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Proceedings for Joint Annual Scientific Meeting 2021: The Hong Kong Paediatric Society, Hong Kong College of Paediatricians, Hong Kong Paediatric Nurses Association, and Hong Kong College of Paediatric Nursing

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Poster Presentation

Clinical Quiz
What is the Diagnosis?

MCQs

In Remembrance

Editorial

Original Articles

Case Reports

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New Series
Supporting Child Health and Development during COVID-19 and Beyond

The number of students in Hong Kong with Special Educational Needs (SEN) has significantly increased in the past few years. There were 42,890 registered students with SEN at public ordinary schools in 2016-2017, with the number increasing by more than 30% to 56,640 in 2020-2021 (28,650 in primary schools and 27,990 in secondary schools). On the one hand, this increase may be related to a greater awareness among parents and professionals, as well as the early identification of SEN children through the new On-site Pre-school Rehabilitation Services (OPRS), which has been extended to more kindergartens in the past few years. On the other hand, there is significant concern about the increasing proportion of children with learning problems due to the impact of COVID-19 pandemic, which has dramatically changed the nurturing environment of many children. Within the wide spectrum of SEN conditions, specific learning difficulties (SLD) and neurodevelopmental disorders including attention deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) are of particular concern. According to the data submitted to Hong Kong Commission on Children by the Education Bureau on 13 December 2021, among the 56,640 registered students with SEN in the 2020/2021 school year, 23,230 have SLD, 14,580 have ADHD, and 11,870 have ASD. In recent years, there have been an increasing number of students receiving help from after-school learning services and support programs (Education Bureau 2021).

The COVID-19 pandemic has had detrimental effects on many aspects of society including significant changes to children's development and their nurturing environment. In particular, preschoolers and young children have been severely impacted not only in terms of disrupted learning, but also from the adverse effects on their psychosocial and physical health. Moreover, children from disadvantaged backgrounds, particularly those with SEN or with parents having chronic illnesses, are especially vulnerable and at high risk of developmental problems and child maltreatment. Neuroscience research in the past few decades has highlighted the importance of a nurturing environment, with adverse experiences and child neglect in early life leading to long-term health, learning, and developmental problems. There is emerging evidence on the potential influence of the environment on school readiness, the influence of different aspects of parenting on children's physical and mental wellbeing, and the effects of parent-child interactions and child-focused activities (including physical exercise, nutrition, diet, sleep, and use of electronic devices) on children's development.

The human brain grows rapidly during the first few years of life and is nearly fully grown by age 5. The brain grows in complexity within only a short period of time along with the development of the central nervous system and critical sensitive pathways, including vision, hearing, language, response to environment, emotional control, and other social skills. The structure and function of the brain can be modified by the environment, relationships, and adverse experiences in early life. Effective early childhood interventions have been shown to improve children's long-term health, development, and psychosocial outcomes. The Comprehensive Child Development Service (CCDS) is a government-led family-oriented service that was first piloted in 2005 and then fully rolled out to the whole territory in the past decade. It is a large-scale comprehensive intervention service targeting young children from high-risk families, including those born to mothers with mental health problems, substance abuse, teenage pregnancy, and domestic violence. The key partners of CCDS include specialties and departments such as Paediatrics, Obstetrics, and Psychiatry under the Hospital Authority.
Maternal Child Health Centre and Child Assessment Service under the Department of Health; Integrated Family Service Centres under the Social Welfare Department; and other Non-Government Organisations, which closely collaborate to provide timely assessment and support for disadvantaged children and their families.9

Child growth and development are critical components of children’s health and well-being, and are closely linked and interact with one another. Wong et al examined the effectiveness of an innovative reading intervention targeted at disadvantaged children under the CCDS. Seventy Hong Kong infants and young children born to mothers with mental health problems, substance abuse, or teenage pregnancy were recruited into the intervention, which prescribed books and provided training to their parents at a community-based clinic.9 The book prescribing program successfully promoted positive parenting and improved the early literacy development of disadvantaged children, with similar outcomes to quality parent-child interactions in Chinese families.10 Meanwhile, Choi et al at the United Christian Hospital studied the outcomes of pregnant teenagers and their babies over a 10-year period from 2008 to 2017. They found that teenage pregnancies in Hong Kong were associated with preterm deliveries, increased risk of low birth weight, and developmental delay. Choi et al also examined the risk factors associated with the developmental problems and discussed an approach to reduce these risks through better social support and parental education.11 The findings from this major cohort study on pregnant teenagers in Hong Kong have extended our understanding of the issues faced by young mothers and their babies in Hong Kong.12,13

One of the two original articles in this issue focused on premature pubertal growth, whereas the other focused on the outcome and prognosis of bacterial meningitis and meningococcemia. The study by Yang et al explored the clinical effects of the gonadotropin-releasing hormone analogue (GnRHa) for treating idiopathic central precocious puberty among 54 girls in Baoding, China. They found GnRH analogue (GnRHa) for treating idiopathic central precocious puberty in girls. HK J Paediatrics (New Series) 2022;27:10-8.


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Original Article

Prescribing Books for Preschoolers under Comprehensive Child Development Service in Hong Kong East: A Pilot Study

Abstract

Aim: To determine if book prescription by paediatrician at community-based clinics can improve literacy orientation and home literacy environment in high-risk families. Patient & Methods: 70 at risk children under Comprehensive Child Development Service aged from 6 to 30 months received book prescription from April to December 2017. Questionnaires on reading aloud were completed by parents just before the intervention and then 6 months later. Results: Before book prescription, 25.7% of parents read book with their child and 17.1% chose reading book with their child as top three preferred activities. After the intervention, the corresponding figures significantly increased to 54.3% and 51.4% (p-values <0.001) respectively. Parents read more frequently with their child every week (p-values <0.001) and had more books at home after intervention (p-values <0.001). Conclusions: Book prescription by paediatrician at community-based clinics can be an effective strategy in promoting positive parenting and early literacy development for high-risk children locally.

Key words Comprehensive child development service; Preschooler; Reading aloud

Introduction

Research showed that reading with young children stimulates optimal patterns of brain development and strengthens parent-child bonding, which in turn builds life-long language, literacy, social and emotional skills. This was particularly important for young children under toxic stress. Paediatric service provider was recommended to promote early literacy development beginning in infancy and provide anticipatory guidance through giving developmentally appropriate books at clinic to these high risk children.

Recommendation by American Academy of Paediatrics (AAP) was based on the widely studied evidence-based literacy program, Reach Out & Read (ROR) in the United States (US). In the ROR program, paediatricians provided free developmentally appropriate picture books and anticipatory guidance about reading aloud as part of routine health supervision for children 6 months to 6 years old while clinics provided literacy rich waiting areas. Research showed that ROR intervention was associated with more positive parenting attitudes in population at risk, better parent-child interaction and language development in early childhood resulted from frequent reading aloud by parents.

Comprehensive Child Development Service (CCDS) in Hong Kong aimed at early identification of at-risk young children (maternal mental illness, perinatal mood disorder, substance abuse and teenage pregnancy) and timely provision of clinical and social support to them and their families. These children with maternal risk factors growing up in high risk families were potentially or already under toxic stress which had negative impact on their development.
The current study was developed based on the concept of toxic stress referred in the AAP recommendation and ROR program. To the best of our knowledge, there have been no previous studies on ROR approach program locally. The aim of this study was to examine the effectiveness of book prescription by paediatrician at local community clinics, as a clinic-based intervention to promote positive parenting behaviour and emergent literacy for high-risk preschoolers under CCDS. The null hypothesis is that book prescription by paediatrician has no effect on literacy orientation, frequency of reading aloud and number of books at home.

Methods

Participants

The study period was from April 2017 to December 2017. Parents of children aged 6 to 30 months born from mothers suffering from active mental or mood disorder, substance misuse or teenage pregnancy under CCDS attending paediatric on-site clinic at Maternal & Child Health Centres (MCHC) in Hong Kong East, namely Chai Wan, Sai Wan Ho and North Point MCHC in April and May 2017 were invited to participate in the study. They were excluded if their children were acutely ill during clinical visits or had significant development problem. Written informed consent was obtained from eligible participating parents.

Procedure

After the participants completed the pre-intervention questionnaire, the paediatrician prescribed a book named "HUG" to them. Procedures of book prescription included: 1) read the book with the child and demonstrate techniques of reading aloud to parents 2) discuss on benefits of reading aloud like mutual enjoyment, social closeness and facilitating language and literacy development 3) provide anticipatory guidance to parents on parenting and development, particularly expected age appropriate behaviour during book sharing 4) encourage parents to read aloud at home and distribute the book with reading tips at the last page for them to take home. This book was age appropriate and suitable to participants as confirmed by local paediatrician and clinical psychologist to be. This colourful board book contains abundant familial animals expressing love by hugging but only very few words. Follow up clinic visits six months after book prescription was arranged and the same questionnaire was completed by the participants.

Assessment Tool

This prospective intervention study, with a before-and-after design used 2 sets of questionnaire on reading aloud at interval of six months. The questionnaire was designed with reference to assessment tools used in previous studies on literacy orientation, child-centered literacy orientation and home literacy environment. It contained 4 questions in Chinese (with English translation):

Q1) Did you read aloud with your child in the past 24 hours?
Q2) How many children books do you have at home?
Q3) How many times do you read with your child per week in average?
Q4) What are your child's top three favourite activities (excluding eating and sleeping)?

Literacy orientation was scored positive if parents' answer to Q1 was yes or "reading" was among the child's three favourite activities for Q4.

Statistical Analysis

The number of subjects to be recruited was estimated based on the number of patients attending paediatric on-site clinics. The demographic, clinical characteristics of participants and questionnaire responses were described. The change in literacy orientation, number of children books at home and frequency of parent reading aloud were calculated according to the questionnaire responses done on the day of book prescription and six months later. Mann-Whitney U test and McNemar’s test were used to compare the change in four questions and literacy orientation for all participants before and after the intervention. Generalised Estimating Equation was used to test whether the effect of the intervention is different among subgroups (teenage pregnancy, substance abuse and mood / mental disorder). Logistic regression analysis was used to measure the possible contributing factors (baby's age & gender, maternal age, marital & employment status, main caretaker and financial assistance) to the intervention effect. Statistical analysis was conducted using SPSS software, with P<0.05 considered as statistically significant in this study.

STROBE statement was used as the reporting guideline.
Results

Parents of 103 children were recruited in the study at start in April and May 2017 with no exclusion or refusal but 33 failed to turn up at the follow up visit 6 months later. Failure to turn up at the scheduled or rescheduled clinical visits within 4 weeks was counted as loss of follow up in the study. Finally, parents of 70 recruited children (38 male, 32 female) completed the study. The age at enrolment of study ranged from 6.07 to 25.8 months with a mean age of 11.66 months old. Majority 134 (95.7%) of parents of participants were Chinese in origin. The participants were divided into three subgroups according to maternal risk factors (3 teenage pregnancy, 6 substance abuses and 65 active mood or mental disorder). Three children were victims of neglect. Demographic data and clinical characteristics of participants were shown in Table 1.

Changes in Literacy Orientation

Responses to the questionnaire before and after intervention were summarised in Table 2. Before the intervention, only 18 (25.7%) of 70 parents read children book with the child and 12 (17.1%) chose reading book with the child as the top three preferred activities. After the intervention, the corresponding figures significantly increased to 38 (54.3%) and 36 (51.4%) respectively (p-value <0.001). Positive literacy orientation, as reflected by positive response to either of the above 2 parameters, increased by 2.35 times in 6 months from 20 (28.6%) to 47 (67.1%) after intervention (p-value <0.001).

Changes in Home Literacy Environment

Before intervention, 49 of 70 participants (70%) had one or more children books at home. Though many participants had books at home, more than half (44, 62.9%) "never" read with their children. After intervention, nearly all (94.3%) had one or more children books at home (P<0.001) and majority of parents (60, 85.7%) read with their children at least once per week (P<0.001). The proportion of parental reading with children 1-4 times per week rose from 20% to 35.7% and reading 5 times per week rose from 17.1% to 50% (P<0.001). Positive changes in home literacy environment were evident from the increase in children books at home and frequency of parents reading with child.

Subgroups Analysis

After subgroup analysis, significant factors for outcome were shown in Table 3. Maternal age was a significant independent factor associated with improvement of literacy orientation (OR=1.139; 95%CI 1.036-1.253, p-value <0.05) and mother at work was negatively associated with

<table>
<thead>
<tr>
<th>Table 1: Demographic and clinical characteristics of participants (n=70)</th>
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</thead>
<tbody>
<tr>
<td><strong>Characteristics</strong></td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>Gender of child</td>
</tr>
<tr>
<td>Age of child at entry of study</td>
</tr>
<tr>
<td>6-12 months</td>
</tr>
<tr>
<td>12-18 months</td>
</tr>
<tr>
<td>18-24 months</td>
</tr>
<tr>
<td>24-30 months</td>
</tr>
<tr>
<td>Parents' country of origin</td>
</tr>
<tr>
<td>China</td>
</tr>
<tr>
<td>Thailand</td>
</tr>
<tr>
<td>Belgium</td>
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<tr>
<td>Pakistan</td>
</tr>
<tr>
<td>Indonesia</td>
</tr>
<tr>
<td>United Kingdom</td>
</tr>
<tr>
<td>Maternal problems (Subgroups)</td>
</tr>
<tr>
<td>Teenage pregnancy</td>
</tr>
<tr>
<td>Substance abuse</td>
</tr>
<tr>
<td>Mood or mental disorder</td>
</tr>
<tr>
<td>Maternal age entry of study</td>
</tr>
<tr>
<td>Maternal marital status</td>
</tr>
<tr>
<td>Married</td>
</tr>
<tr>
<td>Single</td>
</tr>
<tr>
<td>Maternal employment status</td>
</tr>
<tr>
<td>Housewife</td>
</tr>
<tr>
<td>At work</td>
</tr>
<tr>
<td>Maternal education level</td>
</tr>
<tr>
<td>Primary</td>
</tr>
<tr>
<td>Lower secondary</td>
</tr>
<tr>
<td>Upper secondary</td>
</tr>
<tr>
<td>Post secondary</td>
</tr>
<tr>
<td>Financial assistance</td>
</tr>
<tr>
<td>On Comprehensive Social Security</td>
</tr>
<tr>
<td>Assistance (CSSA)</td>
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<tr>
<td>Not on CSSA</td>
</tr>
<tr>
<td>Main carer</td>
</tr>
<tr>
<td>Parents</td>
</tr>
<tr>
<td>Grandparents</td>
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<tr>
<td>Others</td>
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</table>
the improvement (OR=0.228; 95% CI 0.054-0.96, p-value <0.05). Baby’s age and gender, maternal marital status, main caretaker and financial assistance were not associated with improvement in literacy orientation. Mother at work was a significant independent factor negatively associated with improvement in frequency of reading with children (OR=1.115; 95% CI 1.014-1.227, p-value <0.05). No association with these outcomes was found in other potential contributing factors.

With regard to maternal risk subgroups, namely, teenage pregnancy, substance abuse and active mood / mental disorder, there was no significant subgroup difference in the effects of intervention.

Discussion

To the best of our knowledge, this was the first local study on paediatric on-site clinic-based intervention using ROR approach to promote positive parenting behaviour particularly mother-baby interaction and emergent literacy. Studies on ROR approach intervention mainly focus on those families with economic and social risks in other countries like the US and India.5,8,9 The current study focused on mainly Chinese children with maternal high risk factors - mental or perinatal mood problems, substance abuse and teenage pregnancy which were known to be adverse childhood experiences causing toxic stress on their brain development.7 In summary, our local findings were in agreement with the observation of other published reports on literacy orientation, home literacy environment and clinic-based intervention on reading aloud in the US,10-12 India9 and Singapore.7

Literacy orientation describes children’s level of interest or engagement in literacy events. It is a critical factor in children’s language and emergent literacy development.7 This measure was believed to be subject to least reporting bias.6 Needleman et al6 evaluated a pilot program in which paediatrician distributed books to children with anticipatory

<table>
<thead>
<tr>
<th>Response</th>
<th>Pre-intervention Number (%)</th>
<th>Post-intervention Number (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reading with child in the past 24 hours</td>
<td>Yes</td>
<td>18 (25.7)</td>
<td>38 (54.3)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>52 (74.3)</td>
<td>32 (45.7)</td>
</tr>
<tr>
<td>Number of children books at home</td>
<td>0</td>
<td>21 (30.0)</td>
<td>4 (5.7)</td>
</tr>
<tr>
<td></td>
<td>1-4</td>
<td>26 (37.1)</td>
<td>18 (25.7)</td>
</tr>
<tr>
<td></td>
<td>≥5</td>
<td>23 (32.9)</td>
<td>48 (68.6)</td>
</tr>
<tr>
<td>Number of days per week parent read with child</td>
<td>0</td>
<td>44 (62.9)</td>
<td>10 (14.3)</td>
</tr>
<tr>
<td></td>
<td>1-4</td>
<td>14 (20.0)</td>
<td>25 (35.7)</td>
</tr>
<tr>
<td></td>
<td>≥5</td>
<td>12 (17.1)</td>
<td>35 (50.0)</td>
</tr>
<tr>
<td>Reading as child’s top three favourite activity</td>
<td>Yes</td>
<td>12 (17.1)</td>
<td>36 (51.4)</td>
</tr>
</tbody>
</table>

Table 3  Significant factors for each outcome in the multiple logistic regression analysis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Independent factor</th>
<th>Odd ratio</th>
<th>95% C.I.</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of books at home</td>
<td>Maternal working status</td>
<td>0.191</td>
<td>0.048 - 0.764</td>
<td>0.019</td>
</tr>
<tr>
<td>Reading frequency</td>
<td>Age of the child</td>
<td>1.115</td>
<td>1.014 - 1.227</td>
<td>0.025</td>
</tr>
<tr>
<td>Literacy</td>
<td>Age of mother</td>
<td>1.139</td>
<td>1.036 - 1.253</td>
<td>0.007</td>
</tr>
<tr>
<td>Orientation</td>
<td>Maternal working status</td>
<td>0.228</td>
<td>0.054 - 0.960</td>
<td>0.044</td>
</tr>
</tbody>
</table>

All results were adjusted for gender, age of child, main carer, age of mother, marital status, financial assistance, and maternal working status.
guidance at clinic visit and found that 53% subject receiving a book had a positive literacy orientation after book distribution at intervention group and result was more significant for low-income group. A similar study by High et al found that families with intervention had significantly high (69%) child-centered literacy orientation. The positive literacy orientation post intervention (67.1%) in the current study was comparable to these findings.

Home literacy environment can be defined either as the "number" of picture books at home or frequency of parent-preschooler shared reading. A literacy-home environment is important because it is another key factor in children's language and literacy acquisition other than literacy orientation. A Singapore descriptive study on literacy environment of 12-month-old babies found that most families (92.6%) have children books at home; with 62%, 17.5% and 13% owning less than 10, 10-30, more than 30 books respectively. In the current study, only 60% of families have children books at home and the proportion increased significantly to 94.3% after intervention.

In a randomised controlled study for literacy promotion by paediatrician for Hispanic families in the US, 66% of intervention group parents reported reading to their child at least 3 days per week. A similar Taiwan study for Chinese babies found 46% after intervention. Observation of present study in frequency of reading was high with 50% reading to their children 5 days per week after book prescription. Only a few small-scale studies on reading aloud by educators were published locally. The survey of Department of Health carried out in Maternity and Child Health Centres in Hong Kong for normal children below 5 years of age showed that 51% of parents always accompany children to read. Our study in high-risk families for preschoolers showed that frequency of reading aloud was only 25.7% before intervention, reflecting the need for more support in this high-risk group. After intervention the frequency of reading aloud increased to 54.3% and it was comparable with normal children.

We adopted the ROR-approach intervention. The basic ROR model is consisted of 3 components: literacy-rich waiting rooms, a book to take home at each health supervision visit and anticipatory guidance which is the heart of ROR mission. Our intervention program did not include the first component as provision of literary-rich waiting rooms was not feasible, however, our "modified" ROR program as was still effective, with results similar to literacy promoting program which included only the latter 2 components in another study.

These findings support the intervention for promoting literacy at clinic setting by paediatrician. A recent meta-analysis reviews that paediatric provider delivered intervention did demonstrate positive impact on parenting behaviour towards literacy promoting activities. This success may be related to the respect to the profession from the public. In ROR model, book is given by the "primary care provider" and a previous study found positive result with involvement of nurse practitioners. Health care professionals other than paediatrician under CCDS were encouraged to join. The principle behind the effective intervention is to change the parental reading belief and it is an important and significant predictor factor of shared reading. Book "distribution" alone is not effective enough in changing parental attitude and behaviour. Effective program should include both the design of encouraging parental belief and modelling the choice of developmentally appropriate books and shared techniques for reading. In the present study, we "prescribe" rather than just distribute the book at the clinic.

Paediatric on-site clinic in Maternal & Child Health Centre was a non-stigmatising place where parents of at-risk children are more willing to attend and receive guidance from professionals. The practice of book prescription at Hong Kong East may be also beneficial to these high-risk families under CCDS in paediatric on-site clinics at other regions since recruitment criteria is standardised and clinic settings are similar in Hong Kong.

The predictors of home literacy environment and reading frequency namely, mother's education level and parents' national origin were found in previous studies done US and Singapore. Due to high missing data on maternal education level and very low percentage of non-Chinese participants, subgroup analysis did not include these two factors. The present study showing new finding of greater improvement of literacy orientation at higher maternal age may reflect the better receptiveness in older age. Besides, mother at work showing less improvement in both literacy orientation and number of children books at home may reflect their lack of time in taking care of their babies. These results pointed to the need of more support to younger parents particularly the teenage mothers and mothers at work in book prescription.

We start to prescribe books as early as six months old. Benefits of starting reading from infancy include early learning to associate books with enjoyment, promoting joint attention with adults and early reading habit development. Some studies have found the positive effect
of reading during infancy on promoting parent-child interaction at pediatric primary care clinic.\textsuperscript{15,17} Recommendation by AAP was to promote early literacy development by pediatric providers from infancy and continuing at least until the age of kindergarten entry.\textsuperscript{1} The current study found that with increase in baby's age, the improvement of reading aloud frequency became more significant. This finding supported book prescription to be continued after infancy to obtain a sustainable and better outcome for older children.

In Hong Kong, there are only a few small-scaled local studies on shared reading or reading aloud with preschoolers. Unlike other western countries that hold national reading program for raising parents' awareness in reading aloud early and equipping them with skills and resources, there is no centralised literacy program in Hong Kong. Paediatrician can take a proactive role in promoting early literacy, starting from book prescription and develop further on structured reading program with collaboration of early childhood educators and social workers.\textsuperscript{18}

The major limitation of this study was the lack of a control group and no reference for comparing the effect of book prescription with no intervention. Nonetheless, the study findings were comparable with post-intervention group of similar studies in other countries. High-risk families were known to have poor compliance to clinical visits and in the present study the default rate was 32%. These default subjects may represent even higher risk group with more adverse factors and future study on evaluating them was valuable. Relative small sample size can result in error on subgroup analysis of subjects with small numbers. Besides, results based on self-reporting only assessed perception but not behaviour and can be subjected to biases. Home visitation with direct counting of books at home may get more objective and valid data. Other objective measures to assess the improvement of actual literacy rate and the developmental milestone on the long-term effect of language development, reading abilities and school achievement should be used in future studies. Besides, a longer intervention and study period is needed for more books to be prescribed and better reflection on its long-term effect.

This preliminary study suggests that this simple, inexpensive clinic-based intervention by paediatrician at primary care setting can lead to positive changes in attitude of parents of at risk children and their home literacy environment. Paediatricians are recommended to take advantage of clinic visits as an opportunity to counsel high-risk parents on reading aloud and develop literacy promoting program so as to reduce the effect of toxic stress on these high-risk children.

Acknowledgement

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Ethical Approval

The study was approved by the Ethics Committee of Hospital Authority Hong Kong East Cluster (HKECREC-2017-053). Informed consent was obtained from parents.

Declaration

The author has no conflicts of interest to disclose. The author had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

References

Monocyte HLA-DR Expression in Children with Acute Bacterial Meningitis and Meningococcemia: A Predictor of Outcome and Prognosis

C Aydin, F Genel, I Devrim, S Gozmen, O Oluksman

Abstract

Introduction: Acute bacterial meningitis (ABM) and meningococcemia are among the most serious causes of mortality and morbidity in children. Faster tests with high specificity and sensitivity are required to provide early diagnosis and better prognosis. This study aimed to get serial measurements of monocyte HLA-DR expression rate to evaluate the outcome and prognostic value in children with ABM and meningococcemia. Population and Methods: This prospective case-control study was carried out on 18 paediatric patients diagnosed as ABM and meningococcemia and 36 healthy controls between 2011-2017 at Dr. Behcet Uz Children’s Hospital, Izmir, Turkey. Monocyte HLA-DR expression was determined by flow cytometry on admission and the third day of treatment. Results: In the study group, HLA-DR expression was significantly low both on admission and on day 3, as well as HLA-DR mean fluorescence intensity (p<0.001, p=0.001, p=0.001, respectively). When compared to the third day of treatment, monocyte HLA-DR expression was significantly lower on admission (p=0.003). Five patients suffered neurological complications. On day 3, monocyte HLA-DR expression was found significantly lower in patients with neurological complications than the ones with a normal neurological examination (p=0.043). Six patients had used antibiotics before admission. Patients without prior antibiotic usage showed significantly lower monocyte HLA-DR expression (p=0.007). Conclusions: Monocyte HLA-DR expression is down-regulated in patients with ABM and meningococcemia. Higher percentages of monocytes expressing HLA-DR in patients with prior antibiotic treatment supports the importance of early treatment. Low monocyte HLA-DR expression on day 3 also seems to be a valuable predictive marker for neurological complications.

Key words: Acute bacterial meningitis; Meningococcemia; Monocyte HLA-DR expression; Paediatric population
Introduction

The morbidity and mortality caused by acute bacterial meningitis (ABM) in children remains significant worldwide, despite advances in vaccines, chemoprophylaxis, antimicrobial therapy and supportive care. The overall annual attack rate for ABM is 2-5 cases for 100,000 population and the mortality rate is 6-16% in the United States. In developing countries incidence is up to 10 folds and the mortality rate is 2-4 folds higher than the United States. Severe neurological sequelae due to ABM have been reported in 10-20% of the patients. Meningococcemia is a life-threatening bloodstream infection caused by Neisseria meningitidis. Septic shock due to this organism is unique and requires early aggressive management to improve outcome. It is most common in childhood and mortality rates for meningococcemia ranges from 10% in adolescents and 20% in infants.

In children, early diagnosis is very important to improve prognosis both in ABM and meningococcemia. The identification of prognostic factors on admission could alert clinicians and could decrease the occurrence of undesirable events, so faster tests with high specificity and sensitivity are required to predict the outcome and prognosis.

Monocytes are a specific type of leukocytes that have functions in phagocytosis, cytokine production and presentation of antigen to lymphocytes for initiating both cellular and humoral immune responses. Monocytes play an important role in immune regulation and host defence against foreign organisms. HLA-DR molecules are expressed on the majority of monocytes and reflect the activation state of these cells. HLA-DR molecules are important for presenting antigen to the CD4+ cells.

In the paediatric population, significant diminished HLA-DR expression on monocytes in preterm and full-term neonates has been reported. Low monocyte HLA-DR expression was also found to be correlated with lower gestational ages in very low birth weight infants. Downregulation of HLA-DR expression on monocytes has been reported in neonatal sepsis, adult sepsis, different groups of surgical patients, pancreatitis and trauma. It has also been associated with septic complications and increased risk of mortality. Recent studies suggest that decreased monocyte HLA-DR expression is a reliable marker of excessive anti-inflammatory response and immune paralysis. In a study by Shankar-Hari et al, it has been suggested that the optimum biomarker combination associated with subsequent sepsis in emergency department patients with suspected acute infection is the combination of increased neutrophil CD24 and neutrophil CD279 with reduced monocyte HLA-DR expression.

This study aimed to get a serial measurement of monocyte HLA-DR expression rate to predict the outcome and prognosis in children with ABM and meningococcemia.

Population and Methods

Date and Time of Study Conduction / Study Design

This prospective case-control study was carried out between 1st August 2011 and 31st July 2017 at the department of paediatric infectious diseases of Dr. Behcet Uz Children’s Hospital which is a 400-bed paediatric training hospital in Izmir, Turkey. In the study period, 18 children hospitalised with the diagnosis of ABM or meningococcemia were enrolled. The control group consisted of 36 healthy age and gender-matched children that applied to the outpatient departments for routine paediatric follow-up. Neonates were excluded from the study.

Hypothesis

Monocyte HLA-DR expression rate can predict the outcome and prognosis in children with ABM and meningococcemia.

Diagnosis of ABM and Meningococcal Disease

Patients were accepted as ABM according to the following criteria: increased cerebrospinal fluid (CSF) protein >100 mg/dL or decreased CSF glucose <40 mg/dL or CSF leukocyte count >100 white blood cell/mm³ with at least 80% neutrophils, identification of bacterial agents in gram staining, or isolation of bacteria from the CSF samples.

The clinical diagnosis of meningococcemia or meningococcal septic shock was made (in the absence of bacterial isolation) if the ill child had a fever and a petechial or purpuric rash and/or signs of meningitis as described before.

