Editorial
Gut Health, Wealth, and Feelings: This Interface 197
Cheung

Original Articles
The Preliminary Investigation of Faecal Microbiota Transplantation for Paediatric Recurrent Chronic Bowel Diseases and Literature Reviews
Fang, Chen, Yu, Luo, Lou 199

Application of Three Dimensional High Resolution Anorectal Manometry to Demonstrate Anal Sphincter Pressure Asymmetry in Children after Anorectal Surgery: A Pilot Study
Tang, Leung, Hung, Chung, Liu, Chao, Liu 204

Frequency of Refraction Errors among School-age Children in Ankara, Turkey: A Cross-Sectional Study
Aydogan, Ceylan, Nerkiz, Doganer, Tombus, Gokee, Thurston, Mutlu, Altinsoy 209

Paediatric Malone Antegrade Continence Enema (MACE): The Hong Kong Experience
Tang, Chung, Leung, Hung, Yam, Lin, Chao, Leung, Liu, Kwok, Ng 217

Case Reports
A Case Report of Familial Hypocalciuric Hypercaleaemia with a Heterozygous Mutation of the Calcium Sensing Receptor Gene in a Chinese Paediatric Patient
Bao, Ng, Tsui 221

Lipoid Pneumonia Following Aspiration of Lorenzo's Oil in a Child with X-linked Adrenoleukodystrophy
Cheon, Cho, Kim, Wpo 225

Spontaneous Pneumomediastinum in Rhinovirus Infection
Berksoy, Özkul, Saylu 229

Clinical Quiz
What is the Diagnosis?
Cheng, Lo, Luk 232

Abstracts of Articles in Chinese 233

MCQs 236

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Gut Health, Wealth, and Feelings: This Interface Matters

All disease starts in the gut,' remarked Hippocrates more than twenty centuries ago. Perhaps by no means of coincidence, there is the Chinese idiom '病從口入', which literally means the acquisition of illnesses through the mouth. We are all mindful of the embryological development of the gut, with the origin from the foregut of the pharynx, oesophagus, stomach, and proximal duodenum; from the midgut, distal half of duodenum, jejunum, ileum, caecum, appendix, ascending colon, the right two-thirds of the transverse colon; and from the hindgut, the left one-third of the transverse colon, descending colon, sigmoid colon, and the rectum. High school biology students and medical undergraduates should be well versed with the structure of the gut as a tube that extends from the oral cavity through all these passages to the anal sphincter and its function as a conduit for transport, within which the processes of digestion, absorption, and elimination take place. Even at this level of understanding, the importance of gut health cannot be more obvious.

In this issue of the Journal, several original articles have explored the maintenance of gut function and biology. Tang et al performed a pilot study and demonstrated the potential usefulness of a new three-dimensional high resolution anal anorectal manometry in the assessment of anal sphincter function and surgical outcomes in children with various defecation disorders. In another study, the use of paediatric antegrade continence enema in the management of children with faecal incontinence was reviewed. These articles focussed on the tackling of mechanical dysfunction of the gut. On the other hand, Fang et al described the trial of faecal microbiota transplantation in a small cohort of children with chronic bowel diseases including Crohn's disease, ulcerative colitis, and pseudomonas colitis, but found limited effects. While the findings of the latter study should not be over-interpreted, it reminds us of what can be regarded as the wealth of treasure within the gut imparted to us by nature since the very day we are born.

The gut is quick to be colonised by microbes early in life. Microbiota refers to the bacteria, archaea, microeukaryotes, and viruses that share the space within the human body. These microorganisms may engage in a commensal, symbiotic, or pathogenic relationship with our body. While commonly denoted previously as commensal organisms, the gut microbiota is increasingly recognised to have a key role in health and disease. It is no surprise therefore to find that the practice of 'faecal medicine' was documented thirty centuries ago in the 'Collection of 52 Prescriptions' (金匱要略) describing the oral intake of human faecal suspension popularly known as the 'yellow soup' to treat food poisoning by Zhang Zhongjing, and the subsequent adoption of the practice by famous Chinese practitioners including Ge Hong in the fourth century and Li Shizhen in the sixteenth century. In western medicine, faecal microbiota transplantation has shown promise in the management of Clostridium difficile infection, and attracted increasing research interests in its utilisation for management of inflammatory bowel disease, functional gut disorders, and obesity and diabetes.

Beyond its therapeutic potential, the richness of microbes in the gut is linked also to health. Individuals with low bacterial richness have been found to have higher overall levels of body fat and inflammation-associated characteristics than those with higher bacterial richness. An energy-restricted diet may increase microbial richness and decrease inflammation in obese and overweight people who have low microbial richness. Beyond health, gut microbiota may be associated with allergic disease in children, cardiovascular health and disease, and even psychiatric illness.
As the saying goes, 'I feel it in the gut'. An interesting perspective of viewing the brain development in the context of developmental biology of the gut, a 'microbial organ', and its capacity to metabolise the various diets has been proposed recently.\(^{15}\) This awaits rigorous testing of its hypothesis. On the other hand, more robust data have provided evidence on the existence of gut-brain crosstalk in term of a complex, bidirectional communication system that not only ensures homeostasis of the gut but possibly also exerts effects on affect, motivation, and cognitive functions.\(^{16}\)

The gut functions well beyond the role of a conduit. It functions more than a membrane of absorption of nutrients and a passive filter of undigested waste materials. The gut is the interface between the body and the outside world. It represents a large surface, albeit at risk of exposing to vulnerability, for interacting with the outside environment. It must be rendered accessible to nutrient absorption, while at the same time be defensive against pathogenic attacks. It is a platform for establishing a symbiotic and mutually beneficial relationship with the microbiota. It is a large sensory organ that is in constant communication with effector systems including the gut endocrine, neuronal, and immune system.\(^{17}\) The understanding of the gut-brain communication\(^ {16}\) and gut-heart interaction\(^ {12,13}\) is emerging. It becomes intuitive to ensure the well-being of this interface as it matters much beyond it.

When this editorial is read, the 13th Congress of the Asian Society for Paediatric Research hosted by the Hong Kong College of Paediatricians from 6 to 8 October 2017 would have just been concluded successfully, the abstracts of which would be published in the upcoming issue of the Journal. This Congress is an interface whereby basic research meets clinical medicine, personalised medicine translates to public health policies, and scientists interact with clinicians. It is the interface whereby the enormous diversity and wealth of the paediatric research and clinical data mix and synergise to achieve excellence in child health. A healthy gut is but an example of the importance of a diversified, harmonious, and functional interface for the betterment of our health and beyond.

YF Cheung  
Chief Editor

References

The Preliminary Investigation of Faecal Microbiota Transplantation for Paediatric Recurrent Chronic Bowel Diseases and Literature Review

YH Fang, J Chen, JD Yu, YY Luo, JG Lou

Abstract

Background: Faecal microbiota transplantation (FMT) is a potential therapeutic method to treat intestinal diseases with faecal dysbiosis. FMT has demonstrated effectiveness for recurrent *Clostridium difficile* infection (CDI), meanwhile it also showed potential therapeutic effect for some inflammatory bowel disease (IBD) patients. Methods: There were five patients, from 1Y6M to 11 years old. Two patients were diagnosed very early onset Crohn's disease (CD), two patients were ulcerative colitis (UC) and one patient was pseudomembranous colitis. They underwent FMT therapy by nasal jejunal tube or colonoscopy, and were followed up every two to four weeks after FMT. Results: One UC patient and the pseudomembranous colitis patient achieved partial remission after FMT. However, both of the patients' symptoms relapsed six to eight weeks after FMT. Two CD patients and one UC patient did not respond to FMT therapy. All of the IBD patients had moderate to severe disease active index before FMT. For adverse effects: four of the patients had fever after FMT. Other adverse events included abdominal pain, abdominal uncomfortable, they were mild and self-limiting. Conclusions: FMT had limited effect for very early onset CD and UC patients in our preliminary clinical experience. The incidence of adverse effects of FMT was much higher than reported.

Key words Crohn's disease; Faecal microbiota transplantation; Paediatrics; Pseudomembranous colitis; Ulcerative colitis

Introduction

Faecal microbiota transplantation (FMT) was referred to infuse faecal suspension from a healthy donor into the gastrointestinal (GI) tract of a patient through upper or lower way. FMT with a goal to rebuilt microbial community in the gut has become a research hotspot in recent years and was investigated as a new treatment method for a number of GI and non-GI disorders. FMT is effective in the treatment of *Clostridium difficile* toxin-induced recurrent colitis and has been recommend as the first line therapy for the recurrent and refractory *C. difficile* infection (CDI). FMT also showed therapeutic effect for other GI disorders and non-GI disorders such as inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), autoimmune diseases, and metabolic syndromes.

Although the efficiency of FMT for CDI is well admitted, the effect of FMT for other GI diseases is still obscure and without quality research. IBD including Crohn's disease (CD) and ulcerative disease (UC) are both chronic bowel disease, which have a bunch of data support the hypothesis that they result from the immune responses to the intestinal microbiota in genetically susceptible individuals. And such immune responses lead to dysbiosis which induce the inflammatory response. The detailed mechanisms of intestinal dysbiosis involved in the development of IBD are...
still not well elucidated. Decreased bacterial diversity and changes in the abundance of certain bacterial groups have been observed in the faecal samples and colonic biopsies of IBD patients, in comparison with the samples of healthy subjects, monozygotic twins, and multi-centre studies.\textsuperscript{1-4} Several bacterial groups have been associated with IBD, including \textit{Escherichia} and \textit{Bacteroides} \textit{spp.} as well as bacteria belonging to the \textit{Clostridiales}. \textit{Faecalibacterium praunstizii}, an abundant intestinal bacterium belonging to the \textit{Clostridium} cluster IV, was found to be frequently reduced in abundance in CD patients, and there was a reduction in the mucus-degrader \textit{Akkermansia muciniphila} which has been reported in CD and UC patients.\textsuperscript{3,5-7} It is suggested that feces contain a superior combination of intestinal bacterial strains and are more favourable for repairing disrupted native microbiota by introducing a complete, stable community of intestinal microorganisms. Feces also harbour additional substances (proteins, bile acids, and vitamins) which may contribute to the recovery of gut function.\textsuperscript{8} Preliminary case reports of FMT for treating IBD patients revealed a mixed results for the patients were with different age, different disease activity, and different way of administer FMT. The condition of the FMT donator would also affect the treatment result.

Since the effect of FMT on intestinal disease is still exploring the way. This clinical research is a prospective study mainly to confirm the preliminary safety and potential efficacy of FMT in paediatric recurrent chronic bowel diseases including CD, UC and pseudomembranous colitis which failed to respond to regular medical treatment. However, FMT had limited effect for very early onset CD and UC patients in our preliminary clinical experience.

\textbf{Methods}

This was a single-centre open-label study designed to determine tolerability, preliminary safety, and potential efficacy in paediatric patients with chronic recurrent intestinal bowel diseases who did not respond to regular medical treatment. Each participant was followed in the study for more than 12 weeks. Patients were recruited from a tertiary hospital during July 2014 to July 2015. All patients provided written informed consent or assent. This research was also under the ethics of the hospital.

All patients had a diagnosis made by more than two experienced senior gastroenterologist based on history, physical examination, laboratory/radiological studies and gastrointestinal histology. Patients had laboratory tests, including complete blood count (CBC) with differential and platelets, C-reactive protein (CRP), albumin, stool studies for \textit{C. difficile}, bacterial culture, ova and parasite. Donor History Questionnaire was used to evaluate study participant donors for ruling out gastric and intestinal disease, surgery of gastric and intestinal, infectious disease, diabetes, metabolic syndromes, autoimmune disease, allergic disease such as asthma, eosinophilic gastroenteritis. Faecal donor laboratory studies included hepatitis A antibody, hepatitis B serum antigen, hepatitis C antibody, human immunodeficiency virus antibody, rapid plasma reagin and Epstein-Barr viral IgG and IgM, cytomegalovirus IgG and IgM, as well as stool testing for \textit{C. difficile}, bacterial culture, and examination of stool for ova and parasites. The donor for each patient was one of their parents. Donors should also prevent to take antibiotics in three months before the FMT procedure.

Patients received vancomycin 15 mg/kg three times daily for three days until the evening before the procedure. Patients also received omeprazole (0.7 mg/kg intravenous) on the day before and morning of the procedure if via upper gastric way. Transplant recipients received phenolphthalein tablets (<6 years old) or Bisacody (>6 years old) for four days as the same bowel preparation as colonoscopy. For upper gastric way, a nasojejunal (NJ) feeding tube was placed for transplant in the morning of transplantation. Location of the tube was confirmed by X-ray. For lower gastric way, faecal was transplant through colonoscopy or by enema. Approximately 30 g of donor stool was mixed with 100 mL to 200 mL of normal saline and blended with a home used blender at low speed for two to four minutes until a homogenous texture was obtained. The homogenous stool was then filtered two to four times using gauze. Prepared stool was used within half an hour. Infusion was slowly administered through NJ tube over half an hour or through colonoscopy over five to ten minutes period. The NJ tube was flushed with 15 mL of normal saline over 10 minutes. The NJ tube was removed after 15 minutes.

FMT recipients stayed in hospital for at least three days after transplantation and had clinical follow-up at two, four, eight and 12 weeks. CBC, CRP and erythrocyte sedimentation rate were checked when followed up. Clinical manifestations, physical examinations and any possible side effects reported by patients and their parents were recorded.
**Results**

There were five patients received FMT, including four male patients and one female patient. The age of patients were ranged from 1Y6M to 11 years old, among them two patients were under three years old. Case 1 was diagnosed pseudomembranous colitis. Case 2 and case 3 were diagnosed very early onset CD, while the paediatric Crohn's disease active index (PCDAI) sore were 37.5 and 75 respectively before FMT. Case 4 and case 5 were ulcerative colitis, meanwhile the paediatric ulcerative colitis disease active index were 30 and 57.5 respectively before FMT. The duration of disease was from one month to four years, and three of them were longer than one year. The lesion of disease mainly involved colon according to colonoscopy and magnetic resonance enteroclysis, however the disease lesion of case 2 was involved small intestinal bowel as well. All the donors were their mother living together with them except the donor of case 5 was her father.

The general condition and medicines these patients taken before FMT were listed in Table 1. Case 1 and case 4 achieved partial remission after FMT, however the symptoms relapsed around six to eight weeks after FMT. Case 2, case 3 and case 5 did not respond to FMT. Furthermore, the condition of patients got worse with case 5. Case 1 showed response immediately after FMT. He had formed stool without blood the second day after FMT. The colonoscopy also showed great improvement of colon inflammation one month later. However the symptoms relapsed around six weeks after FMT, with a bit fresh blood in the stools. He still had a bit fresh blood at the end of bowel movement after another FMT. Case 4 had fewer times of bloody stools and the stools were of shapes after FMT. He was steroid dependent before, however the dose of steroid was reduced to half of original dosage after FMT. The colonoscopy showed that this patient was improved one month later as well. The inflammation markers were gradually reduced to normal level later. However, his symptoms relapsed around eight weeks after FMT. He still had several episodes of bloody stool after the second FMT. Case 2, case 3 and case 5 had persistent fever with obviously elevated inflammatory markers after FMT, and their symptoms did not get any improvement, case 5 got worse after FMT. Her diarrhoea was deteriorated with fresh and dark blood in the stools.

