patients were <8 months of age. Of the 138 cases (62.73%, 138/220) with pneumonia complications, there were 32 cases of severe pneumonia, 30 cases accompanied with diarrhoea, 25 cases with acute laryngitis, 16 cases with mouth ulcers, 5 cases with febrile seizures, and 4 cases with toxic encephalopathy. In this patient group, complications were more prevalent than in the older children group. A total of 210 subjects were cured, the clinical condition of 7 cases improved and 2 individuals gave up treatment and were discharged from hospital due to expensive treatment charge. One patient died. The clinical manifestations were typical, with a short prodromal period and several complications.

Conclusions: The present study showed that in our population, measles tended to affect the younger age, and that pneumonia was the most common complication. Revaccination of women of childbearing age against measles might reduce the incidence of measles in infants.

Key words Complication; Infant; Measles; Pneumonia

Introduction

Measles is an acute exanthematous infectious respiratory disease caused by the measles virus and is a major threat to the health of children. Since introduction of the live attenuated measles vaccine in 1965 in China, the incidence of measles has reduced appreciably. Nevertheless small-scale epidemics have continued to occur. According to the Chinese National Vaccination Schedule, the first measles vaccine was administered at 8 months of age, the second between 1.5 to 2 years, and the third booster vaccine at 7 years. To understand the clinical characteristics of infant measles and strengthen its prevention and control, 220 cases of infant measles treated in the Central Hospital of Jinhua City from January 2005 to August 2012 are reported here.

Clinical Data

General Information

From January 2008 to August 2015, 220 cases of infant measles were treated at Jinhua Central Hospital.
diagnosis was based on the criteria set in the seventh edition of *Practical Pediatrics* by Futang Zhu.2 The breakdown of cases was 90 cases in 2008, 22 in 2009, 16 in 2010, 48 in 2011, 19 in 2012, 7 in 2013, 5 in 2014 and 13 in 2015. Of these 220 cases, there were 157 boys and 63 girls (ratio, 2.49:1). Eighteen cases (8.18%) were 0-3 months old (minimum was 21 days old), 65 cases were between 3-6 months old (29.55%), 94 cases were between 6-8 months old (42.73%), and 43 cases were between 8-12 months old (19.54%). The distribution of measles outbreaks was: 61 cases (27.73%) from January to March, 98 cases (44.55%) from April to June, 33 cases (15.0%) from July to September, and 28 cases (12.72%) from October to December. A total of 83 cases were from city/urban areas, 72 cases were from rural areas and 65 were from the areas that were none of the above. Seven subjects aged 8-12 months had been vaccinated within 1 day to 3 days, but the others had not been vaccinated. A total of 192 mothers had accepted measles vaccination in their childhood, and 28 mothers had not. Nine mothers of these 220 children with measles had measles during the same period. The general data were showed in Table 1.

### Clinical Manifestations

All cases had fever at the beginning of the disease, with body temperature fluctuating between 37.5°C to 41°C and mucosal plaques (Koplik's spots) on the oral mucosa. They had typical rashes of measles appearing 2-5 days after fever. Pigments subsided in all cases after the disappearance of the measles rash. In these cases, 13 were haemorrhagic measles with worsened disease during measles and a body temperature between 39°C and 41°C. Five had seizures (2.27%) and 30 had gastrointestinal symptoms (13.64%) (Table 2). In 9 cases, both mother and child had measles (4.09%); 3 cases aged 0-3 months and 6 cases aged 3-6 months, and all their mothers had been vaccinated with measles vaccine during their childhood.

### Laboratory Tests

In all cases, measles immunoglobulin M antibodies were found to be positive after eruption; an enzyme-linked immunosorbent assay (ELISA) kit (Jiangsu Huaguan Biological Products Co., Ltd., Jiangsu, China) was used following manufacturer instructions. Routine blood tests, blood biochemistry and myocardial enzymes using venous blood were done for the 220 measles patients. In these cases, 52 cases had a white blood cell (WBC) count >12.0×10⁹/L, 35 cases <4.0×10⁹/L, and 133 cases within the normal range. A total of 189 cases had increased numbers of lymphocytes, 56 with increased levels of C-reactive protein (73±22 mg/L), 82 with increased levels of serum alanine aminotransferase (241±51 U/L), 130 with increased levels of aspartate aminotransferase (239±37 U/L), 90 with increased levels of lactate dehydrogenase (651±72 U/L), 194 with increased levels of creatine kinase up to 379±68 U/L, and 110 with increased levels of hydroxybutyrate catalase up to 357±83 U/L (Table 2).

### Complications

In the chest radiographs of 220 children, 138 cases had pneumonia, 45 cases had bronchitis and 27 cases had normal lungs. Of the 138 cases with pneumonia complications, there were 32 cases of severe pneumonia, 30 cases with diarrhoea, 25 cases with acute laryngitis, 16 cases with mouth ulcers, 5 cases with febrile seizures, and 4 cases with toxic encephalopathy (Table 2).

### Treatment and Prognosis

Integrated treatment was applied: intravenous antibiotic drips, such as cefradine, cefotaxime and ceftriaxone, to

### Table 1  General data of 220 infants with measles

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<tr>
<td>Age</td>
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<td>3-6 months</td>
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<td>6-8 months</td>
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<td></td>
<td>8-12 months</td>
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<td>Distribution of outbreaks</td>
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<td>April to June</td>
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<td>July to September</td>
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<td>October to December</td>
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<td>Area</td>
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<td>Rural areas</td>
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cover for potential bacterial co-infection. Use of antipyretic treatment such as oral ibuprofen at dose of 5-10 mg/kg or acetaminophen at dose of 10-15 mg/kg during the high-temperature period. Also, dehydrating agents such as mannitol at dose of 0.5-1.0 g/kg, every 6-8 hours and methylprednisolone at dose of 1 mg/kg, every 12 hours were used for those with toxic encephalopathy. For those with severe pneumonia, oxygen, diuretics such as furosemide at the dose of 0.5-1 mg/kg, every 12 hours and intravenous gamma-globulin were given. The gamma-globulin was administered at the dose of 1 g/kg for 2 days. Tracheal intubation was performed for respiratory failure and supported by mechanical ventilation, the ventilation model was pressure control ventilation and protective lung ventilation strategy was carried out for the decreased pulmonary compliance. 1 mg budesonide and oxygen-driven atomising inhalation was added to treat any concurrent laryngitis 3 times every day. A total of 210 subjects were cured, conditions of 7 cases were improved and 2 individuals were voluntarily discharged from hospital due to expensive treatment charge. One patient died despite active treatment because of severe pneumonia, respiratory failure and heart failure (Table 2).

### Discussion

Of the 220 cases of measles, infants under 8 months of age comprised 80.46% of the study cohort. The clinical manifestations were typical, with a short prodromal period and several complications. In this patient group, pneumonia was the most common complication reaching 62.73% (138/220), which was similar to the report by Le Roux. Complications were most likely related to the large number of subjects under 8 months of age, their immunocompromised status and strong virulence of the measles virus. The pyrogenic period was long and high fever was common, in which 5 cases had hyperpyretic convulsions. Koplik's spots lasted for a long time, and were often misdiagnosed as infection due to *Candida albicans*. Rashes could be haemorrhagic and could also be commonly misdiagnosed as roseola infantum, scarlet fever or other measles-like diseases. During treatment at the onset of pneumonia and acute laryngitis, because of the widely experienced dyspnoea and cyanosis, the attending physician could misdiagnose without careful checking for rashes. There were several cases with combined hepatic dysfunction and increased levels of myocardial enzymes and the recovery time was long, beyond 3 weeks.

Recently, the incidence of measles in China has changed appreciably with regard to the age at which it strikes individuals. The incidence of measles in infants <1 year of age has increased. In the present study, 80.46% of patients were <8 months of age and the youngest was 21 days of age, which suggested that the incidence of measles tends to affect those of younger age. It has been reported that the prevalence of positive measles antibodies in the body is only 7.14% at 8 months before vaccination. This finding suggests that most infants lose their placenta-transferred antibodies by the time they are 8 months old and that passive immunisation is not possible in some babies due to intrusion of the measles virus after birth. Babies under 8 months of age are entirely dependent upon their placenta-transferred antibodies to resist invasion by the measles virus because they have not been vaccinated against measles. In the present study, both mother and child had measles in 9 cases, and these mothers had previously received the measles

### Table 2  Clinical data of 220 infants with measles

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vaccine during childhood and did not previously develop measles. It has been reported that, if a mother receives the measles vaccine again before pregnancy, the measles antibody levels of cord blood of her baby will be significantly higher than those of babies of mothers without revaccination against measles.\textsuperscript{14-16} Mao et al reported that measles antibody seroprevalence was 95.9% in 2154 women of child-bearing age,\textsuperscript{17} which was consistent with our result that there were 9 mothers and their children infected with measles (4.09%) although the mothers had been inoculated with 2 doses measles vaccine during childhood. It has been recommended that women at childbearing age should receive revaccination against measles before pregnancy. This action could not only improve the measles antibody levels of women of childbearing age, but could also improve placenta-transferred antibody levels to help reduce the incidence of measles in infants.

The local practice in mainland of China is a 2-dose measles containing vaccine programme of the 1st dose at 8 months and a 2nd dose between 18-23 months. While in other territories like Hong Kong, USA and UK, the 1st dose is given at 1 to 1.5 years while the 2nd dose is given at 3-6 years.\textsuperscript{18-20} Vaccine strategies often require strong support from government and healthcare organisations, as well as tailored to culturally appropriate local approaches to optimise outcomes. In the Chinese mainland, the government schedules the measles vaccine for 8 months old, which maybe based on waning of the specific antibodies from the mother. Successful immunisation programmes not only result from high vaccine effectiveness, but also result from local government. It is a great and heavy burden for the inoculation of more than 1.4 billion people, which is all paid by the government. The present study analysed the measles babies under 12 months. The incidence of babies in the 0~3 month age group was the lowest with 8.18%, which might due to the protective antibody from the measles vaccinated mothers. After the inoculation of measles for 8-month old babies, the incidence dropped from 42.73% (6~8 months) to 19.54% (8~12 months), which indicated that the first dose at 8 month could be counted as a valid dose. Considering of the differences of the Chinese mainland measles vaccination from Hong Kong, USA and UK, further vaccine effectiveness study should be performed to explore the pros and cons of administering the 2nd dose at 18-23 months versus giving it later in life.

In summary, pneumonia was the most dangerous and the most common complication of measles infection. As the incidence of measles tends to affect the younger age group of less than 8 months old, we suggest that revaccination against measles for women at childbearing age might reduce the incidence of measles in infants, especially for infants less than 8 months old.

Declaration of Interest

None.

Acknowledgments

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Original Article

Comparison of Conversion Reasons in Paediatric Laparoscopic Surgery to Adult Literature

U Ates, G Gollu, E Ergun, B Turedi, F Mammadov, M Bingol-Kologlu, A Yagmurlu, T Aktug, H Dindar, AM Cakmak

Abstract

Introduction: The aim of this study is to evaluate and analyse the reasons for conversion to open surgery in laparoscopic cases in childhood, compared to the adult literature and differentiate the preventive measures for decreasing the rates for conversions. Patients and methods: The charts of 2068 patients who had appendectomy, Nissen fundoplication, cholecystectomy and splenectomy operations between 2003-2015 were reviewed retrospectively. Laparoscopic and open procedures and the cases that were converted from laparoscopy to open surgery and the reasons of conversions were analysed. Results: Between the years of 2003-2015, total of 2068 cases; appendectomy (1539), cholecystectomy (120), Nissen fundoplication (323) and splenectomy (86) operations were performed. Among these procedures, 181 (8.8%) of them were performed by laparotomy, 1887 (91.2%) of them were intended to be performed by laparoscopy. Among laparoscopically started cases, 1848 (97.9%) of them were completed laparoscopically and in 39 cases (2.1%) conversions were required. The conversion rates were 0.34%, 9.7%, 2.8% and 7.4% in appendectomy, Nissen fundoplication, cholecystectomy and splenectomy, respectively. Conclusion: Preoperative detailed and specific examinations before laparoscopic procedures can decrease the conversion rates in laparoscopic surgery. Complications do not have to be the only conversion indication and elective conversion must be performed without wasting time to avoid complications.

Key words: Children; Conversion; Laparoscopy; Open surgery

Introduction

Since the beginning of the history of surgery, a lot of time and effort has been spent searching for minimally invasive surgery. Introduction of laparoscopy is definitely one of the biggest steps. From Bozzini, who had first reported that he had viewed a bladder using his own invention “lichtleiter” to Semm, who performed first laparoscopic appendectomy in 1982, the development of new devices and less invasive methods has never stopped.1 Because of such reasons as shorter hospital stay, less postoperative pain, fewer wound infections, quicker return to daily life, shortened feeding time, better cosmetic results and so on, laparoscopic approach is in the paediatric surgery armamentarium.2,3 Even though the most common
procedures in paediatric surgery such as appendectomy and Nissen fundoplication as well as splenectomy and cholecystectomy are all routinely performed laparoscopically, in some cases conversion to open surgery is unavoidable. In such cases, the rate of morbidity and complications increase.4

The aim of this study is to analyse and evaluate our conversion reasons and rates and compare it to paediatric and adult literature. We aimed to answer the following questions: Whether the conversion is a problem in laparoscopy or a choice to avoid complications, and what are the conversion rates and reasons in both adult and paediatric surgery.