Determination of Cell Surface Markers by Flow Cytometry

A study designed by Wu et al showed that a single measurement of mHLA-DR within the first week after patient admission had no predictive value regarding mortality. In contrast, results expressed as dynamic parameters (i.e., differences between two-time points)
provided excellent predictive values, especially the difference in mHLA-DR expression between days 0 and 3 or days 0 and 7. Similarly, Zhuang et al found that dynamic monitoring of monocyte HLA-DR expression was more valuable for the diagnosis, prognosis, and prediction of sepsis. In this respect, we also investigated the monocyte HLA-DR expression on admission and the third day of treatment. Measurements were performed via three-colour flow cytometry by one of the authors who knew neither clinical nor laboratory findings of the patients. In the patient group, samples of peripheral blood were collected in EDTA anticoagulant tubes. In the control group, the plasma of the peripheral blood drawn for routine complete blood count was separated and used. Freshly collected blood samples (100 mL) were stained within 15 min after arrival at the laboratory with 10 mL of each conjugated monoclonal antibodies (mAb). The following commercial mAbs were used: phycoerythrin-cyanin 5 (PC5)-labeled CD45 (clone J.33; Beckman Coulter), fluorescein isothiocyanate (FITC)-labeled HLA-DR (clone Immu-357; Beckman Coulter), and phycoerythrin-labelled CD14 (clone RMO52; Beckman Coulter). After completion of the incubation, the erythrocytes were lysed and leucocytes were stabilised and fixed by TQ-Prep (Coulter). The appropriate isotype controls were used. At least 10,000 cells from each sample were analysed on the Cytomics FC500 (Beckman Coulter) flow cytometer, and the data were processed with CXP cytometer software. The cytometer was routinely optimised using the FlowCheck Fluospheres (Coulter, Fullerton, California, USA). Monocytes were identified by gating on forwarding/side scatter in combination with CD45 and CD14. Results were expressed as the percentage of monocytes expressing HLA-DR and as mean fluorescence intensity (MFI) of monocytes showing expression.

**Ethical Considerations**

The study was approved by the "Local Research Ethics Committee of Dr. Behcet Uz Children’s Hospital, Izmir, Turkey" (Protocol number: 21; Date: 17.04.2013) and adhered to the Declaration of Helsinki for Medical Research involving Human Subjects. The parents of the patients gave their informed consent for participation in the study.

**Statistical Analysis**

Data were expressed as the mean, allowing for the Standard deviation of the mean (mean±SD). All data were tested for normality using the Kolmogorov-Smirnov test. Quantitative values were assessed through analysis of variance (ANOVA) when normally distributed, and by the Kruskal-Wallis test in other cases. Comparisons between two groups were made using the Mann-Whitney U-test or t-test, as appropriate. Categorical data were analysed with the chi-squared test ($\chi^2$). Statistical analyses were performed with SPSS software, version 15.0 (SPSS Inc., Chicago, IL). Statistical significance was defined as $p<0.05$.

**Results**

Out of the 18 patients in the study group, 10 were male and 8 were female. The mean age was 55.2 months (4.6 years), ranging from 1 month to 15 years. In the control group, male to female ratio was 1.57 (22/14) and the mean age was 54.1 months (4.5 years) ranging from 1 month to 15 years. Comparison of patients and controls in terms of age and gender did not reveal any statistical significance ($p=0.944$ and $p=0.695$, respectively) (Table 1).

**Demographical Features, Complications and Outcome of Patients**

All of the 18 patients in the study group had fever and meningeal irritations at admission (100%) followed by confusion (n=14, 77.8%), hypotension (n=14, 77.8%), coagulopathy (n=14, 77.8%), vomiting (n=12, 66.7%), headache (n=12, 66.7%) and rash (n=12, 66.7%). Laboratory features of the study group on admission are reviewed in Table 2. Thirteen out of 18 patients had leukocytosis, 1 had leucopenia and 1 had thrombocytopenia. CRP levels of all 18 patients were remarkably high. In 5 patients, the lumbar puncture could not be performed because of haemodynamic instability due to septic shock. Twelve of the patients were diagnosed as meningococcemia with petechial and purpuric skin lesions, confusion, hypotension, prolonged capillary filling time and coagulopathy. CSF analysis of the 13 patients was compatible with ABM. Twelve patients had negative CSF culture and six of these had the history of beforehand

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Comparison of age and gender between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient group</strong></td>
<td><strong>Control group</strong></td>
</tr>
<tr>
<td>(n=18)</td>
<td>(n=36)</td>
</tr>
<tr>
<td><strong>Age, (months)</strong></td>
<td>55.2±60.2</td>
</tr>
<tr>
<td>(mean±SD) (range)</td>
<td>(1-180)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Female (n)</td>
<td>8</td>
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<tr>
<td>Male (n)</td>
<td>10</td>
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</table>
administration of empirical antibiotics that can penetrate through the blood-brain barrier (5 intravenous ceftriaxone, 1 gentamicin+ceftriaxone). While CSF culture of one patient yielded isolation of \textit{N. meningitidis}, another one resulted in \textit{S. pneumoniae}.

Among 18 patients, 5 had neurologic sequelae including seizures, papillary stasis and strabismus, left hemiparesis, ptosis in the left eye and central facial palsy. No death occurred and all patients were discharged after medical treatment.

**HLA-DR Expression**

Mean percentage of monocytes expressing HLA-DR in the study group on admission was significantly lower than the control group (30.1±23.4 vs 93±5.1, p<0.001). In the study group, monocyte HLA-DR mean fluorescence intensity (MFI) on admission was also significantly lower compared to the control group (12±6.1 vs 18±6.1, p=0.001) (Table 3). Representative flow cytometry plots of an ABM patient a healthy control are presented in Figure 1 and Figure 2, respectively. When compared to initial values, the percentage of monocytes expressing HLA-DR significantly increased (49.9±24 versus 30.1±23.4, p=0.003) on the third day of the treatment, but monocyte HLA-DR MFI did not differ significantly (12±6.1 vs 11.3±1.8, p=0.466) (Table 4). On admission, the percentage of monocytes expressing HLA-DR and monocyte HLA-DR MFI were lower in patients with neurological complications compared to patients with normal neurological examination but these differences were not statistically significant (p=0.104 and p=0.217, respectively). The percentage of monocytes expressing HLA-DR was found to be significantly lower in patients with neurological complications on the third day of treatment (p=0.043), however, monocyte HLA-DR MFI values did not differ significantly (p=0.084) (Table 5). Six patients had used empirical antibiotics before admission.

Table 2: Some important laboratory results of the study group on admission (n=18)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean value (range) (±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin (g/dL)</td>
<td>11.3±1.83 (8.8-15.3)</td>
</tr>
<tr>
<td>Thrombocyte count (/mm³)</td>
<td>268,000±120,696 (76,000-498,000)</td>
</tr>
<tr>
<td>Leucocyte count (/mm³)</td>
<td>18,562±9,673 (3,800-33,500)</td>
</tr>
<tr>
<td>Absolute neutrophil count (/mm³)</td>
<td>14,038±8,034 (900-34,000)</td>
</tr>
<tr>
<td>Absolute lymphocyte count (/mm³)</td>
<td>1,866±1,091 (700-4,200)</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate (mm/h)</td>
<td>47±32.8 (3-104)</td>
</tr>
<tr>
<td>C-reactive protein (mg/dL)</td>
<td>14.72±7.2 (3-25)</td>
</tr>
</tbody>
</table>

Table 3: Comparison of percentage of monocytes expressing HLA-DR and monocyte HLA-DR mean fluorescence intensity between the groups on admission

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Study group (n=18)</th>
<th>Control group (n=36)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of monocytes expressing HLA-DR (%)</td>
<td>30.1±23.4</td>
<td>93±5.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Monocyte HLA-DR MFI</td>
<td>12±6.1</td>
<td>18±6.1</td>
<td>0.001</td>
</tr>
</tbody>
</table>

MFI: mean fluorescence intensity
Figure 1  Monocyte HLA-DR expression percentage of an ABM patient on admission (flow cytometry).

Figure 2  Monocyte HLA-DR expression percentage of a healthy control on admission (flow cytometry).
Discussion

In the pathogenesis of sepsis and serious infectious diseases such as meningitis and meningococcemia, the immune system plays a major role in host defence. In the initial phase of the immune response, increased release of pro-inflammatory cytokines leads to an effective immune response against infection. However, excessive production of these cytokines may be associated with excessive cellular injury, multiple organ failure and death. Following this phase, anti-inflammatory mediators are produced to modulate the inflammatory response. Excessive anti-inflammatory stimulation results with a state termed immune paralysis. The percentage of monocytes expressing HLA-DR is found normal or increased in the inflammatory phase. In the anti-inflammatory phase, damaged monocyte functions and activations, inadequate oxidative burst and antigen presentation result in a decreased percentage of monocytes expressing HLA-DR. Decreased monocyte HLA-DR expression is considered as a reliable marker of immune paralysis.

In our study, we found the percentage of monocytes expressing HLA-DR and monocyte HLA-DR MFI significantly lower on admission in the study group. On the third day of treatment, the percentage of monocytes expressing HLA-DR was significantly higher than the initial values. Fortunately, no mortality occurred. However, 5 patients developed neurological complications. Patients with neurological complications had a lower percentage of monocytes expressing HLA-DR and lower monocyte HLA-DR MFI on admission, but these differences were not statistically significant. On the other hand on the third day of treatment, the percentage of monocytes expressing HLA-DR was significantly lower in patients with neurological complications while the monocyte HLA-DR MFI values remained similar.

Percentage of monocytes expressing HLA-DR is considered to be one of the best reflectors of immune functions in adults with serious diseases treated in intensive care units. A low percentage of HLA-DR expression on monocytes has been reported as a poor prognostic factor in septic adults, different groups of surgical patients, pancreatitis and trauma. In adult sepsis, percentage of monocyte HLA-DR expression less than 20% and its persistence on consecutive 5 days are associated with mortality rates as high as 90%. In a study involving adult patients with cryptococcal meningitis, authors defined an immune signature associated with early mortality which was characterised by monocyte deactivation (reduced HLA-DR expression and tumour necrosis factor α response

<table>
<thead>
<tr>
<th>Parameters</th>
<th>On admission</th>
<th>The third day of treatment</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of monocytes expressing HLA-DR (%)</td>
<td>30.1±23.4</td>
<td>49.9±24</td>
<td>0.003</td>
</tr>
<tr>
<td>Monocyte HLA-DR MFI</td>
<td>11.3±1.8</td>
<td>12±6.1</td>
<td>0.466</td>
</tr>
</tbody>
</table>

MFI: mean fluorescence intensity

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Patients with neurological complications (n=5)</th>
<th>Patients without neurological complications (n=13)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of monocytes expressing HLA-DR on admission (%)</td>
<td>14.88±6.39</td>
<td>36.07 ±25.14</td>
<td>0.104</td>
</tr>
<tr>
<td>Percentage of monocytes expressing HLA-DR on the third day of treatment (%)</td>
<td>25.76±20.11</td>
<td>59.31±29.99</td>
<td>0.043</td>
</tr>
<tr>
<td>Monocyte HLA-DR MFI on admission</td>
<td>14.75±7.11</td>
<td>10.98±5.62</td>
<td>0.217</td>
</tr>
<tr>
<td>Monocyte HLA-DR MFI on the third day of treatment</td>
<td>7.69±2.80</td>
<td>13.38±8.42</td>
<td>0.084</td>
</tr>
</tbody>
</table>

MFI: mean fluorescence intensity
to lipopolysaccharide); increased serum interleukin 6, CXCL10 and interleukin 10 levels; as well as increased neutrophil counts; and decreased T-helper cell type 1 responses. Published reports on the relationship between monocyte HLA-DR expression and outcome in children are limited. A study including children after cardiac bypass surgery reported that decreased HLA-DR in the early postoperative period predicts sepsis/systemic inflammatory response syndrome and prolonged stay in the intensive care unit. Hoffman et al, showed the association between persistent low monocyte HLA-DR expression and the risk of post lung transplant pneumonia in children. Döring et al investigated children and young adults after haematopoietic stem cell transplantation. In this study, prior to and during sepsis or bacterial infection, a significant decrease in human leukocyte antigen DR expression occurred. Wakiguchi et al studied the relationship between T-cell HLA-DR expression and intravenous immunoglobulin (IVIG) treatment response in Kawasaki disease (KD). They found increased T-cell HLA-DR expression associated with IVIG resistance in KD patients, indicating that T-cell activation could be a contributing mechanism underlying this phenomenon. A previous study in our centre demonstrated that the percentage of HLA-DR expressing monocytes was significantly lower in the non-survivor late-onset neonatal sepsis group (16.6%), compared with the survivor group (45.2%), and patients with monocyte HLA-DR expression \(\leq 30\%\) had lower survival rate with a 30-fold higher risk of mortality. These results may indicate monocyte HLA-DR expression as an early predictive marker for prognosis in critically ill children and late-onset neonatal sepsis. In the present study, children with ABM and meningococcemia had down-regulated monocyte HLA-DR expression compared with healthy children reflecting compensatory anti-inflammatory response and immune paralysis. The increase on the third day of antibiotic treatment demonstrated improved immune functions. Our study also showed that the percentage of HLA-DR expressing monocytes on the third day may be a predictive marker for the development of neurological complications. In the present study, we found that a mean monocyte HLA-DR expression \(\leq 50\%\) on admission was strongly associated with the diagnosis of ABM. Moreover, we also demonstrated that the patients with monocyte HLA-DR expression still \(\leq 40\%\) on the third day of treatment were more likely to have poor neurological outcome. HLA-DR MFI did not differ significantly either on the first or the third day of follow up. Similarly, we could not find any significant relation between neurological complications and first or third-day monocyte HLA-DR MFI values. In a previous study, Wu et al reported that in survivors of sepsis monocyte HLA-DR MFI values increased significantly after 6 days. In our study, we did not obtain any values further than the third day of treatment.

In ABM and meningococcemia, it is vital to begin antimicrobial treatment as early as possible. Bacterial load must be reduced immediately in order to prevent the complications of uncontrolled infection. Large studies, especially in adults with meningitis indicate that delay in antimicrobial treatment is a strong and independent risk factor for mortality and morbidity. Recent data in children suggest early antibiotics are independently associated with improved outcomes in septic shock. In our study, six patients had used empirical blood-brain barrier penetrating antibiotics (ceftriaxone) before admission. The percentage of monocytes expressing HLA-DR was significantly lower in patients without prior antibiotic usage than the patients who used antibiotics before admission, supporting the importance of early treatment. This result also suggests that early antibiotic treatment may have favourable effects on immune response and regulation in serious infections.

The strength of the current study comes from its being the first study in the current literature that introduces decreased monocyte HLA-DR expression as a reliable predictive marker of outcome and prognosis in paediatric patients with ABM and meningococcemia. On the other hand, the main drawback of the study is the small sample size. Larger scaled prospective studies are required to confirm our findings.

**Conclusion**

According to our findings, monocyte HLA-DR expression is downregulated in paediatric patients with ABM and meningococcemia. Higher percentages of monocytes expressing HLA-DR in patients referred with prior antibiotic treatment supports the importance of early treatment of ABM and meningococcemia. The percentage of monocyte HLA-DR expression on the third day of treatment also seems to be a valuable predictive marker for complications during follow up. Using monocyte HLA-DR expression may help clinicians to save time and effort in the differential diagnosis of critically ill children, leading them in decision making of early antibiotic treatment and prediction of possible complications.
**Conflicts of Interest**

None of the authors declares any conflict of interest.

**Sponsorship**

The authors declare that the present work was supported for laboratory test kits by "Beckman Coulter Biomedical Products, Inc., Bornova, Izmir, Turkey" under application number "2013/H298A-2G-SDDI4246".

**References**


The Clinical Effects of GnRHa in Treating Idiopathic Central Precocious Puberty in Girls

K YANG, HF ZHANG, JX LIU, RM LI, LL ZANG, YN ZHANG, Y WANG, RF QI

Abstract

Purpose: This study will explore the clinical effects of the gonadotropin-releasing hormone analogue (GnRHa) to treat girls with idiopathic central precocious puberty (ICPP). Methods: Fifty-four ICPP girls were treated with triptorelin acetate. To evaluate the clinical effects of GnRHa, measurements were taken of the girls' height, weight, ovaries, and uterus before treatment and at 6 and 12 months after treatment. Findings: During the one-year treatment period, the height growth rate slowed in the second half of the year, and the secondary sexual characteristics retracted to varying degrees. Intracavitary ultrasound showed a decrease in the ovary and uterus volumes and in the ovaries' longitudinal diameter, transverse diameter, and anteroposterior diameter and the uterus's transverse diameter. Conclusions: GnRHa can inhibit the development of the gonads and secondary sexual characteristics and induce significant changes in the volume of the ovaries and uterus, longitudinal ovarian diameter, transverse ovarian diameter, anteroposterior ovarian diameter, and transverse uterine diameter.

Key words BMI; GnRHa; Idiopathic central precocious puberty in girls; Pelvic ultrasound; Secondary sexual characteristics

Introduction

Developing secondary sexual characteristics before the age of eight or menarche before the age of ten is defined as precocious puberty. In recent years, with increasing social and economic growth, the rate of central precocious puberty among girls has increased every year. Idiopathic central precocious puberty (ICPP) refers to precocious puberty without organic lesions. ICPP is caused by the release of the gonadotropin-releasing hormone (GnRH) after early activation of the hypothalamic-pituitary-gonadal axis (HPGA) function. The pituitary gland secretes luteinizing hormone (LH) and follicle-stimulating hormone (FSH), leading to an increase in ovarian and uterine volumes.

Girls with precocious puberty have higher levels of criminal activity, substance abuse, social isolation, early sexual behaviour, and mental health problems. Precocious girls with a history of adolescent behaviour disorder have more depressive tendencies compared to their peers.
The gonadotropin-releasing hormone analogue (GnRHa), including triptorelin, is the first choice for treating ICPP.\(^3\) GnRHa can act as a hypothalamic analogue to competitively inhibit the GnRH secreted by the hypothalamus and reduce the secretion of pituitary gonadotropin, inhibiting or delaying gonadal development and delaying puberty.\(^1\) GnRHa treatment can effectively delay the development of gonads and sexual characteristics and improve adult height, with few side effects.\(^4\)

To develop a therapeutic model and evaluate the clinical effects of triptorelin in ICPP treatment, this study analyzed and compared the changes in height and weight, uterus and ovaries, and other key parameters.

Methods

Subjects

Fifty-four girls diagnosed with ICPP were enrolled in this study. The age range was six to ten years old, with an average age of 8.62±1.15 years old. The study was approved by the hospital's ethics committee. The study protocol was outlined to the girls' guardians, and they signed informed consent.

Inclusion criteria: (1) secondary sexual characteristics developed before the age of eight and menarche or breast development before the age of 10, (2) linear growth acceleration with an annual growth rate higher than that of normal children, (3) bone age at least one year older than the actual age, (4) a pelvic ultrasound showing an increased volume of the uterus and ovaries and multiple ovarian follicles with diameters greater than 4 mm, and (5) activated HPGA with serum gonadotropins and sex hormones at puberty levels. The immunochemiluminometric assay (ICMA) showed that the LH peak value was \(\geq 5\) U/I; the GnRHa stimulation test showed that the LH peak FSH peak was \(>0.6.\)\(^1\)

Treatment of GnRHa

All the girls were treated with triptorelin acetate intramuscularly every 4 weeks, the starting dose was 60-160 \(\mu\)G/kg. We adjust the dose of triptorelin according to the gonadal suppression and the weight changes of the children. The maximum single dose was 3.75 mg.

Detection of height, weight, and body mass index (BMI)

The girls' height and weight were measured and recorded before treatment and at 6 and 12 months after treatment. Height growth rate = height after treatment - the height before treatment; BMI = weight (kg)/square of height (m).

Ultrasound Detection

The girls were examined by transrectal ultrasonography before treatment and at 6 and 12 months after treatment, and the parameters of the uterus and ovaries were recorded. No girl had significant differences between the parameters of the left and right ovaries. The ovaries' longitudinal diameter, anteroposterior diameter, and transverse diameter were defined as the mean values of the parameters of the right and left ovaries. Ovarian volume (ml) = (longitudinal diameter \(\times\) anteroposterior diameter \(\times\) transverse diameter) \(\times\) 0.523. The volumes of the two ovaries and the mean volume were calculated. The uterus volume (ml) = (longitudinal diameter \(\times\) anteroposterior diameter \(\times\) transverse diameter) \(\times\) 0.523. The fundal-cervical ratio (FCR) of the (uterus = anteroposterior diameter of the uterus/ anteroposterior diameter of the cervix).

Statistical Analysis

After the data had been collected, they were statistically analysed using the software SPSS 16.0. The measurement data were expressed as mean \(\pm\) standard deviation (\(x \pm SD\)). In the present study, single-factor, least significant difference analysis was used to compare normally distributed data with homogeneous variance. Non-normally distributed data, such as volumes of the uterus and ovaries, were compared using a nonparametric \(U\)-test. \(P<0.05\) was considered statistically significant.

Results

Secondary Sexual Characteristics

After treatment, the secondary sexual characteristics retracted by varying degrees: the breast glands became softer and smaller in 37 of 54 girls; menstruation disappeared in 24 of 33 girls; and vaginal secretion decreased or disappeared after treatment in 21 girls.

Changes in Height and BMI

In the first six months of treatment, the height growth rate was greater compared to the rate at 6 to 12 months after treatment, and the difference was statistically significant (\(P<0.05\)) (Table 1).

There was no significant change in BMI before and after treatment, and the difference was not statistically significant (\(P>0.05\)).

Pelvic Ultrasound

To facilitate the statistical analysis, the data before
treatment and at 6 and 12 months after treatment began, respectively, were designated as group 1, group 2, and group 3.

**Changes in the Ovaries**

The longitudinal ovarian diameter, transverse ovarian diameter, and anteroposterior ovarian diameter decreased after treatment began \( (P<0.05) \) (Tables 2 and 3), when compared to the measurements before treatment; the reduction in the first six months of treatment was significant \( (P<0.05) \) (Table 4 and Figure 1). The volume of the ovaries shrank during treatment, and this was most obvious in the first six months of treatment \( (P<0.05) \).

**Changes in the Uterus**

The transverse diameter of the uterus decreased during treatment \( (P<0.05) \), and the reduction was most pronounced during the first six months \( (P<0.05) \) (Tables 3 and 5). The results showed no significant changes in the longitudinal uterine diameter, anteroposterior uterine diameter, and uterine FCR before and after treatment \( (P>0.05) \). The results showed that the volume of the uterus decreased during treatment, and this was most obvious during the first six months \( (P<0.05) \) (Table 4 and Figure 2).

**Discussion**

The incidence of ICPP is correlated to race, heredity, environment, and other factors. For example, Jayasena et al reported that the overactivation of the kisspeptin (KISS) gene, which produces a hypothalamic neuropeptide, can lead to precocious puberty in children.\(^5\) Therefore, KISS gene polymorphism was associated with ICPP.\(^6\) A scholar also reported that ICPP is correlated with the mutation of the \( mkrn3 \) gene.\(^6\) In addition, genetic factors, obesity, and environmental factors may be involved in the occurrence and development of ICPP. The widespread presence of endocrine disorder chemicals is suspected of contributing to the trend of the pathogenesis of early puberty.\(^7\)

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### Table 1  Changes in height and BMI before and after treatment (x±SD)

<table>
<thead>
<tr>
<th></th>
<th>Anterior-posterior diameter of the cervix (cm)</th>
<th>Transverse diameter of the cervix (cm)</th>
<th>BMI (kg/m(^2))</th>
<th>Growth value of height (cm/6 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td>1.78±0.43</td>
<td>1.17±0.26</td>
<td>17.88±2.80</td>
<td></td>
</tr>
<tr>
<td>Six months after treatment</td>
<td>1.62±0.42</td>
<td>1.01±0.24</td>
<td>18.50±2.16</td>
<td>3.87±0.90</td>
</tr>
<tr>
<td>One year after treatment</td>
<td>1.67±0.51</td>
<td>1.07±0.33</td>
<td>18.80±2.67</td>
<td>2.64±1.2</td>
</tr>
<tr>
<td>( F )</td>
<td>0.919</td>
<td>2.253</td>
<td>2.094</td>
<td>-3.36</td>
</tr>
<tr>
<td>( P )</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

BMI: body mass index

### Table 2  Changes in the ovary before and after treatment (x±SD)

<table>
<thead>
<tr>
<th></th>
<th>Ovary long diameter (cm)</th>
<th>Ovary anterior-posterior diameter (cm)</th>
<th>Ovary transverse diameter (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td>2.42±0.53</td>
<td>1.46±0.41</td>
<td>1.85±0.46</td>
</tr>
<tr>
<td>Six months after treatment</td>
<td>2.02±0.40</td>
<td>1.13±0.23</td>
<td>1.54±0.36</td>
</tr>
<tr>
<td>One year after treatment</td>
<td>2.16±0.50</td>
<td>1.27±0.28</td>
<td>1.64±0.53</td>
</tr>
<tr>
<td>( F )</td>
<td>4.790</td>
<td>7.818</td>
<td>3.222</td>
</tr>
<tr>
<td>( P )</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>
### Table 3  Comparison of parameters before and after treatment

<table>
<thead>
<tr>
<th></th>
<th>Mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before treatment vs.</td>
</tr>
<tr>
<td></td>
<td>Six months after treatment</td>
</tr>
<tr>
<td><strong>Ovary long diameter</strong></td>
<td>0.40056 (0.1395, 0.6616)</td>
</tr>
<tr>
<td><em>P</em></td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>Ovary anterior-posterior diameter</strong></td>
<td>0.3387 (0.1673, 0.5101)</td>
</tr>
<tr>
<td><em>P</em></td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>Ovary transverse diameter</strong></td>
<td>0.307778 (0.06183, 0.55373)</td>
</tr>
<tr>
<td><em>P</em></td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>Uterus transverse diameter</strong></td>
<td>0.32 (0.063, 0.577)</td>
</tr>
<tr>
<td><em>P</em></td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

CI: confidence interval

### Table 4  Changes in the ovarian volume and uterine volume before and after treatment (x±SD)

<table>
<thead>
<tr>
<th>Time</th>
<th>Ovarian volume (ml)</th>
<th>Uterine volume (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Before treatment</td>
<td>4.07±3.55</td>
<td>5.64±5.44</td>
</tr>
<tr>
<td>(2) Six months after treatment</td>
<td>2.04±1.12</td>
<td>3.16±2.50</td>
</tr>
<tr>
<td>(3) One year after treatment</td>
<td>3.94±3.04</td>
<td>4.05±3.91</td>
</tr>
<tr>
<td>(1) : (2) <em>P</em></td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>(1) : (3) <em>P</em></td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>(2) : (3) <em>P</em></td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

### Table 5  Changes in the uterus before and after treatment (x±SD)

<table>
<thead>
<tr>
<th>Time</th>
<th>Uterus long diameter (cm)</th>
<th>Uterus anterior-posterior diameter (cm)</th>
<th>Uterus transverse diameter (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td>2.41±0.65</td>
<td>2.30±0.57</td>
<td>1.58±0.58</td>
</tr>
<tr>
<td>Six months after treatment</td>
<td>2.08±0.53</td>
<td>1.98±0.51</td>
<td>1.26±1.34</td>
</tr>
<tr>
<td>One year after treatment</td>
<td>2.19±0.67</td>
<td>2.09±0.68</td>
<td>1.34±0.47</td>
</tr>
<tr>
<td><em>F</em></td>
<td>1.913</td>
<td>1.966</td>
<td>3.331</td>
</tr>
<tr>
<td><em>P</em></td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

### Table 6  Changes in the thickness of the vaginal wall (x±SD)

<table>
<thead>
<tr>
<th>Time</th>
<th>FCR of the uterus</th>
<th>Thickness of the vaginal wall (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td>1.33±0.30</td>
<td>0.24±0.07</td>
</tr>
<tr>
<td>Six months after treatment</td>
<td>1.27±0.32</td>
<td>0.21±0.08</td>
</tr>
<tr>
<td>One year after treatment</td>
<td>1.29±0.35</td>
<td>0.22±0.06</td>
</tr>
<tr>
<td><em>F</em></td>
<td>0.264</td>
<td>0.846</td>
</tr>
<tr>
<td><em>P</em></td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

FCR: fundal-cervical ratio
Kim et al\textsuperscript{8} examined 118 ICPP girls and 91 age-matched healthy girls, and the results showed that the plasma levels of daidzein ($P=0.0202$), genistein ($P=0.0021$), and total isoflavones ($P=0.0009$) were higher in ICPP girls than in healthy girls. This result suggests that the increase in serum isoflavones may be correlated to the risk of ICPP in Korean girls.\textsuperscript{7} Zhang et al\textsuperscript{9} reported that concentrations of environmental endocrine disruptors (such as diethylhexyl phthalate, octylphenol, and bisphenol A) were important pathogenic factors of precocious puberty.\textsuperscript{10} Tassinari et al\textsuperscript{11} detected the serum concentration of polybrominated diphenyl ether (PBDEs) in 31 girls with ICPP, and the results showed that the levels were higher than the levels in healthy girls. Girls with higher BMIs had higher serum levels of PBDEs.\textsuperscript{8}

GnRHa is the first choice for treating ICPP globally.\textsuperscript{1} For patients with typical central precocious puberty, GnRHa treatment can effectively improve adult height and does not cause adverse effects on the body and reproductive functions.\textsuperscript{9,11} In addition, Li et al\textsuperscript{12} reported that GnRHa could delay the development of secondary sexual characteristics and ovarian maturity with almost no side effects.\textsuperscript{13} Therefore, this study evaluated the clinical effect of GnRHa triptorelin on ICPP. Fifty-four girls accurately diagnosed with ICPP were treated with GnRHa triptorelin. After treatment began in this study, the secondary sexual characteristics were retracted to varying degrees in 54 girls. The height growth rate was significantly greater in the first six months than in the second six months.

In 2011, Taçcil et al\textsuperscript{14} reported that treating ICPP with triptorelin could increase the BMI, puberty growth hormone secretion, and insulin-like growth factor in the blood. Transient insulin resistance in early and middle adolescence can also increase the adipose tissue content and BMI. Jaruratanasirikul et al\textsuperscript{15} reported that the sexual development of girls was correlated to BMI. The BMI of girls affects the endocrine metabolism regulated by the KISS-1/GPR54 system.\textsuperscript{16} In the present study, there was no significant change in BMI before and after treatment, and no increase in BMI was found in ICPP girls treated with GnRHa.