Adverse effects (Table 2): One patient reported he had mild abdominal uncomfortable, while two patients had mild abdominal pain after colonoscopy. Four patients had fever after FMT. Case 4 had mild fever after the first time of FMT, accompanied with slight elevation of inflammatory makers. Another three patients had persistent fever after FMT accompanied with obviously elevated inflammation markers. All of the three patients considered to have infection although the stool and blood culture were negative. They both received antibiotic treatment intravenously. Additionally, the NJ tube insertion was really an uncomfortable experience for children. The bowel preparation and the colonoscopy for the FMT also bring uncomfortable experience to the children.

### Table 1  General information for patients

<table>
<thead>
<tr>
<th>Patients</th>
<th>Gender</th>
<th>Age</th>
<th>Diagnosis</th>
<th>Disease duration</th>
<th>Symptoms</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>11 years</td>
<td>Pseudomembranous</td>
<td>2 years</td>
<td>Bloody stools</td>
<td>Vancomycine, metronidazole</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>colitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>2-year-1-month</td>
<td>Crohn's disease</td>
<td>2 years</td>
<td>Fever, perianal abscess, diarrhoea</td>
<td>Antibiotics, prednisone, mesalazine</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>1-year-6-month</td>
<td>Crohn's disease</td>
<td>1 month</td>
<td>Fever, diarrhoea, perianal abscess</td>
<td>Antibiotics, TPN</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>7 years</td>
<td>Ulcerative colitis</td>
<td>4 years</td>
<td>Bloody stools</td>
<td>Prednisone, mesalazine, methotrexate</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>10-year-9-month</td>
<td>Ulcerative colitis</td>
<td>4 years</td>
<td>Bloody stools</td>
<td>Prednisone, mesalazine, PN+EN</td>
</tr>
</tbody>
</table>

TPN: total parenteral nutrition, PN: parenteral nutrition; EN: enteral nutrition
Discussion

FMT was an old method which had applied in the modern medicine to treat intestinal and non-intestinal diseases. FMT was well accepted applied to treat CDI. The published experience of FMT for IBD showed potential treatment effect. The first UC patient received FMT therapy was in 1989, after he was transferred by enema, his clinical symptoms and pathological manifestation of intestinal mucosa were all got remission without using any medicine for 11 years. Borody reported six severe UC patients after FMT the symptoms and histological appearance of intestinal mucosa all got improvement in 2002. He analysed 62 UC patients with the treatment of FMT, and found that over 90% of patients got clinical improvement, 67.7% of the patients had complete remission. 24.2% of the patients had partial remission. There were only 8% percent of patients failed to response. Patrizia k reported six chronic active UC patients received FMT through colonoscopy. Both of the six patients' symptoms got improved in two weeks, but only one of them got clinical remission. And the microbiota analysis revealed three of them the microbiota were resemble to the donators. There was UC patient with anal fistula, the regular therapy did not work. After he received FMT therapy four weeks later, the clinical symptoms, endoscopic appearance and pathological manifestation all got remission. However, there were few studies of paediatric study since FMT had applied. David reported four UC children received FMT therapy through NG tube in 2014. These patients were followed 2 weeks, 4 weeks and 12 weeks after FMT. None of them got clinical remission. In 2014, a meta-analysis revealed 111 IBD patients had received FMT therapy. Among these patients, 77.8% of the IBD patients had clinical improved. Nearly 90% UC patients had clinical improved including the clinical symptoms and reduce of UCAI score. Only three studies refer to children. The results of paediatric group varies, but none of them had sever adverse effect. With diagnose of CDI, all the patients including children all got excellent results. It indicated these patients' clinical improvement mostly owning to the improvement of CDI but not UC. As to CD patients, most of the studies did not achieve exciting results except several case reports had inspiring result. David L also reported nine CD patients from 12 to 19 years old with mild to moderate symptoms according to PCDAI received FMT by NG tube and followed up at two, six, 12 weeks after FMT. Based on PCDAI, seven of nine patients were in remission at two weeks and five of nine patients who did not receive additional medical therapy were in remission at six and 12 weeks. Metagenomic evaluation of stool microbiome indicated the evidence of FMT engraftment in seven of nine patients.

In our preliminary clinical study, all the five patients presented chronic recurrent bowel disease. Their symptoms were refractory or persistent after regular medical therapy. The clinical and endoscopic results showed two patients were improved after the FMT therapy. Three patients did not respond to FMT, meanwhile they had persistent fever caused by secondary infection. Case 1 was a pseudomembranous colitis patient, Clostridium difficile test was negative. The therapeutic effect of FMT was as good as reported, however the symptoms relapsed around six weeks. Case 2 and case 3 were both very early onset CD patients and their PCDAI sores reveled moderate to severe disease activity. Both of them had persistent fever with elevated inflammatory makers after FMT, which were considered as secondary infection caused by FMT. One of the UC patients had partial remission after the first FMT, and the symptoms relapsed around eight weeks. Another UC patient failed to respond to FMT therapy. In our study, FMT did not showed positive therapeutic effect for both very early onset CD and UC patients. The most common reported adverse effects were mild to moderate abdominal pain or distension, and they usually were self-limiting. FMT was reported safe for severe case of CD patient even with sepsis patient.

Table 2  Adverse effects of patients and treatment

<table>
<thead>
<tr>
<th>Patient</th>
<th>Adverse effects</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Abdominal distension</td>
<td>Self-limited</td>
</tr>
<tr>
<td>2</td>
<td>Persistent fever, elevation of WBC and CRP, infection</td>
<td>Antibiotic and steroid</td>
</tr>
<tr>
<td>3</td>
<td>Persistent fever, elevation of WBC and CRP, infection</td>
<td>Antibiotic</td>
</tr>
<tr>
<td>4</td>
<td>Transient fever, transient elevation of CRP, abdominal pain</td>
<td>Self-limited</td>
</tr>
<tr>
<td>5</td>
<td>Persistent fever and elevation of WBC and CRP, abdominal pain</td>
<td>Antibiotic and intravenous immunoglobulin</td>
</tr>
</tbody>
</table>

WBC: white blood cells; CRP: C-reactive protein
study, although the stool donators were all exclude infection by stool and blood test before FMT and the patients' stool and blood cultures were all negative, the rate of infection caused by FMT in our study was much higher than reported. It was considered that the high risk of infection rate might had relationship with the high disease activity index and young age. Therefore, we should be more cautious with patients with high disease activity index when apply FMT, which may cause secondary infection. It was a pity that the microbiome of the patients had not been analysed to make sure whether the faecal microbitota from donor was colonised after the FMT in this study. Thus we did not know the colonisation of microbiota from donor was correlated to the effect of FMT.

The pathogenesis of IBD is far more complex than CDI. Although it is related to the microbiota and immune of the intestine, the exact mechanism of IBD pathogenesis has not been clarified yet. The faecal microbiome composition of IBD patients has shown to be different from healthy individuals. A decreased bacterial load and variety are shown in IBD patients. The exact composition of the stool transferred by FMT, the benefit species of bacteria, immune material, and nutrition are not clarified. Moreover, the composition of the microbiota is affected by the species, sex and diet. The efficiency of FTM is affected by a variety of issues. More studies are needed to further verify whether FMT is beneficial for paediatric IBD patients, and how to choose the appropriate receptor and appropriate donor for FMT.

In conclusion, it was suggested that FMT should be more cautious with young age and high disease activity index patients in our preliminary study. And the effect of FMT is limited for paediatric IBD patients as so far.

Acknowledgements

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Conflicts of Interest Statement

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

References

Application of Three Dimensional High Resolution Anorectal Manometry to Demonstrate Anal Sphincter Pressure Asymmetry in Children after Anorectal Surgery: A Pilot Study

PMY Tang, MWY Leung, JWS Hung, KLY Chung, CSW Liu, NSY Chao, KKW Liu

Abstract

**Purpose:** The use of anorectal manometry in the evaluation of anal sphincter function has been well established. The new three dimensional (3D) high resolution anorectal manometry (HRARM) would provide additional information regarding the symmetry of the anal sphincter pressure. **Methods:** We prospectively recruited 17 patients with defaecation disorders: 3 patients with idiopathic constipation, 8 patients with Hirschsprung’s disease and 6 patients with anorectal malformation. 3D HRARM was performed. The resting pressure and squeeze pressure at the physiological sphincter were measured and analyzed. We define the inter-quadrant pressure asymmetry index (Δp) mathematically, Δp = (maximal pressure - minimal pressure)/maximal pressure x 100%. **Results:** There was an increasing inter-quadrant pressure asymmetry index (Δp) observed in the anal pressure profiles in patients with history of Soave pullthrough, myomectomy, Duhamel operation and posterior sagittal anoplasty (PSARP). The asymmetry is more pronounced in squeeze pressure in the Soave pullthrough group, and less pronounced in squeeze pressure in the myomectomy, Duhamel and PSARP group. **Conclusions:** The inter-quadrant pressure asymmetry index (Δp) reflects the post operative status of anal sphincter, which is influenced by the different surgical maneuvers employed in the operations. The symmetry of anal sphincter pressure might provide useful anatomical parameters in the assessment of surgical outcomes.

Key words Anorectal malformation; Anorectal manometry; High resolution; Hirschsprung's disease; Symmetry

Introduction

Anorectal manometry (ARM) has been used extensively in research and in the clinical assessment of patients with defaecation disorders. It has been shown that it can provide reliable analysis of the anal sphincter function.1,2 There are increasing reports of ARM application on paediatric population.3,4

In conventional ARM, a trans-anal water-perfused multi-channel catheter is inserted into the rectum. Serial measurements of resting, squeeze and push pressures at different levels of anorectal region are measured. The catheter is then manually withdrawn by a pull-through technique until it reaches the anal sphincter region.

However, the frequent manipulation of the catheter may be disturbing to a young child, leading to inaccurate results and conclusions. With the evolution of technology, the three dimensional high resolution anorectal manometry (3D HRARM) has been released to the market. It has radially arranged pressure channels in multiple levels; hence the anal pressures along the entire anal canal can be measured simultaneously, obliterating the need of frequent adjustment of the catheter during the procedure. The individual pressure parameters can be integrated by the computer software to
Tang et al

reconstruct a topographic image of anal canal.

The aim of this study is to investigate the feasibility and usefulness of 3D HRARM in the evaluation of patients who had undergone surgery for congenital anorectal anomalies including Hirschsprung’s disease (HD) and anorectal malformation (Mal).

Materials and Methods

From June 2013, we prospectively recruited 14 neurologically healthy children with age 4 years or above, with surgical correction of HD and Mal in our hospital. All the patients were recruited at our multidisciplinary bowel management clinic. Their demographic data and Rintala continence scores are shown in Table 1. Patients with history of HD were further analysed into subgroups according to the surgical techniques employed: five patients had laparoscopic assisted Soave endorectal pullthrough for rectosigmoid HD, two patients had posterior myomectomy for ultra-short segment HD and one patient had Duhamel operation for long segment HD. All the patients in the Mal group had anorectal malformation with posterior sagittal anorectoplasty (PSARP) performed. Three patients with idiopathic constipation were recruited as control group.

With informed consent, all the recruited subjects were given bowel preparation in the form of sodium phosphate rectal fleet enema 3 ml/kg prior to the study. The caretaker was allowed to accompany the child during the procedure to relieve anxiety. A surgeon was present during the entire procedure to conduct and analyse the pressure tracings. A single-use water perfused 24-channel catheter (Figure 1) with four quadrant pressure channels at five 1 cm spacing (Medical Measurement Systems B.V., MMS G-90520 The Netherlands) was used for manometry.

All the patients were awake and non-sedated during the investigation. The physiological anal sphincter was identified at the high pressure zone (HPZ) of the anal canal. The catheter would then be held in place by securing it onto the subject’s buttock with surgical tape. The resting and squeeze pressure at the HPZ were measured.

The orientation and position of the catheter is checked regularly after each manoeuvre to avoid rotation. The pressure parameters were integrated into a topographic image of the anal canal by the 3D HRARM software.

PASW Statistics 18 (SPSS Inc, Chicago, IL, USA) was applied for statistical analysis. Wilcoxon signed ranks test was used to compare non-parametric data, with statistical significance considered at p<0.05. The study was approved by the research ethical committee of the hospital.

Results

All the patients enrolled were able to complete the manometric study with no complications. There is no up-to-date validated data concerning the symmetry of the pressure distribution of the anal canal in children using 3D HRARM. In our study, we define the inter-quadrant pressure asymmetry index (Δp). Δp denotes the inter-quadrant pressure difference divided by the maximal quadrant pressure, in percentage expression.

\[
\Delta p = \frac{\text{maximal quadrant pressure} - \text{minimal quadrant pressure}}{\text{maximal quadrant pressure}} \times 100\%.
\]

For total symmetrical sphincter with equal pressure over the four quadrants, \(\Delta p = 0\%\). For total asymmetrical sphincter, \(\Delta p = 100\%\).

In the control group, \(\Delta p\) ranged from 8-23% in the resting pressure (Figure 2). In the HD group, patients with laparoscopic assisted Soave pullthrough had \(\Delta p\) range from 27-50%; patients with myomectomy and Duhamel operation had \(\Delta p\) range from 56-95%. In the Mal group, patients had \(\Delta p\) range from 59-95% (Figure 3). However, we do not find any correlation of the inter-quadrant pressure asymmetry index with the Rintala score (Table 2).

The squeeze pressures at the HPZ were also measured.

<table>
<thead>
<tr>
<th>Study groups</th>
<th>Control</th>
<th>Hirschsprung’s disease</th>
<th>Anorectal malformation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>3M: 0F</td>
<td>4M: 4F</td>
<td>2M: 4F</td>
</tr>
<tr>
<td>Age (years)</td>
<td>14 (10-17)</td>
<td>8 (6-10)</td>
<td>5(4-9)</td>
</tr>
<tr>
<td>Rintala score (/20)</td>
<td>16</td>
<td>17.6</td>
<td>18.3</td>
</tr>
</tbody>
</table>

Figure 1 Three-dimensional high resolution anorectal manometry catheter.
and the inter-quadrant squeeze pressure asymmetry index ($\Delta'p$) was expressed as the inter-quadrant pressure difference divided by the maximal quadrant pressure on squeezing. $\Delta'p$ were significantly greater than $\Delta p$ in patients with idiopathic constipation or Hirschsprung’s disease with laparoscopic assisted endorectal pullthrough performed (Wilcoxon signed ranks test, $p=0.049$). However, $\Delta'p$ were significantly smaller than $\Delta p$ in patients in HD group after myomectomy/Duhamel operations or Mal group after PSARP ($p=0.021$).