**Patients and Methods**

In the charts of 2068 patients who had appendectomy, Nissen fundoplication, cholecystectomy and splenectomy operations between 2003 and 2015 were reviewed retrospectively. Laparoscopic and open procedures and the cases which were converted from laparoscopy to open surgery, the reasons and rates of conversions were analysed.

**Results**

Between the years 2003-2015, a total of 2068 cases of appendectomy (1539), cholecystectomy (120), Nissen fundoplication (323) and splenectomy (86) operations were performed. Among these procedures, 181 (8.8%) of them were performed by laparotomy, 1887 (91.2%) of them were intended to be performed by laparoscopy. Among laparoscopically started cases, 1848 (97.9%) of them were completed laparoscopically and in 39 cases (2.1%) conversions were required. Of these 39 cases, seven (18%) were forced and 32 (82%) were elective conversions.

In 1539 appendectomies, 1445 cases started laparoscopic and only 5 of them (0.34%) required conversion. When the conversion reasons were analysed, it was seen that conversions were required for appendicular plastron (n=2, 40%), dilated intestines (n=1, 20%), technical difficulty (n=1, 20%) and bladder injury (n=1, 20%).

When analysing 120 cholecystectomies, 13 cholecystectomies (10.8%) were performed by laparotomy, while 107 were intended to be performed laparoscopically (89.2%). Of these 107 cases, 3 were converted to open surgery due to inability to control haemorrhage (n=1, 33.3%), intraabdominal dense adhesions (n=1, 33.3%) and iatrogenic choledochal injury (n=1, 33.3%).

Of 86 splenectomies, 19 (22%) cases were performed by laparotomy and 67 (78%) of them were started laparoscopically. In these 67 cases, 5 (7.4%) of them needed to be converted. The conversion reasons were haemorrhage (n=2, 40%), intraabdominal dense adhesions (n=2, 40%) and splenomegaly (n=1, 20%).

To perform Nissen fundoplication, in which we have the highest conversion rate; among the 323 cases, the operation was performed by laparotomy in 55 (17%) cases. 268 (83%) were started laparoscopically, but 26 (9.7%) of them required conversion at some point. The conversion reasons in Nissen fundoplication were inadequate exposure (n=8, 30.7%), redo surgery (n=6, 23%), hepatomegaly (n=5, 19.2%), unexpected cystic gastrointestinal tract (GIT) duplications (n=4, 15.4%) gastric perforations (n=2, 7.6%) and dense adhesions (n=1, 3.8%). When we analysed the patients, it was found that 14 (54%) of the patients who experienced conversion to open surgery were suffering from cerebral palsy (CP).

**Discussion**

In this study of 2068 cases, we found that similar conversion rates and causes were observed between paediatric and adult literature in laparoscopic appendectomy, cholecystectomy and splenectomy. The results of the laparoscopic Nissen fundoplication, conversion rates and causes were similar to the paediatric literature but conversion rates were higher compared to adult literature and there were different conversion reasons in adult literature besides few similar ones.

It is well known that there are physiological and anatomical differences between paediatric and adult surgery. Preoperative and postoperative complications and reasons of conversion to open surgery may be different in adults and children. For adults, important risks are mostly related to chronic diseases as hypertension, diabetes, lung diseases and vascular diseases. On the other hand, for children the main risks are related to physiological responsive mechanisms such as hypothermia – especially for newborns, even though these procedures are not newborn surgeries, fluid and electrolyte instability and whether they can tolerate the anaesthesia and continuous surgery. The tissues of children are thinner and weaker so the vessels and organs are more vulnerable to the trauma during the surgery. Besides these well-known differences, we tried to show the reasons related with the laparoscopic operations for
The conversion rate of laparoscopic appendectomy in this study was 5/1445 (0.34%). The reason for one of these conversions was a complication and the rest were chosen in order not to prolong the surgery time and to perform a safer surgical procedure. Our conversion rate was lower than the adult literature.

Conversion rates from laparoscopic to open appendectomy range from 0 to 23% and is decreasing in the adult literature. Common reasons of conversion in appendectomy were dense adhesions, fibrosis, acute inflammation, location of appendix vermiformis, iatrogenic injuries, technical difficulties, peritonitis, abscess, long duration of the symptoms, base necrosis, bleeding, difficulties in identifying the organs, older age and comorbidities. Perforation was one of the main reasons of conversion in adult literature.

Laparoscopic appendectomy is one of the most common laparoscopic procedures in paediatric surgery. There are also some conversions in this procedure too but the conversion rate is decreasing with time. The conversion rate varies between 0-32.9 in the paediatric literature.

We started 268 Nissen fundoplications by laparoscopy but in 26 (9.7%) cases, conversion was required. Conversion reasons were; inadequate visualisation in 8, hepatomegaly in 5, hardened laparoscopic manipulations because of redo surgery in 6, unexpected other gastrointestinal pathologies (gastrointestinal cystic duplications) in 4, gastric perforations in two and dense adhesions in one patient.

The highest rate of conversion in our series was in Nissen fundoplication. The latter acceptance in laparoscopy for Nissen fundoplication in children and lack of experience can be the reasons for this high rate (27/268, 9.7%).

In adult surgery, conversion rates vary between 2.2 and 16% in Nissen fundoplication. The most common reasons were bleeding, hiatal hernia, adhesions, gastric perforations, anaesthetic complications, oesophageal complications, peri-oesphagitis, enlarged liver, inability of closing crura, obesity, splenic injuries and technical difficulties.

In the paediatric literature, the conversion rate was between 0-22%. The most common reasons were dense adhesions, bleeding (from short gastric arteries and liver), extreme scoliosis, previously placed gastrostomy tube, patient’s inability to tolerate pneumoperitoneum and gastric perforations.

Even though obesity is one of the major conversion reasons in adult surgery, since children with gastroesophageal reflux tend to have malnutrition and be physically retarded, obesity was not an important reason for conversions in our patients.

Dense adhesions, on the other hand, as it is in all laparoscopic procedures, is one of the important conversion reasons.

High conversion rates do not mean unsuccessful surgery. We tried to start all the cases with laparoscopy, but if the diagnostic laparoscopy reveals a condition, which leads us to laparotomy, we do not hesitate and convert to open surgery at the beginning of the surgery. Conversions due to the inadequate visualisation, hepatomegaly and redo surgeries can be explained by this approach. With this approach we think we can reduce our complication rate, operating time and other morbidities.

For the preoperative preparation, we perform 24-hour pH monitoring and upper gastrointestinal contrast studies before Nissen fundoplication. If further investigations were performed, the unexpected conditions (cystic duplications) could be revealed before surgery via ultrasound or computed tomography imaging.

In this study there were three conversions in 107 laparoscopic cholecystectomies (n=3, 2.8%). One of the conversions was a result of an inability to control the haemorrhage, one was for choledochal injury and one was due to the severe adhesions of the gallbladder.

In the adult literature, the most common conversion reasons in cholecystectomies were haemorrhage, adhesions, technical problems, inadequate visualisation, inability to create pneumoperitoneum, spilled stones, bowel injuries, bile duct injury, gallbladder malignity, and common bile duct exploration. Some authors divided conversions in two groups as elective and enforced. Of 81 conversions in 1238 cases (6.5%), 73 conversions were elective and 8 of them were enforced. As reported by many authors, the rate of conversion was between 0-7.5% in the adult literature. But none of them divided the conversion as Shamim did.

In the paediatric literature, there are fewer articles studying this issue than the adult literature. The common reasons for conversion were similar such as bleeding, adhesions, not being able to clarify the anatomical structures. The rate was also similar as it was between 0-4%.

In adults, the main thought was that if there was a history of previous biliary disease, large stones, ongoing inflammatory process, scarred and fibrosed gall bladder and if the patient was old, laparoscopic procedure will be harder. In paediatric surgery, generally there are not comorbidities and fibrosis and scars as much as in the adult population.
Instead of these conditions, one should be aware of working in a smaller area. Due to the thinner vessels and bile ducts, the dissection is harder. It is difficult to expose anatomical structures properly and variations are as common as in adult population.

There are also adult studies, which aim to predict the conversion risks in laparoscopic cholecystectomy. In one study, the authors have claimed that the predisposing factors for conversion can be predicted before or during the surgery. Jethwani et al revealed the thickness of the gallbladder is relevant with high conversion rates and it can be measured before the operation via ultrasound imaging. Thus the surgeon can be aware of a difficult procedure and, depending on the patient's status, even open surgery can be performed initially. Knowing the difficulty predictors and knowing his/her own abilities and technological facilities gives the surgeon the chance to make better decisions.

In our 67 splenectomies, there were 5 conversions (7.4%). (Two haemorrhage from hilum, two for severe adhesions and one for massive splenomegaly).

The conversion rate in adult literature for splenectomy varies between 3 and 22.5%. Bleeding from the splenic pedicle and splenic artery is the most common reason of conversion in the literature. Besides bleeding from hilum, massive splenomegaly, dense adhesions and bleeding from splenic parenchyma are other common conversion reasons.

Conversion rates vary also in the paediatric literature. The most common reasons are bleeding, splenomegaly and adhesions as they were in the adult literature. In addition to these, technical aspects are conversion reasons worth mentioning. The conversion rate in the paediatric literature for splenectomy is between 1.7 and 6%. Our conversion rate (7.4%) and reasons (bleeding, adhesions and splenomegaly) are similar to both the adult and paediatric literature.

Among all minimally invasive advantages, laparoscopy also has an advantage of facilitating the visualisation of the whole abdomen properly and gives us opportunity to repair minor complications with proper approach. Other than these, since the haemorrhage can be very rapid and life threatening, the surgical team must always be aware of such risk and be ready for laparotomy immediately. We think the surgeon's choices and judgement during a laparoscopy session can be decisive. Especially the insistence of surgeon on laparoscopic procedure can cause more problems for the patient.

Another point of view is the cost of the operation. Pomp et al also claimed that when one converts an operation to open which you started laparoscopically, you combine the high costs of laparoscopic equipment with patient's long hospital stay. So it becomes the most expensive method.

In 39 conversion-required cases, only seven of them (18%) were forced. Thirty two of them were electively converted. The reason why we had low intraoperative complication rates during our laparoscopic cases is our routine of converting directly if we had no proper exposure or the adhesions or other pathologies will prolong our surgery time much more than it would cost. Even though this study shows that our conversion rate is higher in Nissen fundoplication, prolonged anaesthesia time and unnecessary dissections are avoided by this approach.

The highest conversion rate in our series is in Nissen fundoplication. When the conversion rates are analysed, it can be seen that 24 of the conversions were elective. We have only two conversions due to the complications in Nissen fundoplication (two gastric perforations) (n=2, 0.74%). On the other hand, in the appendectomy, which was the first laparoscopic procedure we performed in our clinic, we have the lowest conversion rate (n=5, 0.36%). This low rate can be explained by the existence of common appendectomy procedures in paediatric surgery that allow the surgeons to develop their minimally invasive surgery skill set. The higher number of our conversions in Nissen fundoplication than our appendectomy, cholecystectomy and splenectomy is due to our policy on laparoscopy for the past thirteen years. After a diagnostic laparoscopic glance, if the case does not seem to be appropriate for laparoscopy, conversion is performed quickly.

Besides, preoperative detailed analysis of the relations between the organs and diameters of the liver, fundus and oesophagus may direct us to understand the situation better before the operations.

One of the aims of this study is to attract attention to differences of paediatric laparoscopic procedures since many paediatric procedures are performed by general surgeons all over the world.

**Conclusion**

Even though the surgical procedures are done by similar techniques, the conversion rates and reasons in paediatric surgery show difference in paediatric and adult surgery with some similarities.

Preoperative detailed and specific examinations before laparoscopic procedures can decrease the conversion rates in laparoscopic surgery. Complications do not have to be
the only conversion indication and elective conversion must be performed without wasting time in order to avoid complications.

References

Original Article

Developmentally-induced Hypothyroidism Alters mRNA Expression of Cerebral Angiotensin II Type 1 and Type 2 Receptors of Offspring in a Mouse Model

LL Wu, L Zhang, CC Zou, ZW Zhu, ZY Zhao

Abstract

The impact of hypothyroidism on cerebral renin-angiotensin system (RAS) remains poorly understood. This study was aimed to examine the impact of methimazole (MMI)-induced hypothyroidism on mRNA expression of angiotensin II type 1 receptor-a (AT1a) and type 2 (AT2) receptors in the mouse brain. Pregnant C57BL/6J mice in hypothyroid (H) group received an administration of 0.03% MMI in the drinking water from gestational day 10, and at postnatal day (P) 7, these dams were divided into two subgroups: perinatal hypothyroid (H1) and permanent hypothyroid (H2) groups. Dams in the H1 group stopped receiving MMI, and their litters received pure water after weaning (P21). Dams in the H2 group continued to receive MMI treatment until weaning, and their litters received MMI treatment until sacrifice. The relative expressions of cerebral AT1a and AT2 mRNA were determined by quantitative real-time polymerase chain reaction (PCR). In the H1 group, the cerebral AT1a mRNA expression of offspring was significantly decreased during their first two postnatal weeks, and recovered to normal level thereafter. However, cerebral AT1a mRNA expression of H2 group was reduced persistently during postnatal development. Conversely, cerebral AT2 mRNA expression in the H2 group was significantly increased compared with the controls at P14 and P21. In conclusion, we found that developmentally-induced hypothyroidism may alter mRNA expression of cerebral AT1a and AT2 in the mouse offspring.