Razzaghy-Azar et al\textsuperscript{17-19} reported that uterine and ovarian parameters are significantly correlated with age, height, weight, puberty stage, and puberty development. The parameters of the uterus and ovaries detected by pelvic ultrasound are important for the diagnosis and evaluation of precocious puberty. Ultrasound can directly reflect the development of the gonads by dynamically monitoring the volume change of the uterus and ovaries after treatment.\textsuperscript{20-22}

The present study showed that the longitudinal ovarian diameter, transverse ovarian diameter, anteroposterior ovarian diameter, ovarian volume, transverse uterine diameter, and uterine volume decreased after treatment, and this reduction was most significant during the first six months. However, there was no significant difference between the reduction six months after treatment and 12 months after treatment. The inhibition effect was most obvious when the drugs were used for six months. However, there were no significant changes in longitudinal uterine diameter, anteroposterior uterine diameter, uterine FCR, cervix transverse diameter, and thickness of the vaginal walls before and after treatment. Hence, these changes cannot be used as sensitive indexes to evaluate the effect of treatment.
Conclusions

GnRHa triptorelin treatment for girls with ICPP can retract the secondary sexual characteristics and inhibit gonad development. There was no significant change in BMI. The reduction in the volume of the ovaries and uterus, longitudinal ovarian diameter, transverse ovarian diameter, anteroposterior ovarian diameter, and transverse uterine diameter can be an effective and sensitive index for observation.

Conflicts of Interest

The authors declare that they have no competing interests.

References

Original Article

Perinatal and Developmental Outcomes of Teenage Pregnancy: An Analysis of a 10-year Period in a Local Region in Hong Kong

F Choi, AWF Cheng, WK Chiu

Abstract

Introduction: Teenage pregnancy accounts for 11% of births worldwide. It is associated with poorer perinatal and developmental outcomes when compared to their adult counterparts. Methods: A retrospective cohort study was conducted in a Hong Kong regional hospital, comparing the perinatal outcomes between babies delivered to teenage mothers aged below 20 years and those delivered to mothers aged between 20 and 34 years. Risk factors which may affect developmental outcomes were also analysed. Results: Teenage pregnancy was associated with more preterm deliveries (<37 weeks) (p<0.001), more babies with low birth weight (p<0.001) and more babies who were small for gestational age (p=0.015). They also had significantly higher odds of delivering preterm babies when compared to adult mothers (aORs 9.309, 95% CI 1.918 to 45.173, p=0.006). Amongst the teenage pregnancy cases, those with prior CCDS follow-up had significantly higher number of children with developmental delay (p=0.017). Conclusions: Teenage pregnancy is associated with adverse neonatal outcomes, which may be due to biological immaturity, poor socio-economic status or a combination. Developmental delay is often found in children of teenage mothers. It is essential to identify risk factors to provide social support and education so that children will be able to cope with their everyday activities better.

Key words Developmental outcomes; Perinatal outcomes; Teenage pregnancy

Introduction

Teenage pregnancy refers to pregnancy in girls between 10 to 19 years old. It is estimated 11% of births globally are born to adolescents aged 15 to 19 years. Not only are these teenage girls more vulnerable to poor obstetric outcomes, they are also at increased risk of adverse perinatal outcomes. Many studies reported higher rate of preterm births, low birth weight, intrauterine growth restriction (IUGR), congenital malformations, neonatal intensive care unit (NICU) admissions and perinatal mortality among teenage pregnancies. Some proposed young women who are still growing themselves may compete for nutrients with the foetus, leading to foetal growth impairment, resulting in low birth weight babies or babies who are small for gestational age (SGA). However, there is conflicting evidence as to whether these adverse perinatal outcomes were attributed by the physical immaturity of these teenage mothers or the unfavourable socio-environmental factors. This discrepancy can be explained by the heterogeneity between study settings, small sample size and different sociocultural backgrounds.

Apart from adverse perinatal outcomes, the cognitive development of these children is also of concern. In addition to maternal age, there are many psychosocial factors which may affect the developmental progress of children, such as educational status, financial support and maternal mental health. Although studies on the
relationship between young maternal age and children's cognitive outcome have been performed, most of them were retrospective and did not account for certain confounding factors, for example, smoking and partner status, which were hypothesised to contribute to poorer developmental outcomes. It is essential to identify risk factors which may affect a child's development so that support can be provided earlier, helping the family and child cope with their daily living.

The aim of this study is to investigate whether teenage mothers are at higher risk of adverse perinatal outcomes when compared with their adult counterparts and to identify risk factors amongst teenage mothers which may lead to poorer cognitive outcomes of their offspring.

Methods

This is a retrospective cohort study covering the period from 1 January 2008 to 31 December 2017.

Ninety-five babies born to primiparous women aged under 19 years who were under the Comprehensive Child Development Service (CCDS) follow-up in the Kowloon East cluster during the above period were included. CCDS provides integrated follow-up to most teenage mothers in Hong Kong. 285 babies born to primiparous women aged between 20 and 34 years were matched for comparison.

As advanced maternal age (>35 years) is known to be an independent risk factor for adverse perinatal outcomes, women aged 20 to 34 years are considered to have a reasonably lower risk of age-related pregnancy complications. Multiparous women, women aged above 35 years, and women with multiple pregnancies were excluded.

The sample size was calculated based on the population size of Kwun Tong district. With a confidence interval of 95%, margin of error of 5% and power of 80%, the required total sample size was calculated to be 380.

Demographics, past medical history, clinical parameters and outcomes were collected from the Hospital Authority Clinical Management System / electronic Patient Record system via the Clinical Data Analysis and Reporting System (CDARS). Baseline demographic data included were maternal age, ethnicity, marital status, maternal smoking and drinking status, maternal educational level, maternal past medical history and mode of delivery. The outcome parameters included were gestational age at birth, birth weight, Apgar scores, neonatal complications, for example respiratory distress syndrome, intraventricular haemorrhage and necrotising enterocolitis, neonatal infections, congenital anomalies and birth trauma.

Definitions

Gestational age at birth was defined as the number of completed weeks of gestation between the first day of the last menstrual period and the delivery date.

Perinatal outcomes examined were preterm delivery (<37 completed weeks); very preterm delivery (<32 completed weeks); extremely preterm delivery (<28 completed weeks); low birth weight (LBW) (birth weight <2500g); very low birth weight (VLBW) (birth weight <1500g); extremely low birth weight (ELBW) (birth weight <1000g); small for gestational age (SGA) (birth weight <10th percentile for gestational age); large for gestational age (LGA) (birth weight >90th percentile for gestational age); low Apgar score at 1 minute and 5 minutes of life (Apgar score <7); mode of delivery (spontaneous vaginal delivery, Caesarean section, forceps delivery or vacuum extraction); NICU admission; neonatal complications including congenital anomalies, neonatal infections, respiratory distress syndrome, intraventricular haemorrhage, necrotising enterocolitis and birth trauma were defined according to the International Classification of Disease coding version nine (ICD-9) in the clinical management system and medical records.

Children were considered developmental delay by formal assessment at the Child Assessment Centre (CAC) where available. For those who were not assessed by CAC at the time of data collection, their developmental progress was assessed by the same paediatrician at their Maternal Child Health Care Centre (MCHC) follow-up, who has experience in developmental assessment.

Risk factors included in the subgroup analysis were maternal psychiatric disorder; maternal smoking status; assistance in childcare; prior CCDS follow-up; Comprehensive Social Security Assistance (CSSA) support and history of child abuse.

Statistical Analysis

Categorical variables were compared using the Pearson Chi square test or Fisher’s Exact test (where expected frequencies were <5), as appropriate in univariate analysis. Continuous variables were compared using the Mann Whitney U test and were reported as median and interquartile range. A two-sided p-value of less than 0.05 was considered statistically significant.

Multivariable logistic regression analysis was used to
identify the odd ratios for neonatal outcomes for teenage pregnancies. Crude and adjusted odd ratios (aOR) with their 95% confidence intervals (CI) were used to present the effects among mothers <20 years old compared with those aged between 20 and 34 years.

Statistical Package for Social Sciences for Windows, version 24.0 (SPSS, Chicago, IL, USA) was used for statistical analysis.

Results

Baseline Characteristics

Ninety-five cases were under CCDS follow-up for teenage pregnancy from 1 January 2008 to 31 December 2017, with a mean age at delivery being 17 years (interquartile range: 16 to 18 years). 285 adult mothers were included, with a mean age at delivery being 25 years (interquartile range: 25.5 to 29 years). Table 1 showed the baseline demographics of the two groups. There were more mothers who were smokers (35.8% vs 4.9%), unmarried (1.1% vs 95.8%) and without tertiary education (0% vs 46.7%) in the teenage group. There was significant difference on the modes of delivery (p=0.01), with less spontaneous vaginal delivery (73.3% vs 86.3%) and more instrumental delivery (26.7% vs 13.7%) in the teenage mother group. There was no statistically significant difference in other baseline characteristics.

Neonatal Outcomes

Univariate analysis (Table 2) showed that teenage pregnancy was associated with more preterm babies delivered before 37 weeks (11.6% vs 0.7%, p<0.001), more babies with LBW (9.5% vs 0%, p<0.001), more babies who were SGA (3.2% vs 0%, p=0.015) and more babies with Apgar score less than 7 at 1 minute of life (3.2% vs 0.4%, p=0.05).

Table 3 showed the crude and adjusted odd ratios for neonatal outcomes by maternal age group. Teenage mothers were found to have significantly higher odds of delivering preterm babies when compared to adult mothers (aORs 9.309, 95% CI 1.918 to 45.173, p=0.006).

Developmental Delay in Teenage Mother Group

In this study, the rate of developmental delay in children born to teenage mothers was 25.3%. Further analysis

Table 1  Baseline demographics of teenage and adult mothers

<table>
<thead>
<tr>
<th></th>
<th>Teenage (n=95)</th>
<th>Adult (n=285)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (median +/- IQR)</td>
<td>17 (16-18)</td>
<td>28 (25.5-29)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hong Kong Resident</td>
<td>93 (97.9%)</td>
<td>256 (89.8%)</td>
<td>0.009</td>
</tr>
<tr>
<td>China Tourist</td>
<td>2 (2.1%)</td>
<td>29 (10.2%)</td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>1 (1.1%)</td>
<td>273 (95.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoker</td>
<td>34 (35.8%)</td>
<td>14 (4.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Drinker</td>
<td>3 (3.2%)</td>
<td>5 (1.8%)</td>
<td>0.418</td>
</tr>
<tr>
<td>Educational level</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Secondary</td>
<td>95 (100%)</td>
<td>152 (53.3%)</td>
<td></td>
</tr>
<tr>
<td>Tertiary</td>
<td>0 (0%)</td>
<td>133 (46.7%)</td>
<td></td>
</tr>
<tr>
<td>Religion</td>
<td>0 (0%)</td>
<td>8 (2.8%)</td>
<td>0.209</td>
</tr>
<tr>
<td>Antenatal booked case</td>
<td>88 (92.6%)</td>
<td>278 (97.5%)</td>
<td>0.028</td>
</tr>
<tr>
<td>Spontaneous vaginal delivery</td>
<td>82 (86.3%)</td>
<td>209 (73.3%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Instrumental delivery</td>
<td>13 (13.7%)</td>
<td>76 (26.7%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Psychiatric illness</td>
<td>3 (3.2%)</td>
<td>13 (4.6%)</td>
<td>0.770</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0 (0%)</td>
<td>7 (2.5%)</td>
<td>0.200</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0 (0%)</td>
<td>4 (1.4%)</td>
<td>0.576</td>
</tr>
<tr>
<td>Genitourinary tract infection</td>
<td>8 (8.4%)</td>
<td>13 (4.6%)</td>
<td>0.154</td>
</tr>
</tbody>
</table>
exploring the risk factors among teenage pregnancy group which may lead to children with developmental delay was performed. As shown in Table 4, the cases with prior CCDS follow-up had significantly higher numbers of children with developmental delay (91.7% vs 66.2%, p=0.017).

Discussion

Baseline Characteristics

In this study, it was found that teenage mothers were less likely to have given birth via instrumental delivery when compared to their adult counterparts. This is consistent with previous studies which showed a decreased rate of Caesarean section and instrumental delivery in teenage mothers. However, some studies showed an increased rate of emergency Caesarean sections among teenage mothers with indications of non-reassuring foetal status due to preterm labour or cephalo-pelvic disproportion due to pelvic bone immaturity. By evaluating the nature of Caesarean section being emergency or elective, more insight can be provided on whether the finding of less Caesarean section among teenage mothers is due to biological factors, maternal preference or socio-cultural background. Teenage mothers having higher rates of spontaneous vaginal delivery may be explained by a more favourable myometrial function, greater elasticity of connective tissues, lower compliance of cervix and low birth weight babies, as suggested by a Turkish study.

Neonatal Outcomes

Many studies confirmed that teenage pregnancies are associated with preterm deliveries, which is similar to the findings of this study of teenage pregnancies having a higher rate of preterm deliveries <37 weeks. There is no clear explanation but many studies support that biological immaturity in youngsters give rise to a higher incidence of premature rupture of membrane (PROM), leading to more genitourinary infections, hence preterm deliveries. However, there was no significant difference in the rate of genitourinary tract infections between the two groups in this study, but teenage mothers tend to have a higher rate. Another explanation is the insufficiency in uterine and cervical blood supply maturation, which also leads to an increased susceptibility to infection and increased prostaglandin production, hence a trend towards increased preterm deliveries. Some also gave the explanation of adolescents have a shorter cervix and a smaller uterine volume, which may not be sufficient to accommodate for a term foetus, so they tend to give birth to preterm babies.

However, it is debatable whether these preterm deliveries are more associated with the biological immaturity of young mothers or their unfavourable socio-economic conditions.

International studies have found many social factors contribute to a higher rate of premature deliveries among young mothers, including poor antenatal care, low socioeconomic status and negative lifestyle factors. In this study, it was found there were significantly less number of antenatally booked cases, more smokers and less mothers who have received tertiary education among teenage mothers. These social factors could contribute to the higher rate of preterm deliveries as inadequate antenatal care and risky behaviours are known risk factors for adverse neonatal outcomes.

Although some studies showed teenage pregnancy itself was not a significant risk factor for adverse neonatal outcomes after adjusting for socioeconomic factors, our study confirmed that teenage mothers have a significantly higher chance of delivering preterm babies than the adult mothers after adjusting for maternal smoking, education level, antenatally booked cases and maternal ethnicity.

Teenage pregnancy is complex with many biological and social factors interlinked. It is difficult to determine any causative factors which may give rise to adverse neonatal outcomes. It is likely the adverse neonatal outcomes are due to a combination of gynaecological immaturity and unfavourable socioeconomic factors.

This study also confirmed teenage pregnancies are associated with LBW babies, which is consistent with most studies. However, in accordance with a study in 2009, there was no significance after adjusting for confounding factors. Some studies found there was no significant difference between the mean birth weight and the proportion of LBW babies between teenage and adult mothers. LBW babies may be associated with their prematurity as teenage pregnancies tend to give rise to preterm deliveries. A cohort showed significantly increased risk of delivering babies extremely preterm (<28 weeks) in teenage mothers; and as extreme prematurity and ELBW is intrinsically linked, this may explain the relationship between LBW babies and teenage pregnancy, but may only remain true for extreme preterm babies.4

Teenage pregnancies were also found to be associated with babies who are SGA. However, this is in contrast with the finding in a Swedish study that there was no increased risk for SGA babies in adolescent mothers. This Swedish
### Table 2  Comparison in neonatal outcomes between teenage and adult pregnancies

<table>
<thead>
<tr>
<th></th>
<th>Teenage (n=95)</th>
<th>Adult (n=285)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestation (median +/- IQR)</td>
<td>39 (38-40)</td>
<td>39 (39-40)</td>
<td>0.05</td>
</tr>
<tr>
<td>Preterm &lt;37 weeks</td>
<td>11 (11.6%)</td>
<td>2 (0.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Preterm &lt;32 weeks</td>
<td>1 (1.1%)</td>
<td>0 (0%)</td>
<td>0.250</td>
</tr>
<tr>
<td>Preterm &lt;28 weeks</td>
<td>1 (1.1%)</td>
<td>0 (0%)</td>
<td>0.250</td>
</tr>
<tr>
<td>Birth weight (median +/- IQR)</td>
<td>3095 (2750-3320)</td>
<td>3330 (3152.5-3556.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ELBW</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>-</td>
</tr>
<tr>
<td>VLBW</td>
<td>1 (1.1%)</td>
<td>0 (0%)</td>
<td>0.250</td>
</tr>
<tr>
<td>LBW</td>
<td>9 (9.5%)</td>
<td>0 (0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SGA</td>
<td>3 (3.2%)</td>
<td>0 (0%)</td>
<td>0.015</td>
</tr>
<tr>
<td>LGA</td>
<td>2 (2.1%)</td>
<td>5 (1.8%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Apgar score &lt;7 at 1 min</td>
<td>3 (3.2%)</td>
<td>1 (0.4%)</td>
<td>0.050</td>
</tr>
<tr>
<td>Apgar score &lt;7 at 5 min</td>
<td>1 (1.1%)</td>
<td>0 (0%)</td>
<td>0.250</td>
</tr>
<tr>
<td>NICU admission</td>
<td>36 (37.9%)</td>
<td>117 (41.1%)</td>
<td>0.587</td>
</tr>
<tr>
<td>RDS</td>
<td>2 (2.1%)</td>
<td>0 (0%)</td>
<td>0.062</td>
</tr>
<tr>
<td>IVH</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>-</td>
</tr>
<tr>
<td>NEC</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>-</td>
</tr>
<tr>
<td>Neonatal infections</td>
<td>2 (2.1%)</td>
<td>0 (0%)</td>
<td>0.062</td>
</tr>
<tr>
<td>Congenital anomalies</td>
<td>1 (1.1%)</td>
<td>0 (0%)</td>
<td>0.250</td>
</tr>
<tr>
<td>Birth trauma</td>
<td>1 (1.1%)</td>
<td>1 (0.4%)</td>
<td>0.438</td>
</tr>
</tbody>
</table>

### Table 3  Odd ratios (ORs) in neonatal outcomes in teenage pregnancies

<table>
<thead>
<tr>
<th></th>
<th>Crude ORs</th>
<th>95% CI</th>
<th>P-value</th>
<th>Adjusted ORs*</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm</td>
<td>18.53</td>
<td>4.03-85.25</td>
<td>&lt;0.001</td>
<td>9.309</td>
<td>1.918-45.173</td>
<td>0.006</td>
</tr>
<tr>
<td>LGA</td>
<td>1.20</td>
<td>0.23-6.31</td>
<td>0.826</td>
<td>0.765</td>
<td>0.123-4.766</td>
<td>0.774</td>
</tr>
<tr>
<td>Apgar score &lt;7 at 1 min</td>
<td>9.26</td>
<td>0.95-90.12</td>
<td>0.055</td>
<td>3.281</td>
<td>0.287-37.526</td>
<td>0.339</td>
</tr>
<tr>
<td>NICU admission</td>
<td>0.88</td>
<td>0.54-1.41</td>
<td>0.587</td>
<td>0.757</td>
<td>0.423-1.355</td>
<td>0.348</td>
</tr>
<tr>
<td>Birth trauma</td>
<td>3.02</td>
<td>0.187-48.778</td>
<td>0.436</td>
<td>7.242</td>
<td>0.24-218.358</td>
<td>0.255</td>
</tr>
</tbody>
</table>

* Adjusted for maternal smoking, education level, maternal ethnicity and antenatal booked cases

### Table 4  Subgroup analysis on risk factors for developmental delay in teenage pregnancy group

<table>
<thead>
<tr>
<th></th>
<th>Developmental delay (n=24)</th>
<th>Normal development (n=71)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal mood disorders</td>
<td>2 (8.3%)</td>
<td>7 (9.9%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Maternal smoking</td>
<td>11 (45.8%)</td>
<td>23 (32.4%)</td>
<td>0.235</td>
</tr>
<tr>
<td>Caretaker assistance</td>
<td>24 (100%)</td>
<td>70 (98.6%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Prior CCDS follow-up</td>
<td>22 (91.7%)</td>
<td>47 (66.2%)</td>
<td>0.017</td>
</tr>
<tr>
<td>CSSA</td>
<td>8 (33.3%)</td>
<td>17 (23.9%)</td>
<td>0.366</td>
</tr>
<tr>
<td>Child abuse</td>
<td>1 (4.2%)</td>
<td>1 (1.4%)</td>
<td>0.443</td>
</tr>
<tr>
<td>Maternal drinking</td>
<td>0 (0%)</td>
<td>3 (4.2%)</td>
<td>0.569</td>
</tr>
</tbody>
</table>
study also pointed out maternal smoking appears to be a significant independent risk factor for SGA in all age groups, but has less significance in younger mothers. The difference in socio-economic status may attribute to such adverse neonatal outcomes, although a study found the risk for SGA persisted even after restricting the analysis to women with age-appropriate education level, adequate antenatal care, non-smokers and non-drinkers.

Teenage pregnancies were found to be associated with more babies born with Apgar score less than 7 at 1 minute of life. This is consistent with a study which showed teenage mothers had increased risks for adverse neonatal outcomes, including low Apgar score. The study also attributed the increased risk to maternal physical immaturity with maternal height as a measurement, explaining shorter maternal height relates to smaller pelvic size, thus increasing the risk of preterm deliveries, hence a higher chance of neonatal asphyxia. However, this study did not include maternal height or pelvic size as a measurement of physical maturity and could not demonstrate this relationship. Also, there was only significant difference in the Apgar score at 1 minute of life and not for that at 5 minutes of life. Apgar score is used to report the status of a newborn immediately after birth and assess the response to resuscitation if warranted. A low Apgar score at 1 minute of life does not predict an infant’s outcome but that at 5 minutes of life correlates with neonatal mortality in large populations, but still does not predict future neurologic dysfunction. Although there is statistical significance in the difference in Apgar score at 1 minute of life between the two groups, the clinical significance is yet to be confirmed. By obtaining and comparing Apgar scores at 10, 15 and 20 minutes of life, the clinical impact of teenage pregnancies on adverse outcomes can be further explored.

**Developmental Delay in Teenage Mother Group**

The rate of developmental delay in children born to teenage mothers in this study was 25.3%.

There is a paucity of local data on the epidemiology of developmental delay in the general population. According to a local study by Tang et al in 2008, the rate of developmental delay in children among referrals to Child Assessment Service in Hong Kong was 23%. A child’s developmental progress can be affected by many biological and psychosocial factors. In this study, it was found that cases with prior CCDS follow-up had significantly higher numbers of children with developmental delay.

CCDS is a multidisciplinary service which provides comprehensive support to young children and their families using MCHC as a platform. One of its aims is to improve health and developmental outcomes of three main at-risk groups of children, including mothers who have mental illness, mothers who have history of illicit drug use and teenage mothers.

The results seemed to be a surprise as one would have thought earlier engagement and more support throughout a child’s growth and development should alert both the caretaker and clinician of any signs of delay at a timely manner for formal assessment and intervention. However, on second thought, it was by recruiting these at-risk cases into CCDS which allowed for early identification of developmental delay, prompting for expedient CAC referral and early schooling with appropriate training. Moreover, these cases would be followed up for longer time so that their progress could be monitored closely.

On the other hand, cases with prior CCDS follow-up may not only be looked after early due to teenage pregnancy, but may have co-existing risk factors requiring close monitoring. Further investigation into whether these teenage mothers had mental illness or drug abuse history at the same time which required early CCDS follow-up may be beneficial to determine more associated risk factors leading to delay in their children’s cognitive outcome.

Studies have shown children of teenage mothers are at three to four times higher risk of developmental delay in intelligence, language and social-emotional functions than those of adult mothers. Most studies found that poor financial status, presence of maternal smoking and poor social support were risk factors for developmental delay in children. On the contrary, our study did not show any significant role of CSSA support, maternal smoking and caretaker assistance in the delay in development of children.

Another risk factor contributing to developmental delay is co-parenting conflicts. It commonly occurs in families with complex parent-grandparent relationships. Studies have shown that greater adolescent-mother conflict predicts a greater likelihood of the child being delayed in development.

World-renowned Nurse-Family Partnership program led by Professor David Olds has been shown to be effective in improving birth, health and developmental outcomes, especially for young, first-time mothers and their children. The program starts prenatally, giving support and equipping young mothers with parenting techniques throughout the first two years of childhood. It
is the responsive and engaging parenting which provides secure attachment for children to achieve their best developmental outcome. By making use of CCDS as a platform and with more resources, enhancement can be made by incorporating similar parenting programs to provide easy access to health resources and support to teenage mothers.

Biological factors such as parental intelligent quotient and history of breastfeeding may influence a child’s development. These could be included in future studies to determine their significance. By analysing each domain of development for longer period by formal assessment, potential risk and protective factors can be identified and timely interventions can be provided.

**Strengths and Limitations**

This is the first cohort study in Hong Kong studying the impact of teenage pregnancy on perinatal and developmental outcomes. This study covers certain socio-economic and cultural factors which is important in exploring outcomes that are biologically and socially affected. Through selecting cases with comprehensive follow-up under CCDS, the chance of missing data can be minimised. It also provides a brief insight into the negative impact of teenage pregnancy and the potential consequences it may lead to, hoping to alert the society for the implementation of adequate sexual education to reduce teenage pregnancies and provision of support programs for the families.

However, with the nature of this study being retrospective, it is prone to confounding factors. This study only covers data from a single centre and does not include different sociocultural backgrounds in such a diverse society. More samples from other centres can be included to provide a more comprehensive overview on the sociocultural impact. Although some socioeconomic factors have been included in this study, a more diverse variety for example parental substance abuse history, parental alcohol intake, parental educational level and social services received, can be explored in more detail in future studies for a better coverage. By extending the study for a longer duration and including more potential risk factors, the developmental progress can be monitored in more detail and can provide a better insight into how to prevent developmental delay in the group of at-risk teenage mothers.

**Conclusion**

Teenage pregnancy is associated with adverse neonatal outcomes, like preterm delivery. This may be due to biological immaturity or poor socio-economic status or a combination. Developmental delay is often found in children of teenage mothers and requires intensive support. It is essential to identify risk factors among teenage mothers and their families to provide better social support and appropriate education so that children will be able to cope with their everyday activities better.

**Ethics Approval**

This study was approved by the Kowloon Central / Kowloon East Cluster Research Ethics Committee of the Hospital Authority (KC/KE-18-0210/ER-2) and written informed consent was waived.

**Declaration of Interests**

Nil for all authors.

**References**

A Novel Homozygous PEX1 Pathogenic Variation in a Chinese Newborn with Zellweger Syndrome

S BIAN, Y CHEN, S LIAO, B HAO

Abstract

Zellweger syndrome (ZS) is the most severe phenotype in peroxisomal biogenesis disorders (PBDs). 14 Peroxin (PEX) genes have been identified to attribute PBDs, and about 70% of the ZS patients harbor gene mutations in PEX1. Recently gene mutation screening combined with clinical manifestations such as distinct facial features and congenital malformations is considered a suitable test for ZS patients. Here, a Chinese newborn patient with clinical features of ZS confirmed by molecular findings was reported. A novel pathogenic variation of the PEX1 gene was identified by exome sequencing. The patient is a homozygote of c.1671_1672delAG variation in the PEX1 gene and was inherited from her heterogenous parents, respectively. This variation leads to early termination of translation and produces a non-functional truncated protein. We report a novel pathogenic variation in the PEX1 gene, providing valuable information for genetic counseling and reproductive options.

Key words

Exome sequencing; PEX1 gene; Zellweger syndrome

Introduction

Peroxisomes are dynamic organelles that primarily involve in fatty acid metabolic pathways and contain hundreds of enzymes. Peroxisome disorders including single enzyme deficiency and peroxisome function and assembly defects, which lead to the rare autosomal recessive disorder, peroxisomal biogenesis disorder (PBDs), have highlighted the functional importance of peroxisomes in humans.1,2 About 80% of the patients with PBDs are Zellweger spectrum disorder (ZSD). According to the severity of clinical features, ZSD is classified into Zellweger syndrome (ZS), having the most severe phenotype, neonatal adrenoleukodystrophy (NALD), infantile Refsum disease (IRD) and Heimler syndrome.3,4 The manifestations are clinically heterogeneous, and the affected newborns and infants always have distinctive faces, congenital malformations, severe liver diseases, and die in the first year of life. But cases with milder phenotype only have progressive peroxisome dysfunction and can grow into teenagers or adults.5 Inherited gene mutations in fourteen PEX genes encoding Peroxin have been identified as the causes of PBDs. Nearly 70% of the ZSD patients harbour mutations in the PEX1 gene.1 PEX1 is located on chromosome 7q21-q22 and encodes a 143-kDa cytosolic protein that belongs to the AAA (ATPases associated with diverse cellular activities) protein family. Pex1p functions to recycle the PEX5 receptor and import proteins to the peroxisome matrix.6

In this study, we report a Chinese newborn with clinical features of ZS and identified a novel pathogenic variant of PEX1 (c.1671_1672delAG, p.G558fsX34) that were inherited from the patient’s parents.
Patient Description

This report involves a female newborn who was delivered vaginally with a birth weight of 3,100 g at 39+3 weeks of gestation to a 27-year-old native Chinese female (gravida 1, para 1). Pregnancy was complicated with polyhydramnios from 38 weeks. The baby was born with respiratory distress and needed oxygen administration. The Apgar scores were 6 at 1 minute, 9 at 5 minutes, and 9 at 10 minutes. The infant was hypotonic, neonatal seizures and dysmorphic features were noted, including widely spaced eyes and depressed nasal bridge. The parents were healthy, non-consanguineous, and no family history of any particular disease or mental retardation. The patient was their first baby.