Discussion

HD and Mal are two of the most common congenital anorectal anomalies. Defaecation disorders such as faecal incontinence and constipation can occur after the surgical repair of these conditions. Most of these patients require long-term bowel management program. An objective evaluation of their sphincter function is essential in the evaluation of surgical outcomes. In this study, we limit our application of the manometric study to patient older than 4 years old, because when ARM study is applied in children younger than 4 years old, ketamine sedation is often required because they are too young to cooperate with the study. In the ideal situation, the control group should be children with no gastro-intestinal symptoms (no constipation), however it would be difficult to recruit such children as they would not even come to see us in the first place.

Faecal continence is significantly correlated with anal pressures in post-operative patients. Various studies have also discussed the functional outcome of post-operative patients by means of validated questionnaires and/or bowel function scoring system. Few reports have evaluated the anatomy of the anal canal with endorectal ultrasound and MRI pelvis. Sphincter asymmetry index (SAI) have been described and used for the detection of sphincter defect and to assess the integrity of sphincter after operation for HD, however these studies are often based on adults while using the conventional anorectal manometry.

Recently, the availability of the 3D HRARM has allowed a detailed assessment of pressure distributions in the anal canal. Cheeney et al have suggested that 3D HRARM could improve the understanding of anorectal physiology by permitting concurrent assessment and correlation of anatomy with anal pressures profiles, eliminating the need for subsequent correlation with other imaging modalities. Nonetheless, the experience of using 3D HRARM in the paediatric surgical patients is limited. To the best of our knowledge, this is the first study to evaluate the anal pressure in post-operative paediatric patients by 3D HRARM.

To facilitate communication and understanding, we derived a simplified mathematical model by calculating the pressure difference between the quadrant with the maximal pressure and the quadrant with the minimal pressure, and then we quantify the inter-quadrant pressure asymmetry index ($\Delta p$) by taking the pressure difference in relation to the maximal pressure, the higher value of $\Delta p$, the more the asymmetrical is the anal canal.

We observed that there is a trend of mild asymmetry in the anal pressures in the control group, with $\Delta p <25\%$; moderate asymmetry in the Soave HD group with $\Delta p$ ranges from $25\%-50\%$; and marked asymmetry in the Duhamel HD, myomectomy HD and Mal group with $\Delta p >50\%$.

Ambartsumyan et al had defined the symmetry of the anal canal by incorporating the longitudinal and radial anal pressure distribution, which necessitate the measurement and adjustment of the anal canal length. In our investigations,
we did not take into account of the length of the anal canal as we only focused on the degree of asymmetry of the high pressure zone (HPZ). As we believe that HPZ is the most representative for sphincter function. The variable body size in the paediatric population and the different surgical procedure that had been performed may also lead to imprecise and difficult interpretation of the genuine canal length.

Several studies had discussed the significance of anal pressure asymmetry in nulliparous adult women and it was suggested that the asymmetry was due to the unique "triple looped anatomy" of the puborectalis muscles in the anal canal, which was evident in both high resolution anal manometry and endorectal ultrasound. Hence, the anal pressure profiles of the control group in our study are also not completely symmetrical.

In Soave pullthrough operation, submucosal dissection of the anal cuff with the preservation of anal sphincter was performed. However, we believe inadvertent microscopic damage of the circular fibers may lead to moderate asymmetry in anal pressures.

In both myomectomy and Duhamel operation, the posterior part of the anal sphincter was disrupted, that may account for the moderate to marked asymmetry in anal pressures.

In the Mal group, we expected that by following Pena's principle of adhering to the midline during dissection and by accurate siting of the neo-anus with the nerve stimulator when performing PSARP would preserve the anal sphincter muscle complex. Unfortunately, marked anal pressure asymmetry was found in this group of patient, we postulated that it could be due to the congenital defects of the neuromuscular complex in the anal canal or muscle injury during operation.

It is interesting to note that in constipation and Hirschsprung's disease patients after laparoscopic assisted Soave endorectal pullthrough with mild to moderate anal sphincter asymmetry, Δp' was significant greater than Δp. On squeezing of anal sphincter, contraction of the unique "triple looped puborectalis" muscles in the anal canal may account for the exacerbation of the sphincter asymmetry. However, in patients suffering from Hirschsprung's disease

<table>
<thead>
<tr>
<th>Subject</th>
<th>Diagnosis (Operation)</th>
<th>Resting pressure (mmHg) (max/min.)</th>
<th>Degree of asymmetry (%)</th>
<th>Squeeze pressure (mmHg) (max./min.)</th>
<th>Degree of asymmetry (%)</th>
<th>Rintala score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Constipation</td>
<td>79/67</td>
<td>15</td>
<td>215/161</td>
<td>25</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>Constipation</td>
<td>70/54</td>
<td>23</td>
<td>297/151</td>
<td>49</td>
<td>19</td>
</tr>
<tr>
<td>3</td>
<td>Constipation</td>
<td>74/60</td>
<td>8</td>
<td>134/113</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td>4</td>
<td>HD (Soave)</td>
<td>70/43</td>
<td>39</td>
<td>158/56</td>
<td>64</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>HD (Soave)</td>
<td>70/43</td>
<td>39</td>
<td>302/147</td>
<td>51</td>
<td>18</td>
</tr>
<tr>
<td>6</td>
<td>HD (Soave)</td>
<td>79/58</td>
<td>27</td>
<td>126/74</td>
<td>41</td>
<td>17</td>
</tr>
<tr>
<td>7</td>
<td>HD (Soave)</td>
<td>53/72</td>
<td>49</td>
<td>198/123</td>
<td>38</td>
<td>18</td>
</tr>
<tr>
<td>8</td>
<td>HD (Soave)</td>
<td>109/55</td>
<td>50</td>
<td>116/56</td>
<td>52</td>
<td>18</td>
</tr>
<tr>
<td>9</td>
<td>HD (myomectomy)</td>
<td>85/11</td>
<td>87</td>
<td>103/20</td>
<td>81</td>
<td>18</td>
</tr>
<tr>
<td>10</td>
<td>HD (myomectomy)</td>
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<td>56</td>
<td>206/163</td>
<td>21</td>
<td>18</td>
</tr>
<tr>
<td>11</td>
<td>HD (Duhamel)</td>
<td>113/3</td>
<td>95</td>
<td>137/35</td>
<td>75</td>
<td>19</td>
</tr>
<tr>
<td>12</td>
<td>Mal (PSARP)</td>
<td>86/5</td>
<td>94</td>
<td>124/68</td>
<td>45</td>
<td>20</td>
</tr>
<tr>
<td>13</td>
<td>Mal (PSARP)</td>
<td>85/11</td>
<td>87</td>
<td>103/20</td>
<td>81</td>
<td>18</td>
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<tr>
<td>14</td>
<td>Mal (PSARP)</td>
<td>70/25</td>
<td>64</td>
<td>181/63</td>
<td>65</td>
<td>17</td>
</tr>
<tr>
<td>15</td>
<td>Mal (PSARP)</td>
<td>113/6</td>
<td>95</td>
<td>137/35</td>
<td>75</td>
<td>17</td>
</tr>
<tr>
<td>16</td>
<td>Mal (PSARP)</td>
<td>92/21</td>
<td>78</td>
<td>73/14</td>
<td>81</td>
<td>18</td>
</tr>
<tr>
<td>17</td>
<td>Mal (PSARP)</td>
<td>73/30</td>
<td>59</td>
<td>238/121</td>
<td>49</td>
<td>20</td>
</tr>
</tbody>
</table>

HD: Hirschsprung's disease; Mal: anorectal malformation; PSARP: posterior sagittal anorectoplasty
after myomectomy / Duhamel operation and anorectal malformation after PSARP with marked sphincter asymmetry, Δp' was significant smaller than Δp. The augmenting effect of pelvic floor and gluteal muscles contraction during anal squeeze may account for the compensation of weaken quadrant of anal sphincter.

Based on the above findings, we conclude that the degree of asymmetry (Δp) can reflect the post-operative status of anal sphincter, which is largely influenced by the specific surgical maneuvers employed in the operations for HD and Mal. Therefore, we infer that the study of the pressure distribution in the anal canal can provide useful feedback information to the surgeons and might facilitate subsequent refinement of the surgical techniques.

In this pilot study we were not able to find a clinical correlation of the sphincter pressure status and the functional outcome (in terms of Rintala scores) of these patients. This may also be due to the different response and compliance to the post op bowel management program administered to all our patients after anorectal operations.

A significant limitation of our study lies in the small sample size, with increasing experience and expertise in the application of 3D HRARM, we hope that we can eventually establish some normative data in the assessment of anal sphincter physiology.

The use of 3D HRARM in the assessment of postoperative anal sphincter condition is safe and child-friendly. It may give additional information regarding the degree of the anal pressure symmetry. With further studies and correlation with other investigation modalities, it would become an increasingly useful armamentarium of investigations in the assessment of children with defaecation disorders.

**Declaration of Interest**

None

**References**

Original Article

Frequency of Refraction Errors among School-age Children in Ankara, Turkey: A Cross-Sectional Study

U AYDOGAN, OM CELYAN, P NERKIZ, YC DOGANER, OT TOMBUS, G GOKCE, M THURSTON, FM MUTLU, HI ALTINSOY

Abstract
Uncorrected refractive errors are the most frequent cause of visual impairment in school-age children. The present study sought to evaluate frequency of refraction disorders in school-age children at different socio-cultural levels in Ankara/Turkey. This cross-sectional study was carried out on 1729 children 7-14 years of age. Frequency of refractive errors were determined as 10.8% (n=186) myopia, 3.8% (n=66) hyperopia and 26.3% (n=455) astigmatism. Multiple regression analysis revealed that age (OR:1.23, p<0.001), positive family history of myopia (OR:2.36, p<0.001), number of siblings (OR:0.73, p=0.001) and maternal working status (OR:0.32, p=0.002) were significantly associated with myopia in children. Frequency of myopia as a cause of refractive errors was increased compared with the other developed countries. Regular eye screening programs in school-aged children should be essential practices to prevent vision loss.

Key words
Children; Eye examination; Frequency; Refractive errors

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Introduction

Refractive errors such as myopia and hyperopia are visual impairments, the correction of which leads to potentially high costs. Such visual corrections are defined as a critical reason for public health and economic burden. World Health Organization (WHO) "Vision 2020: The Right to Sight" has adopted the correction of refractive errors, which are the most important preventable causes of visual impairment, as a primary target to eliminate all preventable and treatable blindness. For this reason, screening programs in school-age children are of importance in terms of long-term health conditions across the population. The school-age ocular screening programs increase the chance of early diagnosis of visual impairment risk factors such as amblyopia, diplopia facilitating amblyopia and refractive errors in children.

Uncorrected refractive errors are the most frequent cause of visual impairment in school-age children in either industrial or developing countries throughout the world. The interaction of many factors such as genetics and the environment, socio-economical level, and outdoor activities may contribute to the development of refractive errors. Refractive errors in childhood may result in insufficient and low performance at school but if not detected and treated appropriately may progress to permanent vision loss.

Many studies have been carried out on children at various age groups in different ethnic groups regarding refractive errors. While the frequency of myopia was 24.5% in a study carried out in students between the ages of 12-17 in the USA from 1971-1972, it was 34.8% in a study carried out between the years of 1999-2004. In two studies carried out in Australia, the frequency of myopia was 1.4% in the children at the age of 6 and it was reported as 5.1% in the children at the age of 12. The frequency of myopia in children originating from East Asia as a sub-group in the 12-age group was reported as 41.6%. The frequency of myopia was found at a low rate such as 1.2% in a broad-based study which involved children between the ages of 5-15 in Nepal. While the frequency of myopia was reported at a lower rate of 1.4% in the rural area of India, and it was 7.4% in the urban area. In certain studies carried out in East Asia countries, the frequency of myopia was found to be above 35% in the children of different age groups.

This study evaluated the frequency of ocular pathologies leading to visual impairment such as decreased visual acuity, refractive defects and diplopia in school-age children at different socio-cultural levels in Ankara/Turkey. Additionally, we also sought to identify possible risk factors and demographic features unique to children with myopia.

Methods

Study Design

This study was a cross-sectional study intended to determine the frequency of vision problems such as amblyopia, refractive errors, diplopia and colour blindness in the school-age children ages 7-14.

Questionnaire

A questionnaire included questions regarding socio-demographic characteristics of the parents and their children and an eye health history of the children was completed by their parents. Parent approval about participation in the research study was obtained in order to fill out the survey including questions about their educational levels, working status, number of children, conditions of others who have an eye disorder in the family, whether the child had previously undergone an eye examination, school success, and the time that the child spends on the television/computer. Body mass index (BMI) values of participants were calculated based on the formula of BMI=weight/height² (kg/m²).

Definitions

In order to ensure a complete and valid comparison with other studies, certain definitions were clarified. Myopia was defined as a spherical equivalent (SE) refraction having 0.5 diopter (D) or lower values in one or both eyes. We categorised myopia as mild (-0.5 D to -3.0 D), moderate (-3.1 D to -6.0 D), and high (worse than -6.0 D). Hyperopia was defined as SE refraction’s having +2.0 diopter or higher values in one or both eyes. Hyperopia was categorised as mild (+2.0 D to +3.9 D), moderate (+4.0 D to +5.9 D) and high (≥ +6.0 D). Astigmatism was defined as cylindrical defect’s being ≥0.75 D in one or both eyes. A difference more than 2 lines between eyes in Snellen charts and best corrected visual acuity of each eye lower than 0.6 were considered amblyopia.

Population and Samples

This cross-sectional study was carried out on primary and secondary school-age children in Ankara between the dates of 1st May-1st December 2010. 1729 of 2000 students who were included in the study (86.45%) fulfilled the criteria...
for the parental consent and inclusion into the study. Participants from different socio-cultural levels were included in the study in a randomised manner. Students who were diagnosed with mental retardation, congenital anomaly, ocular opacity and retinal disease and the students of whom consents of their parents were not obtained were excluded from the study. The students were taken into the examination room by their class number. Data from the questionnaire form which was prepared to determine the socio-demographic information of all participants and their previous eye health conditions were recorded.

**Examinations**

The refractive errors of all of the eyes were measured without cycloplegia. Measurement of all of the patients was repeated using Plusoptix S08 refractometers. For measurements with the Plusoptix S08, the examiner adjusted the mobile camera to the face of the patient at a distance of 1 m, and at the end of the measurement, the refractive data indicated in green on the monitor were taken as the baseline. Refractive measurements of the patients were performed by investigators under the same conditions, each device being used by the same investigator. All of the measurements were repeated at least 3 times and the average values of the obtained results were recorded in order to be used in the study.

**Devices Used in the Study**

Plusoptix S08 (Plusoptix GmbH, Nuremberg, Germany) works based on the eccentric photorefraction method. As it performs the measurements from a distance of 1 m, it gives a relaxation of accommodation. Especially in children, its main advantages are that it does not cause a feeling of fear due to the lack of physical contact and it assists in the detection of anisometropia without accommodation difference due to its capability of the binocular measurement. The device also detects the pupil size and inter pupiller distance (IPD) values during refraction measurement.