Key words

Angiotensin II receptor; Hypothyroidism; Renin-angiotensin system; Thyroid hormone

Introduction

The classic renin-angiotensin system (RAS) was initially described as a circulating endocrine system that mediating cardiovascular and body fluid regulation. A major advance in this field is the discovery of a complete local RAS in the brain, independent from the peripheral system. The brain RAS is involved in blood pressure control, drinking behavior, sodium intake and cognitive performance. The functional components of brain RAS include angiotensinogen, peptidases, angiotensin, and specific receptors.

Among them, angiotensin II is the most powerful effector that exerts its action mainly through two principal types of angiotensin II receptors, AT1 and AT2. They are both widely expressed in the brain of the mammals and rodents, and they can be antagonised by losartan and PD123319, respectively. In rodents, there are two homologous AT1
subtypes, AT1a and AT1b. AT1a is predominantly expressed in the central nervous system. Most biological effects of the brain RAS including vasoconstriction, cellular growth, and proliferation are ascribed to the activation of AT1. On the contrary, AT2 may counterbalance the effects of AT1, promoting vasodilatation, apoptosis, and antigrowth effects.

Classic RAS as well as local RAS can be modulated by various kinds of hormones, especially thyroid hormone (TH). There are growing evidences that deficiency of TH during early or adult life has direct effects on RAS functions. One clinical study revealed that the circulating angiotensin converting enzyme level was significantly reduced in children with congenital hypothyroidism. With respect to local RAS, changes in its components induced by TH deficiency seem to be tissue specific. Adult hypothyroidism can cause AT1 and AT2 gene overexpression in the rat heart. Chen et al performed thyroidectomy surgery on fetal sheep and they found AT1 mRNA expression was downregulated but AT2 mRNA expression was upregulated in the kidney. In the rat brain, both perinatal and adult hypothyroidism resulted in a marked decrease of angiotensinogen mRNA. However, little is known about the impact of TH deficiency on cerebral AT1 and AT2 expressions.

It’s now well established that brain AT1 and AT2 expressions are developmentally regulated. Therefore, in the present study, we aimed to compare the expression patterns of cerebral AT1 and AT2 mRNA between the normal mice and those with developmentally-induced hypothyroidism.

Materials and Methods

Animals and Induction of Experimental Hypothyroidism

Pregnant C57BL/6J mice were purchased from the Center of Animal Experiments at Zhejiang University. Dams were randomly assigned to the hypothyroid (H) and control (CN) groups. Dams in the H group were exposed to an anti-thyroid drug methimazole (MMI) (Sigma, USA), at a concentration of 0.03% in drinking water. MMI treatment was started at gestational day 10. And at postnatal day (P) 7, the hypothyroid dams were divided into two subgroups: perinatal hypothyroid (H1) and permanent hypothyroid (H2) groups. Dams in the H1 group stopped receiving MMI, and their litters received pure water and normal diets after weaning at P21. Dams in the H2 group continued to receive MMI treatment until sacrifice. Both dams and their litters in the CN group received pure water and normal diet throughout the experimental period. Animals were housed in a temperature-controlled animal facility with a reversed light/dark cycle. The experimental protocol was approved by the Animal Ethics Committee of Zhejiang University.

Sample Collection

Mouse offspring were sacrificed at P7, P14, P21 and P60. To evaluate MMI-induced changes of cerebral AT1 and AT2 mRNA levels, their cerebrum were immediately removed on ice for RNA extraction. Total cerebral RNA was extracted using an AxyPrep TM Multisource Total RNA Miniprep kit (Axygen Biosciences, USA).

Serum TH Analyses

For each litter, trunk blood was collected upon decapitation and kept on ice until centrifuged to collect serum. Serum total triiodothyronine (TT3) and total thyroxine (TT4) concentrations were analysed by an IMMULITE 1000 immunoassay system (Siemens Medical Solutions, USA).

Quantitative Real-time PCR Analysis

Total RNA was reverse transcribed using a PrimeScript® RT reagent kit (TaKaRa, Japan). The target genes were AT1a (Agtr1a, 11607) and AT2 (Agtr2, 11609). Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used as the endogenous reference gene. Their specific primer sequences are listed in Table 1. The quantitative real-time PCR analyses were performed in Sequence Detection System (SDS 7500; Version 1.4.0; Applied Biosystems, USA) using SYBR Green detection. They were performed according to the following thermo-cycling parameters: 94°C for 180 seconds, followed by 40 two-step cycles at 94°C for 20 seconds and at 60°C for 45 seconds. We used 2-\(\Delta\Delta C_t\) method to analysed the data: \(\Delta C_t\) = (target gene) - (GAPDH) and \(\Delta\Delta C_t\) = (tested sample) - (calibrator). The mean \(\Delta C_t\) (CN group on P7) was used as a calibrator (fold change equals one) for each gene. By using the formula that relative expression = 2\(-\Delta\Delta C_t\) (tested sample)/mean \(\Delta\Delta C_t\) (CN group on P7), the fold change in target gene expression, normalised to GAPDH and relative to mean \(\Delta C_t\) (CN group on P7), was calculated for each tested sample.

Statistical Analyses

Data were analysed using SPSS 22.0 software. All biological data were examined for normal distributions. Normally distributed data were expressed as mean ±
standard deviation (SD). Differences between the normal and hypothyroid groups at P7 were compared by independent-samples t test. Differences between three groups were compared by one-way ANOVA and LSD multiple comparison test. \( P \) values <0.05 was considered significant.

**Results**

**Changes in Serum TT3 and TT4 Levels of the Offspring (Table 2)**

Serum TT3 and TT4 levels of mice offspring were evaluated at P7, P14, P21 and P60. In the H1 group, serum TT3 and TT4 levels were significantly lower than those in the CN group from birth to P14 and P21, respectively. Afterwards they reversed to normal levels. In the H2 group, both of serum TT3 and TT4 concentrations were persistently decreased by approximately 30% to 40% as compared with their controls, and the differences had statistical significances \((P<0.05)\) at all investigated ages.

**Changes in Cerebral AT1a mRNA Expressions of the Offspring (Figure 1)**

AT1a mRNA expression in the normal mouse brain followed a developmental pattern with a general increase with advancing age. There was a four-fold increase in AT1a mRNA expression at P21 compared with that at P7, and the increased expression lasted into adulthood (P60). In the H1 group, the cerebral AT1a mRNA expression level was obviously decreased during the first two postnatal weeks, but it returned to normal at P21, and then significantly exceeded the control level at P60 \((P<0.05)\). In the H2 group, there was a persistent significant reduction in cerebral AT1a mRNA expression compared with the controls during postnatal development \((P<0.05)\).

**Changes in Cerebral AT2 mRNA Expressions of the Offspring (Figure 2)**

The AT2 mRNA expression in the normal mouse brain displayed an opposite developmental pattern of AT1 mRNA. In the CN group, cerebral AT2 mRNA expression

### Table 1  Sequence of specific primers used for quantitative real-time PCR

<table>
<thead>
<tr>
<th>Forward</th>
<th>Reverse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agtr1a</td>
<td>GGACACTGCCATGCCCATAAC</td>
</tr>
<tr>
<td>Agtr2</td>
<td>GTGCATGGGGAGCTGAGTA</td>
</tr>
<tr>
<td>GAPDH</td>
<td>CAATGTGTCCGTCGTGGATCT</td>
</tr>
</tbody>
</table>

Agtr1a: Angiotensin II type 1a receptor; Agtr2: Angiotensin II type 2 receptor; GAPDH: glyceraldehyde-3-phosphate dehydrogenase

### Table 2  Effects of MMI treatment on serum TT3 and TT4 levels (nmol/L) of offspring

<table>
<thead>
<tr>
<th>Groups</th>
<th>TT3 (nmol/L)</th>
<th>P7</th>
<th>P14</th>
<th>P21</th>
<th>P60</th>
</tr>
</thead>
<tbody>
<tr>
<td>CN (n)</td>
<td>2.2±0.32 (7)</td>
<td>2.56±0.31 (8)</td>
<td>2.0±0.28 (7)</td>
<td>1.63±0.28 (7)</td>
<td></td>
</tr>
<tr>
<td>H1 (n)</td>
<td>1.5±0.35 (9)*</td>
<td>1.94±0.17 (7)*</td>
<td>1.94±0.1 (7)</td>
<td>1.5±0.28 (7)</td>
<td></td>
</tr>
<tr>
<td>H2 (n)</td>
<td>1.53±0.42 (9)*#</td>
<td>1.27±0.26 (7)*#</td>
<td>1.21±0.22 (7)*</td>
<td>1.21±0.22 (7)*</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Groups</th>
<th>TT4 (nmol/L)</th>
<th>Postnatal day (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CN (n)</td>
<td>92.5±10.63 (7)</td>
<td>103.26±5.66 (8)</td>
</tr>
<tr>
<td>H1 (n)</td>
<td>63.06±10.03 (9)*</td>
<td>73±7.38 (7)*</td>
</tr>
<tr>
<td>H2 (n)</td>
<td>73.29±6.6 (9)*</td>
<td>64.09±4.56 (7)*#</td>
</tr>
</tbody>
</table>

Serum total triiodothyronine (TT3) and total thyroxine (TT4) concentrations were measured in the normal control (CN), perinatal hypothyroid (H1) and permanent hypothyroid (H2) groups at P 7, 14, 21 and 60.

Data are expressed as mean±SD. *indicates significant differences compared with the CN group, \( P<0.05 \). #indicates significant differences compared with the H1 group, \( P<0.05 \).
was progressively decreased during postnatal development, with a fold change of 0.29 at P60 relative to P7. At P14 and P21, we detected a significant increase in cerebral AT2 mRNA expression of the H2 group comparing with other groups ($P<0.05$). However, there was no significant difference in cerebral AT2 mRNA expression levels between the H1 and CN groups.

Discussion

In the normal mouse brain, AT1a mRNA expression increased gradually during lactation and then maintained a high level, whereas AT2 mRNA expression declined steadily during postnatal development. The pattern of reciprocal changes in cerebral AT1a and AT2 mRNA expression during normal maturation is consistent with several previous protein studies.20-22 This phenomenon may be due to the negative crosstalk between AT1 and AT2 signaling. One previous in-vivo study reported that a sustained peripheral administration of AT2 antagonist PD123319 into adult male rats increased AT1 mRNA expression in the brain.24 In vitro, AT1 blockade increased AT2 mRNA expressions in endothelial cells while overexpression of AT2 significantly decreased AT1 gene expression in vascular smooth muscle cells.25-27

TH is essential for normal brain development and deficiency of TH in early development leads to a series of neurological disorders.28 The anti-thyroid drug MMI can cross the placenta freely and be excreted into milk,29,30 so we duplicated both perinatal and persistent hypothyroid models by orally giving MMI to dams and/or offspring during different developmental time frames.31 We observed a persistent reduction of serum TT3 and TT4 levels in the H2 group and a recovery of reduced serum TT3 and TT4 levels in the H1 group. Serum T4 crosses the blood-brain barrier and has been shown to be toxic to the brain.32-34

Figure 1  Effect of hypothyroidism on cerebral AT1a mRNA expression of offspring.

Total RNA was purified from mice cerebrum in normal control (CN) group, perinatal hypothyroid (H1) group and permanent hypothyroid (H2) group at postnatal day (P) 7, 14, 21 and 60. Total RNA was reverse transcribed and then analysed by quantitative real-time PCR analysis. Data of relative AT1a mRNA expression were obtained by using the $2^{-\Delta\Delta Ct}$ method. The fold change in AT1a mRNA expression, normalised to endogenous reference gene (GAPDH) and relative to mean $\Delta Ct$ (CN group on P7), was calculated for each sample.

Data are expressed as mean±SD. *indicates significant differences compared with the CN group, $P<0.05$. #indicates significant differences compared with the H1 group, $P<0.05$.

Figure 2  Effect of hypothyroidism on cerebral AT2 mRNA expression of offspring.

Total RNA was purified from mice cerebrum in normal control (CN) group, perinatal hypothyroid (H1) group and permanent hypothyroid (H2) group at postnatal day (P) 7, 14, 21 and 60. Total RNA was reverse transcribed and then analysed by quantitative real-time PCR analysis. Data of relative AT2 mRNA expression were obtained by using the $2^{-\Delta\Delta Ct}$ method. The fold change in AT2 mRNA expression, normalised to endogenous reference gene (GAPDH) and relative to mean $\Delta Ct$ (CN group on P7), was calculated for each sample.

Data are expressed as mean±SD. *indicates significant differences compared with the CN group, $P<0.05$. #indicates significant differences compared with the H1 group, $P<0.05$. 
barrier or blood-cerebrospinal fluid barrier more easily than T3. In the brain, T4 undergoes local deiodination into active T3, which is transferred to neurons or oligodendrocytes and then binds to thyroid receptors. As a result, the declined serum TT4 levels in the hypothyroid offspring may affect brain TH levels.

TH functions by regulating target genes, the transcriptional products of which are the essential proteins underlying neurobiological events. To our knowledge, present research findings suggest for the first time that permanent hypothyroidism starting from fetal period significantly down regulates AT1a mRNA expression but up regulates AT2 mRNA expression in the mouse brain. In the H1 group, cerebral AT1a mRNA expression was decreased during first two weeks, but later it was restored to normal and was significantly increased compared with the controls at P60. This interesting phenomenon is indicative of a compensatory of AT1a gene expression in perinatal hypothyroid offspring once anti-thyroid treatment ceases at P7.