Further workup revealed the patient had cloudy cornea with sluggish light reflex, large anterior fontanelle, about 5 cm x 5 cm in size. Her temperature was 32.5°C, pulse: 88 times/min, blood pressure: 62/35 mmHg. After the oxygen-absorption by nasal trachea, breathe 40 times/min, oxygen saturation (SPO2) 90%. She had no spontaneous breathing and activity. The physiologic reflexes such as embracing, sucking, grasping, or foraging reflexes were not elicited. Breath sounds were symmetrical but rough with moist rales. The heart sounds were low and recorded with cardiac murmurs. The hepatomegaly was palpable 3 cm below the costal margin.

Laboratory studies showed hyperbilirubinemia with a marked elevation in liver transaminases, which revealed liver dysfunction. Various biochemical indicators suggested the patient had severe neonatal pneumonia, impaired myocardium, neonatal asphyxiation, and respiratory failure shock. The chest radiograph showed the double lung texture got thickening and fuzzy, thymus participating in the enlargement of the heart. Head B-sonography revealed transparent septum was not closed, bilateral lateral ventricles cyst (Left 20.2 mm, Right 26.4 mm), and high signal of the white matter in the lateral ventricle. Head CT suspected intracranial hemorrhage. Echocardiography showed patent ductus arteriosus, aorta shunted from right to left, patent foramen ovale, room interval shunted from left to right, severe pulmonary arterial hypertension.

Considering the patient’s symptoms (Table 1), doctors treated her with symptomatic therapy, but her vital signs still couldn’t maintain stable. Until the 4th day of age, she died due to her patients’ choice of withdrawing treatment.

Exome Sequencing and Analysis

Genomic DNA extraction from the patients and their parents was extracted from the whole blood by column method. Exome sequencing was performed with the genomic DNA of the patient by using the SureSelect V5 capture kit (Agilent) and HiSeq 2000 sequencer (Illumina). After mapping to the reference human genome (UCSC hg19), the sequence data were sorted, merged, and analysed. We achieved an average percentage of >95% of

Table 1 Patient clinical features

<table>
<thead>
<tr>
<th>Feature</th>
<th>Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0 year</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
</tr>
<tr>
<td>Health care in pregnancy</td>
<td>Polyhydramnios at 38 weeks</td>
</tr>
<tr>
<td>Hyporeflexia</td>
<td>Yes</td>
</tr>
<tr>
<td>Dysmorphic features</td>
<td>Ocular abnormalities with widely spaced eyes, turbid cornea and sluggish light reflex; depressed nasal bridge; large anterior fontanelle and cranial joint dehiscence.</td>
</tr>
<tr>
<td>Head B-sonography</td>
<td>Transparent septum was not closed, bilateral lateral ventricles cyst and high signal of the white matter in the lateral ventricle.</td>
</tr>
<tr>
<td>Liver dysfunction</td>
<td>Yes</td>
</tr>
<tr>
<td>Mutation in the PEX1 gene</td>
<td>NM_000466:exon10:c.1671_1672delAG;p.Gly558fs</td>
</tr>
<tr>
<td>Treatment</td>
<td>Keep warm, intravenous nutrition, ventilator support, prevent bleeding, reduce intracranial pressure, protect liver, anti-infection, anti-shock and improve pulmonary hypertension.</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Died on day 4</td>
</tr>
</tbody>
</table>
Here, we described a Zellweger syndrome case with homozygous variation (c.1671_1672delAG) of the PEX1 gene, which was from heterozygous parents, respectively. The individual was hypotonic and had distinctive facial features of ZS patients, including a high forehead, widely spaced eyes, depressed nasal bridge, and sizeable anterior fontanelle. She is also characterised by developmental malformations of the brain, liver, and kidney.

Although the function of Pex1p is not fully elucidated, previous reports highlighted its essential role in peroxisome assembly and protein import. Pex1p contains PEX-2N, PEX-1N, and AAA domains (Figure 1c). PEX-2N and PEX-1N domains can interact with ubiquitin and proteins with a ubiquitin-like domain. The N terminal region is presumed to contain adapter binding sites allowing for peroxisome biogenesis. The AAA cassette is for ATP binding and ATP hydrolysis.7,8 The two base-pair deletions (c.1671_1672delAG) in the patient results in a frameshift at the 558 aa (p.G558fsX34). Sanger sequencing results confirmed segregation and revealed that the two parents are heterozygous, while the dead patient carried the same homozygous variant (Figure 1a and b). The mutation c.1671_1672delAG of the PEX1 gene had neither been reported before nor in the common genetic variation database. The p.G558fsX34 is predicted to be probably deleterious and disease-causing.

**Figure 1** The pedigrees and sequencing results of the family with PEX1 variation. (A) Sequencing results, the site of the variant was marked by arrows. (B) Family pedigree, the proband was indicated by arrow. (C) Schematic representation of the PEX1 structure showing the localisation of a novel homozygous PEX1 pathogenic variation, the p.Gly558fsX34.

**Discussion**

Here, we described a Zellweger syndrome case with homozygous variation (c.1671_1672delAG) of the PEX1 gene, which was from heterozygous parents, respectively. The individual was hypotonic and had distinctive facial features of ZS patients, including a high forehead, widely spaced eyes, depressed nasal bridge, and sizeable anterior fontanelle. She is also characterised by developmental malformations of the brain, liver, and kidney.

Although the function of Pex1p is not fully elucidated, previous reports highlighted its essential role in peroxisome assembly and protein import. Pex1p contains PEX-2N, PEX-1N, and AAA domains (Figure 1c). PEX-2N and PEX-1N domains can interact with ubiquitin and proteins with a ubiquitin-like domain. The N terminal region is presumed to contain adapter binding sites allowing for peroxisome biogenesis. The AAA cassette is for ATP binding and ATP hydrolysis.7,8 The two base-pair deletions (c.1671_1672delAG) in the patient results in a frameshift at the 558 aa (p.G558fsX34) and predicted to cause premature termination of translation and a truncated protein. Patients with this homozygous mutation generally suffer from severe peroxisome disorders such as Zellweger syndrome.
More than 114 different mutations have been identified in the PEX1 genes, including missense/nonsense mutation, splicing, small deletions/insertions/indels, and gross deletions/insertions/duplications (data from HGMD). Patients with milder phenotypes commonly harbour missense mutations, while nonsense, frame-shifts, and deletions mutations are more likely to be found in severe cases.\textsuperscript{5}

One of the weaknesses of our study is the lack of biochemical analysis. Impaired peroxisomes lead very-long-chain fatty acids (VLCFAs) and branched-chain fatty acids accumulation in tissues and decreased levels of docosahexaenoic acid. These metabolites are predicted to impair the development of the brain, liver, kidneys, and endocrine glands. However, the detection of these metabolites is not inevitable in making a diagnosis of ZS patients. Moreover, the metabolite assay is a technique that requires doctor's experience and can't make an accurate diagnosis. It was reported that VLCFA analysis is hard to dissimilate ZS with other phenotypes.\textsuperscript{9,10}

Exome sequencing has considerable potential in making a more accurate and comprehensive diagnosis for Zellweger syndrome. Our patient only received symptomatic treatment during her illness because there are no uniform guidelines for ZS treatment in China. As a result, our patient was in a dangerous condition and died early. This case is the first report of a Chinese newborn patient with the severe classic form of Zellweger syndrome caused by a novel mutation c.1671_1672delAG in the PEX1 gene using High-throughput exome sequencing. Our findings provide information for genetic counseling and prenatal diagnosis for the family members.

**Conflict of Interest**

The authors declare no conflicts of interest.

**Acknowledgment**

We thank the patient and her families for their collaboration. This study was supported by the National Natural Science Foundation of China (31970836 and 81801549).

**References**

Case Report

Expansion of Phenotype of Lanosterol Synthase-related Disease: A Case Report and Literature Review

S Ho, IFM Lo, HM Luk

Abstract

There are currently fewer than 14 reported families with members suffering from Lanosterol synthase (LSS)-related disease who presented with either cataract or hypotrichosis and non-obligatory mental retardation and/or ectodermal presentation. There is currently only one reported case with an intermediate phenotype of co-existing cataract and hypotrichosis. In this case report, we wish to illustrate a patient suffering from molecularly confirmed LSS-related disease with an intermediate phenotype. In addition, she also has ectodermal manifestations but without any intellectual disability.

Key words Epidermolytic; Cataract; Hyperkeratosis; Hypotrichosis

Clinical Report

The proband (Figure 1) was a 14 years old Chinese girl born at term after an uncomplicated pregnancy and delivery. Parents were non-consanguinous and phenotypically normal. There was no family history. She suffered from alopecia totalis since birth and developed generalised desquamation over the body and limbs (except hands and feet) at day 3-4 of life but had complete recovery at 2 months of age. At 6 months of age, she started to have recurrent episodes of desquamation that began at her fingertips and extended to involve her fingers and palms. Her toes and soles were also affected. Thick scales started to form with time and her fingers developed contractures. The clinical picture and biopsy findings were consistent with palmoplantar hyperkeratosis seen in ichthyosiform erythroderma. She also suffered from congenital cataract diagnosed at 2 months of age with lens extraction done. She had normal development and enjoyed good health otherwise. On physical examination, she had total alopecia with sparse eyebrows and eyelashes but her nails and teeth were normal. There were thick scales and desquamation over her hands and feet. There were mild joint contractures over the proximal and distal interphalangeal joints of all her fingers.

Investigations

Medical exome sequencing was performed on DNA extracted from peripheral blood of the patient. It revealed biallelic pathogenic variants in NM_001001438.2 (LSS): c.818G>A (p.Trp273*) [PVS1, PM3] and c.1025T>G (p.Ile342Ser) [PM2, PM3, PP3, PP5]. The c.1025T>G (p.Ile342Ser) missense variant was previously reported but the c.818G>A (p.Trp273*) nonsense variant was novel. Parents were asymptomatic heterozygous carriers. Both variants were classified as pathogenic according to the ACMG guideline. The diagnosis of LSS-related disease was substantiated. As LSS protein is involved in the cholesterol synthesis pathway, her blood cholesterol levels were tested and revealed no decrease in cholesterol levels or its intermediates.
Discussion

The LSS protein is involved in the biosynthesis of cholesterol, steroid hormones, and vitamin D. It catalyses the rate limiting step in the conversion of (S)-2,3-oxidosqualene into lanosterol. Mutations of the LSS protein have been reported to be associated with cataract (OMIM 616509) and hypotrichosis (OMIM 618275), both inherited in the autosomal recessive manner. There are also reported patients with intellectual disability and ectodermal manifestations.1

Cataract was the first described phenotypical presentation for LSS-related diseases. Two families with members suffering from cataracts were found to harbour homozygous mutation of the LSS.2 Subsequent in vitro and in vivo experiments proved that the LSS mutants failed to demonstrate any cyclase activity and led to a decrease in lanosterol production. The addition of lanosterol, on the other hand, helped reduce the intracellular crystalline aggregation and increase the transparency of the lens. The notion of LSS-related mutations could cause cataracts was therefore substantiated.

LSS mutations related hypotrichosis was reported by Romano et al in 2018.3 Three families suffering from LSS-related hypotrichosis simplex were described. LSS played an essential role in hair follicle biology by encoding the

Figure 1 The proband aged at 10 years old. (a, b) Facial views showing baldness and absence of eyelashes and eyebrows. (c) Palms with hyperkeratosis. (d) Soles with hyperkeratosis.
key enzyme in the cholesterol biosynthetic pathway. It was postulated by Romano et al\textsuperscript{3} that the mutations caused an intracellular mislocalisation of the LSS protein, leading to a degree of cell toxicity only capable of triggering hair follicle damage without disruption of other cholesterol pathways.

However, the notion of LSS mutation only capable of causing hypotrichosis was disproved when Besnard et al\textsuperscript{7} reported 7 unrelated families with members suffering from LSS-related alopecia and intellectual disability in 2019. In addition, affected individuals with LSS-mutations were also described to have variable ectodermal manifestations (e.g. ichthyosis and erythroderma), genital abnormalities (e.g. hypospadias, micropenis), visual or hearing impairment, variable neurological symptoms and abnormal MRI findings. The article concluded that defects in cholesterol biosynthesis could also lead to male genitalia anomalies and have neurodevelopmental implications.

To date, there were 13 reported families with members suffering from LSS-related diseases worldwide (Table 1). All of them have normal blood cholesterol levels except for one (Table 1). It was postulated there is an alternative pathway for cholesterol homeostasis.\textsuperscript{2} Affected members in the same family appear to consistently exhibit same phenotype (i.e. cataract, hypotrichosis with developmental delay or hypotrichosis without developmental delay).

However due to the limited number of families involved, whether this could extend to the conclusion of limited intrafamilial variation in expressivity requires further studies. Amongst all affected individuals with LSS-related disease, only one patient reported by Chen et al\textsuperscript{4} and our patient has the intermediate phenotype, with coexisting cataract and hypotrichosis. In addition to the intermediate phenotype, our proband also has epidermolytic ichthyosis, palmoplantar type, but without intellectual disability. Interestingly, our proband and the patient reported by Chen et al\textsuperscript{4} shared the c.1025T>G mutation. Whether this is a common mutation amongst the Chinese population and whether it contributes to a particular phenotype requires further studies. All the reported mutations appeared to be evenly distributed between the two terminals (Figure 2). It was proposed by Romano et al that the intermediate phenotype in Chen et al's reported patient might be related to the location of the respective nucleotide changes; with one variant in the N-terminus and the other more towards the C-terminus. However, in our patient, both variants were localised towards the N-terminus and thus disproves this hypothesis (Figure 2). Majority of the reported mutations were missense mutations although splice site variants and nonsense variants had also been reported as pathogenic. Further studies are required to arrive at genotype-phenotype correlations.

![Figure 2](image-url)  Schematic diagram of structure of the LSS protein and summary of all reported mutations.
## Table 1  Summary of clinical characteristics

<table>
<thead>
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<th>Family</th>
<th>1</th>
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<th>4</th>
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<th>6</th>
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<tbody>
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<td>Gender</td>
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<td>M</td>
<td>M</td>
<td>F</td>
<td>F</td>
<td>M</td>
<td>M</td>
</tr>
<tr>
<td>Consanguinity</td>
<td>✓</td>
<td>✓</td>
<td>×</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Family history</td>
<td>2 younger brothers</td>
<td>×</td>
<td>×</td>
<td>1 younger sister</td>
<td>1 elder sister</td>
<td>1 younger sister</td>
<td>1 elder brother</td>
</tr>
<tr>
<td>Cataract</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Hypotrichosis</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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</tr>
<tr>
<td>Ectodermal manifestation</td>
<td>N/A</td>
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<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
</tr>
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Compliance with Ethical Standards

Conflict of Interest
All authors have disclosed no conflicts of interest.

Informed Consent
Informed consent for publishing clinical photo and clinical information was obtained from proband and her parents.

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References
Case Report

A Rare Presentation of Cardiac Rhabdomyoma in Children: Sudden Cardiac Arrest

IO Sahin, SM Yucel, S Yüksel

Abstract

Cardiac rhabdomyomas are mostly asymptomatic. Although the mechanism has not been well characterised, cardiac rhabdomyomas can lead to ventricular tachycardia (VT). We report a case of cardiac rhabdomyoma in which the initial presentation was sudden cardiac arrest (SCA) due to VT. Previously healthy 16-year-old boy collapsed after he worked at farm. After successful resuscitation and cardioversion, he was admitted to the hospital. Non-sustained VT was detected on 24-hour Holter monitoring. Transthoracic echocardiography and magnetic resonance imaging showed a mass on the left ventricle apex. After surgical resection, Holter tests were completely normal. The histopathologic study confirmed the diagnosis of rhabdomyoma. Data regarding arrhythmias associated with cardiac rhabdomyoma are limited with small series. Management strategies include antiarrhythmics, cardioverter-defibrillator and surgery, but as to which strategy can be considered as optimal remains unclear. Benign cardiac tumours should be kept in mind as a cause of SCA in children and resection seems to be effective for treating associated VT.

Key words Cardiac rhabdomyoma; Children; Sudden cardiac arrest; Ventricular tachycardia

Introduction

Sudden cardiac arrest (SCA) in children is a rare, but dramatic condition. The incidence of SCA is approximately 0.013%, of which 30% of cases have present cardiac diseases. Common causes of SCA are structural cardiac lesions [cardiomyopathies, coronary artery diseases, myocarditis, congenital heart diseases, arrhythmogenic right ventricular dysplasia (ARVD), etc.], electrical abnormalities (long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia, Wolf-Parkinson-White syndrome Brugada syndrome, complete heart block, etc.) and acquired conditions (drugs/stimulants, chemicals, pulmonary hypertension). Primary cardiac tumours are usually benign and very rare in children with an incidence of 0.2%. However, they have the potential for haemodynamic compromise and life-threatening dysrhythmias. Herein; we present a case of benign cardiac tumour of which the initial presentation was ventricular tachycardia and SCA.

Case Report

A 16-year-old previously healthy boy collapsed on his way home by a tractor after he worked on a farm. The family immediately called emergency medical service (EMS).
Ventricular tachycardia (VT) was observed on the monitor of the cardioverter-defibrillator. After 10 minutes of resuscitation and cardioversion, the patient was admitted to the hospital.

The patient was intubated at admission. Heart rate, blood pressure, oxygen saturation values were within normal limits. After initial stabilisation and treatment in the paediatric intensive care unit (PICU), the patient was evaluated for possible cardiac diseases and arrhythmias.

Detailed medical history and physical examination results were unremarkable. There were no complaint of palpitation or palpitation-associated symptoms such as dizziness, shortness of breath, sweating, headaches and chest pain before and during the attack. Family history revealed no clues for SCA.

The electrocardiography (ECG) of the VT attack was seen on the monitor of the cardioverter-defibrillator but it was not documented during resuscitation. Chest X-ray and 12-lead ECG were evaluated at the PICU. Cardiothoracic index was 0.48 and there were not any clues of long QT syndrome, Brugada syndrome, short QT syndrome or other arrhythmias.

Past medical history, physical examination and baseline ECG of the patient were unremarkable. Pharmacologic treatment was initiated with propafenone and bisoprolol due to the suspicion of VT.

Twelve-lead twenty-hour Holter recording showed multiple ventricular ectopic beats and two unifocal monomorphic non-sustained VT attacks with a rate of 165 beats per minute, which did not cause haemodynamic compromise. The VT was compatible with left sided VT (right bundle branch block pattern, superior axis, QRS transition beyond V3).

Transthoracic echocardiography (TTE) was performed especially for the detection of HCM, ARVD, and congenital heart diseases, which are the most common causes of VT. Echocardiography demonstrated a homogeneous intramural left ventricular mass in the apex. There were not any echocardiographic findings of inflow or outflow obstruction of ventricles.

Cardiac magnetic resonance imaging (MRI) revealed a 2.5x1.5x1 cm, well-demarcated, firm intramural mass unrelated to the intraventricular structures. After gadolinium injection, late contrast-enhanced cardiac MRI images showed a homogeneous and intense bright mass, suggesting rhabdomyoma (Figure 1).

Ventricular tachycardia morphology suggested an origin at the left ventricular apex, coinciding with the cardiac tumour's location. The decision was taken to perform a complete surgical resection of the tumour and hence the mass was resected completely (Figure 2).

Holter recordings after surgery were normal and resection of the mass seemed to be effective for the elimination of VT. The histopathologic evaluation of frozen sections confirmed the diagnosis of rhabdomyoma. After surgery, the patient was evaluated by a paediatric neurologist for tuberous sclerosis and was found to be normal. Holter recording and treadmill test at the 6th month period after the operation were also found to be completely normal.

**Discussion**

SCA is an uncommon and critical condition. For effective management of SCA, clarifying the underlying problem is as important as a successful resuscitation. Cardiac causes of SCA are generally grouped into three categories: structural cardiac defects, primary cardiac electrical abnormalities and acquired diseases.\(^1\) Electrocardiography, TTE, and 24-hour Holter monitoring must be performed after a detailed medical history and physical examination. In the presence of problematic past medical history and ECG clues of arrhythmias, advanced genetic tests of arrhythmias should be planned to diagnose the underlying disease.

Initial TTE generally focusses on systolic cardiac functions, major cardiac defects, HCM and especially ARVD in case of VT suspicion. The echocardiographic evaluation of the patient was normal in terms of these diseases. Although the first 24 hours were uneventful in PICU, 24-hour Holter monitoring showed non-sustained left-sided VT attacks. Therefore, a second TTE was performed carefully and a homogeneous intramural left ventricular mass protruding to inferior was shown in the apex.

Biopsy and histologic assessment evaluation are the gold standards for confirmation of the diagnosis of tumours; although TTE or cardiac MRI imaging is usually adequate to facilitate the diagnosis of cardiac tumours. We planned a cardiac MRI to define the shape, diameter and location of the lesion. Cardiac MRI revealed a 2.5x1.5x1 cm, well-demarcated, firm intramural mass suggesting rhabdomyoma.

Primary cardiac tumours are rare with an incidence of 0.03-0.3% in children.\(^4\) Although the majority are asymptomatic, they can result in cardiac failure,
Figure 1  Protruding mass at the apical portion of left ventricle at MRI (white arrows).

Figure 2  Intraoperative pictures of cardiac rhabdomyoma.
intracardiac obstruction depending on the size and the location of the mass. Data regarding arrhythmias associated with cardiac tumours are limited with small series and case reports. With cardiac tumours, 24% of patients have clinically significant arrhythmias (16% ventricular tachycardia, 2% sudden cardiac arrest). Surprisingly, the patient did not show palpitation, dizziness, presyncpe-syncope, chest pain or any other cardiac symptoms before.

Management strategies for arrhythmias associated with cardiac tumours are pharmacologic treatment, cardioverter-defibrillator implantation and surgical excision; but as to which treatment strategy is optimal remains unclear. We started propafenone and bisoprolol to control cardiac rhythm before a decision of surgical procedure. Holter tests showed that non-sustained left-sided VT attacks persisted even though the patient was not sensing these. The ineffectiveness of antiarrhythmic treatment obligated a surgical resection. Arrhythmic events associated with cardiac tumours are known to be reversible with resection of the tumour.

Surgical resection was performed successfully. Holter tests after surgery were completely normal and resection of the mass seemed to be effective for the elimination of VT. The histopathologic evaluation of frozen sections confirmed rhabdomyoma diagnosis.

Finally, it can be stated that SCA in children is a rare, but dramatic, public health problem. Clarifying the cardiac cause is as important as resuscitating the patient. Unusually, a benign cardiac tumour could result in SCA especially as the first symptom. Surgical resection should be performed for serious VT or SCA related with cardiac tumours. Physicians should keep cardiac masses in mind as a cause of SCA and VT in children which can be treated successfully by the excision of the mass.

Financial Disclosure

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of Interest

All authors declare that they have no conflicts of interest.

References

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The Hong Kong Paediatric Society, Hong Kong College of Paediatricians, Hong Kong Paediatric Nurses Association, and Hong Kong College of Paediatric Nursing
30 October, 2021

Oral Presentation

Poster Presentation
Oral Presentation

Development, Implementation, and Evaluation of a Clinical Practice Guideline for Care of Preterm Infants Receiving Non-Invasive Ventilation: A Before and After Study

SY Chan, J Chau, KL Shu, B But, YM Yeung

Background: Nowadays, noninvasive ventilation is the mainstay of the ventilation strategy in the neonatal intensive care units (NICUs) and most of infants, especially preterm infants, having respiratory problems, are provided noninvasive ventilation (NIV) upon their demands. Nevertheless, complication of NIV device-related pressure injury was common, the incidence of nasal injury ranged from 20% to 60%. Limited studies were found evaluating the nursing care of preterm infants receiving NIV.

Aims: This study aimed to develop an evidence-based clinical practice guideline for preterm infants receiving NIV, implement the guideline in a NICU of a regional hospital, and evaluate infant outcomes including comfort, incidence of NIV device-related pressure injury. Besides, improvement on nurse's knowledge and practice for caring infants under NIV were assessed.

Study Design and Methods: The Iowa Model-Revised was adopted as the theoretical framework to guide the study process. A multidisciplinary workgroup consists of eight stakeholders in NICU was formed for the process and acted as the champions for the new practice. A before and after study design was adopted and included the pre-implementation and post-implementation phases. An integrative review was conducted to identify relevant studies from eight electronic databases before the study. All eligible studies were appraised using the Johns Hopkins University's evidence appraisal tool. Neonatal Pain, Agitation and Sedation Scale (N-PASS) for pain assessment and two self-developed NIV care bundle knowledge test and audit tool were used for the study.

Results: Due to the COVID-19 pandemic in 2020, the study was extended for a month and ended in January 2021. A total of 74 infants in Pre-implementation phase (before group) and 67 infants in Post-implementation phase (after group) were recruited. Logistic regression model was used to compare the incidence of pressure injury between groups after adjusted for all substantial covariates in the study. Infants in after group had an 84% decreased odds of acquiring pressure injury (adjusted OR=0.149, 95% CI 0.045-0.495, p=0.002). Infant's comfort level whilst receiving NIV was not determined in the study as the after group having a significantly lesser mean time (p<0.001) in calm state but lower N-PASS score.

Regarding nurse participants, 71 nurses received the training programme on NIV care bundle, and overall nurses' knowledge level improved immediately (adjusted p<0.001) and at 12 weeks after the programme. Three audits were conducted to evaluate nurses' practice, nurses' compliance rate to the care bundle significantly improved at 12 (p<0.001) and 24 weeks (p<0.001) in comparison with baseline compliance rate in the pre-implementation phase. However, nurses' knowledge retention at 12-week and compliance rate at 24-week after the training programme declined.

Conclusion: The evidence-based clinical practice guideline aims to promote comfort and prevent injury in infants receiving NIV, and outcomes of the infants depend on vigilant nursing care and compliance to this clinical practice guideline. Declining of nurse's knowledge level and practice compliance found in the study indicates the needs of continuous education and audit on the practice to sustain the service quality and patient's safety.

Surgical Intervention Reduces Long-Term Heart Rate Variability During Sleep in Children with Moderate-To-Severe OSA: A Secondary Analysis of an RCT

KTW Cheung, NHY Chow, KCC Chan, AM Li, CT Au

Background: Childhood obstructive sleep apnoea (OSA) is associated with heart rate variability (HRV) but there is no randomised controlled trial to evaluate the effect of OSA treatment on HRV in children.

Purpose: To investigate the effect of surgical intervention on HRV in children with OSA.

Methods: A prospective randomised controlled study was performed in non-obese pre-pubertal children aged 6 to 11 years with polysomnography (PSG) confirmed moderate-to-severe OSA. They were assigned randomly to early surgical intervention (ES) or watchful waiting (WW). The surgical intervention consisting of tonsillectomy with or without adenoidectomy and turbinate reduction was
Acute Kidney Injury in Relation to Nephrotoxic Medication Use Among Critically Ill Children in the Paediatric Intensive Care Unit (PICU)

YPY Chan,1 WF Hui,2 VKW Lok,1 HK Tse,1 C Wong,1 SM Wong,1 KL Hon,2 MH Poon1

1Department of Pharmacy; 2Department of Paediatrics and Adolescent Medicine, Hong Kong Children's Hospital, Hong Kong SAR

Background: Children in the Paediatric Intensive Care Unit (PICU) are vulnerable to acute kidney injury (AKI) and due to the complex nature of the disease, they are often exposed to multiple medications which may individually or in combination have the potential to cause addition risk for renal injury.

Purpose: We presented the result of the interim analysis of an ongoing prospective cohort study on the potential association between nephrotoxic medications and the risk of developing AKI in critically ill children admitted to PICU of Hong Kong Children's hospital (HKCH).

Method: Patients were included if they were aged >1 month to ≤18 years of age and admitted to PICU of HKCH since 6/2020. Patients were excluded if they had pre-existing chronic kidney disease or impaired renal function for ≥3 months prior to PICU admission or admitted for post-renal transplant. The medication records from 14 days prior to PICU admission to PICU discharge would be retrieved and reviewed by an independent pharmacist to determine the number and doses of nephrotoxic medications exposure in relation to the development of AKI. The results of the initial four months of data would be presented.

Findings: A total of 62 patients with 63 admissions fulfilling the study criteria were identified. The overall incidence of AKI during PICU stay was 48.4% (Stage 1: 20.3%; Stage 2: 12.5%; Stage 3: 15.6%). 76.6% of the patients were exposed to one or more of 43 nephrotoxic medications. Altogether 17 (48.5%) of patients with AKI received nephrotoxic medications before development of AKI. The median number of nephrotoxic medication exposure was 1.5 (1, 3). The total medication doses received was 9.5 (1.0, 31.8) doses. Children with AKI were associated with significantly higher nephrotoxic medication exposure during the PICU stay. Patients with AKI received a significantly higher total number of nephrotoxic medications (3 vs 1 medication, p<0.01) and a higher total dose of nephrotoxic medications (21.5 vs 1.0 doses, p<0.01) than those without AKI. Furosemide, vancomycin and co-trimoxazole were the three nephrotoxic medications with the highest total administered doses. Cyclosporine A, foscarnet and ganciclovir were only given to those who had developed AKI.

Conclusion: AKI was commonly encountered among critically ill children in PICU. Critically ill children received a higher number and doses of nephrotoxic medications are at a higher risk of developing AKI. These patients should be monitored frequently and judicious use of nephrotoxic medications should be encouraged.

Unrevealing Parental Mosaicism: The Hidden Answer to the Recurrence of Apparent De Novo Mutations

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Background and Purpose: Mosaicism refers to the co-existence of two or more genetically distinct cell populations in an individual from a single fertilised egg. Previous literatures estimated the percentage of parental mosaicism in rare diseases to be 4-8% (Myers et al., 2018...
Methods: Parents whose children had previously diagnosed with neurodevelopmental disorders with an apparent de novo variant identified through trio sequencing are being recruited (N=15). Blood, buccal swab, and semen sample are being used to detect potential parental mosaicism by sanger sequencing and droplet digital PCR, complemented with the blocker amplification method when possible.