**Statistical Analysis**

While evaluating the data obtained from the study, the package program SPSS 15.0 for Windows (Chicago-USA) was used. Descriptive statistical methods were given in numbers and percentages for categorical variables and as mean ± standard deviation or median (minimum - maximum) for continuous variables. Refractive errors were accepted as primary outcome, whereas gender, age, BMI, parental educational levels, parental working status, the existence of refractive errors in the family, time spent watching TV-computer and number of siblings were accepted as predictors. The conformity of data to a normal distribution was analysed using Kolmogorov-Simirnov test. Chi-square test was used for categorical variables. Spearman correlation analysis was used to evaluate the correlation between factors. The statistical significance was accepted at p<0.05. Multiple logistic regression analysis was applied to detect the impact of independent variables on the refractive errors.

**Ethical Approval**

The parents of school-children were informed and their written consent regarding the study was obtained. The necessary ethical committee approval for the study was received from the Gulhane Military Medical Academy (GMMA) Local Ethics Committee and the required permission was obtained from Ankara Provincial Directorate of National Education. The research adhered to the principles of the Declaration of Helsinki.

**Results**

The mean age of the participants was 9.43±2.06 years (7-14 years) and 47.8% (n=827) of the students were males. The refractive error evaluation carried out on the children was examined in terms of the presence of myopia, hyperopia, and astigmatism in at least one eye. As a result of this evaluation, the frequency of refractive error was determined as 10.8% (n=186) myopia, 3.8% (n=66) hyperopia and 26.3% (n=455) astigmatism. The frequency of myopia-astigmatism was 4.6% (n=80). In the evaluation carried out by considering the presence of amblyopia in at least one eye, the frequency of amblyopia was determined as 8.8% (n=152). When refractive errors and amblyopia rates were evaluated in terms of gender, no statistically
significant difference was found \( p>0.05 \) (Table 1).

Students who were examined in terms of refractive errors were analysed regarding the independent variables including gender, age, BMI, parental educational level, parental working status, the presence of eye disease in the family, time spent on the TV/computer and number of siblings. An analysis of the children having myopia in terms of the independent variables was specified in Table 2. The only significant difference in terms of age was found in those who have hyperopia as compared with those who do not have hyperopia \( (8.86\pm1.92/9.45\pm2.06; \ p=0.023) \). A significant difference in terms of BMI \( (17.88\pm2.93/17.36\pm2.77; \ p=0.001) \) and average time spent on the TV-computer \( (3.02\pm1.48/2.80\pm1.44; \ p=0.005) \) was found in those who have astigmatism as compared with those who do not have astigmatism.

In the study, the relationship between the educational status of the parents and the frequency of myopia of the children was analysed. When the maternal educational level of the children with myopia was compared with the maternal educational level of the children without myopia; the results were as follows: \( (0-8 \text{ years}) 60.8/57\%, \ (9-12 \text{ years}) 36.6/34.7\%, \ (\geq12 \text{ years}) 2.7/8.3\% \ (p=0.025) \) (Table 2). When the relationship between the frequency of myopia of the children and the working status of the parents was analysed, it was found that there was a significant relationship between the children with myopia and the working status of both mother and father \( (p<0.001, \ p=0.024, \ \text{respectively}) \) (Table 2). Furthermore, a positive correlation was detected between the parental educational level and the children who had undergone an eye examination before \( (r=0.073, \ p=0.020; \ r=0.089, \ p<0.001) \).

Myopia and hyperopia defect rating carried out by considering the SE values for both eyes is specified in Table 3. The distribution of the frequency of myopia and hyperopia by the age groups is shown in Figure 1 and Figure 2 \( (p<0.001 \text{ and } p=0.015, \ \text{respectively}) \). In the distribution of the frequencies of astigmatism and amblyopia by the

### Table 2  
Socio-demographic characteristics of the students evaluated in terms of myopia \( (n=1729) \)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Myopia (+)</th>
<th>Myopia (-)</th>
<th>( p^* )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>104 (11.5)</td>
<td>798 (88.5)</td>
<td>0.279</td>
</tr>
<tr>
<td>Male</td>
<td>82 (9.9)</td>
<td>745 (90.1)</td>
<td></td>
</tr>
<tr>
<td>Mother working (+)</td>
<td>10 (5.4)</td>
<td>228 (14.8)</td>
<td>( &lt;0.001 )</td>
</tr>
<tr>
<td>Father working (+)</td>
<td>172 (92.5)</td>
<td>1482 (96)</td>
<td>0.024</td>
</tr>
<tr>
<td>Mother education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-8 years</td>
<td>113 (60.8)</td>
<td>880 (57.0)</td>
<td></td>
</tr>
<tr>
<td>9-12 years</td>
<td>68 (36.6)</td>
<td>535 (34.7)</td>
<td>( 0.025 )</td>
</tr>
<tr>
<td>&gt;12 years</td>
<td>5 (2.7)</td>
<td>128 (8.3)</td>
<td></td>
</tr>
<tr>
<td>Father education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-8 years</td>
<td>78 (41.9)</td>
<td>583 (37.8)</td>
<td></td>
</tr>
<tr>
<td>9-12 years</td>
<td>79 (42.5)</td>
<td>609 (39.5)</td>
<td>0.082</td>
</tr>
<tr>
<td>&gt;12 years</td>
<td>29 (15.6)</td>
<td>351 (22.7)</td>
<td></td>
</tr>
<tr>
<td>Refractive disorders in the family (+)</td>
<td>102 (54.8)</td>
<td>530 (34.3)</td>
<td>( &lt;0.001 )</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>mean±SD</th>
<th>mean±SD</th>
<th>( p^{**} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>10.35±2.06</td>
<td>9.32±2.03</td>
<td>( &lt;0.001 )</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>18.32±2.76</td>
<td>17.39±2.81</td>
<td>( &lt;0.001 )</td>
</tr>
<tr>
<td>TV-PC time (hour/day)</td>
<td>2.88±1.42</td>
<td>2.86±1.46</td>
<td>0.862</td>
</tr>
</tbody>
</table>

*: Student t-test; **: Chi-Square test.

Myopia (+): with myopia; Myopia(-): without myopia.
age groups, no significant difference was found (p>0.05).

Parents were surveyed regarding whether their children had undergone eye examinations before and 45.8% of the children (n=792) had never gone through an eye examination. When the current eye health information of the children was asked to the parents, although 78% (n=1349) notified that their children had no eye problem, 14% (n=242) stated that their children used eyeglass, 2.8% (n=48) stated that their children had amblyopia, 0.3% (n=5) stated that their children had colour blindness, 0.5% (n=9) indicated that their children had diplopia and 4.4% (n=76) stated that their children had other eye diseases in the past. The eyeglass usage rates of the children in which refractive errors and amblyopia were detected during the examination are specified in Figure 3.

Of the parents, 36.6% (n=632) at least one of them had an eye health related problem. Eye pathologies which also include myopia, hyperopia, astigmatism, dyschromatopsia, and colour blindness were found in 17.8% of the mothers (n=307), in 16.5% of the fathers (n=286) and in 12.9% of the siblings. A positive relationship was found between those whose family members have had eye health problems and students having refractive error in terms of myopia (r=0.132, p<0.001) and astigmatism (r=0.048, p=0.045). The total duration that the children spent on the TV and/or computer averaged 2.86±1.45 (0-7 hours) per day.

In a multiple logistic regression analysis carried out, a significant association with age (OR:0.91, CI 95%; 0.86-0.97, p=0.004), BMI (OR:1.08, CI %95; 1.04-1.13, p<0.001) and average duration spent on the TV-computer (OR:1.09, CI 95%; 1.01-1.18, p=0.020) was found in the students diagnosed with astigmatism and a significant association was found in students diagnosed with hyperopia in terms of age as part of the independent variables (OR: 0.83, CI 95%; 0.72-0.97, p=0.020). Multiple regression analysis revealed that age (OR:1.23, p<0.001), positive family history (OR:2.36, p<0.001), number of siblings (OR: 0.73, p=0.001) and maternal working status (OR:0.32, p=0.002) were significantly associated with myopia in children (Table 4).

### Table 3  
Right and left eye evaluation by the severity of the myopia and hyperopia defect (n=1729)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Right eye</th>
<th>Left eye</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy</td>
<td>1515 (87.6)</td>
<td>1519 (87.9)</td>
</tr>
<tr>
<td>Mild myopia (-0,5 D to -3,0 D)</td>
<td>128 (7.4)</td>
<td>122 (7.1)</td>
</tr>
<tr>
<td>Moderate myopia (-3,1 D to -6,0 D)</td>
<td>35 (2)</td>
<td>36 (2.1)</td>
</tr>
<tr>
<td>High myopia (&gt; -6,0 D)</td>
<td>2 (0.1)</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td>Mild hyperopia (+2,0 D to +3,9 D)</td>
<td>43 (2.5)</td>
<td>40 (2.3)</td>
</tr>
<tr>
<td>Moderate hyperopia (+4,0 D to +5,9 D)</td>
<td>5 (0.3)</td>
<td>9 (0.5)</td>
</tr>
<tr>
<td>High hyperopia (≥ +6,0 D)</td>
<td>1 (0.1)</td>
<td>1 (0.1)</td>
</tr>
</tbody>
</table>

![Figure 1](image1.png)  
**Figure 1**  
Distribution of the frequency of myopia by the age groups.

![Figure 2](image2.png)  
**Figure 2**  
Distribution of the frequency of hyperopia by the age groups.

![Figure 3](image3.png)  
**Figure 3**  
Eyeglass usage rates of the children in which refraction errors and amblyopia were detected.
Discussion

Refractive errors are responsible for more than half of the vision impairments in the populations researched. These visual impairments are significant without differentiating age, gender or ethnicity throughout the world. It is important to establish a diagnosis by means of early and rapid diagnosis methods and to ensure healthy vision ability by means of suitable treatment methods. The prevalence of refractive errors can differ by race and geographical region, gender, age and parent training level. In our study, the frequency of amblyopia was 8.8% whereas myopia was determined as 10.8%, hyperopia as 3.8% and astigmatism as 26.3% from all refractive errors.

In the studies carried out in the Far East countries, myopia (≥-0.50 D) was affecting 36.8% of the children at the age of 13; 53.9% of the children at the age of 17, hyperopia (≥+2.00 D) was affecting the children at the rate of approximately 1% in all age groups and astigmatism (≥-0.75 D) rates were affecting 25.3% of all children in the study carried out by He et al in which 2454 total children participated. Saw et al determined the myopia rate as 24.7% at the age of 7 and 49.7% at the age of 9 (approximately two folds greater than at age of 7). In two different studies carried out in the Middle East, myopia was determined at the rate of 1.7%, hyperopia at the rate of 20.5% and astigmatism at the rate of 19.6% in an investigation carried out in children at the age of 6 by Jamali et al. The frequency of myopia was determined as 4.3%, the frequency of hyperopia as 5.4% and the frequency of astigmatism as 11.5% by Rezvan et al in the school-age children ages 6-17. In a study carried out in Northern Ireland, refractive error at ages 6-7 was compared with the age group 12-13; myopia was determined at the rate of 2.8% / 17.7% and hyperopia as 26% / 14.7%. Whereas in Europe, the myopia rate was determined as 11% in 13-year-old children in Poland, and the frequency of myopia (45%) was found to be higher in the same age group in Sweden. In our study, the myopia rates were 4.6% in 7-year-old children and 22.1% in 14-year-old children. The hyperopia rate was 5.3% in the 7-year-old children and 2.4% in 13-year-old children. Hyperopia was not found in children at the age of 14. When we compared refractive error frequencies that we found with the other countries, our myopia rate was not as high as the Far East, and our hyperopia rate was not as high as the European countries.

The spherical equivalency (spheric+cylinder/2) was used in the definition of refractive errors in terms of consistency with the other studies. However, this formulation might lead to faults especially in the patients where the primary problem is high astigmatism in the evaluation of refractive errors. For instance, the SE value was (-0.50) in the eye in the measurement of (+0.50/-2.00), and the main problem was considered as myopia even though it was astigmatism. For this reason, refractive error ratios which are a little bit higher than average might have been found.

There can be many reasons for achieving different results in terms of refractive errors among the different countries. The foremost among them is racial differences. It is considered that the environmental exposure and lifestyle changes play a role even though the factors that increase the genetic sensitivity cannot be clearly explained.

Another reason for the differences between the countries is that there are different refractive error descriptions in the studies. Robinson et al found the frequency of myopia in children at the age of 6 as 6% when they considered myopia as -0.25 D on the horizontal meridian and as 1.8% when they determined the margin as -1.00 D in the study that they carried out by the non-cycloplegic refraction method. For instance, the SE value was (-0.50) in the eye in the measurement of (+0.50/-2.00), and the main problem was considered as myopia even though it was astigmatism. For this reason, refractive error ratios which are a little bit higher than average might have been found.

There can be many reasons for achieving different results in terms of refractive errors among the different countries. The foremost among them is racial differences. It is considered that the environmental exposure and lifestyle changes play a role even though the factors that increase the genetic sensitivity cannot be clearly explained.

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which was most commonly used in previous publications. Compared with the myopia prevalence of children in developed countries, the relatively high myopia prevalence in school-children living in developing countries may arise from the deficiency of public screening interventions during childhood.

In a study carried out by Gao et al, it was found that the eyeglass usage rates in rural area schools are lower than urban area schools. Another important finding that we established was other refractive errors were lower in children diagnosed with myopia and lower eyeglass usage rates in amblyopia. This finding may depend on the fact that wearing eyeglasses is humiliating among students. To cope with this fallacy and to ensure eyeglass usage in necessary cases seems possible by educating the children, their families and their teachers about its importance in preventing other refractive errors and potentially blindness.

It is stated that refractive errors are also related to the educational level and social status of the parents. In our study, a negative significant relationship was found between myopia and the educational level of the mothers and the working status of the parents. We estimate that the parents who are working and the mothers who have high educational level take their children to a regular eye examination and give more value to protective eye health precautions. We could not find a significant relation between the refractive errors and gender. There are also studies which demonstrate that girls are in the majority of the children with myopia, as well as other research studies having parallel findings with our study in terms of the gender difference.

The existence of refractive error history in the family was defined as another independent risk factor. Kaur et al researched the frequency of myopia in three generations (grandparents, parents, and children). It was found that most of the parents who had myopia also had grandparents with myopia. Although the frequency of myopia increases from the older generations to younger generations, no relationship was found between this increase and the myopia of the parents and children. In a study carried out by Jones et al, it was found that parental myopia is a high risk factor in the development of myopia in children. In our study, the presence of the refractive error history in a family increased the development of myopia in children approximately 2.5 times (OR=2.362). These results underline the importance for the students whose families have refractive error history to receive eye health services in terms of preventive care.

The relationship between the children's outdoor playing activities and the frequency of myopia are examined in recent studies. In a study carried out by Dirani et al, a negative significant relationship was found between the increase in the average time spent in the outdoor activities and myopia. This negative significant relationship also continued between the total period spent while doing physical exercise and the development of myopia. In a study carried out on students 12 years of age by Rose et al, however, lower myopia rates were found in the students who were doing outdoor activities (Physical Exercise and leisure time). In a study carried out in students ages 7-12 by Wu et al a significant relationship was found between the TV watching time and myopia. In the analysis that we performed in our study, higher BMI values were found in children with myopia as compared with the children without myopia. These results make us consider that the students in our study group do not spare enough time for sportive and physical outdoor activities, and they spend their leisure time doing activities which cause damage to their eye health such as watching TV, PC games.