The precise mechanism underlying the effect of hypothyroidism on brain AT1a and AT2 gene expression remains unknown. Several previous studies have demonstrated that hypothyroidism in early development results in partial arrest of astrocyte differentiation and down regulates angiotensinogen gene expression in the brain. Astrocyte is the principal cellular source of brain angiotensin II as it produces angiotensinogen; angiotensin II in turn acts on AT1 in astrocytes via different kinase signaling pathways to stimulate astrocyte proliferation. In addition, chronic intraventricular infusion of angiotensin II has been reported to increase AT1 gene expression but decrease AT2 gene expression in the rat brain. Accordingly, we speculate that the delayed astrocyte development and reduced angiotensinogen expression may contribute to changes of AT1a and AT2 gene expression in the hypothyroid brain.

AT2 is highly expressed in the fetal brain and declines rapidly after birth, coinciding with cessation of developmental apoptosis, suggesting a role in cell apoptosis. AT2 was considered to be essential to mediate the effect of angiotensin II on enhancing apoptosis of cultured neurons from newborn rat brain. In addition, the overexpression of AT2 itself is a ligand-independent signal for cell apoptosis. We previously reported that the number of apoptotic neurons was increased in the hippocampus of hypothyroid rat offspring. Thus, hypothyroidism-induced gene overexpression of cerebral AT2 may be implicated in the enhanced neuronal apoptosis observed in the hypothyroid brain.

There was a limitation in our study that we used mRNA expression as the indicator of AT1a and AT2 changes. However, in most studies, there is a rather good agreement in the direction of changes between their mRNA and protein expression.

In conclusion, our findings indicate an important role of TH in regulating cerebral AT1a and AT2 mRNA expression. Further research work is needed to investigate the impacts of hypothyroidism on the related protein expression.

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Declaration of Interest

We declare no conflict of interest.

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7. Lenkei Z, Palkovits M, Corvol P, Llorens-Cortes C. Distribution
**Update on Clinical Practice**

*Update on Helicobacter pylori Infection in Children*

**CO SHAM**

**Abstract**

*Helicobacter pylori* infection is a common worldwide infection. It is an important cause of gastric cancer, but an overwhelming majority of those get infected will not suffer any consequences during their lifetime. The indication of testing, diagnosis and management of this bacterial infection are also different in children and in adult. This article serves to highlight the important points included in the two guidelines, difference in management of adult and children patients, and discuss the applicability of the guidelines in the Hong Kong setting.

**Key words**

Children; Diagnostic tests; Eradication; *Helicobacter pylori*; Triple therapy

**Introduction**

*Helicobacter pylori* (*H. pylori*) infection is a well-recognised aetiology for peptic ulcer disease and gastric cancer. The infection is often chronic and usually acquired in childhood, but it rarely causes complications in childhood and adolescence, in contrast to adults. Significant scientific advances have been made in this field throughout these years. The European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)/ the North American Society of Paediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) and the American College of Gastroenterology (ACG) have issued new guidelines in management of this disease in 2016 and 2017.\(^1,2\) This article serves to highlight the important points included in the two guidelines, difference in management of adult and children patients, and discuss the applicability of the guidelines in the Hong Kong setting.

**Who Should Be Tested and Treated?**

All adult patients with an evidence of active *H. pylori* infection should be treated.\(^2\) However, this statement may not be true in children.\(^1\) In children with peptic ulcer disease, eradication of the infection may lower the risk of ulcer recurrence. For other situations, treatment is controversial. This is because there are no data showing that *H. pylori* cause symptoms or complications in children in the absence of peptic ulcer disease. *H. pylori* associated gastritis can be an incidental finding which is picked up during upper gastrointestinal endoscopy for work up of other conditions such as inflammatory bowel disease or coeliac disease, but this condition rarely gives rise to complications such as peptic ulcer disease and gastric cancer in childhood. Moreover, some young children can be re-infected with *H. pylori* after its successful eradication. A study in Bolivia has shown that the re-infection rate in 1 year can be up to 20% in young children.\(^1\) Furthermore, there is epidemiological evidence for an inverse association between *H. pylori* infection and allergic diseases in young children.\(^1\) Indeed, eradication of *H. pylori* in these children may not
relieve the symptoms, but may also expose the child to potential risk of treatment such as treatment failure, cramps, diarrhoea and undesirable alteration of the gut microbiome. Of course, in discussion with parents and older patient, these problems should be addressed as well as the risk of complications related to infection, such as peptic ulcer disease and gastric cancer, later in life.

For iron deficiency anaemia, testing and treatment of H. pylori remains controversial. A recently published systematic review and meta-analysis showed that there was a significantly increased likelihood of iron deficiency anaemia in H. pylori infected individuals compared with un-infected ones. A study in Texas also found out that children with H. pylori infection eradicated had a significant 3-fold increase in ferritin over baseline level. However, such changes were not noted in a study conducted in Bangladesh. A review in Iran concluded that there was not enough evidence to conclude that there was association of H. pylori eradication therapy and refractory childhood iron deficiency anaemia.

Table 1 listed the indications of H. pylori testing and its treatment in adults and children:

<table>
<thead>
<tr>
<th>Indications of H. Pylori testing and its treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adults</strong></td>
</tr>
<tr>
<td>Testing indicated:</td>
</tr>
<tr>
<td>• Active peptic ulcer disease</td>
</tr>
<tr>
<td>• Past history of peptic ulcer disease without cure of H. pylori infection documented</td>
</tr>
<tr>
<td>• Low grade gastric mucosa associated lymphoid tissue (MALT) lymphoma</td>
</tr>
<tr>
<td>• History of endoscopic resection of early gastric cancer</td>
</tr>
<tr>
<td>• Uninvestigated dyspepsia below the age of 60 without alarming features (point 1)</td>
</tr>
<tr>
<td>• Patients taking long term low dose aspirin</td>
</tr>
<tr>
<td>• Patients initiating chronic treatment with a non-steroidal anti-inflammatory drug (NSAID) (point 2)</td>
</tr>
<tr>
<td>• Unexplained iron deficiency anaemia despite appropriate evaluation</td>
</tr>
<tr>
<td>• Adults with idiopathic thrombocytopenic purpura</td>
</tr>
</tbody>
</table>

Note points:
1. Number needed to treat to cure functional dyspepsia was 14.
2. Benefit of testing and treating H. pylori in NSAID-treated patients remains unclear.
3. In the author’s opinion, treatment of GERD may involve prolonged use of proton pump inhibitors (PPI), and eradication of H. pylori infection before starting this treatment may prevent the progression to atrophic gastritis.
4. Beware of warning signs, which include persistent right upper or right lower quadrant pain, dysphagia, odynophagia, persistent vomiting, gastrointestinal blood loss, involuntary weight loss, deceleration of linear growth, delayed puberty, unexplained fever, and a family history of inflammatory bowel disease, coeliac disease or peptic ulcer disease.
Test and Treat Strategy

The ACG Guideline endorsed this treatment strategy for *H. pylori* infection for patients under 60 years of age who have dyspeptic symptoms and without warning features. In areas that *H. pylori* is prevalent, non-invasive tests for this bacterium may be performed in this group of patients, and eradication therapy should be offered if test positive. Otherwise, the patient can be given a trial of proton pump inhibitors (PPI) and see if his or her symptoms will improve. In case of treatment failure in both situations, upper gastrointestinal endoscopy may then be arranged. The test and treat strategy was found to be more cost effective than proceeding with endoscopy right away or empirical acid suppression with PPI. In children, as there was no data showing that *H. pylori* causes symptoms in the absence of peptic ulcer disease, if organic cause of dyspepsia is suspected, upper gastrointestinal endoscopy should be arranged. The test and treat strategy is not recommended.

Diagnosis

In adults, diagnosis of *H. pylori* can be made easily by non-invasive tests such as urea breath tests and stool antigen test. The sensitivity and specificity of both tests are above 90%. However, because of low prevalence of *H. pylori* infection in children, especially in Europe and North America, the positive predictive values of these tests are low. The ESPGHAN/NASPGHAN Guideline recommended that *H. pylori* infection in children should be diagnosed either by positive culture or by finding *H. pylori* gastritis on histopathology plus one more positive test such as rapid urease test (RUT). To achieve this diagnosis, the current standard is to obtain at least six gastric biopsies, including two from antrum and two from corpus for histopathological evaluation as well as one from antrum and one from corpus for *H. pylori* culture. One more gastric biopsy should be obtained for additional diagnostic test such as RUT. Urea breath test or stool antigen test may help to support the diagnosis of *H. pylori* infection.

Note: The ACG Guideline recommends to collect biopsies of normal-appearing gastric mucosa for *H. pylori* detection during endoscopy in patients with dyspeptic symptoms; while the ESPGHAN/NASPGHAN Guideline recommends that during endoscopy if antral nodularity without mucosal lesions (gastric/duodenal erosions or ulcers) is visualised, biopsies for RUT and culture to diagnose *H. pylori* infection and guide treatment should only be taken if treatment is likely to be offered upon confirmation of infection.

Table 2  Treatment options recommended by ESPGHAN/ NASPGHAN

<table>
<thead>
<tr>
<th><em>H. pylori</em> antimicrobial susceptibility</th>
<th>Suggested treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Known susceptibility to clarithromycin and to metronidazole</td>
<td>PPI + amoxicillin + clarithromycin for 14 days</td>
</tr>
<tr>
<td>Known resistance to clarithromycin but susceptibility</td>
<td>PPI + amoxicillin + metronidazole for 14 days or bismuth</td>
</tr>
<tr>
<td>to metronidazole</td>
<td>based</td>
</tr>
<tr>
<td>Known resistance to metronidazole but susceptibility to</td>
<td>PPI + amoxicillin + clarithromycin for 14 days or bismuth</td>
</tr>
<tr>
<td>clarithromycin</td>
<td>based</td>
</tr>
<tr>
<td>Resistance to both clarithromycin and metronidazole</td>
<td>PPI + amoxicillin + metronidazole for 14 days with high dose</td>
</tr>
<tr>
<td></td>
<td>amoxicillin or bismuth based</td>
</tr>
<tr>
<td>Unknown</td>
<td>PPI + amoxicillin + metronidazole for 14 days with high dose</td>
</tr>
<tr>
<td></td>
<td>amoxicillin or bismuth based, or concomitant therapy</td>
</tr>
<tr>
<td></td>
<td>(PPI + amoxicillin + clarithromycin + metronidazole) for</td>
</tr>
<tr>
<td></td>
<td>14 days</td>
</tr>
</tbody>
</table>

* PPI dose 1.5-2.5 mg/kg/day refer to esomeprazole and omeprazole and should be adapted if other PPIs are used
Table 3  Standard dosing regimen as recommended by ESPGHAN/NASPGHAN Guideline

<table>
<thead>
<tr>
<th>Drug</th>
<th>Body weight range</th>
<th>Morning dose, mg</th>
<th>Evening dose, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPI</td>
<td>15-24 kg</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>25-34 kg</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>35 kg or more</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Amoxycillin</td>
<td>15-24 kg</td>
<td>500</td>
<td>500</td>
</tr>
<tr>
<td></td>
<td>25-34 kg</td>
<td>750</td>
<td>750</td>
</tr>
<tr>
<td></td>
<td>35 kg or more</td>
<td>1000</td>
<td>1000</td>
</tr>
<tr>
<td>Clarithromycin/metronidazole</td>
<td>15-24 kg</td>
<td>250</td>
<td>250</td>
</tr>
<tr>
<td></td>
<td>25-34 kg</td>
<td>500</td>
<td>250</td>
</tr>
<tr>
<td></td>
<td>35 kg or more</td>
<td>500</td>
<td>500</td>
</tr>
</tbody>
</table>

Table 4  First line treatment options recommended by ACG Guideline

<table>
<thead>
<tr>
<th>Name of regimen</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarithromycin triple</td>
<td>PPI + clarithromycin + amoxicillin or metronidazole for 14 days</td>
</tr>
<tr>
<td></td>
<td>(The only regimen approved by US Food and Drug Administration)</td>
</tr>
<tr>
<td>Bismuth quadruple</td>
<td>PPI + bismuth + tetracycline + metronidazole for 10-14 days</td>
</tr>
<tr>
<td>Concomitant</td>
<td>PPI + clarithromycin + amoxicillin + nitroimidazole for 10-14 days</td>
</tr>
<tr>
<td>Sequential</td>
<td>PPI + amoxicillin for 5-7 days then PPI + clarithromycin + nitroimidazole for 5-7 days</td>
</tr>
<tr>
<td>Hybrid</td>
<td>PPI + amoxicillin for 7 days then PPI + amoxicillin + clarithromycin + nitroimidazole for 7 days</td>
</tr>
<tr>
<td>Levofoxacin triple</td>
<td>PPI + levofoxacin + amoxicillin for 10-14 days</td>
</tr>
<tr>
<td>Levofoxacin sequential</td>
<td>PPI + amoxicillin for 5-7 days then PPI + levofoxacin + nitroimidazole for 5-7 days</td>
</tr>
<tr>
<td>LOAD</td>
<td>Levofoxacin + PPI double dose + nitazoxanide + doxycycline for 7-10 days</td>
</tr>
</tbody>
</table>

The ACG Guideline recommends enquiry of patients' previous antibiotic exposure, particularly macrolides and fluoroquinolones, when choosing a treatment regimen (Table 4). Previous macrolide therapy for longer than 2 weeks in 20 years is associated with higher risk of treatment failure with clarithromycin triple therapy. Previous macrolide therapy for longer than 2 weeks in 20 years is associated with higher risk of treatment failure with clarithromycin triple therapy. For those with reported penicillin allergy and failed first line H. pylori eradication therapy, the ACG Guideline recommends that these patients should be referred for allergy testing since the vast majority, who do not have true penicillin hypersensitivity, can ultimately be safely given amoxicillin-containing salvage regimens. Enquiry about previous antibiotic exposure and penicillin allergy testing are not mentioned in the paediatric guidelines but the author believes that these are good practice (and paediatricians should consider to follow).