Findings: We report here 2 positive results that demonstrated asymptomatic parental mosaicism with 2 mechanisms: (1) Somatic mosaic mutation is observed in the father of two affected fetus with CHARGE syndrome. The splice site variant CHD7:c.7164+1G>A was found in both affected fetus and in the semen of the father but not detected in paternal lymphocytes. Such mutation might have arisen during spermatogenesis due to paternal age effect, given the age of father at conception is already 36 years old. (2) Gonosomal mosaic mutation in FLNC: c.4916G>A (p.Cys1639Tyr) is observed in the semen, buccal and lymphocytes of the father of two children with restrictive cardiomyopathy, demonstrating that the mutation had arisen from early embryogenesis.

Conclusions: Obtaining the right sample type and implementing sensitive detection method to identify mosaicism is currently limited but of great importance. Carrying a hidden mutation in the germ cells will have an impact on reproductive risk for next pregnancies, which could have a recurrence rate of as high as >50% (Shu et al., 2021).

Acknowledgement: This study is supported by the Society for the Relief of Disabled Children and the Seed Funding for Basic Research (201910159064) from the University of Hong Kong.

Incidence and Outcome of Electrolytes Disturbances Among Critically Ill Children

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Introduction: Electrolyte disturbances are common yet overlooked conditions in paediatric critical care. The local incidence and outcome of electrolytes disturbances among critically ill children are largely unknown.

Purpose: We described the epidemiology of electrolytes disturbances among children admitted to the paediatric intensive care unit (PICU) of the Hong Kong Children's Hospital. This is the interim analysis of the prospective cohort study (E-AKI-DRUG) conducted in our PICU.

Methods: All children aged 1 month to 18 years old would be enrolled. Exclusion criteria included those with pre-existing chronic kidney disease, impaired renal function for ≥3 months, immediate post-renal transplant and short PICU stay of ≤1 days. AKI would be defined using the KDIGO criteria. The serum electrolytes profiles on sodium, potassium, calcium, phosphate and magnesium were reviewed. Appropriate urinary investigations were performed to look for tubular dysfunction among those with electrolytes disturbances. The data of initial four months would be presented.

Findings: We identified 63 episodes of admission for analysis. 59% were male and the median (interquartile range) age was 6.1 (6.6) years old. 49.2% of patients had an oncological diagnosis and 9.5% were recipient of bone marrow transplantation. The median number of types of electrolytes disturbances was 4 (3) types. Hypophosphatemia (85.5%), hypocalcaemia (77.4%) and hypokalaemia (61.3%) were the three types of electrolyte disorders with highest incidences. Children with AKI (p<0.001), requiring inotropic support (p<0.01) and mechanical ventilation (p<0.01) had higher number of electrolytes disorders. Tubular dysfunction was common among children with electrolytes disturbances. The proportions of children with urinary wasting of potassium (25%), phosphate (50%) and magnesium (87.5%) were high among those with hypokalaemia, hypophosphatemia and hypomagnesaemia. Abnormal urinary beta-2-microglobulin (median level of 0.9 [5] μg/ml) occurred in 64.7% of children with ≥2 types of electrolytes disturbances. Tubular dysfunction may occur independent of AKI as various urinary indices showed no significant difference between those with and without AKI. The number of electrolytes disturbances were associated with increased duration of ventilation (p=0.011) and PICU length of stay (p<0.001) and higher risk of PICU mortality (relative risk 4.3 [95% CI 1.4, 12.7]).

Conclusion: Electrolytes disturbances were common among critically ill children and may contribute to PICU morbidity and even mortality. Proximal tubular dysfunction was associated with multiple electrolytes disturbances.
Relationship Between Eczema Severity and Skin Microbial Biodiversity and Compositions in Hong Kong Infants

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Background: Eczema is the commonest chronic skin disease in children. Skin microbiome modulates the susceptibility and severity of childhood eczema, but there is limited data on its role for eczema severity in infants.

Objective: To characterise early-life skin microbial profiles and its effect on infantile eczema.

Methods: This birth cohort followed 120 Chinese infants at 1, 6, 12 and 24 months. Eczema diagnosis was made according to Hanifin and Rajka criteria, and severity was assessed using SCORing Atopic Dermatitis (SCORAD). Patients with objective SCORAD ≥15 were categorised as having moderate-to-severe eczema. Serial skin swabs taken at left antecubital fossa were subjected to 16S rRNA sequencing, and differentially abundant taxa for eczema phenotypes were analysed by Analysis of Compositions with Bias Correction.

Results: Twenty-nine, 29, 7 and 3 subjects in this cohort had moderate-to-severe eczema at 6, 12 and 24 months respectively. Compared with mild eczema at 24 months, patients with moderate-to-severe eczema had lower alpha diversity of skin microbiome at 6 months as indicated by Shannon (P=0.03) and Simpson (P=0.03) biodiversity indices. The relative abundances of Janibacter (adjusted P<0.001) and Acinetobacter (adjusted P<0.001) at 1, 6 and 12 months were consistently lower in patients who had moderate-to-severe eczema than those with mild eczema at 12 and 24 months old.

Conclusions: Skin microbial biodiversity and compositions during infancy may predict the presence of moderate-to-severe eczema by 24 months in Chinese toddlers. (Fund by Health and Medical Research Fund [reference no. 06170466])

Identification of Common Variants in Vitamin D Binding Protein (GC) and Vitamin D Receptors (VDR) in Affecting Serum 25(OH)D Level in Han Chinese Healthy Infants and Toddlers

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Background: Infancy represents an important period of development and vitamin D plays an essential role in it. Hypovitaminosis D is associated with long-term health issues and diseases development in children and infants. Recent findings in Vitamin D genetics illustrated an important role in determining serum 25(OH)D concentration, with genes controlling vitamin D metabolic pathway. Specifically, GC gene and VDR gene, encoding the vitamin D binding protein and vitamin D receptor are both involved in vitamin D metabolism and found to be associated with serum 25(OH)D. While associated key environmental factors have been extensively identified in children, adolescent and adults, the effects of genetic variation in relation to the serum vitamin D in Han Chinese infants warrant further exploration.

Objective: This study aimed to examine the effects of genetic variability in vitamin D binding proteins (GC) and vitamin D receptor (VDR) on the serum 25(OH)D levels among Chinese infants. A local set of hypovitaminosis D risk haplotype will be constructed to lay down the genetic basis specifically for the infants.

Method: Stratified random sampling was adopted to recruit infants and toddlers aged 2 to 24 months in the period of 1 June 2019 to March 2021. DNA was extracted from the collected whole blood samples and genotyping was performed by allelic discrimination and validated by Sanger Sequencing. Serum 25(OH)D was measured by Liquid Chromatography Tandem Mass Spectrometry (LC/MS-MS) and the measurement accuracy passed the proficiency testing of Vitamin D External Quality Assessment Scheme (DEQAS) by Endocrine Laboratory, London, UK.

Results: A total of four single nucleotide polymorphisms were genotyped among 243 infants. GCrs7041 and rs2282679 were significantly associated with serum 25(OH)D levels in Hong Kong infants, in which GCrs7041T and GCrs2282679C were identified as risk alleles. Further analysis on VDBP haplotype (rs7041-rs4588) revealed that the VDBP protein isoform GC1F was significantly associated with lowered 25(OH)D levels in the combined haplotype manner and GC1S demonstrated with the highest
Tetraspanin CD9 Drives Immune Evasion and Disease Progression in Paediatric Acute Myeloid Leukaemia

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Introduction: We have previously reported that long-term survivors of childhood cancer in Hong Kong demonstrated low awareness in treatment-related late effects. There is emerging evidence in the Western literature that demonstrated improved health literacy in this population after the provision of a survivorship care plan.

Methods: We recruited survivors (or caregivers) diagnosed with cancer before 18 years old and were ≥2 years post-treatment. Upon recruitment (T0), we assessed the awareness of their own cancer diagnosis, treatment history, and treatment-related health risks using a structured questionnaire. We then provided a personalised treatment summary and counselling on the potential therapy-related late effects as per the Children's Oncology Group guidelines. The participants' cancer-related knowledge was assessed again at 1-month post-intervention (T1). The Wilcoxon signed-rank test was conducted to evaluate changes in cancer-related knowledge scores from T0 to T1.

Results: The intervention was administered to 185 survivors (67.4% hematological cancer; current age 18.6 [SD=6.6] years old; range: 4 to 38 years) who were 9.0 [SD=5.0] years post-treatment. The current analysis included 82 participants (44.8%) who completed post-
AI-Driven Delineation of Distinct Phenotypes Associated with N-Terminal Truncations of the MN1 Gene - Beyond a New Syndrome Discovery from Hong Kong

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Background: MN1 C-Terminal Truncation (MCTT) syndrome is a rare autosomal dominant disorder characterised by intellectual disability, mid-face hypoplasia, severe expressive speech delay, and an atypical form of rhombencephalosynapsis (Mak et al. Brain 2020 and GeneReviews9). The MN1 gene is comprised of only two exons. Individuals with distinct features of MCTT harbour truncating variants at the C-terminal (within exon 2 or the last 55bp of exon 1), which are predicted to escape nonsense-mediated decay (NMD). Individuals affected by N-terminal (MNTT) truncations (predicted to induce NMD) have milder developmental phenotypes than MCTT patients.

Methods: Since our discovery of the syndrome, an expanded clinical case series was recruited to review 45 subjects (mean age 12.9, range 2-44) from North America, Europe and Asia. We performed deep phenotyping on patients affected by MNTT (n=13) and MCTT (n=32) mutations both clinically and using AI-based facial recognition software GestaltMatcher (Hsieh et al.). GestaltMatcher trains deep convolutional neural networks on 22,619 frontal images with 299 different rare disorders to learn the facial features, and it further converts facial images into feature vectors to form a Clinical Face Phenotype Space. The facial syndromic similarities among the patients are quantified by cosine distance in this space.

Results: Delineation of phenotype both clinically and by GestaltMatcher identifies two distinct groups when comparing MNTT with MCTT. Clinically, patients with MNTT have unique facial features, a disproportionate abundance of cleft palate (33% vs 7%) and conductive hearing loss (82% vs 35%). Compared to the MCTT group where 33% of individuals with MCTT rely on non-verbal communication only, and the remaining expressing first words at the mean age of 4.03 (range 2-6.75 years). Speech delay is less severe in the MNTT group with mean age first words at 2 (range 1.3-3 years). The distinction of MNTT and MCTT is supported by GestaltMatcher where clustering of MNTT and MCTT facial gestalt is observed and delineates from other syndromes in an unsupervised manner. Using this approach, GestaltMatcher also helps identify atypical cases where the phenotype does not follow the predicted rule of NMD.

Conclusions: Truncating mutations can have a region-specific effect on phenotype. Supported by AI-based approaches, MNTT and MCTT are two distinct facially recognisable syndromes in the same gene and are distinct from other known syndromes.

Acknowledgement: This study is supported by the Society for the Relief of Disabled Children.

Enhanced Pain-Management for Children Undergoing Cleft-Palate Repair to Shorten the Length-of-Hospital-Stay

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Standardised enhanced pain-management program after palatoplasty was implemented as collaborative Enhanced-
Recovery-After-Surgery project, promoting early discharge postoperatively.

**Purpose:** To provide an interim-review of the 'ERAS-effectiveness' of this enhanced pain-management program after palatoplasty.

**Methods:** Setting-up standardised postop-medication protocol for analgesia (+ antibiotics)
- Post-op-Day(POD)0-1: regular IV-Paracetamol + PR-Diclofenac (+ IV-Esmeprazole)
- POD2+: regular PO-Paracetamol and Ibuprofen (+Famotidine). If unfeasible oral route, continue IV-Paracetamol + PR-Diclofenac
- Rescue analgesic for breakthrough pain: IM-/PO-Tramadol (+ Ondansetron)

All patients undergoing palatoplasty after program implementation were prospectively included. Parents were given questionnaires to chart pain-score, vomiting, feeding-tolerance and need of extra analgesics on POD0-3.

**Findings:** Fourteen patients recruited, 14 questionnaires received.
- 64% reported minimal/mild pain only on POD1. 78% tolerated oral-fluids on POD1. 78% discharged on POD2/3. Nil reported significant breakthrough pain. All parents expressed satisfaction towards pain-control and early discharge.
- 57% reported moderate-to-severe pain with no rescue medication given.

Hypotheses:
- Parents unaware of available rescue medication
- Reluctant/afraid about extra analgesics
- Nurses could not identify correct timing for rescue analgesic for breakthrough pain
- Promulgation/education on using rescue medication is important, to both parents and nurses

**Conclusions:** This project aims to enhance recovery after palatoplasty in children. Preliminary review suggests the pain-protocol shortens LOS by expediting adequate feeding via optimal pain-control. Future improvement measures and further studies to substantiate findings are considered.

**Validation of the Sonographic Measurement of Lateral Parapharyngeal Wall Thickness in Children**

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**Background:** Lateral parapharyngeal wall (LPW) thickness is a potentially useful anatomic marker of childhood obstructive sleep apnoea (OSA). Measuring LPW thickness by ultrasonography (USG) is technically feasible but its validity has not been verified in children.

**Purpose:** To assess the intra- and inter-operator reliability of the sonographic measurement of LPW thickness in children and to validate the measurement against MRI measurement.

**Methods:** Prepubertal children aged 6-11 years with suspected OSA were recruited. Using USG, LPW thickness was measured as the distance between the internal carotid artery and the echogenic surface of the pharynx in an oblique coronal plane. The measurement was repeated on the same day by the same operator twice and by another operator. By MRI, oblique dimension of LPW was measured at the retropalatal level. Intraclass correlation coefficient (ICC) was used to examine the intra- and inter-operator reliability. The agreement between the LPW thickness measured by USG and MRI was assessed by ICC and Bland-Altman plot.

**Findings:** Thirty-two children (mean age: 8.83±1.58, 25 male) were recruited. The intra- and inter-operator reliability of the LPW thickness by USG were good (ICC = 0.91 and 0.84, respectively). The agreement between the USG-measured and MRI-measured LPW thickness was acceptable (ICC = 0.65). The Bland-Altman plot demonstrated a mean difference of 0.075 cm and a 95% limits of agreement from -1.10 to 1.25 cm.

**Conclusions:** The sonographic measurement of LPW thickness in children demonstrated good intra- and inter-rater reliability and acceptable agreement with MRI measurement. Ultrasonography is a valid method to assess LPW thickness in children.

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The Impact of Nusinersen Treatment on Musculoskeletal Progression in Patients with Spinal Muscular Atrophy

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Background: Spinal muscular atrophy (SMA) is a neuromuscular condition associated with multiple comorbidities. Scoliosis and hip instability are common due to progressive deterioration and imbalance in muscle strength.

Purpose: Nusinersen, an intra-thecal delivered medication to treat SMA, has documented effects on improving strength and motor function. However, there is no published literature regarding the long term effects of nusinersen on scoliosis progression and hip instability. Our study aims to evaluate musculoskeletal progression of SMA patients after nusinersen treatment.

Methods: Under the current IRB approved prospective study, detail demographic and clinical information is gathered to document clinical outcome of all SMA patients undergoing nusinersen treatment. We excluded those who received surgery for the hip and/or spine within the study period. For all patients, scoliosis X-ray series were taken before the starting of nusinersen treatment and at regular intervals every 6 to 9 months. Cobb's angle was measured and average rate of progression per year post nusinersen treatment was calculated. For hip instability assessment, baseline X-rays taken at pre-nusinersen screening were compared to the latest in-patient X-rays using Reimer's migration index (RMI). Clinically significant changes were defined as 1) if hip changes from reduced to subluxed or dislocated and from subluxed to dislocated, 2) if RMI was <0.5 and progressed to >0.5, or 3) if RMI was >0.5 and progressed to >0.8.

Findings: By June 2021, a total of 24 SMA patients have started on nusinersen treatment in our institution. Sixteen patients had scoliosis in their latest X-rays and 1 was excluded due to a short follow-up period. The median age of patients was 8.0 years (range 2.2-18.0 years). The average follow-up period was 27 months (range 15-47 months). At baseline prior to nusinersen treatment, scoliosis was present in 5 out of 6 SMA type 1 patients, 4 out of 7 SMA type 2 patients, and 2 out of 2 SMA type 3 patients. At final follow-up, 3 out of 5 SMA type 1 patients experienced curve progression, whilst 2 patients remained stable; all 4 SMA type 2 patients had progressed; and both SMA type 3 patients had curve progression. The average rate of Cobb's angle progression for type I patients was 6.9 degrees/year, type II patients was 13.6 degrees/year, and type III patients was 5.2 degrees/year. Eighteen patients were included for hip analysis. Those who did not have a hip X-ray for comparison after the loading doses of nusinersen and those who underwent surgery were excluded. The median age of patients was 7.9 years (range 2.1-26.7 years). The average follow-up period was 22 months (range 14-36 months). RMI progressed in 10 out 16 hips in SMA type I patients, 7 out of 16 hips in SMA type II patients, and 2 out of 4 hips in SMA type III patients. In hips with RMI progression, 4 were clinically significant in type I, 3 were clinically significant in type II, and none were clinically significant in type III.

Conclusion: SMA patients treated with nusinersen show significant musculoskeletal progression, particularly in the more severe, non-ambulatory group. SMA patients on nusinersen should be placed on closer monitoring for scoliosis progression and hip instability. More aggressive interventions should be considered. Large scale studies with longer follow-up periods are warranted to confirm the findings of this study.

Investigating the Health-Related Quality of Life of Rare Disease Patients in Hong Kong

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Background: Rare disease (RD) affects less than one in 2,000 individuals, often causing life-long physical or intellectual disability. In Hong Kong (HK), approximately 470 types of RDs were identified, affecting one in 67 people. Nonetheless, the health-related quality of life (HRQoL) of RD population as a group was never reported in HK.

Purpose: To investigate the HRQoL of RD patients in HK.

Methods: EuroQol 5-Dimension (EQ-5D) was used to describe HRQoL. RD patients and caregivers were
recruited through Rare Disease Hong Kong, the largest RD organisation in HK, between March and October 2020. The five health dimensions assessed were usual activities, pain/discomfort, mobility, anxiety/depression, and self-care. Utility scores were generated with reference to the HK value set. Meta-analysis was conducted using a random-effect model for studies investigating the HRQoL of RD patients using EQ-5D.

**Findings:** Overall, 289 independent participants were recruited, covering 116 unique RDs. The mean age was 31.6 (S.D. 19.8), where 30.8% were patients ≤18 years. The mean utility score of patients was 0.52 (S.D. 0.36), with 10.4% reported negative scores indicating worse-than-death health states. Patients with rare neurologic diseases had significantly lower mean scores than other patients (p<0.001). Comparing to existing literatures, RD patients had significantly lower mean utility scores than the general population (0.92), patients with diabetes (0.87), hypertension (0.88), heart disease (0.88), and cancer (0.87) in HK. Caregivers of RD patients also reported significantly lower utility scores compared to the HK general population (0.80 vs 0.92). In the meta-analysis including 6 studies comprising 2395 patients, the pooled mean utility score was found to be 0.58 (95% CI 0.47-0.69, I² 98.8%).

**Conclusions:** This is the first study in HK to illustrate the significant impact of RDs on HRQoL, which warrants exceptional care from policy makers and society.

**Acknowledgement:** We would like to thank the Society for the Relief of Disabled Children for their funding support, and all patients and care-givers who participated in this study.
Poster Presentation

The Establishment and Benefit Impact of Donor Milk Bank of Hong Kong University Shenzhen Hospital: 8 Months Experience

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Background: Mother's own milk (MOM) is the best choice for preterm infants and sick neonates. When MOM is not available or not enough, donor milk can be an alternative.

Purpose: To integrate the benefit and experience in establishing a Human Donor Milk Bank (HMB) in the Hong-Kong University ShenZhen Hospital to promote nutrition status and exclusive breastfeeding rate.

Method: A multidisciplinary team was established to prepare and manage the HMB. To ensure the safety of human donor milk, we adopted guidelines from Human Milk Banking Association of North America (HMBANA) and operation standard issued by the dietitian society of China. Several critical control points were identified for close monitoring including donor recruitment and donor milk pasteurisation. All donor milk can be traced back for its donation and processing information, such as name of donor, donor's virology status, date of donation, mode of sterilisation and handling staff etc.

Findings: Total 256 mothers donated 13,2800 mls of donor milk since operation of the HMB. Twenty-eight infants with mean GA of 30+2 weeks (SD±40.15 days) and mean birth weight 1510.93g (SD±948.27g) in NICU received donor human milk during hospitalisation, 82.14% of whom were VLGA. The average length of stay was 38.54 days (SD±32.54 days). An increased in the exclusive breastfeeding rate upon discharge was observed before and after the operation of HMB from 13% to 40%.

Conclusion: Through establishment of human milk bank and maintain a safe and sustainable management system is an important means to promote breastfeeding.

Implementation of a Family-Centered, Multidisciplinary Clinic for Early Diagnosis of Neurodevelopmental Impairment and Cerebral Palsy of Critically Ill Preterm Neonates in Shenzhen, China

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Aim: To compare the time to diagnosis of neurodevelopmental impairment (NDI) and cerebral palsy (CP) in preterm neonates (<29 weeks) at a Multidisciplinary Assessment and Care (MDAC) clinic with that of a conventional high-risk infant follow-up clinic.

Methods: All eligible surviving preterm neonates born at <29 weeks gestation at the University of Hong Kong-Shenzhen Hospital between January 2015 and December 2019 were followed up in conventional (2015-2017) and MDAC (2018-2020) clinics up to 2 years of corrected age with clinical demographic information collected in a prospective database. The MDAC team used standardised developmental assessments. The rates and timing of diagnosing NDI and CP in two epochs were compared.

Results: The rates of NDI and CP were not different in two epochs (NDI: 12(50%) vs. 12(41%); CP: 3(12%) vs. 2(7%) of 24 and 29 surviving infants assessed in conventional and MDAC clinics, respectively). Infants followed up in the MDAC clinic were diagnosed with NDI and CP earlier than those in the pre-MDAC epoch (6 vs. 14 months corrected age, respectively, P<0.05).

Conclusion: High-risk preterm neonates can be followed more effectively in a family-centered, child-friendly multidisciplinary clinic leading to an earlier diagnosis of NDI and CP. Early counselling and interventions could be implemented accordingly.
Use of Different Device in Handling Haemodialysis Catheter to Streamline the Procedure Time and Catheter Revision Rate

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Introduction: Different from adult renal patients, cuff central venous haemocatheter (CVC) are majority used in children on chronic haemodialysis (HD) in Hong Kong. A bundle of strategies is used to minimise the rate of central line- associated blood stream infection (CLABS), thrombosis and catheter malfunction. In the past, a sterile reusable renal set and blind-end device is used to capped the CVC with prescribed anti-coagulant. Since the year 2020, A needle-free capping device (Tego connector, TC) was introduced to the current practice. After each HD session, a sterile disposable dressing set and a TC was use to cap the CVC. The current study was to compare the past and new practice of cap device in a haemodialysis center so to improve the patients' comfort and the procedure cost.

Methodology: The study was conducted from 1/3/2020 till 28/2/2021. The patients' inclusion criteria were those patients with a cuff CVC and the exclusion criteria of the study were those patients' CVC are incompatible with TC and arterial- venous fistula. The catheter function such as any blockage, thrombosis formation and rate of CLABS was reviewed every HD session by renal nurses and monthly medical review.

Result: Total 14 patients were recruited in the study period. Eight female and 6 males whose age range was 3 years - 31 years. The CLABS was remaining zero between two devices. No clot formation inside the catheter lumen and connector dislodgement was not detected after using the TC. The catheter revision rate in patients using TC was lower from 1.0 to 0.71 per 1000 catheter days as compared with using the blind-end capped. The current study showed a better catheter survival rate than the McAfree & Seidal study (2010) in USA 0.78 per 1000 catheter days. The disinfection procedure using a sterile disposable dressing set at the end of the HD session was reduced from 15 minutes to 10 minutes in each patient. It implies that the paediatric patients no need to hold the same position in every HD session for more than 15 minutes. In fact, holding same position for was not easy especially the younger age patients. Total nursing time saved was 174 hours in the study period. Furthermore, there are 40% decrease the usage of sterile reusable renal set which replaced by sterile disposable dressing set. It implies to save the administrative cost to handle sterile set from Sterile Supply Unit (SSU), ward manual daily checking.

Conclusion: In the study, the change of practice using TC for HD paediatric patients could promote the patients' comfort to reduce the time of holding same position during the HD therapy and the cuff CVC survival rate. The change of practice also streamlines the procedure time and decrease the administrative cost in handling reusable set.

A COVID-Adapted Neonatal Resuscitation Workshop for Teaching Neonatal Resuscitation – A Regional Hospital’s Experience

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Background: A good and effective neonatal resuscitation training (NRT) program is important for retaining skills and achieving good outcome. A stimulation based Neonatal Resuscitation Workshop (NRW) has been held quarterly for Paediatric, Obstetric and Emergency Department trainees since 2011. The NRW was suspended since July 20 due to COVID-19 pandemic. A web-based COVID-adapted NRW (CaNRW) was developed in January 21 to achieve the objectives of providing NRT and abiding infection control measures.

Methods: A CaNRW was developed with the Multi-Disciplinary Simulation and Skills Centre (MDSSC), Queen Elizabeth Hospital in January 21. It consists of a 1-hour lecture delivered in YouTube; a 1-hour video on skills and a birth related drill performed at MDSSC. All trainees participate it online except those involved in the drill. Trainees can join the drill and debriefing online simultaneously. Upon competition, they were asked to complete an evaluation.

Results: Total 113 trainees joined three CaNRW in 21. Trainees didn't report difficulties in viewing. Facilitators felt more comfortable in executing this CaNRW. Seventy-three evaluations were analysed. Trainees reported this CaNRW was useful with high level of satisfaction (Score: 4.41/5). Trainees strongly recommended it to their colleagues (Score: 8.53/10). Nurses and midwives were granted Continuous Nursing Education and PEM credits respectively.
Conclusions: This innovative web-based CaNRW provides a simple and structured model for NRT during COVID-19 pandemic. Trainees welcomed and enjoyed it. Thus, this CaNRW is worth promoting and should be made available to more trainees and departments. More studies should be performed to testify its clinical values.

Measuring Compliance to Ketogenic Diet Among Obese Children and Adolescents

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Background: Ketogenic diet, low in carbohydrate and rich in fat, have been used for weight loss but compliance is challenging among obese children and adolescents. Assessing compliance is important for evaluating its effectiveness.

Purpose: To review reported compliance to ketogenic diet among obese children and adolescents.

Methods: A systematic search for literature was performed using PubMed to identify intervention studies on the effect of ketogenic diets among obese children or adolescents. Additional hand search was performed. Full text studies in English with primary data on compliance to ketogenic diet (claimed ketogenic or very-low-energy diet) were included. Subjects' characteristics, dietary prescription, duration, use of pre-made food, frequency of dietitian counselling, instructional menus, family involvement, self-reported side-effects, measures of compliance, calculated compliance and retention rate were extracted.

Findings: Eight papers are included. Majority were carried out in the U.S. on 6-to-18-year-old subjects. Intervention periods ranged from 6 weeks to 6 months. Recommended carbohydrate content was 10-60 grams per day. Four studies also limited fat and/or protein consumption. Subject retention rate was 57-100%. Most had weekly or bi-weekly dietitian counselling. Side effects including constipation, nausea and headache were generally mild and infrequent. One study provided pre-made food which seems to increase compliance (62.5%). Studies mainly used food records to measure compliance with 1 using >5% weight loss and 4 monitoring urinary/blood ketones.

Conclusions: Assessing the compliance to ketogenic diet is important in clinical studies and yet complicated. More convenient assessment of ketosis is required for design and analysis of studies on ketogenic diet.

Proactive Intervention Program for Pregnant Ladies with Substance Abuse at Antenatal Period

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Background: Multidisciplinary case conferences (MDCC) will be conducted for every newborn with positive urine result of illicit drugs since 2016. Moreover, court hearing for care or protection order will be arranged for those require out of home care. In 2018, our team implemented a new program of screening illicit drugs for all pregnant ladies with history of substance abuse during antenatal period. Urine screening for toxicology were arranged at the first visit and antenatal welfare plan meeting will be attended by paediatrician and social workers during one of the antenatal checkup visit for those with positive urine result. Explanation of harmful effect of drugs to fetus, appropriate detoxification programs and child care plan will be discussed.

Objectives:
1) To reduce the harmful exposure of illicit drug to the fetus,
2) For early engagement of detoxification program to the addicted pregnant ladies,
3) To reduce the burden in conducting MDCC and Court hearing,
4) To reduce the length of hospitalisation of the affected newborns and
5) To increase the rate of discharge of babies back to drug-free mothers.

Methodology: Under Comprehensive Child Development Service (CCDS), all pregnant ladies with history of substance abuse were recruited prospectively with written consent in 2018. The mother-child dyad would be followed up until the child at 24 months.

Result: In 2018, there were 41 pregnant ladies of mean age of 28.2 years old with history of substance abuse recruited. The mean age for the first intake of illicit drug was 17.9 years old. Twenty-six (63%), 19 (46%) and 16 (39%) of them reported using ketamine, cocaine and
amphetamine respectively. Twenty-six (63%) of them were using multiple drugs at the same instant. Antenatal urine screening for toxicology were conducted in 30 (73%) of them and 11 of them refused to provide urine sample or poor attendance in further antenatal visits. Thirteen of them (43.3%) with at least one urine sample tested positive of any kind of illicit drugs during antenatal period. Ten of them (76.9%) quitted drugs after engaged to the proactive program. Moreover, the hospital stay of the babies was shortened from in average of 29 days to 8 days for those newborns with positive to negative urine. Refusal for antenatal urine screening and/or defaulting antenatal visits were predictive for active drug abusing as reflected by the high rate of drug being detected in the newborn (54.5%). Developmental assessments were performed in 40 children (97.5%) at the age of 24 months. Ten (25%) of them were diagnosed to have developmental delay with no correlation to the antenatal drug status. Three out of 18 (18.7%) from the group of mother tested negative were delay. Incident of developmental delay is higher than normal population (10%). Four ladies in this cohort were persistently active in taking drugs, three of them were under the "refused" group. Five of the mothers relapsed in taking illicit drugs and 2 of their children suffered from developmental delay. Five of the mothers had another pregnancy within next 36 months, two of the newborns had positive urine result of illicit drug at birth.