**Study Limitation**

The major limitation of the study is not that it is a study that is based on population distribution, but that it is a study that is based on demographic characteristics at schools. The differences between rural and urban region schools were researched with questions regarding the socio-economic level. The use of cycloplegic and mydriatic agents could not be applied since the research was designed as a comprehensive field study.

**Conclusion**

The frequency of myopia within the refractive errors was determined moderately high compared with the other developed countries although it was determined as lower than the Far Eastern countries. It was remarkable that the eyeglass usage rate in the refractive error groups other than myopia was not high. Study results indicate that refraction errors in children may differ based on demographics and public health policy should be rearranged in terms of visual screening programs. Visual disorders occurring in childhood may persist to adulthood and become a significant barrier to achieve educational goals and pursue certain career paths through an individual's life. The performance of regular eye screening programs, mainly in
the regions with low socio-economic development will potentially prevent vision losses later in life. Meanwhile, effective interventions could provide healthy neurodevelopmental improvements during the childhood period.

**Declaration of Interest**

None

**References**

Paediatric Malone Antegrade Continence Enema (MACE): The Hong Kong Experience

PMY Tang, KLY Chung, YCL Leung, JWS Hung, FSD Yam, CSW Liu, NSY Chao, MWY Leung, KKW Liu, YCF Kwok, CWH Ng

Abstract

Introduction: Faecal incontinence in children is a common and socially embarrassing condition. Surgical intervention may be required when medical treatment fails. Malone antegrade continence enema (MACE) is a well-established way to achieve social continence via regular evacuation of the colon through the appendiceal conduit. Methods: We retrospectively reviewed the clinical records of patients who have undergone the MACE procedure in our center from 2009 to 2016. Results: Eight patients were recruited in the review and all of them were able to achieve a Rintala score of $\geq 15$ after the MACE procedure. Conclusions: The MACE procedure is safe and effective in the management of children with faecal incontinence and refractory constipation. Careful patient selection and a team of dedicated specialty nurses are essential for optimal outcome.

Key words Faecal incontinence; MACE; Rintala

Introduction

Faecal incontinence is usually broadly divided into overflow incontinence and non-retentive incontinence. It is socially embarrassing and when it occurs in children, it is usually associated with spinal cord anomalies, anorectal malformation or Hirschsprung's disease. Irregardless of the aetiology of the faecal incontinence, the Rome III criteria have been established to distinguish between functional constipation and functional non-retentive faecal incontinence in children with a developmental age of at least 4 years. Conservative management of faecal incontinence includes stool softeners, bulking agents, suppositories, rectal enema and biofeedback. Social continence can often be achieved when the colon is kept evacuated by means of regular rectal enema. In 1990s, Malone first described the use of appendix as a conduit for the delivery of antegrade continence enema. Many modifications have been developed over the years, including the minimally invasive
approach. The theory is that the antegrade enema is to be administered with faecal elimination – thus preventing constipation and faecal continence. The improvement in the quality of life in paediatric patients pre and post Malone antegrade continence enema (MACE) procedure has been established. However, the data on the MACE procedure in Chinese children is lacking.

Methods

We retrospectively reviewed the clinical records of patients who have undergone the MACE procedure in our hospital from 2009 to 2016. Their demographic data, original diagnosis and related complications were reviewed. The operative details of the MACE procedure is shown in Figure 1.

Results

Eight patients were recruited in the review. Their age at the MACE operation, gender, original diagnosis and the details of the MACE procedure performed are shown in Table 1. All of the patients recruited has a Rintala score of below 6 prior to the operation. Rintala score is a clinical score for the evaluation of faecal continence. The score is derived from standardised questionnaires and physical examination is not required (Table 2). The score consists of seven factors, which are scored from 0 to 3, except the factor of frequency of defaecation, which is scored 1-2. The maximum bowel function score is 20. Patients with "poor" results scored 6-9 points and usually had to use daily enema because of severe constipation or had constant soiling.

The mean age of the patients was 13.5 years old (range: 10-18 years old). The mean follow up duration was 42 months (range: 6-78 months). There were two laparoscopic assisted MACE procedures and six open MACE procedures, one of which had simultaneous bladder augmentation surgery and Mitrofanoff procedure. There was no peri-operative blood transfusion or mortality. Three minor complications were recorded including one exit site leakage, one exit site stricture and one persistent peri-anal soiling after the MACE procedure. The patient with exit site leakage was successfully treated with ultrasound guided deflux injection at the exit site under local anaesthesia.

![Figure 1](image)

**Figure 1** Intra-operative photos of the MACE procedure.

<table>
<thead>
<tr>
<th>Age</th>
<th>Gender</th>
<th>Initial diagnosis</th>
<th>MACE procedure</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>M</td>
<td>Anorectal malformation</td>
<td>VQZ flap</td>
<td>Post MACE peri-anal soiling</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>Myelomeningocele</td>
<td>VQZ flap, CIC post op via urethra</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>Visceral myopathy</td>
<td>VQZ flap</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>Spinal bifida</td>
<td>VQZ flap, post op CIC via urethra</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>M</td>
<td>Anorectal malformation</td>
<td>VQZ flap</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>Anorectal malformation</td>
<td>VQZ flap</td>
<td>Stoma site leakage, treated with deflux injection</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>Spinal bifida</td>
<td>VQZ flap, simultaneous bladder augmentation and Mitrofanoff</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>F</td>
<td>Myelomeningocele</td>
<td>Laparoscopic assisted, VQZ flap</td>
<td>Stoma site stricture</td>
</tr>
</tbody>
</table>
Table 2  Rintala score for evaluation of fecal continence

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ability to hold back</td>
<td>Always</td>
<td>3</td>
</tr>
<tr>
<td>defaecation</td>
<td>Problems &lt; x1/week</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Weekly problems</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No voluntary control</td>
<td>0</td>
</tr>
<tr>
<td>Feels urge to defecate</td>
<td>Always</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Most of the time</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Uncertain</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>Frequency of</td>
<td>Every other day to</td>
<td>2</td>
</tr>
<tr>
<td>defaecation</td>
<td>twice a day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>More often/less often</td>
<td>1</td>
</tr>
<tr>
<td>Soiling</td>
<td>Never</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Staining less than x 1/week.</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>No change of underwear</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Frequent staining, change of underwear required</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Daily soiling. Requires protective aids</td>
<td>0</td>
</tr>
<tr>
<td>Accidents</td>
<td>Never</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Fewer than x 1/week</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Weekly accidents</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Daily accidents</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>No constipation</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Manageable with diet</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Manageable with laxatives</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Manageable with enemas</td>
<td>0</td>
</tr>
<tr>
<td>Social problems</td>
<td>No social problems</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Sometimes (foul odors)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Restrictions to social life</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Psychic problems</td>
<td>0</td>
</tr>
</tbody>
</table>

All the patients were followed up at the paediatric surgical gastrointestinal nurse clinic. The technique of the antegrade administration of normal saline was regularly monitored (Figure 2). The volume of fleet enema and normal saline required in the antegrade washout were adjusted periodically according to patient's body weight and the effectiveness of the washout. All patients were able to achieve a Rintala score of >= 15 after the MACE procedure.

Conclusions

MACE procedure is safe and effective in the management of children with faecal incontinence, although minor complications can occur. In our review, 7 patients (88%) achieved complete faecal continence after the MACE procedure. All the patients were able to administer the antegrade continence enema via the MACE exit site by themselves independently. And most patients can reduce the use of the phosphate enema and be able to maintain complete faecal continence with the use of antegrade NS irrigation. Moreover, as the normal saline solution could be formulated at home using the standard recipe of 1000 ml of tap water with 1½ teaspoon table salt (or 500 ml of tap water with ¾ teaspoon table salt), cost and time would be saved tremendously as well.
Discussions

For children with faecal incontinence, they often are faced with only three options: daily soiling, diverting colostomy and undergoing the bowel management programme.

A successful bowel management programme should include daily enema, diet manipulation and medications. The goal of such programme is to keep the child clean 24 hours a day, and to allow normal daily activities without the use of protective wear. However, as the child grows older, daily rectal enema may not be sufficient to adequately evacuate the colon for the child to keep dry and clean for 24 hours. Moreover, they may also seek more autonomy and independence as they enter adolescence, and may become reluctant to let the caretaker to assist in the administration of rectal enema.

Careful patient selection for the MACE procedure and a team of dedicated specialty nursing care are essential. We believe with increased awareness, more patients with faecal incontinent and refractory constipation would be able to benefit from the MACE procedure.

Declaration of Interest

None.

References

Case Report

A Case Report of Familial Hypocalciuric Hypercalcaemia with a Heterozygous Mutation of the Calcium Sensing Receptor Gene in a Chinese Paediatric Patient

JWK Bao, KL Ng, TKC Tsui

Abstract

The differentiation of familial hypocalciuric hypercalcaemia from the more common primary hyperparathyroidism harbours clinical significance, as unnecessary investigations and treatment could be avoided. We report a 22-month-old asymptomatic Chinese patient with an incidental finding of hypercalcaemia with biochemical features suggestive of familial hypocalciuric hypercalcaemia. The diagnosis was confirmed by mutation analysis of the CASR gene. Genetic analysis of the family showed the inheritance of familial hypocalciuric hypercalcaemia in an autosomal dominant manner.

Key words

Calcium sensing receptor; CASR; Familial hypocalciuric hypercalcaemia

Introduction

There are three types of familial hypocalciuric hypercalcaemia (FHH). FHH Type 1 is the commonest caused by loss-of-function mutation of the CASR gene while type 2 and 3 are caused by the GNA11 and AP2S1 mutations respectively. The biochemical profile of FHH includes hypercalcaemia, elevated or inappropriately normal parathyroid hormone level and hypocalciuria. It poses clinical significance to differentiate FHH from primary hyperparathyroidism as this could avoid unnecessary investigations and procedures.

Case Report

Case Presentation

The proband is a 22-month-old girl who first presented in August 2015 to the outpatient clinic with a complaint of poor growth. Her birth history and perinatal history was unremarkable. She enjoyed good past health. Upon reviewing the family history, patient’s mother reported incidental finding of hypercalcaemia during antenatal checkup. Otherwise, both parents and elder sister enjoyed good past health. Developmental milestones were met. Growth charts were reviewed showing a decreasing centile of body weight since introduction of solid food, and was at the 3rd centile on the day of the first consultation. Examination was unremarkable except presence of a soft ejection systolic murmur compatible with a flow murmur. An impression of inadequate caloric intake was made at the end of the consultation.

Investigations

There was incidental finding of hypercalcaemia upon the workup for failure to thrive. Serum total calcium level was 3.03 mmol/L (Reference range: 2.25-2.75 mmol/L). Rechecked level was 3.13 mmol/L. Blood ionized calcium was 1.67 mmol/L (Reference range: 1.13-1.32 mmol/L). Serum phosphate level was 1.57 mmol/L (Reference range: 0.97-2.10 mmol/L). Serum magnesium level was
1.02 mmol/L (Reference range: 0.70-0.99 mmol/L). Plasma intact parathyroid hormone level was 3.0 pmol/L (Reference range: 1.6-6.9 pmol/L) which was inappropriately normal. Serum total 25-hydroxyvitamin D level was 52 nmol/L, which was sufficient. 24 Hour urine was collected with a urine volume of 846 ml, urine calcium level of <0.15 mmol/L and urine creatinine level of 1.2 mmol/L. The concurrent serum total calcium and serum creatinine levels were 3.18 mmol/L and 33 umol/L respectively. The calcium to creatinine clearance ratio was <0.001, which confirmed hypocaliuria using a cut-off of <0.01. Ultrasound kidney, X-ray for long bone and echocardiogram were normal.

**Genetic Analysis**

In view of hypercalcaemia with low urinary calcium excretion, the diagnosis of FHH was suspected. Mutational analysis of the CASR gene (OMIM#601199) was performed on the peripheral blood leukocytes of the patient with informed consent from parents. Genomic DNA was extracted from leucocytes using a standard procedure. Polymerase chain reaction (PCR) amplification of all the coding exons (exon 2 to exon 7) and flanking introns of the CASR gene was performed. The PCR products were purified and sequenced in both forward and reverse directions using the BigDye cycle sequencing kit and analyzed with ABI-3100 automated sequencer. The patient was heterozygous for a missense mutation c.652T>C (p.Tyr218His) in exon 4 of CASR gene (GenBank Reference NM_000388.3) (Figure 1). The missense mutation changes the codon from TAT to CAT, leading to the change of amino acid residue from tyrosine to histidine at codon 218, which has been reported as a pathogenic mutation in patient with FHH.\(^1\) The mutant residue is located in and disrupts one of the five calcium-binding sites within the extracellular domain of the calcium (Ca\(^{2+}\)) sensing receptor (CaSR) and affects the ability of the CaSR to bind Ca\(^{2+}\) in a cooperative fashion.\(^1,2\)

**Family Study**

The patient's family, and subsequently the extended family on the maternal side were referred for cascade screening. Both the proband's mother and maternal grandfather showed the same heterozygous CASR mutation. The inheritance of FHH in an autosomal dominant manner is shown in the pedigree in Figure 2.

**Treatment and Follow Up**

The patient remained asymptomatic upon subsequent follow up. She was referred to our dietitian. Her body weight caught up to 25th centile. No pharmacological treatment for hypercalcaemia was required.

**Discussion**

The CASR is a G protein-coupled receptor highly expressed on the renal tubules and parathyroid gland. It has three domains, namely the intracellular, transmembrane and extracellular domain.\(^1\) The mutation of such causes an abnormal set point of calcium dependent PTH secretion. Higher calcium level is required to suppress the PTH secretion. Renal tubular reabsorption of calcium is also affected. Patient with activating mutation of CASR would result in autosomal dominant hypocalcaemia, causing severe hypocalcaemia.\(^1\) Inactivating mutation would cause either severe neonatal hyperparathyroidism (NSHPT) or FHH, depending on whether it is a heterozygous (FHH) or homozygous/compound heterozygous (NSHPT) mutation.\(^3\)

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**Figure 1** (A) Electropherogram of the heterozygous missense mutation c.652 T>C (p.Tyr218His) in exon 4 of the CASR gene detected in the proband. The nucleotide c.652T>C is marked by an arrow. (B) The corresponding wild-type sequence detected in a normal control.
The degree of hypercalcaemia in FHH and NSHPT reflects a gene dosage effect. However, the phenotypes of \textit{CASR} mutation may not always correspond to the genotypes.\textsuperscript{4} Some \textit{CASR} mutations may have a dominant negative effect causing a higher degree of hypercalcaemia that is usually seen in heterozygotes. However, some mutations may have mild effect on calcium homeostasis. Thus some patients with heterozygous mutation may be normocalcemic.