Outcome Assessment

The ESPGHAN/NASPGHAN Guideline mentioned that levofoxacin or tetracycline may be considered in the rescue regimen if an adolescent patient failed treatment with first line therapy options. Paediatricians may worry about the safety profile of these two groups of drugs. A study published in 2014 has shown that levofoxacin may be safe for use in children. Doxycycline has been used for treatment of macrolide resistant Mycoplasma pneumoniae in children and so-far no significant adverse events have been reported.

The ACG and the ESPGHAN/NASPGHAN Guidelines recommend testing to prove eradication of H. pylori at least 4 weeks after completion of antibiotic therapy, and after
PPI therapy have been withheld for two weeks. This may be carried out by the urea breath test or stool antigen test.1,2

**Probiotic**

The ESPGHAN/NASPGHAN Guideline does not support the routine addition of probiotic to *H. pylori* eradication therapies due to the lack of evidence that this treatment can reduce the side effects.

**Further Research Questions**

A study published in 2008 involving 2480 Hong Kong children aged 6-19 years has shown that 13.1% of the population had positive urea breath test that suggested *H. pylori* infection.11 A continuous surveillance of the situation is needed as disease prevalence will affect the positive predictive value and cost effectiveness of different diagnostic tests, as well as our recommendation in diagnosing *H. pylori* infection among local children.

Research should also be conducted on whether the test and treat strategy is suitable for management of Hong Kong adolescents with apparent dyspepsia. Dyspeptic symptoms are not uncommon in adolescents in Hong Kong, and *H. pylori* infection is much more prevalent in Hong Kong than in countries in Europe and North America.12,13 This may be a cost-effective strategy in the management of this group of patients.

**Applicability**

Although the prevalence of *H. pylori* infection in children is different, there are similarities between the situation in Hong Kong and that in Europe and North America (Table 5). There are no data showing that *H. pylori* cause symptoms or complications in children in the absence of peptic ulcer disease in Hong Kong, Europe and North America. Due to the even higher prevalence of *H. pylori* infection in Hong Kong, the risk of re-infection after eradication may even be higher. There is so far no evidence that eradication of *H. pylori* infection in childhood can lower the risk of stomach cancer in adulthood in Hong Kong. Therefore the author believed that the Joint ESPGHAN/NASPGHAN Guideline can be applied in Hong Kong.

**Summary**

1. Management of *H. pylori* infection is different between adults and children because of different treatment aims, different risk of disease complications such as peptic ulcer disease and gastric cancer, and different re-infection rate.
2. *H. pylori* associated gastritis without peptic ulcer disease does not cause symptoms in most children. Therefore, treatment of such condition may not relieve the gastrointestinal symptoms of children. Children with functional abdominal pain should not undergo testing for *H. pylori* infection.
3. The traditional 7-day triple therapy regimen should not be used to eradicate *H. pylori* in view of its low efficacy. The ACG Guideline recommends that triple therapy should be given for 14 days in the North America.2

**Competing Interest**

None declared.

**Acknowledgement**

The author would like to thank the Hong Kong Society of Gastroenterology, Hepatology and Nutrition (HKSPGHAN) for reviewing the article.

**References**


<table>
<thead>
<tr>
<th>Area</th>
<th>Prevalence estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hong Kong</td>
<td>13.1%11</td>
</tr>
<tr>
<td>Iran</td>
<td>64.2%14</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Less than 5%15</td>
</tr>
<tr>
<td>Turkey</td>
<td>23.6%16</td>
</tr>
<tr>
<td>United States</td>
<td>Less than 5%16</td>
</tr>
</tbody>
</table>


Café Au Lait Spots: What is the Diagnosis If It Is Not Neurofibromatosis Type I?

PT Yu, HM Luk, IFM Lo

Abstract

Multiple café au lait spots is a common referral indication for assessment of possible syndromal disorder. Neurofibromatosis type 1 (NF-1) is a common disease in paediatric population, which characterised by café au lait spots, intertriginous freckling, neurofibroma, lisch nodules and/or osseous lesions. Plexiform neurofibroma, optic nerve and other central nervous system gliomas are occasionally seen. Legius syndrome is a relatively new disorder that being described in the literature since 2007, which present with NF-1 like features, including café au lait spot, freckles, macrocephaly and learning disability. However, it is not associated with benign or malignant tumours. Therefore, the differentiation between these two entities are important that not only for diagnosis, but also for prognosis counselling and follow up surveillance. Here, we report a child who initially referred for suspected NF-1, who is subsequently diagnosed to have Legius syndrome. Also, we have summarised and compared the clinical features of NF-1 and Legius syndrome, their difference in counselling and surveillance are also being discussed.

Key words

Legius syndrome; NF1-like; \textit{SPRED1} gene

Introduction

Neurofibromatosis type 1 (NF-1) is one of the most common neurocutaneous syndrome in paediatric population that presented with multiple café au lait spot. Legius syndrome is a recently reported disease entity that manifested with NF-1 like features. The two diseases may be indistinguishable in early childhood. Here, we reported a 15 years old boy presented with NF-1 features, who was subsequently diagnosed to have Legius syndrome by \textit{SPRED1} gene testing. This is the first reported Chinese case in the literature.

Case Report

A 15-year-old boy was referred to clinical genetic clinic in July 2016 for suspected NF-1, due to multiple café au lait spots and axillary freckles. He was the first child from a non-consanguineous Chinese couple, born at full term with birth weight of 3.8 kg. Antenatal follow up revealed mild dilated renal pelvis, which was eventually normalised in the postnatal renal ultrasound. Otherwise, he enjoyed good health and normal development. There was no skeletal dysplasia and ophthalmological assessment was normal. He had no neurological symptoms all along. Family history was unremarkable. Physical examination showed mild macrocephaly (head circumference 59 cm, 0.5 cm >97th percentile), multiple café au lait spots more than 6 patches with size more than 1.5 cm. The maximal size was around 8 cm at the longest diameter (Figure 1). There were also axillary and groin freckles but no neurofibroma nor plexiform neurofibroma. There was also no scoliosis or skeletal dysplasia. Examinations of other systems were normal. Based on the clinical diagnosis of NF-1, genetic testing included Multiplex ligation-dependent probe
amplification (SALSA P081-B1/P082-B1 kit) and sequencing of $NF1$ gene (reference sequence NM_000267.3) were performed, but no pathogenic variant or copy number change in coding region of $NF1$ gene was detected. Since there was no other stigmata of neurofibromatosis type 1 apart from café au lait spots and freckles at his adolescent period, Legius syndrome was suspected. Sequencing of $SPRED1$ gene was performed that showed a heterozygous 4 base pair deletion $c.1149_1152\text{delAGAG}$ pathogenic variant in exon 7 of $SPRED1$ gene. This is a reported mutation in the literature\(^1\) and the diagnosis of Legius syndrome was substantiated. Parental testing showed it is a denovo change.

**Discussion**

Multiple café au lait spot is a common indication of referral for genetic assessment and counselling. Among the list of differential diagnoses (Table 1A), neurofibromatosis type 1 is one of the most common and well-known cause of café au lait macules. Neurofibromatosis type 1 (OMIM #162200) is an autosomal dominant genetic disorder with incidence of 1 in 3000 live births. The main features include café au lait spot, intertriginous freckling, neurofibroma, lisch nodules and osseous lesions. Learning disability presents in 50% of cases. More serious but less frequent features included plexiform neurofibroma, optic nerve and

---

**Figure 1**  This showed multiple café au lait spots, pigmentary macules and Intertriginous freckling in our patient. There is no neurofibroma, plexiform neuroma or skeletal deformity.
other central nervous system gliomas. Legius syndrome (OMIM #611431) is an autosomal dominant disorder that have many overlapping features with NF-1 particularly cutaneous changes like café au lait spots, with or without intertriginous freckling, intellectual disability and macrocephaly. But there are no non-cutaneous features like neurofibroma, plexiform neurofibroma, optic gliomas, sphenoid wing dysplasia. Also, Legius syndrome is not associated with increased risk of malignancies (Table 1B). Therefore, distinction of the two entities is important in clinical management and counselling of disease prognosis.

Legius syndrome is caused by heterozygous germline pathogenic variant in \( SPRED1 \) gene. \( SPRED1 \) gene is located on chromosome 15q13.2 that encodes a protein spred1 which negatively regulates Ras-MAPK signaling. Mutation in \( SPRED1 \) gene would result in dysregulation of Raf1 kinase activation and downstream Raf-MEK-ERK signaling. As NF-1 is caused by mutation in \( NF1 \) gene that is a key component of same pathway, therefore it would explain the overlapping clinical features between two disease entities.

Studies showed that about 1-4% of individuals with multiple café au lait spots and clinical NF-1 like features have \( SPRED1 \) mutation. Different prevalence in publications is due to the difference in clinical practice like age of testing and availability of genetic testing.

### Table 1
Differential diagnoses of multiple café au lait spots and the comparison of clinical features between Neurofibromatosis type 1 and Legius syndrome

<table>
<thead>
<tr>
<th>(A) Differential diagnoses of multiple café au lait spots</th>
<th>Neurofibromatosis type 1</th>
<th>Legius syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noonan syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autosomal dominant café au lait spots</td>
<td></td>
<td></td>
</tr>
<tr>
<td>McCune Albright syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bloom syndrome</td>
<td></td>
<td></td>
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<tr>
<td>Fanconi anaemia</td>
<td></td>
<td></td>
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<tr>
<td>Russell-Silver syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bannayan Riley Ruvalcaba syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Costello syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiofaciocutaneous syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tuberous sclerosis complex</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(B) Comparison of clinical features between Neurofibromatosis type 1 and Legius syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>NF-1</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Multiple café au lait spots</td>
</tr>
<tr>
<td>Intertriginous freckling</td>
</tr>
<tr>
<td>Neurofibromas</td>
</tr>
<tr>
<td>Plexiform neurofibroma</td>
</tr>
<tr>
<td>Optic gliomas</td>
</tr>
<tr>
<td>Lisch nodules</td>
</tr>
<tr>
<td>Macrocephaly</td>
</tr>
<tr>
<td>Learning disability</td>
</tr>
<tr>
<td>Malignant peripheral nerve sheath tumour</td>
</tr>
<tr>
<td>CNS tumour</td>
</tr>
<tr>
<td>Leukaemia</td>
</tr>
</tbody>
</table>
Distinguishing the two disease entities clinically in early childhood is difficult. But more specific characteristics of NF-1 may evolve when the child grows up. Until now, there is no consensus in the indications for \textit{SPRED1} gene testing. But in the literature, there was a study to demonstrate it is cost effective in testing \textit{NF-1} negative patients after puberty. They recommended that \textit{SPRED1} gene test should be considered in \textit{NF-1} like individual but without characteristic features of \textit{NF-1} at age between 10 and 14 years old.

In summary, we have reported the first molecularly confirmed Legius syndrome in Chinese. In patient with multiple café au lait spots, although NF-1 is the most common cause, alternative diagnosis like Legius syndrome should be considered. Differentiating patient with Legius syndrome from NF-1 is important as NF-1 patients require regular surveillance of the extra-cutaneous manifestations like optic pathway glioma and possible neurological tumours, which would not happen in the patient with Legius syndrome. Therefore, the diagnosis of Legius syndrome may not only avoid unnecessary medical intervention, but it would also relieve the psychological burden of patient and families, who are expecting less serious complications of Legius syndrome as compared with NF-1.

References

Case Report

Long-term Extrauterine Survival in a Triploid Infant: A Review of the Clinical Features of Live-born Infants with Triploidy

S Hashimoto, L Igarashi, M Kobayashi, H Tsutsumi

Abstract

Almost all triploid fetuses abort spontaneously in the first trimester; live-born triploid infants are rare. We herein report a triploid infant who survived for 250 days. The infant was delivered at 33 weeks 4 days of gestation because of severe fetal growth restriction. The birth weight was 1108 g, and multiple malformations were present. Chromosomal analysis demonstrated a karyotype of 69,XXY. At the time of this report, she lived at home and was 280 days old. A review of triploid infants revealed that the relatively unique clinical features of triploidy were syndactyly of the third and fourth fingers and abnormal erythrocyte indices. The associated karyotypes were 69,XXX and 69,XXY but not 69,XYY. Two of five infants died of pneumonia. Two infants, including the infant described herein, developed infantile spasms after the age of 200 days. Triploid infants with long-term survival are at high risk of developing pneumonia and infantile spasms.

Key words

Erythrocyte indices; Fetal growth restriction; Long-term survivor; Syndactyly; Triploidy

Introduction

Triploidy is a chromosomal abnormality that occurs in 1% of pregnancies. Almost all triploid fetuses abort spontaneously in the first trimester; therefore, live-born triploid infants are rare. In addition, live-born triploid infants usually die soon after birth. We herein report a triploid infant who survived for more than 250 days and was discharged home. We also performed a review of the long-term survival of triploid infants to understand the relevant clinical features.