**Conclusion:** Antenatal proactive screening for substance abuse in pregnant ladies is effective in reducing (1) the drug exposure to fetus, (2) number of MDCC and court hearing, (3) length of hospitalisation of newborns. Moreover, it also increased the rate of abusing pregnant ladies in quitting the drug dependent habit. This program also served to identify those ultra-high risk ladies in terms of their refusal in conducting the screening test and poor attendance to antenatal visits. Higher incident of developmental delay is noted, possible the effect of perinatal drug exposure or the weak parenting skill might be the origin. Further long study would be needed for identify the cause.

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**Immunosuppressive Therapies in Children with Biopsy-Proven IgA Vasculitis Nephritis: A Tertiary Centre Experience**

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**Background:** IgA Vasculitis Nephritis (IgAVN), also referred as Henoch-Schönlein purpura nephritis, can lead to persistent proteinuria in children. The aim of this study is to determine the efficacy of immunosuppressive therapies in the management of IgAVN in children.

**Methods:** A retrospective review was conducted for all IgAVN patients under the care of the Paediatric Nephrology Centre in Hong Kong between January 2009 and December 2019. Patients with biopsy-proven IgAVN with persistent moderate or severe nephrotic-range proteinuria despite Renin-angiotensin-aldosterone system inhibitor (RAASI), including angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), were included. Patient demographics, clinical and laboratory data, details of medical treatment and clinical outcomes were evaluated.

**Results:** Of the 177 Chinese children with IgAV, 42 children developed proteinuria. Twenty-one patients (16 boys) had persistent proteinuria despite the use of RAASI. Kidney biopsy confirmed IgAVN at a median age of 8.5 years. At baseline, 3 (14%), 14 (66%), 3 (14%) and 1 (5%) patient had moderate proteinuria, nephrotic-range proteinuria, nephrotic syndrome and nephritic-nephrotic syndrome with renal impairment, respectively. Cellular crescents were found in 76% of renal biopsies. Over a median follow-up period of 6.0 years, 18 patients (86%) attained complete remission at a median of 139.5 days since the initiation of immunosuppression. Upon the most recent follow-up, all patients had normal kidney function and the median UPCR was 0.11 mg/mg (IQR 0.10-0.16).
Conclusion: Immunosuppressive therapies were associated with favourable renal outcomes in children with biopsy-proven IgA VN presented with persistent moderate or nephrotic range proteinuria despite RAASi.

Pulmonary Complications in Premature Infants Using Beractant or Poractant for Respiratory Distress Syndrome in A Local Neonatal Intensive Care Unit
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Background: Beractants or poractants are the two types of surfactants utilised in treatment of respiratory distress syndrome (RDS) in premature infants. This was a retrospective cohort study comparing the outcomes between the two groups of surfactants.

Purpose: It compared the incidence of pulmonary complications and neonatal outcomes of premature infants receiving beractants or poractants.

Methods: Seventy-two patients in beractant group, and 54 patients in poractant group, were included. The primary outcome was to measure the incidence of air leak syndrome (ALS) and pulmonary haemorrhage. The secondary outcomes assessed mortality, pulmonary performance and outcomes. Logistic regressions were performed to identify independent risk factors for significant primary outcome.

Findings: There was significantly higher incidence of pulmonary haemorrhage in poractant group, measuring 2.8% in beractant group and 13% in poractant group ($p=0.038$). The difference in the incidence of ALS was not significant ($p=0.883$). Presence of coagulopathy was the only significant independent risk factor (OR=18.672, 95%CI [1.681-207.450], $p=0.017$). Patients in poractant group had longer mechanical ventilation duration ($p=0.019$), duration of oxygen supplement ($p=0.037$), length of stay in hospital ($p=0.005$), and higher percentage of patients fulfilling the criteria of BPD ($p=0.014$).

Conclusion: The study showed higher incidence of pulmonary haemorrhage in poractant group. Only coagulopathy, but not the type of surfactant, was identified as an independent risk factor for pulmonary hemorrhage incidence in multivariate analysis.

Fracture Burden in Paediatric End Stage Kidney Disease
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Background: Paediatric patients with chronic kidney disease are known to have an increased risk of fracture, however relevant data is limited.

Purpose: To determine the incidence of fracture and associated factors in children with end stage kidney disease (ESKD) receiving renal replacement therapy (RRT).

Methods: A retrospective review on all paediatric patients with ESKD at the tertiary Paediatric Nephrology Centre in Hong Kong. Children who presented before 18 years with active follow-ups for 12 or more months by November 2020 were included.

Results: RRT was initiated in 69 children (55% boys), with 21 (30.4%), 10 (14.5%) and 38 (55.1%) patients received peritoneal dialysis, haemodialysis and kidney transplant. 10 fracture episodes were observed in 7 patients (10.1%) at a mean duration of 7.8 years since RRT initiation, corresponding to a cumulative fracture incidence of 227.8 per 10000 patient year. This rate was 5-folds higher than the published data from our local general paediatric population (45 per 10,000 person-years; $p=0.01$).

Children who sustained fractures were significantly younger at the time of RRT initiation (3.5 vs 10.4 years; $p=0.02$) with a longer time on dialysis (12 vs 2.7 years; $p<0.001$). Other associated factors included metabolic bone disease, difficulty in walking, radiological evidence of renal osteodystrophy, parathyroid hyperplasia/adenoma, a higher parathyroid hormone level and more use of cinacalcet.

Conclusions: Children with ESKD receiving RRT have a higher risk of fracture. Longer duration of dialysis and a higher parathyroid hormone level were potential modifiable factors associated with fractures.
Five Years Data on Department of Health Child Assessment Service (CAS) Preschool Children at Risk of Dyslexia and Their Comorbidities
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Background: Dyslexia is known to be associated with a number of comorbidities, including developmental language disorder (DLD), attention-deficit/hyperactivity disorder (ADHD), and developmental coordination disorder (DCD). Previously, most reading at risk cases could not be identified before school age. With the development of new assessment tools including the Hong Kong Dyslexia Early Screening Scale (HKDESS) (2016) and Hong Kong Comprehensive Assessment Scales for Preschool Children (HKCAS-P) (2014), the number of preschool children shown to be at risk of dyslexia increased dramatically.

Purpose: This study reviewed CAS cases diagnosed in the recent 5 years as being "at risk of dyslexia" together with their comorbidities, with the purpose of enhancing vigilance to coexisting developmental problems for early management.

Methods: A search was performed on the CAS database. Data on children coded as "at risk of dyslexia" were retrieved from June 2015 to May 2020. Comorbidities of ADHD, DLD, and DCD diagnosed during preschool or at subsequent assessments during school age were searched and analysed.

Findings: A total of 5689 children were diagnosed as "at risk of dyslexia" for the 5-year period. Their ages at diagnosis ranged from 4 years 6 months to 6 years 2 months. The prevalence of comorbidities in these children were as follows: (i) ADHD 41.1% (n=2338), (ii) DLD 46.7% (n=2659), (iii) DCD 23.1% (n=1312).

Conclusions: As early as pre-school age, children at risk of dyslexia showed high prevalence of developmental comorbidities. The data provides an overall picture of this disease pattern in Hong Kong for future clinical and educational services planning.

Improved Neonatal Outcomes by Multidisciplinary Simulation - A Contemporary Practice in the Demonstration Area of China
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Aim: To investigate the impact of collaborative in-situ neonatal resuscitation simulation in reducing the incidence of neonatal asphyxia and related morbidity.

Methods: Neonatal in-situ resuscitation simulation training has been conducted by neonatal and obstetrical collaboration once per week in the University of Hong Kong – Shenzhen Hospital (HKU-SZH) since 2019. Each simulation was led by two instructors, accomplished by three health care providers from obstetrics and neonatal intensive care unit, followed by participatory feedback by the providers and several observers. The incidence of neonatal asphyxia, severe asphyxia, hypoxic-ischemic encephalopathy (HIE) and meconium aspiration syndrome (MAS) before (2017-2018) and after (2019-2020) the regular simulation was analysed.

Results: There were 82 simulation cases including resuscitation of preterm neonates with different gestational age, fetal distress, meconium-stained amniotic fluid, congenital heart disease, etc. After multidisciplinary in-situ simulation, the incidence of neonatal asphyxia decreased from 8.4‰ to 6.4‰ (P=0.045). The incidence of HIE and MAS dropped from 1.0‰ to 0.1‰ (P=0.003), from 1.9‰ to 0.87‰ (P=0.014), respectively.

Conclusion: Weekly collaborative resuscitation simulation improves acute neonatal outcomes, with decreased rate of neonatal asphyxia, hypoxia ischaemic encephalopathy and meconium aspiration syndrome. Implementation of regular resuscitation training is feasible and may improve the quality of neonatal resuscitation with better neonatal outcomes.
Discuss and Share Experiences in Implementing FCC Models in University of Hong Kong – Shenzhen Hospital (HKU-SZH)

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Aim: To discuss and share experiences in implementing Family centered care (FCC) models in Hong Kong - Shenzhen Hospital (HKU-SZH).

Methods: At present, FCC has not been well implemented in China and most NICU adopt closed management. Since December 2013, our department has introduced the FCC concept and implemented 24-hour opening ward, providing family members with a series of services including ward rounds, progressive health education, palliative care, breast-feeding, cold chain support of breast milk, breast milk bank, family visit, follow-up after discharge, and mutual support group for family members. The above services were maintained during the COVID-19 period.

Results: 10,615 newborns were treated from December 2013 to December 2020, the minimum gestational age of preterm infants treated successfully was 22+6 weeks and the minimum weight was 500g. The patient satisfaction rate in 2020 was 99.9%, and the average breastfeeding rate in 2020 was 84% while 83.4% of full-term infants and 90.2% of premature infants were breast-fed. (A multi-center survey of 974 cases of nutrition-related status of preterm infants in NICU in China reported that 13.6% of preterm infants were breast-fed during 2005-2006) The nosocomial infection rate from 2014 to 2020 was controlled between 0.41% and 2.02%. Literature showed that the incidence rate of nosocomial infection in neonatal care units of 17 grade A general hospitals in China from 2013 to 2014 was 3.35%.

Conclusion: An open NICU based on the FCC concept is feasible and contributes to increased breastfeeding rates and patient satisfaction without increasing the incidence of nosocomial infections.

Hypoxic Obstructive Sleep Apnoea in Children: A Subtype Associated with Higher Cardiovascular Risk

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Background: Childhood obstructive sleep apnoea (OSA) is a heterogeneous disease with variable clinical and polysomnographic manifestations that may contribute to the individual differences in cardiovascular outcomes even in patients with a similar level of conventional severity indexes.

Purpose: To investigate the differences in blood pressure (BP) outcomes between children with hypoxic and non-hypoxic OSA.

Methods: This retrospective study reviewed the records of OSA patients aged 5 to 14 years who had undergone both overnight sleep study and 24-h ambulatory blood pressure monitoring in Prince of Wales Hospital from July 2014 to December 2020. A patient was defined as having hypoxic OSA when >50% of the respiratory events were associated with a drop of ≥3% in oxygen saturation level. Patients with mild (obstructive apnoea hypopnoea index (OAHI) 1-5/h) and moderate-to-severe (OAHI ≥5/h) OSA were analysed separately.

Results: Respectively 99 (45 with hypoxic OSA) and 44 (23 with hypoxic OSA) patients with mild and moderate-to-severe OSA were included in this analysis. No significant differences in daytime and nighttime BP were observed between hypoxic and non-hypoxic OSA groups in both mild and moderate-to-severe subgroups. However, patients with hypoxic moderate-to-severe OSA had significantly less nocturnal dipping of both systolic BP (7.7%±4.7 c.f. 10.7%±4.1, p=0.035) and mean arterial pressure (8.2%±5.9 c.f. 11.9%±5.7, p=0.047) than the non-hypoxic counterparts despite having similar age, gender distribution, body mass index z score and OAHI.

Conclusion: Children with moderate-to-severe OSA and respiratory events that were predominately associated with oxygen desaturations had less nocturnal BP dipping, suggesting hypoxia might have an independent effect on cardiovascular risk.
The Demographics and Long-Term Outcomes of Paediatric Kidney Replacement Therapy in Hong Kong

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Background and Purpose: To evaluate the demographics and outcomes among children with End-stage kidney disease (ESKD) in Hong Kong.

Methods: We conducted a cohort study at the Paediatric Nephrology Centre, the designated site providing kidney replacement therapy (KRT) for children in Hong Kong. All children who initiated chronic KRT before 19 years, between 2001-2020, were included. Demographics, trend and survival outcomes of ESKD were examined.

Findings: 147 children (50% male) received KRT at a mean age of 11.4±5.7 years. The incidence of ESKD was 6.28 per million age-related population (pmarp). The leading cause of ESKD was congenital anomalies (33%). Ten children (7%) had pre-emptive kidney transplants, 104 (71%) and 33 (22%) patients received automated peritoneal dialysis and haemodialysis as initial KRT. The incidence of ESKD increased over time, and were 4.38, 5.07, 6.15 and 9.17 pmarp during 2001-2005, 2006-2010, 2011-2015 and 2016-2020, respectively (p=0.005). The mortality rate was 9.1 deaths per 1000-patient-years (95% CI 4.6-16.2). The survival probabilities at 1-, 5-, 10- and 15-year were 100%, 94.8% (95% CI 90.7-98.9%), 89.7% (95% CI 83.4%-95.9%), 87.1% (95% CI 79.3%-94.9%), respectively. Standardised mortality ratio was 54.5. >70% of deaths were due to infections. Young infants and those without kidney transplants were associated with worse survival (ps<0.01). Multivariate analysis demonstrated that patients receiving dialysis only had a significantly higher risk of death (HRadj 12.9, 95% CI 2.7-63.2, p=0.002).

Conclusion: There is an increasing incidence of paediatric ESKD in Hong Kong. Mortality risk is comparable to other developed countries and is highest among dialysis population.

Recto-Urethral Fistula with a Normal Anus in a Boy with VACTERL Association: A Case Report and Literature Review

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Anorectal malformation (ARM) is a congenital malformation that has an incidence of 1 in 5000. It is classified into different types according to the Krickenbeck classification. Recto-urethral fistula with a normal anus is a rare variant among all ARM with very few cases reported in previous literature. We hereby report a case with H type recto-urethral fistula with a rare clinical presentation of recurrent epididymo-orchitis, with our subsequent workup, surgical management and literature review.

Impact of School Closure on Children'S Sleep Pattern During the COVID-19 Pandemic

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Background: School closure is one of the main global health policies performed worldwide during the coronavirus disease 2019 (COVID-19) outbreak. Despite all of the advantages, there may be some risks for children who are quarantined. This study aimed to objectively measure and compares the sleep patterns of Hong Kong school students before and during the COVID-19 outbreak.

Methods: Baseline assessment was performed before the first wave of the COVID-19 outbreak in Hong Kong. The sleep pattern was recorded by a physical activity monitor (Actigraph wGT3X-BT, Pensacola, Florida, USA). The follow-up assessment was conducted in early 2020.

Findings: In total, 718 students were collected in the baseline. Subsequently 140 students joined the reassessment between March and April 2020. Analysis of sleep timing shows that 98.0% primary students, 78.0% secondary students and 79.9% primary school students and 58.8% secondary school students go to bed before midnight before and after the outbreak, respectively (p<0.001). Mean sleep duration (hours) was 6.81 (0.62) and 8.09 (0.07) at baseline and during the outbreak, respectively. The differences in the mean sleep features for total sleep time,
sleep fragmentation index and sleep fragmentation were 0.92 (1.64), 1.64 (6.95) and 2.49 (9.18), respectively. The overall sleep quality was poorer as evidenced by delays in bedtime and wake up time, increased duration in bed, longer sleep latency, increases in the movement and fragmentation indices.

**Conclusion:** This exceptional longitudinal study reported objective data on the change in sleep patterns before and during the COVID-19 outbreak with school closures.

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**A Chinese Boy with a Novel Compound Heterozygous Mutation of the DGKE Gene and Membranoproliferative Glomerulonephritis**

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**Background:** Diacylglycerol kinase epsilon (DGKE) gene mutation is known to cause atypical haemolytic uremic syndrome. With its gene pleiotropy, a small number of patients were found to present with isolated membranoproliferative glomerulonephritis (MPGN).

**Method:** We report a ten-year-old Chinese boy with steroid-resistant nephrotic syndrome and a pathological diagnosis of immune-complex mediated MPGN. He first presented at the age of four with generalised oedema, hypoalbuminaemia, nephrotic-range proteinuria (urine pr/cr 13.9 mg/mg) and hyperlipidaemia. He responded poorly to full dose prednisolone and renal biopsy confirmed immune-complex mediated MPGN. He attained partial remission eventually with the use of Cyclosporin A. Four years later, he developed urinary relapse (urine pr/cr 1.57 mg/mg) after discontinuation of immunosuppressants.

**Findings:** Next-generation sequencing revealed compound heterozygous mutations in the DGKE gene. These included a c.1068_1071del p.(Asn356Lysfs*6) frameshift mutation and a c.1282_1284+18del deletion, both were classified as pathogenic (ACMG/AMP classification). Repeated renal biopsy showed immune-complex mediated MPGN and features of mesangiolyis, suggestive of previous glomerular thrombotic microangiopathy (TMA). This might represent a previous episode of subclinical TMA related to the DGKE mutations, in addition to an immune mediated process. Our patient showed good response to angiotensin converting enzyme inhibitor, prednisolone and mycophenolate mofetil and is now in complete remission.

**Conclusion:** This is the first Chinese patient of DGKE nephropathy presenting as nephrotic syndrome with MPGN picture. These two DGKE pathogenic mutations are also first to be reported among DGKE-patients with MPGN. Of interest, our patient responded promptly to immunosuppressants. This case highlights the importance of genetic testing in children with atypical course of nephrotic syndrome.

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**The Hidden Costs of Rare Diseases Beyond Healthcare Setting**

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**Background:** In Hong Kong (HK), one in 67 people is living with at least one rare disease (RD). While the impact is often perceived as the immediate healthcare burden, the broader socio-economic consequences of RDs are important for healthcare and related planning, yet challenging to estimate.

**Purpose:** To estimate the socio-economic cost of RDs in HK.

**Methods:** The Client Service Receipt Inventory for the RD population (CSRI-Ra) was used to collect direct and indirect cost-related data in the RD population in HK. RD patients and carers were recruited via multiple RD organisations in Hong Kong. Costs were estimated from the societal perspective using a bottom-up approach.

**Findings:** A total of 286 independent participants were recruited between April and August 2020, covering 106 unique RDs. Over 80% of RD patients (n=230) took medications over the reported period, with an average of 3.66 inpatient days, 9.5 outpatient attendances, 3.6 accident and emergency visits, 10.2 day-care attendances, and 31.0 allied health visits per year among those who utilised the respective service. Of those who utilised residential medical services, there was an average annual cost of 29.7 visits per patient. Total hospital and community health service costs was found to be $25,703,312. A total of 176 patients (61.5%) took medications over the reported period, with an average of
5.5 drugs per patient (range: 1-27), equivalent to an annual
total cost of $43,433,933. Over 70% (n=210) of RD
patients required care from a paid or unpaid carer. Annual
costs of paid care and informal care support were
found to be $4,281,545 and $36,834,569, respectively.
Due to the patient’s RD condition, labour productivity loss
in the form of annual leave and reduced working hours was
equivalent to an annual cost of $28,577,883. The total
annual cost for the 286 RD patients was estimated to be a
minimum of HKD$138,831,242, with a minimum average
cost of HKD$485,424 per patient per year.

**Conclusion:** This is the first study to estimate the
socio-economic costs of RDs in the healthcare and
community settings in HK. Hidden costs in the form of
informal care support and productivity losses are significant
in this population, reflecting the importance of rare
diseases in health policies.

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**Theory of Mind (ToM) Profiles in Children with
Autism Spectrum Disorder (ASD) and
Developmental Language Disorder (DLD)**

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**Background/ Introduction:** Theory of Mind (ToM) is a
fundamental social cognitive skill necessary for
understanding of intentions, emotions, desires, taking
perspective and making predictions about other's behaviour.

ToM is a composite function requiring visual/auditory
input, language, central coherence and executive function
and may be affected in different neurodevelopmental
disorders such as autism spectrum disorder (ASD),
developmental language disorder (DLD), attention deficit
hyperactivity disorder (ADHD), hearing impairment and
visual impairment.

The Hong Kong Scales for Assessment of Theory of Mind
(HKAToM) was published by the Child Assessment Service
(CAS) in 2020 for evaluating ToM of children aged 5 years
to 12 years 1 month.

**Purpose:** To review HKAToM performance profiles in
85 children with suspected language impairment or ASD
in CAS from 2019 to 2020.

**Method:**

(1) Language abilities and ToM performance
was compared in 35 children with suspected language
impairment aged 5-12 years. (2) ToM abilities were
analysed in 50 children with ASD and normal intelligence
aged 6-12 years.

**Findings:**

(1) Among children with suspected language
impairment, there was a significant correlation between total
score of HKAToM and specific subtests of Hong Kong
Cantonese Oral Language Assessment Scale (HKCOLAS).
(2) Among children with ASD, performance on basic ToM
tasks was comparable to norm but they presented significant
difficulty in more advanced ToM tasks.

**Conclusions:** Language impairment is correlated with
poor ToM. In children with ASD, compensatory reasoning
supported basic but not advanced ToM tasks. These
findings provide useful information for understanding the
social interaction difficulties of these children, and for
guiding their training.

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**Volume-Targeted Versus Amplitude-Targeted High
Frequency Oscillatory Ventilation: A Retrospective
Case Control Study**

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**Background:**

High-frequency oscillatory ventilation (HFOV) is widely used in neonatology. Fluctuations in
pCO2 increase risk of intraventricular haemorrhage and hypocarbia is associated with cerebral ischaemia in preterm infants. Carbon dioxide (CO2) elimination during HFOV correlates with the diffusion coefficient of CO2 which is very sensitive to changes in tidal volume. Volume-guaranteed HFOV (HFOV-VG) is an advanced ventilation mode that allows clinicians to target the tidal volume delivered rather than the amplitude, potentially reducing pCO2 fluctuations.

**Purpose:** To retrospectively evaluate the difference in
pCO2 variability between preterm neonates receiving
HFOV-VG and conventional HFOV.

**Methods:**

Preterm infants who received HFOV-VG in
the Prince of Wales Hospital were identified. Each infant
who received HFOV-VG was gestational age-, birth weight-
and sex-matched with two infants who received
conventional HFOV. The mean and standard deviation
(s.d.) of pCO2 levels, and percentages of hypercarbic and
hypocarbic readings were compared using Mann-Whitney
U test and unpaired t-test as applicable.
Findings: Results showed significant difference in the pCO2 s.d. between the HFOV-VG and conventional HFOV groups (p-value=0.0451; mean difference=0.496). Incidence of hypocarbia (pCO2 <4 kPa) was significantly lower in the HFOV-VG group (p-value=0.002).

Conclusions: Preterm neonates receiving HFOV-VG had less fluctuations in pCO2 and lower incidence of hypocarbia than those receiving conventional HFOV. It suggests that HFOV-VG might be preferred in preterm neonates who are susceptible to cerebral vascular injuries. To confirm our findings, larger-scale randomised controlled trials are needed.

Paediatric Adrenocortical Tumours in Hong Kong - 25 Years of Experience
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Background: Adrenocortical tumours (ACTs) are rare neoplasms in children encompassing benign adenoma (ACA) and malignant carcinoma (ACC). Endocrinologic dysregulation is frequent and underlying cancer predispositions have to be considered.

Purpose: To review the characteristics and treatment outcome of paediatric ACTs in Hong Kong leveraging a population-wide childhood cancer database.

Methods: Retrospective review of the Hong Kong Paediatric Haematology/Oncology Study Group database for patients diagnosed <18 years-old with ACTs from May 1996 to April 2021.

Findings: Thirteen patients with ACTs were identified (ACC=11, ACA=2; M:F=6:7). Median age of diagnosis was 8.2 years (range: 6 months-15 years). Most patients (n=8) presented with virilisation or precocious puberty, whereas hypertension (n=3), abdominal pain (n=3), hypokalemia (n=1) were less common features. Biochemically, excessive androgen (n=10) was most frequent, followed by cortisol (n=3) and aldosterone (n=1) excess. COG staging was I in 6 patients, II in 3, III in 1 and IV in 3. Twelve patients received surgical resection of primary tumour which was preceded by biopsy in 4. Chemotherapy was given in 5 patients (Stage I=1, III=1, IV=3) using cisplatin/etoposide/doxorubicin with mitotane. All 5 patients progressed among which 4 died within 2 years despite further second-line treatment. In contrast, all 8 patients (Stage I/II disease) who had resection alone remained disease-free (median follow-up 9.8 years). Germline TP53 mutations were detected in 4/7 patients (pathogenic=3, variant of unknown significance=1) tested; one patient had Beckwith-Wiedemann syndrome.

Conclusions: The management of ACT requires multi-disciplinary input and advanced-stage disease remains a challenge direly requiring novel strategies.

Hearing Impairment in Children with Waardenburg Syndrome
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Background and aims: Waardenburg syndrome (WS) is a rare condition characterised by hearing loss and pigmentation deficiencies. Other anomalies vary depending on the type. This study aims to review the hearing impairment (HI) in children with WS and their developmental profiles.

Methods: CAS data was collected on children born from 2013 to 2020 with WS and significant HI. Reasons for referral, hearing thresholds, use of hearing aids or cochlear implantations (CI) and developmental findings were analysed.

Results: Six cases were identified. The hearing ranged from moderate to profound sensorineural hearing loss. The developmental profile ranged from mild language delay to mild intellectual disability.

Four cases of HI were detected at universal newborn hearing screening (UNHS) and confirmed with significant HI. The remaining two children presented with bilateral blue iridis without dystopia canthorum. There was no confirmed HI at referral to CAS. One child presented at 2 years 2 months for developmental delay and suspected autism spectrum disorder. Profound SNHL in one ear and severe SNHL in the other were diagnosed. The second child presented at 1 year 3 months for language delay, hypotonia and gross motor delay. Bilateral severe to profound SNHL was found. CIs were done for both children, which improved hearing thresholds to conversational levels.

Conclusions: We should be alert of WS and consider hearing assessment for children with bilateral blue iridis without dystopia canthorum.
Vaccines that elicit mucosal immune responses against SARS-CoV-2 could potentially be of exceptional importance in providing first line defence at the site of viral entry. In order to understand the mucosal immune response profiles of SARS-CoV-2 vaccines, we examined both the mucosal and systemic responses of subjects vaccinated by two different vaccination platforms: mRNA (Comirnaty) and inactivated virus (CoronaVac). Nasal epithelial lining fluid (NELF) and peripheral blood samples were collected in subjects who had received two doses of CoronaVac or Comirnaty. We quantified IgA and IgG specific to SARS-CoV-2 S1 protein, neutralisation antibody by ELISA in NELF and plasma samples. Only Comirnaty induced nasal S1-specific IgA and IgG responses, which were evident as early as on 14±2 days after the first dose. The NELF samples of 72% of subjects became IgA+IgG+, while in 62.5% of subjects the samples were neutralising by 7±2 days after the second dose. In 45% of the subjects their NELF remained neutralising 50 days after the booster. In plasma, 91% and 100% Comirnaty subjects possessed S1-specific IgA+IgG+ on 14±2 days after the first dose and 7±2 days after booster, respectively. The plasma collected on 7±2 days after booster was 100% neutralising. The induction of S1-specific antibody by CoronaVac was IgG dominant, and 70% of the subjects possessed specific IgG by 7±2 days after booster and were all neutralising. This study reveals that Comirnaty is able to induce S1-specific IgA and IgG response with neutralising activity in the nasal mucosa in addition to a consistent systemic response.
**Innate Immune Response of Human Influenza A Virus and Rhinovirus A16 in Patients' Nasopharyngeal Aspirates and Human Airway Models**

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**Background/Introduction:** Rhinovirus (RV) and influenza A virus (IAV) are prevalent respiratory viruses found in children. RV infection is considered to induce a milder response than IAV in general. Whether the parameters measured in the mucosal fluid of patients can reflect by the in vitro cell models remain elusive.

**Purpose:** To compare the mucosal inflammatory profiles of hospitalised RV- and IAV-positive children and verify if the air-liquid interface (ALI) culture of the human nasopharyngeal (NP) and bronchial epithelia-derived epithelial cell culture and the corresponding airway organoids (AOs) are good models to reflect the local immune response.

**Methods:** Nasopharyngeal aspirates (NPA) from hospitalised paediatric patients with respiratory symptoms are collected during admission. The presence of respiratory virus was detected by multi-plex PCR and RV was genotyped by VP4-VP2 sequencing. The cell pellet of the NPA was extracted for measuring host gene expressions. ALI and AO cultures were cultured from human NP and bronchial tissue, and infected with RV-A16 and IVA H1N1. Viral replication and gene induction were assessed.

**Findings:** A total of thirteen RV-A and fifteen IAV positive paediatric subjects were identified. RV-A patients were significantly younger than IAV patients. Influenza virus induced a stronger chemokine response in patients' NPA, including CCL8, CXCL11 and CCL5 than RV-A, as detected in their NPA. IAV may induce stronger IFN response in ALI and AO culture.

**Conclusion:** We identified distinct innate immune responses of RV-A and IVA in patients' NPA and human airway models. AOs serve as a novel model for IVA pathogenesis.

**Teamwork on Early Mobilisation for a Critically Ill Patient on Continuous Renal Replacement Therapy (CRRT) in the Paediatric Intensive Care Unit (PICU) - A Case Study**

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**Introduction:** Recent studies showed early mobilisation during CRRT in PICU is safe to minimise the risk of deep vein thrombosis (DVT) and alleviate patients' post-PICU symptoms. This case study demonstrates the teamwork in PICU to achieve early mobilisation for a critically ill patient on CRRT.