FHH is a benign condition. Suspicion should arise if a young asymptomatic patient was found to have hypercalcaemia. FHH does not require any treatment. In particular, standard subtotal parathyroidectomy is unindicated, as it would not result in lowering of serum calcium level, opposed to that in primary hyperparathyroidism. Hence, the diagnosis of FHH has clinical importance as its differentiation from primary hyperparathyroidism could avoid unnecessary investigations and treatment. The main differences between FHH and primary hyperparathyroidism would be the presence of symptomatic hypercalcaemia, decreased bone density and previous normocalcemia in patients with primary hyperparathyroidism. The major differentiation tool in clinical practice is the calcium to creatinine clearance ratio. A ratio of less than 0.01 is suggestive of FHH, while a ratio of higher than 0.02 suggests primary hyperparathyroidism.\textsuperscript{5} However, the definitive diagnosis of FHH depends on mutation analysis. There are three genetic types of FHH. FHH type 1 accounts for 65% of cases caused by inactivating mutations in the \textit{CASR} gene. The other 35% have either a mutation in the \textit{GNAI1} gene in FHH type 2 or \textit{AP2S1} gene in FHH type 3.\textsuperscript{6} Analysis of the \textit{CASR} gene can be considered first in patients suspected of FHH. A negative \textit{CASR} analysis by sequencing cannot exclude the diagnosis FHH. It has been postulated that \textit{AP2S1} missense mutations affecting Arg15 residue represented a mutational hotspot in FHH Type 3 and might account for $>20\%$ individuals with definite clinical and biochemical diagnosis of FHH without \textit{CASR} mutations.\textsuperscript{6} It remains unclear whether clinical relevant phenotypic differences are present in patients with different types of FHH. However, a recent study suggested that \textit{AP2S1} mutations affect calcium homeostasis more severely than \textit{CASR} mutations evidenced by higher plasma calcium concentrations in patients with FHH type 3 than patients with FHH type 1, despite having similar PTH concentrations and urinary calcium excretion.\textsuperscript{7} Although genetic analysis is definitive and superior, biochemical screening tests (e.g. serum total calcium and 24 hour urine calcium to creatinine clearance ratio) are still useful as first line investigations. It is recommended to include calcium to creatinine clearance ratio as an essential part upon the workup for hypercalcaemia to differentiate between FHH and primary hyperparathyroidism.\textsuperscript{8} Once the disease causing mutation of FHH is identified for the proband, subsequent family screening by target mutation testing could be performed.

Although FHH is believed to run a benign course, there

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**Figure 2** Pedigree of the studied family. Squares represent male and circles represent female. Hatched symbols represent affected individuals with \textit{CASR} gene mutation. Arrow indicates the proband.
are rare reported cases of FHH associated with pancreatitis, nephrolithiasis, gallstones, articular chondrocalcinosis and premature vascular calcification. Some of the reported complications were observed during middle age. Before more evidence is available, it is recommended to follow up FHH paediatric patients till adulthood.

Declaration of Interest

There is no conflict of interest to declare.

References

Case Report

Lipoid Pneumonia Following Aspiration of Lorenzo's Oil in a Child with X-linked Adrenoleukodystrophy

KR Cheon, HJ Cho, SS Kim, YJ Woo

Abstract

Background: Exogenous lipoid pneumonia (LP) is caused by the aspiration or inhalation of lipid substances into the respiratory tract. The clinical symptoms are non-specific and variable, ranging from asymptomatic to life-threatening. Since there is very limited disease-modifying treatment to prevent the onset or slow the progression of X-linked adrenoleukodystrophy (X-ALD), Lorenzo's oil can be used, although its effect is still controversial. Case presentation: Here, we report a case of LP in a 6-year-old boy with X-ALD who was treated with Lorenzo's oil. To our knowledge, this is the first case report demonstrating an association between Lorenzo's oil therapy and LP in a paediatric patient with X-ALD. Conclusions: Patients with X-ALD suffer from various neurological deficits, including swallowing difficulty and oromotor dysfunction. In X-ALD patients with oromotor dysfunctions are at high risk of LP while using Lorenzo's oil, where physicians should be aware and avoid if possible. This awareness can enable early diagnosis and treatment of LP and improve prognosis by discontinuing exposure to the offending agent or to an appropriate treatment.

Key words

Adrenoleukodystrophy; Lipoid pneumonia; Lorenzo's oil

Background

Lipoid pneumonia (LP) is an uncommon disease caused by the presence and accumulation of lipid compounds in the pulmonary tract and alveoli.1,2 The clinical symptoms are non-specific, such as dyspnoea and/or cough and variable, ranging from asymptomatic to as severe as life-threatening.1 It can be classified into endogenous and exogenous forms. Exogenous LP has various causes, including oils present in food, radiographic contrast media, and oil-based medications such as laxatives.2

Here, we report a case of LP occurring secondary to treatment with Lorenzo's oil in a patient with childhood cerebral form X-linked adrenoleukodystrophy (X-ALD). To our knowledge, this is the first case report demonstrating an association between Lorenzo's oil therapy and LP in a paediatric patient with X-ALD.

Case Presentation

A 6-year-old boy was admitted to hospital presenting with a 1-week history of cough and sputum. At the age of 5 years, he was diagnosed with the cerebral form of X-ALD with rapid regression and motor weakness. On admission, he could not walk or sit by himself however required per
oral feeding without any gastric tube. Genetic analysis confirmed the diagnosis by identifying an ABCD1 gene mutation. At the time of the genetic analysis, increased levels of very long-chain fatty acids (VLCFAs) were also detected (C26:0 = 4.74 mmol/L (normal <1.30 mmol/L) and C26:0/C22:0 = 0.072 (normal <0.023)). Brain magnetic resonance imaging (MRI) revealed bilateral hyperintense lesions involving the frontal and occipital periventricular white matter, internal capsule, genu and splenium of the corpus callosum and corticospinal tract. In addition, linear and nodular enhancements in the corpus callosum and internal capsule were also noted. These findings were compatible with ALD. As there is no disease-modifying treatment to prevent the onset or slow the progression of this disease, the parents of the patient were informed of several treatment options including haematopoietic stem cell transplantation. However, the parents refused these options. Although the effect of Lorenzo's oil is still controversial, the patient had been taking 20 cc Lorenzo's oil twice daily for the last 3 months, together with supportive care and rehabilitation. Although his neurological status deteriorated, Lorenzo's oil was administered orally. While taking the oil, he had a history of frequent choking and coughing.

On physical examination, crackles were auscultated bilaterally without any signs of chest retraction or tachypnoea and the saturation of $O_2$ was 95–98% in room air. Chest radiography showed multifocally increased opacity in both lung fields (Figure 1A). High-resolution computed tomography (HRCT) of the chest showed diffuse bilateral ground glass opacity and smooth interstitial thickening with a crazy-paving pattern in both lungs, predominantly in the posterior and lower lung zones. These findings were compatible with LP (Figure 1B).

The patient underwent diagnostic bronchoscopy with bronchoalveolar lavage (BAL). The bronchoscopic findings indicated no endobronchial lesions, but whitish secretions were drained from the posterior segmental bronchi of the right upper lobe and superior segmental bronchi of the right lower lobe and BAL was performed from this lesion. Bacterial, mycobacterial and fungal analyses of the BAL fluid were negative, and the BAL fluid was also negative for malignant cells.

The BAL fluid showed a milky whitish appearance. Oil red O staining demonstrated numerous lipid-laden macrophages (Figure 2). The patient was confirmed to have LP and was hospitalised for 10 days with supportive care. His symptoms gradually improved and after the occurrence of LP, he discontinued taking Lorenzo's oil. Due to the early development of complications after a short period of Lorenzo's oil use, the effectiveness of its use could not be assessed. Post Lorenzo's oil VLCFA level and brain MRI will be repeated later after the child has fully recovered.

**Discussion**

X-ALD is a neurometabolic disorder that primarily affects the central nervous system, white matter and the adrenal cortex, which is caused by a defect in the ABCD1 gene encoding the adrenoleukodystrophy protein (ALDP),...
a transporter present in the peroxisomal membrane. ALDP defects lead to accumulation of saturated VLCFA, such as hexacosanoic acid (C26:0), in the adrenal glands and nervous system, white matter and other tissues, and in plasma. At present, only very limited disease-modifying treatments exist to prevent the onset or slow the progression of X-ALD. Several treatment options have been indicated in clinical trials, including Lorenzo’s oil, antioxidants, allogenic haematopoietic stem cell transplantation and bone marrow transplantation.

Lorenzo’s oil is a 4:1 mixture of glyceryl trioleate and glyceryl trierucate. Oral administration of this oil, combined with a moderate reduction in fat, normalises or significantly lowers the plasma levels of VLCFA in patients with X-ALD. It is available worldwide, however its clinical efficacy or indications has not been established. Basu et al have analysed medical data of 116 male asymptomatic paediatric patients who were administered Lorenzo’s oil which proved actual improvements in health status as well as MRI findings. Moser et al have reported a single arm study to assess the effect of Lorenzo’s oil and they concluded that hexacosanoic acid reduction by Lorenzo’s oil was associated with decreased risk of developing abnormalities in MRI. However, despite this reduction, some patients still have progressive characteristics of the disease. Although the efficacy of Lorenzo’s oil is still controversial, we opted for supportive care and rehabilitation in our patient, as he was already manifesting neurological impairment consistent with the cerebral form of X-ALD.

Neurological impairment and associated swallowing dysfunction are significant risk factors for aspiration and exogenous LP. The histories of neurological impairment and frequent choking during administration of Lorenzo’s oil suggested LP in our case, but a history of oil ingestion

Figure 2  Cytologic findings of bronchoalveolar lavage fluid. Variable sized bubble-like vacuoles are observed within the foamy histiocytes (arrow, A-C). They were stained by oil red O stain and were bright red in color (C). Scattered ciliated bronchial epithelial cells (arrowhead) were admixed with lipophages (B, C). Smeared lipoid material was also stained by oil red O stain (D). (A, Papanicolaou stain, original magnification X400; B, Giemsa stain, original magnification X400; C, D, oil red O stain, original magnification X400).
Lipoid Pneumonia Following Aspiration of Lorenzo’s Oil

is often overlooked and exposure to the oil is often identified retrospectively after a diagnosis of LP is made.²

The clinical symptoms of LP can vary significantly among individuals, ranging from asymptomatic to life-threatening, according to the patient’s age, amount and type of oil aspirated and duration of oil intake.²

A diagnosis of LP is initially made based on history of oil exposure to oil and radiological findings.² The best type of imaging study to establish a diagnosis of LP is HRCT of the chest. The features of HRCT in children with LP are air-space consolidations and ground-glass attenuation, occasionally with a crazy-paving pattern, distributed bilaterally in the posterior and lower zones of the lungs, but none of these radiological features were specific to LP.¹ In addition, there is a discrepancy in severity between the radiological and clinical findings, i.e., patients are often asymptomatic despite extensive imaging findings.²

Bronchoscopy with BAL is a good diagnostic tool for LP. BAL fluid is macroscopically whitish or turbid with fat globules on the fluid surface, and specific staining of recovered lipid-laden alveolar macrophages is consistent with a diagnosis of LP.¹⁰ The presence of extracellular oily droplets is more specific to exogenous LP.² In our case, a definitive diagnosis was made by bronchoscopy and specific staining of the BAL fluid with Oil Red O.

The natural history and outcome of LP are variable and depend on the type, volume and distribution of oil aspirated.¹ There have been no studies defining the best therapeutic option for LP. Treatment is primarily supportive and generally conservative, followed by treatment of the complications.¹² However, there is a consensus that the key objective is to identify and discontinue exposure to the offending agent, and that the best treatment for this disease is prevention.²

To our knowledge, this is the first case report in a paediatric patient with X-ALD who suffered LP after administration of Lorenzo’s oil. Patients with X-ALD suffer from various neurological deficits, including swallowing difficulty. In X-ALD patients with oromotor dysfunctions are at high risk of LP while using Lorenzo’s oil, where physicians should be aware and avoid if possible. Such awareness can enable the early diagnosis and treatment and improve the prognosis by discontinuing exposure to the offending agent or to an appropriate treatment.

Competing Interests

All authors have no competing interests.

References

Spontaneous Pneumomediastinum in Rhinovirus Infection

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Abstract

Background: Spontaneous pneumomediastinum (SPM), a spontaneous mediastinal air-leak without any trauma or mechanical ventilation, is a rare paediatric emergency that typically occurs secondary to asthma attack in children. Herein, we report a case of SPM with subcutaneous emphysema in a 3-year-old child following rhinovirus (RV) infection. Case: A 3-year-old male patient was referred from another medical centre when respiratory distress, tachypnoea, and wheezing developed in addition to an ongoing cough and runny nose. It was the first wheezy attack and there was no history of atopy and no allergic diseases, foreign body aspiration, or trauma. Upon examination of the patient, who was admitted to emergency services, there were no pathological findings except for respiratory distress, common crepitations in the bilateral neck and chest walls, and bilateral wheezing during the respiratory system examination. Chest radiograph findings were compatible with pneumomediastinum and RV was detected in his nasal swab sample based on multiplex polymerase chain reaction methods. The patient improved spontaneously with conservative treatment. Conclusions: RV infections in children can lead to serious, life-threatening complications such as pneumomediastinum without pneumothorax. Thus, it should be considered a triggering agent of SPM in children even without a history of asthma.

Key words: Child; Pneumomediastinum; Rhinovirus

Introduction

Spontaneous pneumomediastinum (SPM) is the presence of air in the mediastinum without mechanical ventilation, trauma, or interventional procedures. It is rare in children and is commonly seen in tall, slender male adolescents. Although the most common cause in children is asthma, vomiting, screaming, violent coughing, and intense sports activities can also lead to SPM. Human rhinovirus (RV), which is a member of the family of Picornaviruses, can cause many diseases – such as cold, bronchiolitis, and lower respiratory tract infections such as pneumonia, and may also lead to an acute asthma attack.

Here, we present a case that was admitted to the emergency department with signs of respiratory distress and subcutaneous emphysema, without a history of asthma or airway sensitivity; the diagnosis was SPM caused by RV.

To the best of our knowledge, this is the second report in the English literature of RV-induced SPM.

Case

A 3-year-old male patient was admitted to our hospital's emergency department with ongoing cough for 2 days, runny nose, and wheezing complaints.

Concerning his anamnesis, it was discovered that, the day
before, he took salbutamol nebuliser treatment in an outer health centre. He had no trauma history. He was born as a term baby and his medical history was not significant; he had no history of wheezing or atopy, and there was no history of asthma in his family. He also had no history of foreign body aspiration.

When the patient was referred to the hospital, he was restless and had increased respiratory effort, but the circulation and skin findings were normal. Upon physical examination, his pulse was 150/min, respiratory rate was 40/min, blood pressure was 90/45 mmHg, body temperature was 37°C, and oxygen saturation was 95% (normal room air saturation).