We obtained permission from the patient's parents to publish the features of this case.

Case Report

The infant's father was 43 years old and unrelated to the mother, who was 40 years old. The mother was 7 gravida, 1 para and had undergone 6 abortions (4 spontaneous abortions, 2 induced abortions). There was no significant family or medical history. Because severe fetal growth restriction was noted from 19 weeks of gestation, the infant was delivered at 33 weeks 4 days of gestation by cesarean section.

The birth weight was 1108 g (below 1st percentile), length was 36.5 cm (below 1st percentile), and head circumference was 27.5 cm (just below 5th percentile). The Apgar score was 3 points at 1 minute and 6 points at 5 minutes. The infant had multiple external malformations including sparse eyebrows, blepharoptosis, bilateral syndactyly of the third and fourth fingers, bilateral overlapping of the third and fourth toes, and labial adhesions.

The placenta weighed 360 g and had no cystic villi. A complete blood count obtained at birth showed that the mean corpuscular volume, mean corpuscular haemoglobin, and mean corpuscular haemoglobin concentration were 129.8 fL, 47.2 pg, and 36.4%, respectively. These three abnormal erythrocyte indices are reportedly increased in infants with triploidy. Bilateral colobomas were noted upon eye
examination. Brain magnetic resonance imaging demonstrated brain atrophy (mainly in the frontal lobe) and agenesis of the corpus callosum; however, whole-body computed tomography and ultrasound scanning revealed no major congenital anomalies.

Chromosomal G-banding of peripheral blood samples demonstrated a karyotype of 69,XXY in all 100 cells analysed. Although a Y chromosome was detected, the external genitalia were female; therefore, we determined that the infant was female. We recommended a chromosomal analysis and further analysis of other tissues, including the buccal mucosa or skin; however, the parents did not grant approval.

The patient required intratracheal intubation and ventilator management for treatment of respiratory failure until the age of 15 days, and indomethacin was administered twice to manage a patent ductus arteriosus. Administration of intravenous glucose for hypoglycemia was necessary until the age of 21 days, and indomethacin was administered until the age of 55 days. She developed bacteremia caused by Enterobacter cloacae at 66 days, which resolved after antibiotic treatment. It was vaccinated after 90 days; however, she developed a high fever, poor general condition, and elevation of her C-reactive protein blood concentration soon after vaccination. Because she had mild apnea and a respiratory disorder, she required oxygen therapy until 148 days of age. Oral feeding was difficult to perform after a corrected age of 1 month; therefore, she required tube feeding. At the age of 222 days (corrected age of 5 months), she required no medical treatment except tube feeding and was discharged home.

At the age of 248 days, she was readmitted because of convulsive seizures. An electroencephalogram demonstrated an abnormal electrical pattern consistent with hypersrrhythmia; therefore, we diagnosed her with infantile spasms. Antiepileptic drugs were administered, and her seizures were gradually controlled. At the time of this report, she was 280 days old and still at home.

Discussion

Long-term survival (>150 days) of triploid infants is very rare. The clinical features of such triploid infants are reviewed in Table 1. All parents except those in the present case were <40 years of age. There are no characteristic antenatal features with which to diagnose triploidy during the fetal period. The features of live-born triploid infants are various; therefore, there are no absolute clinical findings of triploidy. Nevertheless, bilateral syndactyly of the third and fourth fingers is not often reported in other chromosome disorders. In addition, abnormal erythrocyte indices are unique to triploidy. These findings might be helpful for diagnosis.

The karyotype of triploid infants with long-term survival is 69,XXX or 69,XXY, but not 69,XYY. Some infants were diagnosed by analysis of both peripheral blood lymphocytes and skin; therefore, the infant described herein may have had mosaic triploidy. A previous report has described live-born mosaic triploid infants. In most such cases, triploid cells were not detected in the peripheral blood, but they could be detected using fibroblast cultures derived from the skin or bone. In the present case, triploidy was confirmed in all 100 blood cells tested; therefore, we assumed that she was a complete triploid infant. In cases involving investigation of the origin of the extra haploid set of chromosomes in triploidy, the extra set was of maternal origin in all infants. Such analysis was not performed in this case because the parents did not grant permission. However, we considered that the extra set of chromosomes was of maternal origin because the infant showed fetal growth restriction, a large head relative to body size, and no cystic villi in the placenta, which are all characteristics of maternal origin.

Only six infants survived for >150 days, and the longest surviving infant was aged 312 days. Two of the five infants died of pneumonia. Our patient developed bacteremia and strong side effects of vaccination; therefore, triploidy might cause immune system dysfunction. We believe that adequate and rapid treatment of infection is important for long-term survival of triploid infants.

Seizures due to infantile spasms were reported in the longest surviving infant with triploidy. That infant and the present infant developed seizures at the age of 225 and 248 days, respectively; therefore, long-term survival might be associated with the development of infantile spasms after the age of 200 days.

In conclusion, our patient had similarities with previously described live-born triploid infants and showed the second-longest survival at the time of this report. Clinical findings of triploidy are difficult to diagnose in the fetal period and at birth; however, several unique features, including bilateral syndactyly of the third and fourth fingers and abnormal erythrocyte indices, might be useful for diagnosis. This disease has a poor prognosis, and very few infants live for >150 days. Prevention of infection (including pneumonia) and seizures caused by infantile spasms are important for long-term survival of triploid infants.
Table 1  Clinical features of long-term survival (>150 days) of triploid infants

<table>
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<td>Oligohydramnios</td>
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<td>1,850</td>
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<td>Hypertelorism</td>
<td>Small palpebral fissures</td>
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<td>Low-set ears</td>
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<td>Hypertelorism Low-set ears Cleft lip, alveolus and palate</td>
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<td>221 days</td>
<td>164 days</td>
<td>312 days</td>
<td>27 weeks</td>
<td>23 weeks</td>
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<td>Cardiorespiratory problems</td>
<td>Pneumonia</td>
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<td>Dyspnorea</td>
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</table>

FGR, fetal growth restriction
Disclosure Statement

All the authors declare that there is no conflict of interest.

Acknowledgment

We thank Angela Morben, DVM, ELS, from Edanz Group (www.edanzediting.com/ac), for editing a draft of this manuscript.

References


Case Report

Neonate with Congenital Myotonic Dystrophy Conceived via In Vitro Fertilisation by an Asymptomatic Mother

BN KIM, YT LEE, IG LEE, JY HAN

Abstract
Congenital myotonic dystrophy 1 (CDM1) is characterised by severe hypotonia with difficulty in swallowing and respiration, facial diplegia, and increased risk of prematurity. We report a neonate with CDM1 born to an asymptomatic mother after in vitro fertilisation. Molecular analysis for the cytosine-thymine-guanine (CTG) triplet related DM1 was carried out and revealed over 1,000 CTG repeats, which was consistent with the clinical impression of CDM1. Gene analysis was carried out on the proband's family. In this family, the expanded CTG repeats were transmitted maternally, and earlier age of onset and increasing severity of the disease occurred in following generations.

Key words
Congenital myotonic dystrophy

Introduction

Myotonic dystrophy is an autosomal dominant, multisystemic disorder characterised by myotonia, progressive muscle weakness and atrophy, disturbances of heart rhythms, hypogonadism, frontal balding, and cataracts.1 Usually there is weakness of distal muscles, especially those of face, ankle, and feet. The two types of myotonic dystrophy (DM1 and DM2) are both caused by gene mutations. DM1 results from an expansion of a cytosine-thymine-guanine (CTG) trinucleotide repeat in the 3'-untranslated region of the dystrophia myotonica protein kinase gene (DMPK gene) on chromosome 19q13.3. DM2 is due to mutations in the cellular nucleic acid-binding protein gene (CNBP gene) on chromosome 3q21.3 and generally milder. Myotonic dystrophy has heterogeneous clinical phenotype, ranging from the congenital form to an asymptomatic form. We report a neonate with congenital myotonic dystrophy 1 (CDM1) born to an asymptomatic mother after in vitro fertilisation (IVF) for a history of infertility.

Case Reports

The male proband was born via Caesarean section to non-consanguineous parents at 37+1 weeks of gestation and his birth weight was 2,960 g. He was admitted to the neonatal intensive care unit with mild respiratory distress, increased sleep duration, arthrogryposis, and decreased movements. Physical examination revealed bradycardia, respiratory problems, poor feeding, narrow palpebral fissure with antimongoloid slant. The patient had several episodes of bradycardia (70-90 beats per minute) most frequently in the first few days, but he was haemodynamically stable. He lay in a frog-like position and showed weak spontaneous movements and developmental reflexes such as Moro, grasp and sucking. He showed profound hypotonia (e.g., head lagging, inverted U posture in prone suspension). Deep tendon reflexes were normal and no fasciculation of the tongue was seen. Owing to transient tachypnoea with mild chest wall retraction, assisted oxygen via nasal prong was
continued until 13 days as muscle tone improved. Blood parameters including creatine kinase, lactate, ammonia, serum amino acids, urine organic acids, and thyroid function tests were all within normal range. Echocardiogram showed no abnormality. Holter monitoring revealed borderline PR interval prolongation. Visual and auditory evoked potentials were normal. Ophthalmological assessment revealed evidence of cataracts. Brain magnetic resonance imaging and electroencephalography were normal for the gestational age.

Electromyography and nerve conduction velocity done at 18 days of age showed no evidence of a myopathic process.

Main problems were global hypotonia, along with insufficient sucking and swallowing, which required in gavage feeding in the first week. He was discharged after 23 days without gavage tube and with consistent weight gain. During early infancy, he showed gradual improvement of motor function and was able to sit without support at 12 months of age. Walking was accomplished at the age of 19 months and the proband's speech was limited to pronouncing just his parent's names at the age of 20 months.

Blood karyotype with G-banding and a genomic microarray showed no abnormalities. FMR1 mutations for the fragile X syndrome were not detected and the Prader-Willi methylation test was normal. Molecular analysis for the CTG triplet related DM1 was carried out and revealed over 1,000 CTG repeats, consistent with the clinical impression of CDM1.

There was no striking family history of any neuromuscular disease reported by his parents up to this point. They were both unaware of muscle weakness or myotonia. However, on examination, the mother had minimal evidence of muscle wasting in the face. Characteristically she had mild symptoms and was not diagnosed until after the birth of the affected baby. She menstruated irregularly once every 2-3 months. The pregnancy was achieved by IVF owing to fertility problems. Grip myotonia and percussion myotonia were not observed in the hands. She had no history of frontal balding, fatigue, or developmental delay. However, she revealed exercise intolerance. Photographs at age of 36 showed clear evidence of wasted facial and bitemporal muscles and ptosis (Figure 1). The electromyography demonstrated myotonia and myopathic changes and cataracts were not detected.

The grandmother (I-2) developed cataracts and mild weakness of hands later in life. Being diagnosed at age of 28, the 1st uncle (II-3) denied any symptoms of hand or wrist weakness or myotonia. Ophthalmological assessment and echocardiogram were normal. He was able to finish college as a normal person without any problems. His face showed some wasting facial muscles but no apparent signs of DM1. The detailed neurological test of the patient (II-3) was completely normal. At age of 25, he (2nd uncle, II-4) was unaware of muscle weakness or myotonia. Neither the patient's father nor grandfather exhibited any signs of DM1. The family was referred for medical genetic consultation for screening and counselling. Several family members were identified as carriers of the mutation (Figure 2). The presence of a pathological expansion of CTG repeats was revealed in the proband, mother, grandmother, and the 1st uncle. The mother (II-2) had 400 repeats, grandmother (I-2) had 160 repeats, and 1st uncle (II-3) had 220 repeats. But the father (II-1) and 2nd uncle (II-4) were within the normal range at 20 to 25.

![Figure 1](image1.png)  Patient's mother (II-2), at age of 36 years (A) showing wasting of facial muscles and lack of facial expression. The proband at age of 9 months (B) showing lack of facial expression.

![Figure 2](image2.png)  Family pedigree.
Discussion

CDM1 is characterised by severe hypotonia with difficulty in swallowing and respiration, facial diplegia, and prematurity after birth. Overall perinatal mortality is 11% and mortality is associated with cardiorespiratory complications. Children who survive the critical neonatal period later show improved motor functions, but typically still have global developmental delay compared to normal children. Clinical myotonia do not appear until late in childhood although electromyographic myotonia may develop after the first year. CDM1 is therefore a biphasic disease and should be considered as a possible diagnosis to neonates with hypotonia. Previous studies have documented a general tendency for the repeat number to increase with passage of generations because instability of the expanded CTG repeat during gametogenesis, which results in larger repeat size in the progeny. Moreover, there is a fairly strong correlation between earlier onset/greater severity and increasing repeat size. Normal populations have 5 to about 30 CTG repeats, whereas DM1 patients have 50-2,000 repeats. Patients with a CTG repeat size of 100 or less are likely to be either asymptomatic or only mild symptomatic. Neonatal form is associated with hypotonia, cardiorespiratory and feeding problems and may showed 1,000-2,500 CTG repeats. Although repeat size does seem to play a decisive role in the aetiology of the DM1 phenotype, it does not entirely explain it. The variability of the CTG repeat sizes among different tissues resulting from the somatic instability provides a basis for heterogenous expressivity of this pleiotropic disease. Inheritance of CDM1 is overwhelmingly maternal. This phenomenon emerges from the much greater likelihood for anticipation (e.g., expansion of CTG repeats) to occur in maternal compared with paternal transmission.