**Methodology:** A 7-year-old boy with hepatoblastoma and lung metastasis was admitted to the PICU. His condition deteriorated with ventilator support, CRRT and latter intermittent haemodiafiltration (IHIF). Medical and physiotherapy records were reviewed. Children's Chelsea Critical Care Physical Assessment Tool (cCPAx) and maximum inspiratory and expiratory pressures (MIP & MEP) were measured. Any adverse effect were documented.

**Results:** Chest physiotherapy were practiced since admission. Inspiratory muscle training via endotracheal tube (ETT) initiated to promote the respiratory function (intubated MIP and MEP: 20 cmH2O). Anti-embolism stockings accompanied with mobilisation were administrated.

During the CRRT, an active video gaming incorporated into rehabilitation promoted exercise compliance. Strategies for early sit out of bed (SOOB) were discussed in weekly PICU round i.e., IHF catheter was repositioned into right internal jugular vein. SOOB for IHF successfully achieved since day10.

Since extubation on day18, assisted walking and tricycling were practiced with improvement at MIP and MEP (31 and 33 cmH2O on day20) and cCPAx total score (from 2/50 (admission) to 35/50 (day 45)). No adverse event was reported.

**Conclusion:** Teamwork between the PICU team and physiotherapists provides a safe example for early mobilisation for PICU care with CRRT. This serves a platform for further development of early mobilisation protocol in PICU.
A Challenging Case for Genetic Counselling: Blended Phenotype of Familial Hypocalciuric Hypercalcaemia, Haemophilia A and Turner Syndrome with Interaction Between Isochromosome X and Duplication in F8

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Introduction: Blended phenotype, a complex phenotype affected by more than one defective gene, is not as rarely seen as it used to be because of the advancement of whole exome sequencing. Retrospective analysis of WES data of 7374 patients shows 4.9% of patients were diagnosed with two or more monogenic diseases (Posey et al., 2016).

Case Report: This case report describes a patient with a blended phenotype of familial hypocalciuric hypercalcaemia, type I (FHH1), haemophilia A and Turner syndrome. At age of 1 year old, she was noticed to have spontaneous bruising with abnormal cloting. Blood test revealed she has more severe haemophilia A, with factor VIII <1% clotting activity, than her father. Constitutional karyotyping was performed to determine the genetic cause of the severe expressivity of haemophilia A and identified an Xq11.1-28 duplication affecting the F8 gene in addition to the F8 genetic defect inherited from her father in another X chromosome. Besides, mosaic Turner syndrome was substantiated.

Single gene testing of CASR was arranged because of positive family history and found a paternally inherited heterozygous mutation (NM_000388.4:c.196C>T, p.Arg66Cys) in CASR associated with FHH1, an autosomal dominant disease requiring no treatment but monitoring.

Conclusion: This is a challenging case for genetic counselling because it is uneasy to educate the patient about the modes of inheritance of the three distinct genetic diseases. Since the two defective genes segregate independently, a dihybrid cross model has to be used to explain the integrated recurrence risk. There were also difficulties in the diagnostic journey and provision of preimplantation genetic testing to the family.

Associations Between Childhood Maltreatment and Psychiatric Disorders: Findings from a Population-Based Cohort Study

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Background: High-quality evidence regarding links between childhood maltreatment and psychiatric diagnoses is lacking particularly for Axis II disorders.

Purpose: This study used electronic health record data to explore the association between childhood maltreatment experiences and Axis I and Axis II mental disorders.

Methods: In this study, the exposed group (n=7,473) comprised patients aged 0 to 19 years with a first-time record of maltreatment episode between January 1, 2001 and December 31, 2010, whereas the unexposed group (n=26,834) comprised individuals with the same gender, age, and admission hospital and time who did not have any record of maltreatment episode between January 1, 2001 and December 31, 2010. Data on their psychiatric diagnoses recorded between the date of admission and January 31, 2019 were also retrieved. A Cox proportional hazard regression model was fitted to estimate the hazard ratio (HR, plus 95% CIs) between childhood maltreatment exposure and psychiatric diagnoses, adjusting for age at index visit, sex, and government welfare recipient status.

Findings: Childhood maltreatment exposure was significantly associated with subsequent diagnosis of conduct disorder/oppositional defiant disorder (adjusted HR, 10.99 [95% CI 6.36, 19.01]), attention deficit...
hyperactivity disorder (ADHD) (7.28 [5.49, 9.65]), and personality disorders (5.36 [3.78, 7.59]). The risk of subsequent psychiatric disorder in maltreated children did not vary by exposure to sexual abuse, age at exposure, and gender.

Conclusions: Maltreated children are vulnerable to psychiatric disorders. Findings highlight the need for early provision of integrated family support services to address the long-term psychosocial needs of maltreated children.

Association Between Chronic Inflammation and Telomere Length Among Overweight and Normal-Weighted Adolescents

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Background: Rising prevalence of obesity in children and adolescents over the past decades has become a worldwide health concern. Recent research found that overweight and obese children and adolescents are more likely to have shorter telomere length (TL), which is recognised as one of the biomarkers of ageing. However, the biological pathways underlying these associations remain to be unknown.

Purpose: The purpose of this study is to investigate the association between serum cytokine levels and telomere length among overweight and normal-weighted adolescents.

Methods: A total of 278 adolescents aged 12 to 15 years were included in the analyses of this study. Buccal swabs and peripheral venous blood samples were collected from the adolescents for measuring telomere length and serum cytokines levels respectively. Anthropometric measurements on parameters including weight and height in barefoot and light clothing were also obtained.

Findings: Among the 278 participants, 180 were boys (64.7%) and 98 were girls (35.3%) with an average age of 13.35 years. About one-third of the adolescents (31.3%) were overweight with the average BMI of 19.97. Adjusted regression models showed that the levels of interleukin (IL)-1β, tumour necrosis factor (TNF)-α, IL-6, and IL-8 were significantly associated with TL. Only IL-18 and IL-1β were significantly associated with TL in normal-weighted adolescents.

Conclusions: This study adds to the current evidence that TL among overweight adolescents are more vulnerable to the elevated levels of peripheral monokines. This indicates the potential involvement of macrophages in the process of cellular aging, especially among obese and overweight population.

Bedside Surgical Release of Tongue Tie in Babies with Breastfeeding Difficulties: A Report on the Local Experience

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Background: Tongue tie is a common anatomical variation found in 1.7-10% of the population. While it seldom carries functional impairment into older age, there were studies showing babies with tongue tie experience more difficulties with direct breastfeeding. A few randomised controlled trials suggested the benefit of surgical release of tongue tie in this context. These had led to the recommendation from National Health Service and the Canadian Pediatric Society on the surgical procedure. In Hong Kong, despite increasing awareness on the benefits of breastfeeding, a comprehensive service is yet to be established for babies encountering difficulty in breastfeeding associated with tongue tie.

Purpose: We report our experience in the surgical release of tongue tie in conjunction with assessment and review by lactation consultants.

Method: A retrospective review was carried out in babies with surgical release of tongue tie who presented with difficulty with breastfeeding difficulties. Preoperative complaints were documented. All of them had reassessment on breastfeeding by a lactation consultant immediately after the procedure.

Findings: In the study period of 26 months, a total of 46 babies had bedside release of tongue tie performed in Prince of Wales Hospital. Forty-one (89%) of them had pre-operative and post-operative assessment by lactation consultants. Presenting complaints included ineffective sucking/slow feeding (30%), poor latching (61%) and sore nipples (37%). No complication has been raised from the procedures.

All babies were immediately assessed for breastfeeding after the procedure. All of them had the symptoms
improved. Only 30 babies were followed up after the procedure day, at a median follow up of 8 days. Twenty-six (87%) were continuing direct breastfeeding. Thirteen mothers had a delayed interview on the scale of improvement (rated 0-10) from the procedure, mean score was 8.7.

Conclusions: In the local setting, surgical release of tongue tie at bedside brought immediate improvement in the symptoms from tongue tie in breastfeeding babies. A standardised follow up practice is needed to study the longer term effect of the procedure.

Effects of an Evidence-Based Educational Programme for Improving Nurses' Knowledge and Self-Efficacy About the Ponseti Method of Clubfoot Treatment: Service Innovative Project
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Background: Clubfoot, also known as congenital talipes equinovarus, is one of the most common deformities of the lower limbs in newborns. It is treatable and can be corrected by Ponseti method with 90% of successful rates. However, relapse is the most common problem affecting long term successful outcome. Poor adherence with Ponseti method is regarded as the major cause of relapse. A lack of knowledge and skills about Ponseti method and misunderstanding about the importance of brace compliance among healthcare providers and family caregivers of clubfoot children are the common cause. Hence, researchers suggested that relevant training or education should be provided to health care providers so that they can acquire the knowledge and skills of clubfoot management. Unfortunately, relevant training for health care providers were mostly provided in low- and middle-income countries and there is insufficient education or training about clubfoot management in Hong Kong. Also, the admission rate of clubfoot is increasing in these few years so there is a need to implement evidence-based educational programme for nurses to improve the knowledge and self-efficacy about the Ponseti method of clubfoot treatment.

Aims & objectives: The aim of this service innovative project is to develop and pilot testing an evidence-based educational programme for nurses who take care of clubfoot children undergoing Ponseti method of treatment. Specific objectives are: (1) to evaluate the effectiveness of the educational programme on nurses' knowledge and self-efficacy related to clubfoot and Ponseti method of clubfoot treatment; and (2) to evaluate the level of satisfaction and feasibility of the educational programme among nurses.

Potential setting: The educational programme will be conducted in an indoor seminar room in the hospital.

Potential participants: Nurses, regardless of age and clinical experiences, who are currently working in the paediatric wards and need to take care of children with clubfoot in an acute public hospital will be recruited.

Project plans: The educational programme involves two face-to-face education sessions taught by an orthopaedic surgeon and an orthopaedic nurse consultant, who are experienced in Ponseti method. There will be two face-to-face education sessions in two consecutive weeks. Each face-to-face education session will last for around 3 hours. Two face-to-face education sessions include theoretical and practical sessions. Through theoretical sessions, knowledge about clubfoot and Ponseti method of clubfoot treatment will be delivered to nurses through lectures. Each nurse will receive a booklet which comprised of lecture notes with powerpoint slides. Through practical sessions, skills of cast and brace application will be demonstrated to nurses and they need to return demonstration on cast and brace application. Question & answer session and group discussion are also provided after each education session.

Project outcomes: Demographic data of nurses will be collected before the start of educational programme. Also, primary outcome is to assess nurses' knowledge of clubfoot and Ponseti method. Secondary outcome is to assess nurses' self-efficacy regarding to take care of clubfoot children undergoing Ponseti method. Outcomes will be measured before and after the implementation of intervention.

Discussion: This educational programme is feasible in applying to clinical settings due to its high degree of practicality, implementation and demand. The cost of education materials and settings are relatively low. Also, it is facilitated and supported by Department of Paediatrics and Adolescent Medicine. Flexible arrangement of duty can be done to encourage nurses to participate in the training.

Conclusion: Through the service innovative project, nurses are expected to increase the knowledge and self-efficacy to take care of the clubfoot children during different phases of Ponseti method of treatment. Thus, they can provide appropriate care and education to patients and family caregivers to increase their satisfaction of treatment,
enhancing patient outcomes and finally improving the quality of health care service about clubfoot in our working paediatric unit.

**ESS is an Independent Predictor of Systolic Blood Pressure in Sleep-Deprived Schoolchildren**

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**Introduction:** In Hong Kong, sleep deprivation is common amongst schoolchildren. While it is associated with numerous psychosocial and health consequences, for example worse daytime functioning, emotional disturbances and obesity, recent studies also evaluated its impacts on systolic blood pressure (SBP) in the paediatric population. Various cohorts have reported higher SBP in sleep-deprived schoolchildren when compared to those who have sufficient sleep. However, the predictors of a higher SBP in sleep-deprived subjects remain unclear.

**Purpose:** A cross-sectional study was conducted to assess the potential predictors of SBP in Hong Kong schoolchildren.

**Methods:** 53 sleep-deprived subjects aged between 12-16 were included after excluding those with obesity, sleep disorders and any known conditions or medications that may affect sleep. Their body weight, height, BMI, pulse rate, blood pressure and sleep duration were recorded. The Paediatric Daytime Sleepiness Scale (PDSS) and Epworth Sleepiness Scale (ESS) were completed at baseline. Sleep deprivation was defined as sleep duration <8 hours at baseline. The association between baseline characteristics and SBP was evaluated by simple linear regression. A backward multiple regression model was used to assess the effects of PDSS and ESS on SBP.

**Findings:** 53 sleep-deprived subjects with a mean sleep duration of 6.63 hours per day were included in our study. ESS [F(1,51)=6.351, p=0.015, R^2=0.111, R^2_adjusted=0.093], age [F(1,51), p=0.004, R^2=0.150, R^2_adjusted=0.133] and BMI [F(1,51)=4.607, p=0.037, R^2=0.083, R^2_adjusted=0.065] are associated with SBP using simple linear regression. However, sleep duration in sleep-deprived schoolchildren is not associated with SBP [F(1,51)=2.272, p=0.138, R^2=0.043, R^2_adjusted=0.024]. Three independent variables, including ESS, age and BMI, were included in the multiple regression analysis [F(3,49), p<0.001, R^2=0.290, R^2_adjusted=0.247]. The association between ESS and SBP remains statistically significant [β=-0.336, p=0.010].

Another multiple regression analysis was conducted, which included BMI, age and PDSS. PDSS is not associated with SBP in this multiple regression model [β=-0.212, p=0.103].

**Conclusions:** ESS is an independent predictor of higher SBP in sleep-deprived schoolchildren.

**Photogrammetry as a Screening Tool for Childhood Obstructive Sleep Apnoea - A Pilot Study**

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**Background:** Cranio-facial profile is an important component in the aetiology of childhood obstructive sleep apnoea (OSA). Different craniofacial features can be captured by photogrammetry, which is making measurements by photographs. Whether photogrammetry findings together with clinical parameters would yield a clinically acceptable screening tool for OSA has not been explored.

**Purpose:** To develop a prediction model for childhood OSA using both clinical parameters and photogrammetric craniofacial features.

**Method:** Prepubertal children suspected of OSA were recruited. All subjects underwent craniofacial photogrammetry and overnight polysomnography. Data was split into 70% training data and 30% test data. The prediction models were built from the training data using logistic regression and evaluated on the test data using receiver operating characteristic curve analysis.

**Results:** This study included 90 children (mean age: 8.2±1.6 years, 66 males). Non-OSA, mild OSA and Moderate-to-severe (MS) OSA groups consisted of 32, 31, and 27 subjects, respectively. Four prediction models were built. Model 0 was built with only clinical measurements which included age, sex, BMI z-score and the presence of large tonsils as predictors (AUC=0.683). Models 1 and 2 used clinical measurements and one photogrammetric feature, which was the maxillary-mandibular relation angle (sn-n-sl) for model 1 (AUC=0.778), and the anterior mandibular height to whole face length ratio (sto-gn/gn) for model 2 (AUC=0.806). Model 3 used clinical measurements and the two photogrammetric features, giving the highest accuracy (AUC=0.861).

**Conclusion:** Craniofacial features obtained from photogrammetry could improve the prediction accuracy for childhood OSA.
Genetic Diagnosis of Mitochondrial Diseases by Detection of Aberrant Expression and Splicing Events in RNA Sequencing Data

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Background and objective: Mitochondrial diseases (MDs) are the commonest group of inborn errors of metabolism. Genetic diagnosis is crucial for disease management but challenging owing to phenotypic and genetic heterogeneity. MitDNA sequencing and whole exome sequencing (WES) are useful diagnostic tools, but a proportion of the patients remains undiagnosed. In this study, we aim to investigate the power of RNA sequencing (RNAseq) to overcome the limitation of WES for genetic diagnosis.

Methods: We studied a cohort of 25 undiagnosed patients with suspected MDs after WES. RNAseq was undergone for the fibroblasts of these 25 patients together with 6 genetic confirmed positive controls, 2 undiagnosed patients with other diseases and 8 unaffected controls. We implemented a recently established workflow, Detection of RNA outliers pipeline (DROP), to detect aberrant expression and splicing events.

Results: A total of 95 significant expression outliers and 1847 splicing outliers have been identified in the patients. Two significant abnormally expressed genes, MFSD1 and GFCI, were found in one of the undiagnosed MD patients. These two genes are located with high proximity on chromosome 3 and a possible deletion covering MFSD1 is suggested. Further studies are needed to investigate whether the deletion will affect cis-acting elements controlling the expression of GFCI associated with oxidative phosphorylation deficiency. An aberrant splicing event was identified in another patient resulting in partial exon 2 retention in POLRMT encoding mitochondrial RNA polymerase. Functional study is essential to evaluate the effect of the intron retention on protein function.

Conclusion: Here we have investigated a transcriptome-directed approach for molecular diagnosis of MDs. Further investigation by alternative prioritisation of outliers and functional confirmation will be proceeded to identify candidate genetic defects to explain the patients' phenotypes.

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Neurofibromatosis, Old and New: A 16 Years Clinical and Molecular Characterisation in Hong Kong

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Background: Neurofibromatosis type 1 (NF1) is the commonest multi-systemic neurocutaneous tumour-predisposition disorder. It has an age-related complete penetrance but a highly variable inter- and intra-familial expressivity.

Purpose: To explore the incidences of features in the NIH clinical diagnostic criteria and the molecular characterisation in our cohort, report on novel variants and discover new genotype-phenotype correlations.

Methods: The clinical features and molecular characteristics of 832 clinically or molecularly confirmed NF1 patients from 697 unrelated families recruited from a single centre in Hong Kong diagnosed during the 16 years period from January 2005 to January 2021 were summarised and analysed.

Findings: While the majority of the reported figures in terms of clinical features and molecular findings appeared to be concordant with what had been described in the literature, we would like to highlight the newly found association of a heightened risk of congenital heart anomalies and pulmonary stenosis in individuals harbouring in-frame variants in the entire RAS-GAP domain, accompanied with a "Noonan-syndrome-like phenotype" with a higher incidence of short stature, relative macrocephaly, pectus abnormalities and lower incidence of cutaneous neurofibroma. On the other hand, the incidences of hypertension, stroke, epilepsy, vascular abnormalities and malignancies appeared much lower in our cohort than reported figures from previous literature, whether these findings reflect genuine ethnicity-related differences, or environmental factors and modifications present in our locality, requires further studies.

Conclusions: In this study, we have revisited the incidences of NIH clinical diagnostic criteria features and molecular characterisation, reported on novel variants and discovered new genotype-phenotype correlations.
Fathers' Involvement in Pregnancy and After Childbirth – A Qualitative Study

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**Background:** There was a significantly global trend in discussing fathers' experience and involvement in pregnancy and childbirth since 1960s. The number of fathers who were participated in engagement during pregnancy were also increasing. Some of the famous articles identified the importance of the presence of fathers' involvement such as attending antenatal care or cutting umbilical cord in delivery ward. In Hong Kong and Chinese culture, most of the family units are belonging to nuclear family. The tradition mother roles are full of domestic duties and mainly provide care to children. Mothers are playing a fundamental role in the children's life and they are having a magical power to take care the children and whole family. Usually, pregnancy and care during childbirth were primary focused on the expectant mothers. Much published papers were discussing about mother's experience and how they can cope in pregnancy. But conversely people always neglect the presence of fathers during their partner's pregnancy and after the childbirth. Fathers, in traditional Chinese culture, they are playing a dominant role in a family.

Fathers also recognising as a pillar in the development of the children and fathers are the protectors, the adult who was holding unchallenged power. Their presence and engagement must have a huge impact to their family. Considerable studies have already proven the presence of fathers in pregnancy has great impact to children development. In recent decades, the encouragement of fathers' engagement with children has increased because such kind of involvement were shown improved child cognitive and socio-emotional development. Not only for children, literature review in 2021 reported, shared care with fathers providing greater support to mothers in terms of relieving some of the burden of housework and childcare. Also, may help to improve maternal wellbeing levels and reduce mother’s stress. Especially in Hong Kong, no studies have examined the involvement of fathers' during their partner's pregnant also the aspects of the engagement not yet discussed.

**Objectives:** Aims to shed light and understanding on the experiences of Hong Kong fathers during the period form their partner's pregnancy and childbirth, to bridge the gaps between fathers' involvement and practice in this study. Discover the fathers' experiences in the transitional pathway to fatherhood. To explore and to promote fathers' involvement in their partner's pregnancy and childbirth, an overview of father's involvement should be explored. The following are the research questions in this study:

1. What are the fathers' perceptions/attitude during pregnancy and after childbirth?
2. How did the fathers' involvement impact the family?
3. What are the mothers' perception/attitude on father's involvement during pregnancy?

**Methods:** A qualitative study will be conducted. Purposive sampling of a sample of couples will be recruited in antenatal clinic. Following with an interview with interview guides, generate data used to explore the Hong Kong fathers' views and experience during pregnancy. Participants will be interviewed again one month after their partners' delivery. All the data were transcribed and analysed using thematic analysis.

**Study implications:** Healthcare professionals should identify the fathers' experiences, changes and their needs such as source of informational support, fathers' attitude, relationship with partner and the health outcomes for children. The findings in this study will promote our understanding of the transitional process and aspects of fathers' involvement in Hong Kong during the beginning of their fatherhood life.

Except the process of transitional to fatherhood will be discussed, Family-centred caring (FCC) is the main central idea which should be promoted in the future obstetric care. Support from midwives and nurses appeared to facilitate fathers' involvement during labour. At the moment of birth have already awakening of fatherhood in men, midwives are essential in supporting not only the mothers, but also the fathers. Midwives have the roles to offer them the opportunities to take part and participate in all decision-making process. Therefore, it is absolutely suitable to apply the FCC concept in obstetrics in order to provide the best care to the whole family.
A Quality Improvement Program to Enhance Safety Administration of Expressed Breast Milk (EBM) in Neonatal Unit (NNU)

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**Introduction**: With the Baby-Friendly Hospital Initiative promote among hospitals, more women are breastfeeding and providing breastmilk to hospitalised infants.

Ensuring safe breastmilk handling and administrating in neonatal unit is a complex process with many potential points for error, of which one of the most serious is administration of the wrong milk to the wrong baby.

Although, our unit has our own guideline specially for proper handling and preparation. We still had few incidents of giving wrong expressed breast milk (EBM) to the wrong babies.

Hence, a new 2D scanning system for milk scanning was employed to promote patient safety and reducing risk of misadministration. A pilot study was initiated from February 2021.

**Objectives**:
1. To examine the feasibility of using 2D barcode scanning system for EBM identification
2. To ensure the safe administration of EBM for all infants
3. To enhance staff competence on using the new barcode system

**Methodology**:
1. To estimate the usages and search for the supply of scanning systems
2. To raise staff awareness on the EBM incidents by providing briefing and training sessions
3. To implement pilot study for testing of efficacy
4. To monitor the efficacy and efficiency of implementation
5. To obtain the evaluation and feedback from staff
6. To compare the number of errors before and after the implementation.
7. To monitor the staff's competence

**Results and outcomes**: There is no wrong EBM incident in the span of a year (2021).

All staff has shown competence on using the new barcode system.

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Rare Thoracic Tumour in a Young Girl: A Call for Multidisciplinary Intervention

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**Introduction**: Primary thoracic tumours are uncommon in children. The application of next-generation sequencing allows robust disease classification while proactive interventions are required to mitigate potential morbidities associated with mediastinal syndrome.

**Purpose and Methods**: To describe the clinical course of a child diagnosed with primary thoracic low-grade fibromyxoid sarcoma (LGFMS).

**Findings**: A previously healthy 9-year old girl presented with six months of dyspnea. Examination showed reduced air entry over the right lung with tracheal deviation contralaterally and facial puffiness. Imaging revealed a giant mass expanding the right thorax with significant compression on the mediastinum. Frozen section on biopsy specimen demonstrated abnormal spindle cells. Chemotherapy was started with the presumed diagnosis of pleuropulmonary blastoma for the life-threatening clinical picture, but with lack of response noted. Subsequently, histologic analysis indicated MUC4 positivity by immunohistochemistry, and *FUS-CREB3L2* fusion was detected by RNA-sequencing, confirmatory of LGFMS. Understanding that surgery is the mainstay, a multidisciplinary team was assembled to devise the peri-operative plan. With pre-operative cannulation of the femoral vessels, embolisation of feeding arteries, and meticulous intra-operative monitoring, near-total resection was achieved without complications. Post-operatively, the patient was pre-emptively maintained on extracorporeal membrane oxygenation due to pulmonary hypertension, and made an uneventful recovery other than
Overcoming the Diagnostic and Management Challenges in Metastatic BCOR-Altered Primitive Myxoid Mesenchymal Tumour of Infancy
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Introduction: Primitive myxoid mesenchymal tumour of infancy (PMMTI) with BCOR alteration is a rare entity newly added to the 2020 WHO Classification of Soft Tissue Tumours.

Purpose and Methods: To illustrate the diagnostic dilemmas and clinical course of the first reported case of PMMTI in Hong Kong.

Findings: A six-month-old girl presented to Hong Kong Children's Hospital with progressive, congenital left dorsal foot swelling. Differential diagnoses considered included infantile haemangioma, overgrowth syndrome and infantile fibrosarcoma. Clinical examination and imaging showed numerous metastatic lesions in the lungs, cervical and inguinal lymph nodes, gluteal muscle, paraspinal region, and subcutaneous tissue. Immunohistochemistry and FISH of left foot biopsy specimen indicated BCOR-positivity with absence of EWSR1-rearrangement. BCOR internal tandem duplication was then confirmed by RNA-Seq, compatible with diagnosis of PMMTI. Apatinib, temozolomide and irinotecan (AIT) was started with palliative intent. Tumour progressed after 5 cycles, so a course of vincristine, doxorubicin and cyclophosphamide (VDC) was offered, but was complicated by septic shock. VDC was withheld and AIT resumed. Surprisingly, the patient demonstrated partial response and disease stabilisation with continued AIT cycles (21 cycles given to-date). The regimen was well tolerated other than transient hypertension and proteinuria that resolved with apatinib dose reduction. With tumour shrinkage, the girl is now ambulatory and enjoys good quality of life.

Conclusion: Our case highlights the challenges in diagnosing and managing rare paediatric cancers and the critical role of refined histopathologic-molecular workup. Without an established treatment strategy, combination of multikinase inhibitor and chemotherapy resulted in durable disease control.

Evolution of Childhood OSA Phenotypes After Adenotonsillectomy: Latent Class and Latent Transition Analysis of the Childhood Adenotonsillectomy Trial
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Introduction: The severity of obstructive sleep apnoea (OSA) is classically graded by apnoea hypopnoea index (AHI) which is, however, not well correlated with disease complications and treatment outcomes. Identifying phenotypes and evaluating their response to treatment will help to personalise treatment strategy.

Purpose: To classify childhood OSA patients into different phenotypes and to investigate their associations with clinical outcomes and moderating effect on the response to adenotonsillectomy.

Methods: Latent class analysis (LCA) was applied to identify symptom phenotypes using variables from the Paediatric Sleep Questionnaire (PSQ) from the baseline clinical data of the Childhood Adenotonsillectomy Trial (CHAT). The associations of phenotypes with clinical parameters including polysomnography (PSG) measurements, biochemical results, neurobehavioural outcomes and quality of life (QOL) were tested. Differences in phenotypes' response to adenotonsillectomy were further evaluated in two-way ANCOVA (repeated measures). Latent transition analysis (LTA) was performed to assess the phenotype change after adenotonsillectomy.

Findings: Three phenotypes were identified: Phenotype1 (Heaviest "nocturnal and daytime symptoms" burden), Phenotype 2 (Predominantly daytime inattention burden), and Phenotype 3 (Minimal symptoms).
symptoms), and Phenotype 3 (Predominantly nocturnal symptoms).

The three phenotypes differed significantly from each other in PSQ and QOL score (all \( p < 0.05 \)). Phenotype 3 had significantly lowest cognitive testing score in (Behaviour Rating Inventory of Executive Function) BRIEF, (Child Behaviour Checklist) CBCL, (Conners Rating Scale-Revised) CRSR when compared with Phenotypes 1 and 2 after adjustment for age, gender, BMIs, IgAHI (all \( p < 0.001 \)).

After adjustment of age, gender, BMIz, BMIz change, phenotype \( \times \) time point interaction was significant in PSQ \( (P < 0.001) \), OSA18 \( (P < 0.001) \), CBCL \( (P = 0.029) \) and CRSR \( (P = 0.008) \). However, phenotype \( \times \) time point \( \times \) study arm interactions were significant only in IgCRP \( (P = 0.006) \) and PSQ \( (P = 0.040) \).

After adenotonsillectomy, the majority (67\%) of Phenotype 1 patients transitioned into Phenotype 2 with the cognitive symptoms unresolved. However, 66\% of Phenotype 2 remained as the same phenotype after treatment. 81\% of Phenotype 3 patients resolved from the nocturnal symptoms and transitioned into the disease resolution group Phenotype 4.

Conclusions: Using the machine learning algorithms, our study identified three symptom patterns in childhood OSA, with differential associations with clinical outcomes and response to adenotonsillectomy. Phenotype with heaviest symptom burden had higher resistance to improvements. This study provides insights that symptom phenotyping may help to predict treatment outcomes.

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Paediatric Fiberoptic Endoscopic Evaluation of Swallowing: Service Review with Clinical Audit on Documentation

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Background: Fiberoptic endoscopic evaluation of swallowing (FEES) provides direct visualisation of the anatomy and physiology of swallowing. There is a lack of standardised protocol for FEES performed in children.

Purpose: This study was aimed at systematically evaluating the collaborative ENT and Speech Therapy paediatric FEES performed at Hong Kong Children's Hospital (HKCH) since its inception. The results could guide subsequent service planning and development of paediatric FEES protocol.