When palpated, there were crepitations in the front side of the chest and neck of the patient; there were also subcostal and intercostal retractions, bilateral rhonchi in the lungs, and a prolonged expiration time on auscultation. The other systemic examinations, excluding sinus tachycardia, were normal. There was no Hamman's sign. Based on laboratory investigations, haemoglobin was 12 g/dL, white blood cell was 25.9 x 10⁹/L, neutrophil was 18.0 x 10⁹/L, C-reactive protein was 48.86 nmol/L, blood gas pH was 7.38, pCO₂ was 4.39 kPa, pO₂ was 11.97 kPa, and total immunoglobulin E (IgE) was 10 kU/L. On posterioranterior (PA) chest radiography, linear air density – starting from the neighboring area of the left lung and extending parallel to the wall of the left ventricle, which is compatible with pneumomediastinum and cervical, axillary, and bilateral chest wall subcutaneous emphysema – was observed. Pneumothorax was not observed (Figure 1). Viral (RV) load was detected based on viral panel real-time polymerase chain reaction (PCR) from the nasopharyngeal swab material. The patient was diagnosed with RV infection-caused SPM based on clinical findings and PA chest radiography.

The patient was treated with bed rest, a 6 L/min moistened oxygen mask, intravenous maintenance fluid, and salbutamol nebuliser solution. Possible heart failure and cardiac tamponade were discussed with the Department of Cardiology. Cardiologic and echocardiographic examinations were normal. Respiratory distress symptoms regressed from the third day of observation. The findings of subcutaneous emphysema began to diminish after the 5th day, and findings on chest radiography improved. After all respiratory symptoms had regressed, the patient was discharged on the condition that he be followed-up at the Children Allergy Polyclinic in case asthma occurred. During 8 months of follow-up, the patient had no wheezing attack until the present time.

**Discussion**

Despite the reported incidence of SPM being 1/8,302, it is believed that the condition is more common than estimated because it is not well-known and has a good prognosis in children.⁶,⁷ SPM is most commonly seen in children under 4 years of age and adolescents.⁶ Our patient was 3 years old.

The most common reason for SPM is asthma attack during the childhood years.⁶⁻⁸ Gasser and colleagues reported that asthma was the most common concomitant disease of SPM (49%); in order, the next most common diseases were cough (45.6%), severe vomiting (10.3%), and foreign body aspiration (8.3%).⁷ Our case had not had an attack of wheezing previously; moreover, there was no family history of allergic rhinitis, atopy, or asthma. There was also no history of foreign body aspiration and the chest radiograph did not show foreign body aspiration. Furthermore, symptoms such as runny nose began with upper respiratory tract infections. The patient had no vomiting but did experience a vigorous cough. He was aged above 2 years and was not diagnosed with bronchiolitis. However, RV may trigger severe episodes of lower airway dysfunction in children with asthma and in atopic individuals.⁹ Because of the absence of atopy and wheezy history, as well as the normal total IgE value, we did not consider an asthma attack in our patient. We believed that this could be the first attack of late occurring wheezing triggered by RV. Therefore, there

![Figure 1](image) Chest radiography showed linear aeration around the left heart border and subcutaneous emphysema without pneumothorax or pulmonary infiltration.
were no identifiable risk factors other than the cough in addition to serious RV infection.

Having RV infections in the first 3 years of life increases asthma risk 10-fold after 6 years of age. The mechanism by which RV infections lead to the development of asthma remains unclear, but the virus is thought to increase airway inflammation through T2 helper cells. A previous study suggested performing respiratory function tests (RFT) after SPM attacks, but our patient was not eligible for RFT because of his age. We believe that serious RV infections may be a marker for future development of asthma, so after discharge we directed our patient to the Allergy and Asthma Department.

Subcutaneous emphysema is the most common finding with SPM, despite not being pathognomonic. Another characteristic finding is Hamman's sign, which is characterised by a crunching sound; however, it is seen in only 11.6% of cases. In our case, Hamman's sign was not present, but the presence of subcutaneous emphysema extending through the chest wall and neck led us to consider a diagnosis of SPM.

PA chest radiography was sufficient for diagnosis. According to some reports, if the diagnosis is confirmed based on PA chest radiography, and intrathoracic organ perforation is not seen, further investigations are not required for differential diagnosis. In our patient, PA chest radiography was sufficient for diagnosis; therefore, we did not perform any further examinations.

If the SPM is not complicated, the treatment should be supportive, as in our case.

Conclusions

Subcutaneous emphysema that occurs with SPM is rare in children without chest trauma. Because of being self-limiting, as well as the high possibility of missing the diagnosis, paediatricians should be aware of SPM signs and symptoms. RV infections can cause SPM without asthma attack. Children diagnosed with SPM that is triggered by RV infection should be followed due to the risk of asthma.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

References

Clinical Quiz

What is the Diagnosis?

SSW Cheng, IFM Lo, HM Luk

The proband is a 4-year-old boy. He was born at full term with body weight of 2.27 kg to a non-consanguineous Chinese couple. Antenatal course was uneventful except he had mild IUGR since 30 weeks’ gestation. Postnatally he was noted to have cardiac murmur with echocardiogram showed he had mild supravalvular aortic stenosis. He also had mild to moderate developmental delay that studied in special school. He was then referred to genetic clinic for assessment. Physical examination showed he had unremarkable growth parameters with body height of 50th centile, body weight of 25th-50th centile and head circumference of 10th centile. However, facial dysmorphism (Figure 1) was noted that including periorbital puffiness, flat nasal bridge, malar hypoplasia, full nasal tip, long philtrum, prominent lips, small and widely spaced teeth and wide mouth. Cardiovascular examination revealed Grade 3 over 6 ejection systolic murmur at left upper sternal border that radiated to neck. The rest of examinations were normal. He is very talkative and friendly during consultation.

Figure 1 Clinical photo of our patient (consent has been taken for publication).

The clinical quiz was prepared by:
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Answer to "Clinical Quiz" on Pages 239-242
N.B. The Editors invite contributions of illustrative clinical cases or materials to this section of the journal.
Abstracts of Articles in Chinese

粪便菌群移植治療兒童反覆慢性腸道疾病的初步研究和文獻綜述


背景：粪便菌群移植（FMT）是治療伴有異體菌群失調的小腸疾病的一種有希望的治療方法。對反覆時感梭菌感染（CDI），FMT 有效，而且對部份炎症性腸道疾病（IBD）病人可能有效。方法：病人5名，1歲6月至11歲。診斷發性克隆恩氏病（CD）二例，潰瘍性結腸炎（UC）二例，假膜性結腸炎一例。用鼻空腸管或結腸鏡進行FMT治療，病人治療後每2至4週覆診追蹤。結果：FMT後一例UC和一例潰瘍性結腸炎病人達到部份緩解，治療後6-8週均症狀復發。二例CD和一例UC病人對FMT治療無效。FMT治療前，全部IBD病人均有中等至重度的疾病活躍指數。關於副作用，FMT後發熱有四例。其他副作用包括腹痛和腹部不適，均為輕度和自限性。結論：在作者初步臨床經驗中，FMT對發性CD和UC療效有限。FMT副作用的發病率大大高於以往所報告的數據。

關鍵詞：克隆恩氏病、糞便菌群移植、兒科、假膜性腸炎、潰瘍性結腸炎

3D高解析度直腸肛門測壓在分析直腸肛門手術後兒童中肛門括約肌壓力非對稱性分佈中的應用：一項初步研究


目的：肛門直腸測壓在評估肛門括約肌功能方面已得到廣泛應用。新的方法是3D高解析度直腸肛門測壓將提供關於肛門括約肌壓力分佈與稱性方面的額外資訊。方法：作者先選17例排便功能障礙的病人：3例特發性便祕，8例先天性巨結腸術後，6例直腸肛門畸形術後。病人均進行了3D高解析度直腸肛門測壓。作者測量並分析了括約肌的靜息壓和收縮狀態下壓力。定義了Δp為壓力不對稱參數計算：Δp = (最大壓-最小壓) /最大壓 x 100%。

結論：Soave術，括約肌切開術，Duhamel術和後矢狀入路壓腔術肛門括約肌功能狀態，而選擇的術式影響術後肛門括約肌的功能狀態。肛門括約肌壓力分佈對稱性參數可能在分析手術效果方面提供幫助。

關鍵詞：肛門直腸畸形，肛門直腸測壓，高解析度，先天性巨結腸，對稱性
橫斷面研究：土耳其安卡拉學齡兒童屈光不正的發病率


未矫正的屈光不正是引致學齡兒童視力受損的最常見原因。本研究擬評估土耳其安卡拉的不同社會文化階層學齡兒童屈光性疾病的發病率。對1729名7-14歲兒童進行橫斷面研究。屈光不正的發生率為：近視10.8% (n=186)，遠視3.8% (n=66)，散光26.3% (n=455)。多重回歸分析提示年齡 (OR:1.23, p<0.001)，近視家族史陽性 (OR: 2.36, p<0.001)，兄弟姊妹數目 (OR: 0.73, p=0.001)，母親工作狀態 (OR: 0.32, p=0.002)，與兒童近視顯著相關。作為屈光不正的原因之一，近視的發病率高於其他發達國家。在學齡兒童中進行常規眼睛篩查計劃，是預防視力下降的重要方法。

關鍵詞：兒童、眼睛檢查、發病率、屈光不正

兒童 Malone 順行自主灌腸（MACE）：香港經驗


引言：兒童大便失禁常導致其無法參加正常的社交活動。內科治療失敗的患兒需外科介入。Malone順行自主灌腸法 (MACE) 通過闊尾造口有規律的清洗結腸，使患兒可解除大便失禁的尷尬，更好的融入社會。方法：回顧性分析了我們中心 2009 年—2016 年做過 MACE 手術的患兒。結果：8 例患兒獲得隨訪，他們手術後 Rintala 評分均大於等於 15。結論：MACE 手術治療兒童大便失禁和頑固性便秘方面是安全和有效的。如果想獲得滿意的手術效果，謹慎的選擇患兒和專科護士團隊的護理是必需的。

關鍵詞：大便失禁、MACE 、 Rintala

病例報告：一例華裔兒童患有家族性低尿鈣性高鈣血症伴鈣感應受體基因突變


鑑別家族性低尿鈣性高鈣血症與更常見的原發性甲狀旁腺素亢進，具有臨床重要性，可避免不必要的檢查和治療。作者報告一例 22 月大無症狀的華裔病人，意外發現高鈣血症，並伴有家族性低尿鈣性高鈣血症的生化特徵。對 CASR 基因的突變檢查確定該診斷。家族的基因檢查顯示，家族性低尿鈣性高鈣血症以常染色體顯性方式遺傳。

關鍵詞：鈣感應受體、CASP 基因、家族性低尿鈣性高鈣血症
貢獻：外源性脂質肺癥（LP）是由於呼吸道吸入油性物質所引起。其臨床症狀為非特異性和多樣性的，患兒可全無症狀，但一些症狀則可致命。因為針對X-連鎖闊腺腦白質營養不良症的發病預防，以及控制進展的疾病改善治療手段十分有限，Lorenzo氏油是可使用方法，但其效果仍然有爭論。病例彙報：作者報告一例脂質肺癥，見於一名用 Lorenzo氏油治療中，患有X-ALD的6歲男童。據作者所知，這是首例報告，提示在X-ALD 兒童中，Lorenzo氏油和脂質肺癥相關。結論：X-ALD 病人可出現不同的神經性缺陷，包括吞咽困難和眼球運動障礙。伴有限運動障礙的 X-ALD 病人，在使用 Lorenzo氏油時具有高度脂質肺癥風險，醫生應該有所認識，盡可能避免。這種認識可對脂質肺癥患者進行早期診斷和治療，停止使用不當的藥物和進行適當治療，改善預後。

關鍵詞：腺運動障礙症，脂質肺癥，Lorenzo氏油

鼻病毒感染中的自發性縫膈氣腫


背景：自發性縫膈氣腫（SPM）指在沒有任何創傷和機械通氣下，自發性的縫膈空氣洩露。此乃一種少見的兒童急症，典型病例見於兒童哮喘發作。特此，作者報告一例3歲兒童鼻病毒感染後出現 SPM 伴皮下氣腫。病例：1名3歲男童由外院轉介，當時有呼吸窘迫、呼吸短促、喘息發作、持續咳嗽和流涕。此為首次喘息發作，無濕疹和過敏性疾病史，無異物吸入史，無外傷史。送入急症室後檢查結果，除呼吸系統檢查發現呼吸窘迫、雙側胸廓和胸壁遊走性音、和雙側喘息外，無其他病理生理學發現。胸部X-光片發現縫膈氣腫，用巢式PCR方法從鼻拭子監測到鼻病毒。經保守治療後，病人自行好轉。結論：兒童鼻病毒感染可導致嚴重致命性併發症，如無氣胸的縫膈氣腫。因此，儘管病童沒有哮喘歷史，此鼻病毒可作病童 SPM 的觸發病原。

關鍵詞：兒童，縫膈氣腫，鼻病毒
MCQs

(A) The Preliminary Investigation of Faecal Microbiota Transplantation for Paediatric Recurrent Chronic Bowel Diseases and Literature Review

1. Which of the following diseases could be effectively treated by faecal microbiota transplantation (FMT)?
   a. Crohn's disease
   b. Ulcerative colitis
   c. Clostridium difficile toxin-induced recurrent colitis
   d. Irritable bowel syndrome
   e. Autoimmune diseases

2. Which of the following descriptions about inflammatory bowel disease (IBD) patients is NOT correct?
   a. Decreased intestinal bacterial diversity in IBD patients
   b. Escherichia coli and Campylobacter species are increased in Crohn's disease (CD)
   c. Bacteroidetes is decreased in CD patients
   d. Mycobacterium avium is increased in CD patients
   e. Firmicutes phyla is increased in CD patients

3. Which of the following mechanisms does NOT account for the benefit of FMT to treat Clostridium difficile toxin-induced recurrent colitis?
   a. Direct competition
   b. Restoration of secondary bile acid
   c. Repair of the gut barrier.
   d. Reduced secretion of inflammatory cytokines
   e. Rebuilt microbial community

4. Which of the following is NOT the major adverse effect of FMT that were observed in the clinical trial?
   a. Fever
   b. Abdominal distension
   c. Vomiting
   d. Transit increase of serum inflammatory markers
   e. Abdominal pain

5. Which of the following preparations is NOT necessary for patients prior to FMT?
   a. Take donor's History Questionnaire
   b. Pathogen testing of donors' and patients' stool samples
   c. Fasting for several days
   d. Bowel preparation of patients
   e. Vancomycin treatment for patients

(B) Application of Three Dimensional High Resolution Anorectal Manometry to Demonstrate Anal Sphincter Pressure Asymmetry in Children after Anorectal Surgery: A Pilot Study

1. Which of the following is NOT a characteristic of the three dimensional high resolution anorectal manometry (3D HRARM)?
   a. Radially arranged pressure channels in multiple levels
   b. Anal pressures along the entire anal canal can be measured simultaneously
   c. Topographic image of the anal canal can be reconstructed by the computer software upon integration of the pressure parameters
   d. Requirement for manual manipulation of the catheter by pull-through technique to locate the anal sphincter region
   e. Relatively new technology to be applied on the paediatric population