There is a 50% risk of the offspring being affected and 3-9% chance of having a severely affected child. The estimated incidence of CDM1 is very broad, ranging from 2.1 to 28.6 per 100,000 live births. In this family, the expanded CTG repeats were transmitted maternally, and earlier age of onset and increasing severity of the disease occurred in following generations. The proband's echocardiography revealed intermittent bradycardia and PR interval prolongation. Conduction delays are seen from 5 to 25% in DM1 patients.

Because DM1 is a known aetiology of infertility and is one of the most frequent adult myopathies, our experience shows the need to consider DM1 in infertility clinic. DM1 patients of both sexes can suffer from problems of infertility due to different causes, which are at times concomitant (ovarian dysfuncion, multiple miscarriages, or azoospermia). About 20% of affected females show menstrual irregularities, infertility, miscarriage or early menopause. The development and generalisation of reproductive techniques have opened the possibility that asymptomatic carriers of the disease can conceive fetuses affected by more serious clinical phenotypes. Therefore, infertility clinics should test for DM1 with detailed history and exact physical examination of the couples.

Declare of Interest

None to declare.

Declaration of Informed Consent

We obtained informed consent to include photographs in this case report.

References

Epiploic Appendagitis with Chronic Abdominal Pain in an Obese Adolescent

HJ Kim

Abstract
Epiploic appendagitis is a rare non-specific disease that can be confused with other diseases. Herein, we report a case of epiploic appendagitis with chronic abdominal pain in a 15-year-old boy with a body mass index of 31 kg/m², who visited our emergency room with a complaint of acute-onset abdominal pain and intermittent fever. Examination of the abdomen revealed tenderness and rebound tenderness in the right lower quadrant (RLQ). Computed tomography (CT) imaging demonstrated a 2.2-cm low attenuating lesion abutting the ascending colon with pericolic fat stranding. Because of the persistent RLQ pain and tenderness, follow-up CT was performed and it showed a decreased lesion without complications. This indicates that epiploic appendagitis may be associated with chronic pain, although this association is very rare.

Key words
Abdominal pain; Child; Chronic; Obesity

Introduction
Epiploic appendages are fat-filled, small pedunculated structures that are present along the colon wall and are accompanied by one or two arterioles and a venule. Spontaneous venous thrombosis of an appendage-draining vein or torsion of the epiploic appendages can cause inflammation, and acute abdominal pain is a major symptom of epiploic appendagitis. Mild fever may be present in some patients; however, other symptoms such as nausea, vomiting, and diarrhea are rare. These symptoms usually resolve within 2 weeks. Obesity and heavy exercise are risk factors for the development of epiploic appendagitis. This report describes a case of epiploic appendagitis with chronic abdominal pain in a 15-year-old obese boy.

Case Report
A 15-year-old boy who had been previously diagnosed with irritable bowel syndrome (diarrhea type) visited the emergency room complaining of acute-onset abdominal pain lasting for 1 day, which remained localized in the right lower quadrant (RLQ). He had intermittent fever and watery diarrhea. The body mass index (BMI) of the patient was 31 kg/m². Examination of the abdomen showed tenderness and rebound tenderness in the RLQ. Laboratory study findings were unremarkable, except for increased alanine aminotransferase. Because of RLQ tenderness, a computed tomography (CT) scan was obtained, which demonstrated a 2.2-cm low attenuating lesion abutting the ascending colon with pericolic fat stranding and diffuse fatty infiltration in the liver without focal lesions (Figure 1A). The patient was managed conservatively with oral anti-inflammatory medication. On the third day in the outpatient clinic, the fever and watery diarrhea were resolved; however, RLQ abdominal pain and tenderness persisted for 2 months. Abdominal pain did not disturb social life. A follow-up CT performed 2 months after diagnosis demonstrated a slightly decreased lesion, but a 1.7-cm low attenuating lesion abutting the ascending colon was still noted (Figure 1B). A few days later, the abdominal pain was resolved.
Discussion

Epiploic appendages are peritoneal pouches that are present in the serosal surface of the colon. The length of these appendages range from 0.5 to 5 cm and they consist of adipose tissue and blood vessels. Ischaemia due to torsion or venous occlusion is the main cause of acute epiploic appendagitis.1,3

Previous studies have reported an association between obesity, unaccustomed exercise, and epiploic appendagitis.4,5 Our patient with a BMI of 31 kg/m² had also non-alcoholic fatty liver disease as a complication of obesity. In addition to this being a rare disease, it is noteworthy also because obese patient had chronic clinical symptoms.

Epiploic appendagitis can occur at any age. However, it occurs most commonly in the 4th to 5th decades of life, and predominantly in men. The sigmoid colon and the caecum are the predominant sites of occurrence.6

The clinical signs and symptoms of epiploic appendagitis are non-specific. Thus, it is difficult to diagnose and is often confused with other diseases based on its occurrence site. It can mimic acute appendicitis, if the right side of the body is involved. Moreover, it may mimic diverticulitis or acute cholecystitis when it occurs in the sigmoid colon or proximal part of the transverse colon.7,9

Occasionally, an unnecessary procedure may have been performed. Rashid et al7 presented a 7-year-old boy misdiagnosed preoperatively with acute appendicitis and subsequently, during surgical exploration, was found to have caecal appendagitis. In the present case, it was first thought that the patient had appendicitis, but the diagnosis was changed based on CT findings; experienced radiologists can help clinicians in this regard. The most common CT finding is an oval lesion less than 5 cm in diameter that has an attenuation equivalent to that of fat, which abuts the anterior colonic wall, and is surrounded by inflammatory changes. Another finding is the thickening of the parietal peritoneum secondary to the spread of inflammation.6

These CT findings can persist for 6 months after diagnosis, but clinical signs and symptoms may be self-limiting within 2 weeks in most cases.10 However, our case had clinical symptoms that persisted for 2 months. Therefore, a follow-up CT was performed to find complications or other lesions, but without success. Persistent abdominal pain without any complications may occur.

In conclusion, this report details the first case of epiploic appendagitis with chronic pain. This condition can be confused with other diseases and knowledge of CT features is especially important in obese patients.

Declaration of Interest

Author reports no conflicts of interest.

Figure 1  CT image showing a 2.2-cm low attenuating lesion abutting the ascending colon with pericolic fat stranding (A) slightly decreased, however, a 1.7-cm low attenuating lesion can be observed abutting the ascending colon with improved pericolic fat stranding (B).
References

Dear editor,

**Interpreting Neonatal Serum Triglyceride Levels Against Reference Intervals**

The case of hypertriglyceridaemia associated with neonatal subcutaneous fat necrosis after hypothermia therapy for asphyxia was interesting. However, it would be clearer to the reader if the authors had quoted the reference range of serum triglyceride of their laboratory, the test method and the condition of blood sampling. Then one would know how far above normal the levels were.

It is complex to interpret serum triglyceride levels, which rise above baseline postprandially. Similarly, they would be higher when lipid is infused continuously. European nutrition authorities accepted serum triglyceride level up to 2.83 mmol/L (250 mg/dL) in neonates on continuous intravenous lipid infusion. Fasting triglyceride reference values were obtained from adults for meaningful comparison with fasting levels in patients to avoid the variations due to recent meals. This is obviously not feasible in neonates, who have to be fed every few hours. Hence preprandial sampling may be more practical for monitoring of neonates and following the trend. An excellent set of reference data on 'spot' triglyceride levels in infants is the CALIPER database of Toronto, which was derived mainly from well multi-ethnic (including Chinese) neonates to be discharged from maternity wards and from selected outpatients with low chance of having metabolic disorders. Values were obtained on the Abbott ARCHITECT c8000 system. For neonates 0-14 days, the normal reference interval was 0.93-2.93 mmol/L (82-259 mg/dL); for babies aged 15 days-<1 year, it was 0.60-2.92 mmol/L (53-258 mg/dL). These intervals bracketed the middle 95% of 'normal' babies.

It is probable that this infant was fed after one to two weeks of fasting. Comparison with the upper limits of these reference intervals may be relevant if the reported levels were mostly spot levels. The 95% confidence interval for the upper limit was 2.83-3.06 mmol/L (250-271 mg/dL) for babies 15 days - <1 year. Therefore, any spot level above ~3 mmol/L would be likely to be truly elevated.

**References**


KH POON
Paediatrician, Hong Kong

**Correspondence to:** Dr KH POON
Email: poon-kinhung@graduate.hku.hk
Reply

Dear editor,

I would like to show our appreciation to Dr Poon's letter. His letter about normal range of triglyceride in neonates/infants is indeed educational. According to a reference provided by Dr Poon, the 95% confidence interval for the upper limit from 15 days of life to age of 1 year was 2.83-3.06 mmol/L (250-271 mg/dL). Dr Poon further pointed out that any spot level above ~3 mmol/L would be likely to be truly elevated. In our case the triglyceride level was mostly between 3.35-3.80 mmol/L with peak level of 4.20 mmol/L on day 23. This was in agreement with Dr Poon's reference concerning the definition of hypertriglyceridaemia.

RSY Lee
Department of Paediatrics and Adolescent Medicine,
Pamela Youde Nethersole Eastern Hospital,
3 Lok Man Road, Chai Wan, Hong Kong

Correspondence to: Dr RSY Lee
Email: leesyr@netvigator.com
**Clinical Quiz**

**What is the Diagnosis?**

SSK Ho, TCW Wong

This 12-year-old girl presented with one-week history of running nose, sore throat and dry cough that did not improve with symptomatic treatment. She was afebrile and there was no systemic upset. Over the past few years, she has experienced multiple episodes of "bronchitis" and abdominal pain that were treated with antibiotics and antispasmodics intermittently. Antenatal and postnatal history were unremarkable. There was no history of trauma or surgery.

On examination, she was afebrile without respiratory distress. Her throat was mildly congested. There was reduced breath sounds on the left side of the chest and 'coarse crackles' at the left axilla. Blood results including complete blood picture, C-reactive protein and erythrocyte sedimentation rate were all normal. A postero-anterior chest radiograph was taken (Figure 1).

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The clinical quiz was prepared by:

SSK Ho
TCW Wong
Bachelor of Medicine and Bachelor of Surgery Undergraduate Year 5, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong

Answer to “Clinical Quiz” on Pages 317-318
N.B. The Editors invite contributions of illustrative clinical cases or materials to this section of the journal.
Abstracts of Articles in Chinese

220例12月龄以下婴儿麻疹的临床分析


目的：观察麻疹婴儿的临床特徵及加強预防措施。検查方法：於2008年1月至2015年8月間，金華市中心医院共收治220例麻疹婴儿。我院常採用ELISA検查特異性麻疹病毒IgM的方法以確立麻疹诊断，對所有患兒均進行了血常規、血生化、心肌酶譜的検查。结果：所有患兒均有發熱（體溫波動於37.5-41℃）及口腔粘膜斑（柯氏斑）；所有患兒在出疹後的麻疹病毒IgM抗体検測結果均為陽性。發病年齡而言，8個月以下佔比高達80.46%；併發症方面，138例患兒（62.73%）合併有肺炎，其中32例为重症肺炎；30例患兒有腹瀉表現，25例患兒合併有急性喉炎，16出现粘膜潰瘍，5例患兒出現高熱驚厥，4例患兒出現中毒性腦病。發病年齡低於8月的患兒發生上述併發症的概率高於大於8月的患兒：220例患兒中，有210例治癒，其餘10例中，有7例臨床症狀好轉但因治療費用昂貴而自行出院，有2例放療治療，另有1例患兒死亡，此例患兒臨床表現較典型，前駱期持續時間短，合併有許多併發症。结论：本研究發現低月齡患兒相對較為容易感染麻疹，肺炎為麻疹患兒最常見併發症。對生育年齡的女性進行麻疹疫苗的復種可減少嬰兒麻疹的發生。

鍵词：併發症、嬰兒、麻疹、肺炎

對比成人文獻分析兒童腹腔鏡手術中轉為開腹原因


前言：本研究旨在評估和分析兒童腹腔鏡手術轉換為開放式手術的原因，並與有關的成年人病例的文獻進行比較，對降低中轉開腹率的預防措施進行分辨。方法及方法：回顧性分析2003-2015年間共1208例開腹手術、尼森胃底折疊術、膽囊切除術和脾切除術的病例。分析了腹腔鏡手術與開放手術的異同，和由腹腔鏡轉開放手術的病例以及中轉開腹的原因。結果：2003-2015年共2068例；行胃底切除術（1539例）、膽囊切除術（120例）、尼森胃底折疊術（323例）和脾切除術（86例）。其中181例（8.8%）為剖腹手術，1887例（91.2%）為腹腔鏡手術。在腹腔鏡手術開始的病例中，1848（97.9%）完成了腹腔鏡手術，39例（2.1%）需要轉為開放式手術。開腹切除術、尼森胃底折疊術、膽囊切除術和脾切除術的中轉開腹率分別為0.34%、9.7%、2.8%和7.4%。結論：腹腔鏡手術術前詳細細緻的以及特異性檢查可降低腹腔鏡手術的中轉開腹率。併發症不一定是唯一的中轉開腹適應症，為了避免併發症必須進行選擇性中轉開腹時也無需猶豫。

鍵词：兒童、轉化、腹腔鏡、開放手術
在小鼠模型中因發育引致甲狀腺功能減退以改變子代的大腦血管緊張素 II 受體 1 型和 2 型的 mRNA 表達

LL Wu, L Zhang, CC Zou, ZW Zhu, ZY Zhao. Developmentally-induced Hypothyroidism Alters mRNA Expression of Cerebral Angiotensin II Type 1 and Type 2 Receptors of Offspring in a Mouse Model. HK J Paediatr (new series) 2018;23:282-287

甲狀腺功能減退對腦腎素—血管緊張素系統 (RAS) 的影響仍然知之甚少。本研究旨在驗證甲狀腺抑制（MMI）誘導的甲狀腺功能減退對小鼠大腦血管緊張素 II 1 型受體 (AT1a) 和 2 型 (AT2) 的 mRNA 表達。懷孕的 C57BL/6j 小鼠在甲減組 (H) 從妊娠期第 10 天到生後第 7 天 (P) 0.03% MMI 飲用水飼養，這些 Dams 被分成兩個亞組：圍產期甲減組 (H1) 和永久性甲減 (H2) 組。在 H1 組的停止接受 MMI，他們的幼崽斷奶後純水飼養 (P21)。H2 組繼續接受 MMI 直到斷奶，他們的幼崽持續接受 MMI 直到結實。腦 AT1a 和 AT2 mRNA 的相對表達是由定量即時聚合酶鍵反應 (PCR) 確定的。在 H1 組，產後最初 2 週，子代大腦的 AT1a mRNA 表達顯著減少，而後恢復到正常水平。然而，在 H2 組，大腦 AT1a mRNA 的表達在產後持續減少。相反，在 P14 和 P21，大腦 AT2 mRNA 的表達在 H2 組與對照組相比顯著增加。總之，我們發現發育階段誘導甲狀腺功能減退可能改變小鼠子代的大腦 AT1a 和 AT2 mRNA 的表達。

關鍵詞：血管緊張素受體 II、甲狀腺功能減退、甲狀腺激素、血管緊張素系統

周佳瑩醫師

兒童幽門螺桿菌感染的最新進展

CO Sham. Update on Helicobacter pylori Infection in Children. HK J Paediatr (new series) 2018;23:288-293

幽門螺桿菌感染是一種常見的世界性感染。它是引致胃癌的一個重要原因，但絕大多數受感染的人在他們的一生中不會遭受任何影響。這種細菌感染的檢測、診斷和治療的適應症在兒童和成人中也有所不同。本文旨在強調這兩項指導的重點，即成人及兒童病人的管理差異，並討論該指導在香港的適用性。

關鍵詞：兒童、診斷試驗、根除、幽門螺桿菌、三合一療法
牛奶斑—如果不是神經纖維瘤1型，還會是甚麼診斷？

PT Yu, HM Luk, IFM Lo. Café Au Lait Spots: What is the Diagnosis If It Is Not Neurofibromatosis Type I ?. HK J Paediatr (new series) 2018;23:294-297

病童身體多處出現咖啡牛奶斑是評估其可能患上綜合徵病症時常用的參考指徵。神經纖維瘤病(NF-I)型是兒科常見病，其特點為咖啡牛奶斑、間擦雀斑、神經纖維瘤、虹膜色素損害和／或骨損害。偶爾可見囊狀神經纖維瘤、視神經及其他中樞神經系統結實病。Legius綜合徵是一種較新的疾病，自2007年以來已有文獻描述此綜合徵，具有NF-1樣的特徵，包括咖啡牛奶斑、雀斑、大頭畸形和學習障礙。然而，它與良性或惡性腫瘤無關。因此，區分這兩個病不僅要診斷，而且對預後諮詢和隨訪監測也很重要。在這裏，我們報告了一名兒童最初因懷疑患上NF-1而轉介到另一中心接受治療，後來被診斷出患有Legius綜合徵。此外，我們還對NF-1和Legius綜合徵的臨床特點進行了總結和比較，並對兩者在諮詢和監測方面的差異進行了討論。

關鍵詞：Legius綜合徵、類1型神經纖維瘤病、SPRED1基因

長期宮外存活的三倍體嬰兒一例：存活三倍體嬰兒的臨床特點回顧


幾乎所有三體胎兒在孕早期均會出現自發性流產，活產的三體症狀十分罕見。我們在此報告一例存活時間長於250天的三倍體嬰兒。此患兒因嚴重的宮內發育遲緩於孕33+4周出生，出生體重1180g，出生時即發現其有多種先天畸形。染色體組型分析結果為69XXX，目前，此患兒在家中已存活超過280天。通過對三倍體症狀的回歸，發現三倍體症狀對應特殊的臨床特點包括：第5、14指並指以及異常的血紅細胞指標。相關的組合包括：69 XXX, 69 XXY，而非69 XYY。5例三體症狀中有兩例死於肺炎。其中兩例，包括我們目前報告的此例，在出生200天後出現嬰兒症。長期存活的三倍體症狀出現肺炎及嬰兒症的風險高。

關鍵詞：紅細胞指標、胎兒宮內發育受限、長期存活，並指、三倍體
BN Kim, YT Lee, IG Lee, JY Han. Neonate with Congenital Myotonic Dystrophy Conceived via In Vitro Fertilisation by an Asymptomatic Mother. HK J Paediatr (new series) 2018;23:302-304

先夭性強直性肌營養不良新生兒1例（新生兒為試管嬰兒，母親無臨床症狀）

HJ Kim. Epiploic Appendagitis with Chronic Abdominal Pain in an Obese Adolescent. HK J Paediatr (new series) 2018;23:305-307

肥胖青少年伴有慢性腹痛的腸脂垂炎

關鍵詞：先夭性強直性肌營養不良，肥胖青少年伴有慢性腹痛的腸脂垂炎

關鍵詞：腹痛、兒童、慢性、肥胖
**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) Clinical Analysis of 220 Infants Less Than 12 Months Old with Measles**

1. Which of the following is not a manifestation of measles?
   a. Fever
   b. Koplik’s spot
   c. Pigment
   d. Diarrhoea
   e. Haematuria

2. What is the most common complication of measles?
   a. Pneumonia
   b. Fever seizure
   c. Diarrhoea
   d. Laryngitis
   e. Liver dysfunction

3. When does the measles outbreaks mostly occur?
   a. January to March
   b. April to June
   c. July to September
   d. October to December
   e. Whole year

4. Which age of infants suffer the highest morbidity of measles?
   a. <3 months
   b. 3~6 months
   c. 6~8 months
   d. 8~12 months
   e. None of the above

5. When is the first dose of measles vaccine performed in mainland of China?
   a. At 8 months
   b. At 12 months
   c. At 18 months
   d. At 3 years
   e. At 2 years

**(B) Comparison of Conversion Reasons in Paediatric Laparoscopic Surgery to Adult Literature**

1. Which of the following is not an advantage of laparoscopic surgery?
   a. Less postoperative pain
   b. Shorter hospital stay
   c. Quicker return to daily activities
   d. Cheaper devices
   e. Better cosmesis

2. Which one of the following is a common surgical challenge for infants and children?
   a. Diabetes Mellitus
   b. Hypertension
   c. Chronic Lung Diseases
   d. Vascular Diseases
   e. Hypothermia

3. Which one of the following is not a risk factor for conversion in laparoscopic appendectomy?
   a. Comorbidities
   b. Dense adhesions
   c. Long appendix vermiformis
   d. Technical difficulties
   e. Difficulties in identifying organs

4. Which one of the following is not a common conversion reason for laparoscopic Nissen fundoplication?
   a. Hepatomegaly
   b. Oesophagitis
   c. Inadequate visualisation
   d. Redo surgery
   e. Gastrointestinal duplication cysts

5. Which one of the following is the correct strategy of conversion?
   a. One should convert if only there is excessive bleeding
   b. Conversion should not be an option in any situation
   c. One should not hesitate to convert in any condition which seems to make laparoscopy difficult
   d. Conversion should be thought if only it is not expensive
   e. Conversion reasons are same in all kind of operations
(C) Developmentally-induced Hypothyroidism Alters mRNA Expression of Cerebral Angiotensin II Type 1 and Type 2 Receptors of Offspring in a Mouse Model

1. What is the functional component of brain renin-angiotensin system?
   a. Angiotensinogen
   b. Peptidases
   c. Angiotensin
   d. Specific receptors
   e. All of the above

2. Which kind of biological effect is ascribed to the activation of AT2?
   a. Vasoconstriction
   b. Cellular growth
   c. Proliferation
   d. Apoptosis
   e. None of the above

3. Where does the renin-angiotensin system exist?
   a. The circulatory system
   b. Heart
   c. Kidney
   d. Brain
   e. All of the above

4. The brain renin-angiotensin system is involved in?
   a. Blood pressure control
   b. Drinking behaviour
   c. Sodium intake
   d. Cognitive performance
   e. All of the above

5. In the brain, which type of cell is the principal cellular source of brain angiotensin II?
   a. Neuron
   b. Oligodendrocyte
   c. Astrocyte
   d. Microglia
   e. Ependymal cell

(D) Update on Helicobacter pylori Infection in Children

1. In children, which of the following situations is the testing of Helicobacter pylori indicated?
   a. Abdominal pain
   b. Constipation
   c. Peptic ulcer disease
   d. Weight loss
   e. Chronic diarrhoea

2. According to a study in Bolivia, how high was the re-infection rate at 1 year after successful eradication of Helicobacter pylori infection in young children?
   a. 1%
   b. 3%
   c. 7%
   d. 10%
   e. 20%

3. Which of the following is NOT the risk of eradication treatment of Helicobacter pylori infection in children?
   a. Iron deficiency anaemia
   b. Abdominal cramp
   c. Diarrhoea
   d. Undesirable alteration of the gut microbiome
   e. Treatment failure

4. According to a population-based study, what was the prevalence of Helicobacter pylori infection in Hong Kong Chinese children?
   a. 1%
   b. 5%
   c. 8%
   d. 13%
   e. 40%

5. Which of the following antibiotics is NOT recommended by both ESPGHAN/ NASPGHAN and ACG Guidelines for the treatment of Helicobacter pylori infection?
   a. Amoxicillin
   b. Vancomycin
   c. Clarithromycin
   d. Metronidazole
   e. Levofloxacin

Answers of July issue 2018

(A) 1. c; 2. b; 3. d; 4. e; 5. c
(B) 1. d; 2. e; 3. c; 4. a; 5. c
(C) 1. e; 2. b; 3. d; 4. a; 5. b
(D) 1. c; 2. b; 3. e; 4. c; 5. a
**What is the diagnosis?**

The middle and lower zones of the left chest are filled with bubbly shadows without fluid levels. The left hemidiaphragm is not well visualised. The gastric bubble is absent. Cardiac apex is obscured. There is also mild scoliosis. The radiological features are compatible with left sided diaphragmatic hernia. The diagnosis was confirmed by CT thorax and the defect was successfully repaired by thoracoscopic technique.

**What is late presenting diaphragmatic hernia?**

Diaphragmatic hernia is a condition where a defect in the diaphragm results in herniation of abdominal viscera into the thoracic cavity. The majority of diaphragmatic hernias are congenital in nature, known as congenital diaphragmatic hernia (CDH). In contrast, acquired diaphragmatic hernias are due to trauma and are less common. The underlying pathophysiology of CDH is believed to be due to the persistence of the posterolateral pleuropertoneal canal in the diaphragm which allows abdominal viscera to herniate into the thoracic cavity.1,2

CDH can be diagnosed prenatally with ultrasonography. Cases without prenatal diagnosis commonly present shortly after birth with acute respiratory distress and the classical "scaphoid abdomen", as a result of pulmonary hypoplasia and pulmonary hypertension associated with abdominal visceral herniation. Less than 3% of the patients remain undiagnosed within the neonatal period.3 This is believed to be due to a milder degree of visceral herniation, lesser compression onto the lungs and absence of pulmonary hypoplasia.4 Another possible reason for late presentation is thought to be due to bowel herniating through a diaphragmatic defect that has previously been occluded by the spleen and liver during early period of life.4 These patients may present anytime beyond the neonatal period and are called late-presenting CDH.

**Clinical presentations of late presenting CDH**

Compared to early presenting CDH where the diagnosis is usually straightforward, the symptoms are usually more vague and less acute in late presenting CDH.5 A study on late presenting CDH suggested three types of presentation: acute respiratory and gastrointestinal symptoms, chronic nonspecific symptoms such as abdominal pain and constipation, and lastly, incidental discoveries in asymptomatic patients.5

Clinicians most often use chest radiographs to help guide diagnosis. To confirm the diagnosis, additional imaging including abdominal radiographs, upper and lower gastrointestinal contrast studies and CT thorax with contrast may be necessary.6 However, owing to the variable clinical presentations as well as the low incidence of congenital anomaly in older children, there is often a delay in diagnosis and frequent misdiagnosis. The commonest initial misdiagnosis is pneumonia.6 Furthermore, studies have found that 25% of initial chest radiographs were misinterpreted as tension pneumothorax or pyopneumothorax.7

**Complications of CDH**

Complications of late CDH occur in around 10% of patients most commonly with both large bowel strangulation and necrosis as well as gastric volvulus. There are also reported cases of gastric perforation due to strangulation.8 Misdiagnosed cases treated as pneumothorax or pleural effusion may also suffer from iatrogenic complications during chest drain insertion leading to gastric perforation.3
Treatment

All patients with CDH require surgical intervention to repair the defect on the diaphragm. Prognosis of a late presenting CDH is generally excellent but delayed diagnosis may significantly increase morbidity. Clinicians should always include congenital lesions in their differential diagnoses if the clinical presentations are recurrent or atypical.

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References

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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.

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4. SI units should be used or included in parentheses.

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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.

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