2. Which of the following is part of the preparation prior to the 3D high resolution anorectal manometric measurement?
   a. Pre-operative assessment by the anaesthetist for fitness for general anaesthesia
   b. Fasting for at least 12 hours prior to the procedure
   c. Digital evacuation of the rectum to ensure empty rectum
   d. Sodium phosphate rectal enema 3 ml/kg as bowel preparation after informed consent
   e. Insertion of urinary Foley catheter to empty the urinary bladder
3. Which of the following is NOT observed during the 3D high resolution anorectal manometric procedure?
   a. Presence of a caretaker to accompany the child and to relieve anxiety
   b. Orientation and position of the catheter is well preserved to avoid rotation
   c. Secure placement of the catheter onto the child's buttock with surgical tape
   d. Correct naso-gastric tube placement to decompress the stomach
   e. The patient remains awake and non-sedated

4. Which of the following is NOT a common form of evaluation of the bowel function in children after operation?
   a. Endorectal ultrasound
   b. Pelvic MRI
   c. Validated questionnaires and bowel function scoring system
   d. Endoscopy
   e. Anorectal manometry

5. Which of the following could be the potential cause for the anal pressure asymmetry in nulliparous adult women?
   a. Injury to the anal canal during childbirth
   b. Congenital under-developed muscles
   c. Imbalance of the muscle development
   d. Triple looped anatomy of the puborectalis muscle in the anal canal
   e. Over zealous stretching

(C) Frequency of Refraction Errors among School-age Children in Ankara, Turkey: A Cross-Sectional Study

1. Which of the following is the most frequent cause of visual impairment in school-age children?
   a. Congenital cataract
   b. Tumours
   c. Uncorrected refractive errors
   d. Premature retinopathy
   e. Keratoconus

2. Which of the following may affect the development of refractive errors?
   a. Genetics
   b. Environment
   c. Socio-economical level
   d. Outdoor activities
   e. All the above

3. "Myopia was defined as a spherical equivalent (SE) refraction having...... diopter (D) or lower values in one or both eyes". Please, fill in the blank with appropriate word for this study.
   a. 0.25
   b. 0.50
   c. 0.75
   d. 1.00
   e. 1.25

4. What is the formulation of the spherical equivalency (SE) used in this study?
   a. spheric + cylinder/2
   b. spheric x cylinder/2
   c. spheric - cylinder/2
   d. spheric + cylinder/3
   e. spheric + cylinder/2 - spheric - cylinder

5. "Hyperopia was defined as SE refraction's having...... diopter or higher values in one or both eyes." Please, fill in the blank with appropriate word for this study.
   a. +0.25
   b. +0.5
   c. +1.0
   d. +1.5
   e. +2.0

(D) Paediatric Malone Antegrade Continence Enema (MACE): The Hong Kong Experience

1. Conservative management for faecal incontinence in children includes:
   a. Stool softener
   b. Bulking agent
   c. Biofeedback
   d. Rectal enema
   e. All of the above

2. What is the theory of antegrade enema in the management of faecal incontinence?
   a. A diverting stoma for stool diversion
   b. To facilitate digital evacuation
   c. Regular faecal elimination to prevent constipation and faecal incontinence
   d. To alter the microbiota of the colon
   e. To excise redundant bowel
3. Which of the following could be a cause of faecal incontinence in children?
   a. Spinal cord anomalies
   b. Anorectal malformation
   c. Hirschsprung disease
   d. Myelomeningocele
   e. All of the above

4. Which of the following is considered as part of the bowel management programme?
   a. Medications, dietary manipulation and daily enema
   b. Fluid restriction
   c. Avoiding physical exercise
   d. Alarm system
   e. Electric shock therapy

5. How is antegrade continence enema (ACE) superior to rectal enema?
   a. Allows autonomy and independence to a growing child
   b. Potentially able to reduce the use of phosphate by replacing it with normal saline
   c. Eliminate the need for an assistant to administer the rectal enema
   d. Effectively keep child dry and clean for 24 hours
   e. All of the above

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**Answers of July issue 2017**

(A) 1. c; 2. e; 3. b; 4. d; 5. d  
(B) 1. d; 2. b; 3. b; 4. e; 5. c  
(C) 1. d; 2. c; 3. c; 4. b; 5. b  
(D) 1. e; 2. a; 3. a; 4. d; 5. e
CLINICAL QUIZ (p232) ANSWER

What is the diagnosis?

The clinical features of this child (facial dysmorphism, developmental delay and supravalvular aortic stenosis) were compatible with Williams syndrome (WS, also known as Williams-Beuren syndrome). Genetic investigation by using Multiplex ligation-dependent probe amplification (MLPA) showed he had heterozygous deletion of \textit{ELN} gene in the chromosome 7q11.23 region. Therefore the clinical and molecular diagnoses of WS in this child were substantiated.

Williams syndrome is a multisystem disorder characterised by cardiovascular disease (elastin arteriopathy, supravalvular aortic stenosis, peripheral pulmonary stenosis, hypertension etc.), distinctive facial features, connective tissue abnormalities, intellectual disability, outgoing personality characteristics, growth abnormalities and/or endocrine problems (hypercalcaemia, hypercalciuria, hypothyroidism and early puberty etc.). The prevalence of WS is approximately 1 in 7500 live births.

When to consider WS as one of the differential diagnosis clinically?

WS should be considered clinically with distinctive clinical features. Scoring system was developed for clinical diagnosis (Table 1). Children with WS usually have characteristic facial profile include periorbital fullness, short nose and full nasal tip, malar hypoplasia, long philtrum, wide mouth, full lips, dental malocclusion and mild micrognathia. These tend to become more distinctive with advancing age. Mild prenatal growth deficiency and postnatal growth problem are also consistently observed. As children with WS are generally smaller than the children of their age, specific growth charts for WS would be used during clinical evaluation.

What are the major complications associated with WS?

The majority of children with WS have cardiovascular anomalies. The most common cardiovascular defect is supravalvular aortic stenosis. It is usually progressive and requires surgical repair. For peripheral pulmonary artery stenosis, it is often present in infancy and tends to improve with time. Mitral valve prolapse and aortic insufficiency have been reported in adults. Other vascular problems, e.g. coarctation of aorta, renal artery stenosis and systemic hypertension may worsen over time if presented.

Idiopathic infantile hypercalcaemia is another special feature of WS that can lead to extreme irritability, vomiting, constipation and muscle cramping. Symptomatic hypercalcaemia usually resolves when children grow older, however, lifelong abnormalities of calcium and vitamin D metabolism may persist. Hypercalciuria will predispose to nephrocalcinosis. The aetiology of hypercalciuria and hypercalcaemia in WS are still unknown.

Most children with WS have some degree of intellectual disability which can range from severe to mild. WS children also have special cognitive profile. WS children had strength in verbal short-term memory and language but extreme weakness in visuo-spatial construction. The characteristic personality profile of WS includes social disinhibition, excessive empathy, overfriendliness and attention problem.

Other medical problems, e.g. gastrointestinal reflux, colic, Chiari I malformation, strabismus, chronic otitis media, hypodontia, malocclusion, bowel or bladder diverticula, hernias, joint laxity, spinal problems, urinary tract malformations, hydronephrosis, hypothyroidism and rectal prolapse have also be reported in WS children.
### Table 1  Scoring system for Williams syndrome (WS)

<table>
<thead>
<tr>
<th><strong>Growth (Past or Present Evidence of)</strong></th>
<th>1 point</th>
</tr>
</thead>
<tbody>
<tr>
<td>If 3 of 5 items are checked, score 1 point</td>
<td></td>
</tr>
<tr>
<td>1. Post-term birth &gt;41 wk gestation</td>
<td>4. Prolonged colic &gt;4 m irritability</td>
</tr>
<tr>
<td>2. Failure to thrive / height and weight &lt;5th percentile</td>
<td>5. Chronic constipation</td>
</tr>
<tr>
<td>3. Vomiting or gastroesophageal reflux</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Behaviour and Development</strong></th>
<th>1 point</th>
</tr>
</thead>
<tbody>
<tr>
<td>If 3 or 6 items are checked, score 1 point</td>
<td></td>
</tr>
<tr>
<td>1. Overly friendly personality</td>
<td>4. Developmental delay or mental retardation</td>
</tr>
<tr>
<td>2. Hypersensitivity to sound</td>
<td>5. Visuospatial problems</td>
</tr>
<tr>
<td>3. Anxiety</td>
<td>6. Delayed speech acquisition, followed by excessive talking</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Facial Features</strong></th>
<th>3 points</th>
</tr>
</thead>
<tbody>
<tr>
<td>If 8 of 17 items are checked, score 3 points</td>
<td></td>
</tr>
<tr>
<td>1. Bitemporal narrowing</td>
<td>10. Broad brow</td>
</tr>
<tr>
<td>2. Epicanthic folds or flat nasal bridge</td>
<td>11. Periorbital fullness</td>
</tr>
<tr>
<td>3. Strabismus</td>
<td>12. Stellate lacy iris pattern</td>
</tr>
<tr>
<td>4. Short nose or anteversion of nares</td>
<td>13. Bulbous or full nasal tip</td>
</tr>
<tr>
<td>5. Full cheeks</td>
<td>14. Malar hypoplasia (flat cheek bones)</td>
</tr>
<tr>
<td>6. Long philtrum</td>
<td>15. Full prominent lips</td>
</tr>
<tr>
<td>7. Small, widely spaced teeth</td>
<td>16. Malocclusion</td>
</tr>
<tr>
<td>8. Wide mouth</td>
<td>17. Small jaw</td>
</tr>
<tr>
<td>9. Prominent ear lobes</td>
<td></td>
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<table>
<thead>
<tr>
<th><strong>Cardiovascular Problems (by Echocardiography) (a)</strong></th>
<th>5 points</th>
</tr>
</thead>
<tbody>
<tr>
<td>If 1 of 2 items are checked, score 5 points</td>
<td></td>
</tr>
<tr>
<td>1. SVAS*</td>
<td>2. Peripheral pulmonary artery stenosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Cardiovascular Problems (b)</strong></th>
<th>1 point</th>
</tr>
</thead>
<tbody>
<tr>
<td>If 1 of 3 items are checked, score 1 point</td>
<td></td>
</tr>
<tr>
<td>1. Other congenital heart disease</td>
<td>3. Hypertension</td>
</tr>
<tr>
<td>2. Cardiac murmur</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Connective Tissue Abnormality</strong></th>
<th>2 points</th>
</tr>
</thead>
<tbody>
<tr>
<td>If 2 of 6 items are checked, score 2 points</td>
<td></td>
</tr>
<tr>
<td>1. Hoarse voice</td>
<td>4. Long neck or sloped shoulders</td>
</tr>
<tr>
<td>2. Inguinal hernia</td>
<td>5. Joint limitation or laxity</td>
</tr>
<tr>
<td>3. Bowel or bladder diverticula</td>
<td>6. Rectal prolapse</td>
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</tbody>
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<table>
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<tr>
<th><strong>Calcium Studies</strong></th>
<th>2 points</th>
</tr>
</thead>
<tbody>
<tr>
<td>If 1 of 2 items are checked, score 2 points</td>
<td></td>
</tr>
<tr>
<td>1. Hypercalcaemia</td>
<td>2. Hypercalciuria</td>
</tr>
</tbody>
</table>

If the score is <3, a diagnosis of Williams syndrome is unlikely. If the score is >=3, genetic studies should be considered. (Mean score for Williams syndrome was 9 [standard deviation=2.86].)¹

*If supravalvular aortic stenosis (SVAS) is present, referral to geneticist and genetic studies are recommended.
How is the diagnosis established in WS?

The diagnosis of WS is confirmed by demonstrating heterozygous deletion of the William-Beuren syndrome critical region (WBSCR) that encompasses the elastin gene (ELN) in the proband. WBSCR is located at long arm 11.23 region of chromosome 7 (7q11.23). More than 99% of individuals with the clinical diagnosis of WS have this gene deletion which can be detected using fluorescent in situ hybridization (FISH) and/or dosage testing like multiplex ligation-dependent probe amplification (MLPA) or chromosomal microarray (CMA). WS is an autosomal dominant condition with penetrance of almost 100%. However, the phenotypic features are highly variable. The WBSCR deletion comprises 1.55 megabases (Mb) in 95% of individuals with WS and 1.84 Mb in 5% of WS. A more severe phenotype with lower cognitive ability is found in patients with very large deletion (e.g. >2Mb ) that include the WBSCR than in individuals with typical WBSCR deletion.

What are the recommendations for management and surveillance for WS?

Concerning the management of WS, some baseline and regular surveillance are recommended (Table 2). Clinical guideline for the management of WS in different age groups is also available.

Table 2  Recommended investigations in WS

<table>
<thead>
<tr>
<th>Clinical features of WS</th>
<th>Baseline investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital heart defects</td>
<td>Full cardiac assessment by cardiologist including blood pressure (4 limbs), echocardiogram, ECG</td>
</tr>
<tr>
<td>Failure to thrive / feeding problem / reduced growth velocity</td>
<td>Plotting of growth parameters on WS specific growth charts at regular intervals</td>
</tr>
<tr>
<td></td>
<td>Routine paediatric investigations for FTT and reduced growth velocity</td>
</tr>
<tr>
<td>Calcium metabolism problems</td>
<td>Serum concentration of calcium or ionised calcium</td>
</tr>
<tr>
<td></td>
<td>Calcium / creatinine ratio on spot urine sample</td>
</tr>
<tr>
<td>Thyroid function abnormalities</td>
<td>Measure TSH level</td>
</tr>
<tr>
<td></td>
<td>If elevated, consider thyroid scan and refer to endocrinologists.</td>
</tr>
<tr>
<td>Urinary tract abnormalities</td>
<td>Renal ultrasound annually. If nephrocalcinosis is present, refer to nephrologist for 6 monthly screening.</td>
</tr>
<tr>
<td></td>
<td>Serum concentration of BUN and creatinine</td>
</tr>
<tr>
<td></td>
<td>Urinalysis</td>
</tr>
<tr>
<td>Behavioural problems</td>
<td>Look out for attention deficit and anxiety in patients</td>
</tr>
</tbody>
</table>
There are special considerations for the children diagnosed with WS. Multivitamin preparations should be avoided due to potential deleterious effects of vitamin D. Diligent use of sunscreen to minimise autologous production of vitamin D is recommended. There is general management guideline for hypercalcaemia in WS patients. Periodic cardiovascular assessment including hypertension evaluation should be performed despite baseline examination with normal findings.

For our patient, his cardiac problem was continued to follow up by cardiologist. His growth, calcium and thyroid condition would be regularly monitored in Paediatrics clinic.

Acknowledgement

We would like to thank the patient and the family for their contribution.

References

3. Colleen A. Morris, MD; Frank Greenbery, MD; Paige Kaplan, MD; Martin Levinson, MD; and Barbara Pober, MD; with data analysis by Carolyn B. Mervis, PhD and Byron F. Robinson, MA; presented at the 1994 Williams Syndrome Association Convention; July 31, 1994; San Diego, CA.
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Results
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