Method: A retrospective analysis of 18 FEES performed from October 2019 to August 2021 was done. Demographics of patients, FEES reports and post-FEES progress notes were analysed. They were reviewed independently by two speech therapists using a binary rating system for presence or absence of items based on the protocol used by Cincinnati Children's Hospital Medical Center.

Findings: Half of the patients were below 1-year-old and 61\% were female. Oncological disorder was the most common primary diagnosis (50\%). The complication rate was 5\% (1/18). For FEES documentation, all areas under the four sections of standard protocol were addressed with a reporting rate of 11\% to 100\%. Some areas were described in details with a reporting rate up to 92\% (e.g. location of pharyngeal residue), while some other details were lacking (e.g. amount of aspiration).

Conclusions: Findings indicated FEES is feasible in infants and older children with a low complication rate in HKCH. Clinical documentation covered the essential items including past medical history, anatomy and physiology, secretion management, swallowing deficits. However, inclusion of more detailed documentation varied greatly. The FEES protocol, particularly clinical documentation, should be adhered to in greater details, to facilitate clinical care of patients with dysphagia.

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Inferior Endothelial Function Improved Following Optimisation of Anti-Inflammatory Treatment in Asthmatic Children

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Background: Prior research has explored the potential association between asthma and cardiovascular disease (CVD). However, data has been inconsistent. Confirming the relationship between the two conditions may allow future CVD burden to be lessened following good asthma control.

Purpose: To serially assess endothelial function in physician-diagnosed asthmatic children and to assess the changes in measurements after initiation or up-titration of inhaled corticosteroids (ICS) in those with uncontrolled asthma.

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**Method**: Children aged 6 to 16 years with asthma were recruited to undergo assessment including symptom control (Asthma Control Test (ACT) and Functional Symptom Score (FSS)), spirometry, fractional exhaled nitric oxide (FeNO), and flow-mediated dilation (FMD). FMD is a proven and valid marker of endothelial function. Age-, gender- and body mass index (BMI)-matched non-asthmatic healthy controls was selected for baseline comparison. Asthma subjects were treated with inhaled corticosteroids (ICS) therapy, with repeat measurements carried out at 2 and 4 months from baseline. Linear mixed models were employed to examine effects of ICS therapy across time points.

**Findings**: Forty subjects were studied, 23 had uncontrolled asthma. Subjects with uncontrolled asthma had significantly lower baseline FMD compared to matched controls ($8.0 \pm 0.8\%$ vs $8.6 \pm 0.7\%$, $p=0.012$). Subjects with uncontrolled asthma after treatment showed significantly greater improvements in FMD when compared to the stable asthmatic group after adjustment for age, gender, BMIz ($p (visit*gp)=0.017$). Corresponding improvements were also demonstrated in symptom control, lung function, and FeNO.

**Conclusion**: Children with uncontrolled asthma had reduced endothelial function compared to matched healthy controls. Significant improvement in endothelial function was demonstrated following better asthma control, suggesting poorly controlled childhood asthma could be an important early-life risk factor for future CVD.

**Sleep Duration in Pre-Schoolers is Overestimated by Their Parents**

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**Background**: Parent-reported sleep diary is the most commonly used tool to collect sleep duration data on pre-schoolers. However, there is a lack of research looking into its accuracy.

**Purpose**: To validate the sleep duration obtained from 7-day parent-reported sleep diary against objective measurement.

**Methods**: Data was obtained from a sleep education workshop for pre-schoolers with insufficient sleep (parent-reported sleep duration <25th percentile of a community-based sample). Sleep duration was both reported by parents with a sleep diary and recorded by actigraphy for a week. Data acquisition through actigraphy involved continually wearing a movement (acceleration) sensor on the non-dominant wrist. Levels of agreement between actigraphy and diary recordings were examined by intra-class correlation coefficient (ICC) and Bland-Altman plot.

**Findings**: Data was successfully obtained from 39 preschoolers (13 male, mean age=$4.8 \pm 0.7$) at baseline. The parent-reported average sleep duration was significantly greater than the actigraphy-measured sleep duration ($560 \text{ min} \pm 45$ vs. $545 \text{ min} \pm 49$, $p<0.001$). The ICC between the two measurements was 0.84 (95% CI 0.59-0.93). The agreement between actigraphy-derived and parent-reported sleep of the baseline visit was Mean=$15.0$ and SD=$23.5$ min. The 95% CI limits of agreement was -31 to 61 min, with no significant proportional bias.

**Conclusion**: Despite an acceptable agreement, 7-day parent-reported sleep duration was an over-estimation when compared to the actigraphy-measured sleep duration.

**Rehabilitation Outcome of Severe Feeding Disorder in Children with Chronic Illness**

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**Background**: Children with chronic illness frequently have feeding problems as a result of complex interactions between medical, developmental, behavioural and psychosocial factors.

**Purpose**: This study aims to review the feeding outcome in children with severe feeding disorder due to chronic illness after participating in a multidisciplinary feeding program.

**Methods**: In this retrospective study, we reviewed the medical records of children admitted to a paediatric rehabilitation centre for intensive feeding program between January 2017 and December 2018, with follow-up up to July 2021. Patient demographics, anthropometric parameters, medical background, swallowing assessment and tube feeding duration were recorded.

**Findings**: Among the 18 children (age 2m to 13yr) who completed the training program, ten (55%) successfully achieved full oral feeding. Four (22%) weaned off feeding tube at the end of program. Six (33%) weaned off feeding tube when receiving follow-up out-patient service. The
median tube feeding duration was 18 months (range 8 to 50 months) in children who achieved full oral feeding. Among them, seven children (70%) developed behavioural feeding problems, a complication associated with prolonged tube feeding. Six out of fourteen (43%) children with medical complexity achieved full oral feeding after training. Global developmental delay was common (94%) in our cohort, indicating multidisciplinary neurodevelopmental training in addition to feeding program.

**Conclusion:** In children with severe feeding disorder due to chronic illness, oral feeding rehabilitation took time and required multidisciplinary approach. Besides medical follow-ups, the patients and their families often required resources to help them face challenges in developmental, behavioural and psychosocial aspects.

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**Back-To-Back Comparison of Diagnostic Efficacy Between Genome Sequencing and Exome Sequencing Reanalysis in Primary Ciliary Dyskinesia Cohort**

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**Background:** Primary ciliary dyskinesia (PCD) is a heterogenous genetic disorder with more than 44 genes correlated. With the rapid improvement of next generation sequencing, exome sequencing is frequently utilised in the clinical setting for molecular diagnosis. However, there is still an ongoing debate on whether to proceed with genome sequencing (GS) or perform exome sequencing reanalysis (rES) if the initial results return negative. By using a back-to-back double-blinded comparison, this study aims to evaluate between the two methodologies. This comparison serves as the first to inform clinicians and clinical geneticist on the optimal next action after a negative exome sequencing result.

**Methods:** In this study from 2015 to 2020, 55 participants (29 males and 26 females) suspected of PCD were recruited into this study and exome sequencing was performed. Negative or inconclusive exome sequencing results were considered for GS due to high genotype-phenotype correlation. GS was then performed on 30 (13 males and 17 females) inconclusive exome sequencing results. In GS, 50% concordant CNVs calls from ERDS and CNVnator were analysed in this study. Two teams of genome analysts and bioinformaticians were randomly allocated to GS or rES and were blinded to the other team's analysis. The time for bioinformatics, analysis, and discussion were also recorded for evaluation.

**Findings:** Exome sequencing revealed 5 positive cases in the initial batch of exome sequencing. The positive case included mutations in RSPH4A, CCDC40, DNAH11, and CFTR (2 cases were correlated to cystic fibrosis). GS and rES, in this cohort, achieved one new diagnosis and identified eight VUS results with potential clinical relevance. The new diagnosis in DNAH11 was made due to an update in medical literature which upgraded a VUS to likely pathogenic, thereby confirming the diagnosis. This variant was identified in both GS and rES. GS was also able to detect an additional VUS result due to low coverage in rES within exon 3 of the DNAAAF3 gene. The patient's functional result matches previously reported DNAAAF3 static ciliary movement.

**Conclusion:** Beyond deep intronic changes, CNVs, and SVs, GS had an additional advantage of uniform coverage over the exons. Here we have investigated a back-to-back comparison in diagnostic efficacy between GS and rES. Further investigations are needed to explore deep intrinsic mutations and structural variations in cases with one VUS mutation found.

**Acknowledgement:** This study was supported by the Society for the Relief of Disabled Children, the Health and Medical Research Fund (HMRF), Li Ka Shing Donation Account: Enhanced New Staff Start-up Packages, and the Edward and Yolanda Wong Fund.
Establishment of Hong Kong Neuromuscular Disorder Patient Registry

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**Introduction:** Neuromuscular disorders (NMDs) are a group of diseases affecting the peripheral nervous system (1). Many NMDs cause disability or even premature death (2). We aim to design and establish a robust NMD patient registry in Hong Kong.

**Methods:** By modelling international NMD patient registries, we designed patient-professional reported questionnaires to collect the demographic, clinical characteristics, genetic details, family history, investigation findings and specific treatment of NMD patients. Patients were recruited through Hong Kong West Cluster (DKCH, QMH) and Kowloon Central Cluster (HKCH). We also developed self-registration online platform. \( p<0.05 \) was considered statistically significant.

**Findings:** Since June 2019, 125 NMD patients have been enrolled in the registry with 12 participants registered online. The registry recruited 13 types of NMDs, including spinal muscular atrophy (SMA) (n=31), Duchenne muscular dystrophy (DMD) (n=19) and congenital myopathy (n=18). The age range was 7 months to 63 years old. 65.6% of those enrolled were children (<18 years old). 63.2% were male. 64.8% of the patients had genetic diagnosis. The registry has contributed to two studies. The first one is a prospective study of clinical efficiency of Nusinersen in SMA patients (n=22). 14/16 SMA patients showed improvement in at least one of motor performance (CHOP intend/RULM/HINE/HFMSE) and health-related quality of life after 1st year of treatment. The second study is the reactogenicity and immunogenicity study of the COVID-19 vaccine in DMD patients (n=4). Data will be available in October.

**Conclusion:** Hong Kong Patient registry has contributed to ongoing and new research study to optimise medical care.

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Natural History of Acute Kidney Injury Among Critically Ill Children

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**Introduction:** Acute kidney injury (AKI) among critically ill patients contributes to both morbidity and mortality. Local data on progression of AKI among critically ill children is lacking.

**Purpose:** We described the epidemiology of AKI among children admitted to the paediatric intensive care unit (PICU) of the Hong Kong Children's Hospital. This is the interim analysis of the prospective cohort study (E-AKI-DRUG) conducted in our PICU.

**Methods:** All children aged 1 month to 18 years old would be enrolled. Exclusion criteria included those with pre-existing chronic kidney disease, impaired renal function for \( \geq 3 \) months, immediate post-renal transplant and short PICU stay of \( \leq 1 \) days. Children with no urinary catheter would be excluded from urine calculation. AKI would be defined using the KDIGO criteria. The data of initial four months would be presented.

**Findings:** We identified 62 children with 63 episodes of admission for this analysis. Male accounted for 59% of the admissions and the median (interquartile range) age was 6.1 (6.6) years old. The overall incidence of AKI during PICU stay was 48.4% (Stage 1: 20.3%; Stage 2: 12.5%; Stage 3: 15.6%). 33.3% of children already developed AKI on PICU admission and 53.3% of children attained the highest stage of AKI on day 1 of admission. The median duration of AKI during PICU stay was 1 (3) day. Most children with AKI were non-oliguric with their urine output during PICU stay being 3.9 (2.9) ml/kg/hour. Among children with AKI, only 32.3% of them had their serum creatinine level (SCr) returning to baseline level. The duration from peak SCr to lowest SCr was significantly longer among those with higher stage of AKI (\( p=0.002 \)). CRRT was required among 6.3% of children. Upon PICU discharge, AKI was not yet resolved among 38.7% of patients (Stage 1: 12.9%; Stage 2: 16.1%; Stage 3: 9.7%) and 3.1% of the patients remained dialysis-dependent. The staging (\( p<0.001 \)) and the duration of AKI (\( p=0.018 \)) were both associated with worse stage AKI at PICU discharge. Overall PICU mortality was 4.7% and AKI was associated with longer PICU stay (5 vs 3 days, \( p=0.003 \)) and higher mortality (12.9% vs 0%. \( p=0.05 \)).
Conclusion: AKI was common among critically ill children and most of them acquired the condition on 1st day of PICU admission. AKI was not resolved in a significant proportion of children upon PICU discharge, and a higher AKI stage and longer AKI duration were associated with worse renal outcome at PICU discharge.

Acute Kidney Injury and Electrolytes Disturbances Among Critically Ill Children with Malignancy
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Introduction: Acute kidney injury (AKI) and electrolyte disturbances are common among critically ill children and contributes to both morbidity and mortality. Children with oncological diagnosis is at risk of developing both conditions. We described the epidemiology of AKI and electrolytes disturbances among children with malignancy admitted to the paediatric intensive care unit (PICU) of the Hong Kong Children's Hospital.

Methods: This is the interim analysis of the prospective study on the epidemiology of AKI and electrolytes disturbances (E-AKI-DRUG) conducted in our PICU. All children aged 1 month to 18 years old would be enrolled, except those with pre-existing chronic kidney disease, impaired renal function for ≥3 months, immediate post-renal transplant and short PICU stay of ≤1 days. Children with no indwelling urinary catheter would be excluded for urine calculation. AKI would be defined using the KDIGO criteria and serum electrolytes profiles on sodium, potassium, calcium, phosphate and magnesium were reviewed. The data of initial four months would be presented.

Findings: Altogether 63 episodes of admission were enrolled. 59% were male and median (interquartile range) age was 6.1 (6.6) years old. 49.2% of patients were oncology patients. The overall incidence of AKI during PICU stay was 48.4% (Stage 1: 20.3%; Stage 2: 12.5%; Stage 3: 15.6%). Children with malignancy had a significantly higher PIM3 score (p=0.014), more use of mechanical ventilation (p=0.041) and higher number (p<0.01) and doses (p=0.023) of nephrotoxic medication exposure than those without malignancy. Oncology patients had a significantly higher incidence of AKI compared to non-oncological patients (62.5% vs 34.4%, p=0.024). Hypophosphataemia, hypocalcaemia and hypokalaemia were the most common electrolytes disturbances among oncology patients (incidence of 87.5%, 77.4% and 56.3% respectively). There was significantly more hyponatraemia among oncological patients (43.8% vs 9.7%, p<0.01). Tubular dysfunction was common among children with electrolyte disturbance and oncological patients had significantly more urinary phosphate wasting than those without malignancy (66.7% vs 33.3%, p=0.046).

Conclusion: Children with malignancy admitted to the PICU had a higher risk of developing AKI and electrolytes disturbances. Tubular dysfunction, especially urinary phosphate wasting, was commonly observed among children with malignancy having electrolyte disturbances.
prioritised by gene burden analysis. The excess of rare protein-altering variants strengthened the gene-disease association of three established genes (GATA6, NOTCH1, TBX1) for tetralogy of Fallot. This study also provided additional evidence for the potential roles of other prioritised genes (ANKRD11, ARID1A, MYH6, SOS1, STRA6, TRAF7) in the complex aetiology of CTD. Four of these genes were previously reported to be related to syndromes with extracardiac features but not identified as genetic causes of isolated CTD.

**Conclusion:** Our results substantiated the important genotype-phenotype associations in the largest Chinese cohort of CTD in Hong Kong. Candidate genes associated with CTD related syndromes were enriched in this nonsyndromic cohort, providing novel insight into the complex genetic architecture of CTD.

**Acknowledgements:** This study was supported by grants from the Society for the Relief of Disabled Children and the Children's Heart Foundation of Hong Kong.

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**Establishment of a Paediatric Palliative Care (PPC) Team in Department of Paediatrics**

**SP Law**

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**Background:** Palliative care should be commenced once illness is diagnosed, rather than at decline, and it should be continued. With the increasing number of children with complex chronic conditions or sudden complex illnesses, as well as the needs of family-centered care, Paediatric Palliative care (PPC) is crucial and should not be delayed. In HK, the PPC service provided by Hong Kong Children's Hospital and NGOs were not always 24/7 available, and therefore it was necessary to form a local PPC team to readily intervene for those patients and families in need.

**Purpose:** To establish a team to provide PPC service.

**Methods:** A PPC workgroup was formed in 2020. PPC policy and documentation were standardised to improve workflow and clinical handover. Collaboration among professionals across different sectors and NGOs was facilitated for comprehensive intervention. Patients and families were supported for their physical, psychological, social and spiritual problems. PPC trainings were provided for nurses and doctors to raise awareness and enhance their skills and knowledge.

**Findings:** Total 36 referrals were made by physicians, the families were interviewed by PPC team within 0 to 3 days. The families were being referred to the professionals across different sectors and NGOs for support according to their problems and needs. End-of-life care and bereavement care were provided to the families of all the deceased patients.

**Conclusion:** A systematic PPC service could not only increase the quality of care, but also enhance family-centered care, and promote quality of life for the patients and their families.

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**Eczema in Hong Kong: Prevalence Trends and its Association with Breastfeeding**

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**Introduction:** Eczema is a common childhood allergic disease which significantly affects patients' quality of life.

**Purpose:** To review the trend of childhood eczema in Hong Kong and investigate its association with breastfeeding.

**Methods:** Parents were recruited from kindergartens in Hong Kong from late 2020 to mid-2021, to complete a standardised questionnaire adapted from the ISAAC. The local prevalence of childhood eczema was retrieved from two territory-wide cross-sectional studies conducted in 2001 and 2009. The prevalence of childhood eczema was expressed as a proportion with a 95% confidence interval (CI). The association between child eczema and the aforementioned factors was evaluated using univariate and multivariate analysis.

**Findings:** The prevalence of lifetime eczema and current eczema increased significantly from 31.9% in 2009 to 37.2% (95% CI: 0.35-0.40, p<0.001) in 2020 and from 4.5% in 2001 to 11.5% (95% CI: 0.10-0.13, p<0.001) in 2020 respectively. Childhood eczema was positively associated with a family history of eczema (OR=2.71, p<0.001) and breastfeeding (OR=1.41, p=0.006). After controlling for family history, the odds of having eczema increased by 1.05 times (95%CI 1.01-1.07, p=0.002) per 6-month increase in breastfeeding time, and 1.05 times (95%CI 1.02-1.08, p=0.002) per 2-month increase in exclusive breastfeeding time. Yet, children with an early onset of eczema were significantly more likely to be breastfed (p=0.001) and exclusively breastfed (p=0.002) for a longer duration.
Conclusion: The prevalence of childhood eczema has significantly increased over the decade. While genetic factor is the key determinant of childhood eczema, breastfeeding is a risk factor for eczema after controlling for family history in this study.

Noise Reduction Program in Neonatal Intensive Care Unit (NICU)

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Introduction: Infants in NICU are constantly exposed to ambient noise that often exceeds recommended levels. Premature Infants are particularly vulnerable to elevated noise levels due to their immature auditory pathway. Many studies showed that such excessive noise will lead to many adverse health consequences. We noted that noise level in our NICU was ranged from 52 to 79 dB that often exceeded the AAP recommended (45dB) levels. Although some loud noise in the NICU is unavoidable, strategies were implemented to decrease the noise levels in our busy NICU.

Objectives:
1. To explore the sources of excessive loud noise in our NICU
2. To implement the strategies to alleviate noise sources, and
3. To enhance staff awareness of maintaining a quiet environment

Methodology:
1. To perform literature review on the evidence of noise source in NICU
2. To study the current noise sources and staffs' perception on sources of noise in local NICU
3. To raise staff awareness on the impact of loud noise by providing briefing and training sessions
4. To implement strategies for noise reduction
5. To monitor the noise level in NICU
6. To compare the noise level before and after the program.
7. To monitor the staff’s behavioural change after implementation of the noise reduction program

Results and outcomes: The mean ambient noise level was lowered within NICU by 9% from baseline measurements in the span of a year. There was also decreasing in individual items from 0.3 db to maximum 19.7 db after implementation of difference strategies. Staff’s behaviour was continuous monitoring, and the program was sustaining.

Challenges in Nutritional Support for Children with Brain Tumour: An Adaptive Solution Against All Odds

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Introduction: Feeding disorders are commonly observed in paediatric neuro-oncology patients. The causes are multifactorial involving neurological dysfunction, treatment related emesis, mucositis and behavioral changes. Potential complications of malnutrition including electrolyte disturbances, growth deprivation, increased risks for infection and poor quality of life are often overlooked.

Method: Case-report: A 5-year-old boy initially presented with obstructive hydrocephalus. Imaging and pathology confirmed the diagnosis of classic medulloblastoma group-3 with extensive leptomeningeal metastasis. Tumour excision was performed, followed by multiple ventriculoperitoneal-shunt revisions and chemoradiotherapy. Poor feeding and weight-loss persisted despite strategic nutritional consultations because of continued vomiting with intolerance to nasogastric/nasojejunal tube placement. Prolonged rescue total-parenteral-nutrition was required to regain weight from <3rd to 25th percentile. Feeding-gastrostomy was considered while isotope-milk-scan demonstrated significant delayed gastric-emptying. Primary transgastric-jejunal (TGJ) tube insertion proceeded eventually upon optimal recovery of blood-counts after cycle-2 maintenance-chemotherapy plus G-CSF therapy. Intraoperatively, ventriculoperitoneal-shunt in-situ at gastric-position was localised and safe-guarded fluoroscopically and laparoscopically prior to siting of gastrostomy in close proximity; low-profile-TGJ tube was inserted ‘Seldinger’ fashion uneventfully. With expectant suboptimal wound healing postoperatively, extended antibiotic-prophylaxis and proton-pump-inhibition was adopted to minimise shunt-contamination risks.

Outcomes: Recovery was uneventful with early escalation to full jejunal-feeding. Adaptive/alternating gastric and jejunal-feeding regimen correlating subsequent chemotherapy-cycles was adopted and well-tolerated at home, regaining weight from 25th to >50th percentile.

Conclusion: Primary TGJ placement is novel in our local experience. All due technical challenges and oncological/operation-risks must be considered in
transdisciplinary setting. It facilitates adaptive enteric feeding regimen when appropriate, a promising strategic option amongst paediatric neuro-oncology patients acquiring difficult feeding-disorders.

**Urinary Tract Infection in Infants Younger Than 2 Months – Which Imaging Approach to Adopt?**

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**Aims:** A well-established imaging guideline for urinary tract infection (UTI) in infants younger than 2 months old is lacking. We analysed the characteristics of this group of patients to look into the possibility of adopting a more selective imaging approach for investigation.

**Methods and Material:** This is a post-hoc analysis using data of the patient cohort collected between 2005 and 2006 for the study by Wong et al in 2010.

**Results:** 170 patients were selected and reviewed. Eleven patients with significant urological abnormalities were identified. They had at least one of the following characteristics: (1) atypical features, (2) abnormal urinary ultrasound (USG) report and (3) UTI recurrence within the follow-up period.

**Conclusions:** Following first occurrence of UTI, infants younger than 2 months old presenting with atypical features, abnormal USG of the urinary system, or recurrence of UTI may warrant more extensive investigations with micturating cystourethrogram (MCUG) and dimercaptosuccinic acid (DMSA) scans. For those with typical features at presentation, USG of the urinary system alone may be adequate as basic screening, unless UTI recurs. Further studies are required to establish a specific guideline for this group of patients.

**Challenges in the Management of an Infant with Matthew Wood Syndrome Having Pulmonary Hypoplasia and Visual Impairment: A Case Report**

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**Background:** Matthew Wood syndrome (MWS) is a rare entity in which the two main characteristics include anophthalmia and pulmonary hypoplasia. Other problems such as diaphragmatic entration, duodenal stenosis, pancreatic malformations, intellectual disability, cardiovascular abnormalities, and intrauterine growth retardation have also been reported.

**Purpose:** This is a case report discussing the challenges encountered in the long-term care of a patient with MWS.

**Findings:** We report a five-year-old boy who had MWS diagnosed in the neonatal period presenting with bilateral microphthalmia, bilateral pulmonary hypoplasia, diaphragmatic entration, and congenital cardiac defects. Misalignment between the light-dark cycle and the endogenous circadian timing causes circadian rhythm sleep disorder (CRSD) – nonentrained type. With nonentrained type CRSD, MWS patients might be somnolent during the day while insomnia is experienced at night. Sleep disturbances have a great impact on the quality of life of this group of patients and limit their opportunity of training in the daytime.

On the ground that they have visual impairment, cognitive delay and craniofacial dysmorphism, numerous difficulties are encountered during the initiation of non-invasive ventilation. We did not target a perfectly normal blood gas reading as the treatment goal, rather a balance on optimal ventilatory support against safety and patient's comfort are of a pivotal importance.

**Conclusion:** Main clinical features of MWS include anophthalmia/microphthalmia and pulmonary hypoplasia or agenesis. CRSD in this group of patients and constraint on optimising ventilatory support were important issues in their long-term care.
Clinical Quiz

What is the Diagnosis?

SSW Cheng, SKL Ho, IFM Lo

The proband is a 17-year-old boy. He was born full term in Hong Kong to a non-consanguineous Chinese couple. Antenatal checkup was normal. He was referred to genetic clinic for short stature. His height centile drifted away from 25th centile at birth to below 3rd centile at 34 months of age. X-ray showed mildly metaphyseal spraying of distal radius and ulna, slight bowing of distal radial shaft and delayed bone maturation at two years of age (Figure 1 C). On examination at 34 months of age, he had macrocephaly with head circumference of 52.5 cm (above 97th centile). His body weight was 12.5 kg (25th centile) and body height was 84 cm (3 cm <3rd centile). He had frontal bossing, hypertelorism, downslanting palpebral fissures, short nose, lumbar lordosis, normal teeth with tibial bowing especially left lower limb. He had normal intelligence. His mother had short stature of 144.8 cm (<3rd centile). His mid-parental height was 163.7 cm (10-25th centile). He had mild hearing loss at high frequency without need of hearing aids. Biochemical result showed low serum phosphate level 0.73 mmol/L (1-1.95 mmol/L), normal calcium level, elevated alkaline phosphatase 638 IU/L (104-345IU/L) and reduced tubular resorption of phosphate corrected for glomerular filtration rate (0.5 mmol/L). He was put on phosphate supplement, hydrochlorothiazide and vitamin D since 34 months of age. Later, his renal ultrasound showed nephrocalcinosis at 5.5 years old. His current height was 143 cm at 17-year-old (15 cm <3rd centile). He had regular knee pain and on acupuncture for pain relief.
Figure 1  (A) Facial profile of proband at 10 months of age;  (B) Facial profile of proband at 17 years of age;  (C) X-ray hand of the patient at 2 years of age showing splayed distal radial and ulnar metaphysis with slight bowing of distal radial shaft and delayed bone maturation;  (D) Mild bowleg was noted at 2 years of age;  (E) Body stature of proband at 2 years of age;  (F) Body stature of proband at 17 years of age;  (G) Bowlegs were more prominent at 17 years of age (with consents for publication by parents).
MCQs

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

(A) Prescribing Books for Preschoolers under Comprehensive Child Development Service in Hong Kong East: A Pilot Study

1. Which of the following young children was included in the study?
   a. Maternal mental illness
   b. Maternal perinatal mood disorder
   c. Maternal substance abuser
   d. Maternal teenage pregnancy
   e. All of the above

2. Which of the following(s) is / are the essence of book prescription?
   a. Change parental belief
   b. Model book choices
   c. Demonstrate reading aloud techniques
   d. a & c
   e. a, b & c

3. What is / are the components of Reach Out & Read Model adopted in this study?
   a. Provide free developmentally appropriate picture books
   b. Anticipatory guide about reading aloud during clinical consultation
   c. Provide literacy-rich waiting area in clinic
   d. a & b
   e. a, b & c

4. In this study, which of the following is false?
   a. Higher maternal age predicts greater literacy orientation improvement
   b. Higher maternal age predicts higher reading aloud frequency
   c. Mother at work predicts less improvement in number of books at home
   d. Mother at work predicts less literacy orientation improvement
   e. Increase in baby’s age predicts higher reading aloud frequency

5. What is / are the benefits of start reading from infancy?
   a. Associate books with enjoyment
   b. Promote joint attention
   c. Develop reading habit
   d. Improve mother-baby interaction
   e. All of the above

(B) Monocyte HLA-DR Expression in Children with Acute Bacterial Meningitis and Meningococcemia: A Predictor of Outcome and Prognosis

1. What is the causative agent of meningococcemia?
   a. Escherichia coli
   b. Neisseria meningitidis
   c. Streptococcus pneumoniae
   d. Haemophilus influenzae type b
   e. Pneumocystis jiroveci

2. What are the possible outcomes of meningococcemia?
   a. Loss of life
   b. Peripheral gangrene
   c. Coma
   d. Neurological deficits
   e. All of the above

3. Which of the following is not one of the monocyte functions?
   a. Phagocytosis
   b. Cytokine production
   c. Antibody production
   d. Presentation of antigens to lymphocytes
   e. Oxidative burst response
4. Which of the following is true about monocyte HLA-DR expression?
   a. HLA-DR molecules reflect the activation state of monocytes
   b. HLA-DR molecules are important for presenting antigens to the CD4+ cells
   c. Decreased monocyte HLA-DR expression is considered as a reliable marker of immune paralysis
   d. All of the above
   e. None of the above

5. The low percentage of HLA-DR expression on monocytes could be a valuable predictive marker for poor prognosis in;
   a. Neonatal sepsis
   b. Major surgery and trauma
   c. Bacterial meningitis and meningococcemia
   d. Pancreatitis
   e. All of the above

(C) The Clinical Effects of GnRHa in Treating Idiopathic Central Precocious Puberty in Girls

1. What is the cause of ICPP?
   a. The increased release of TSH
   b. The decreased release of FSH
   c. The increased release of GnRH
   d. The inactivation of HPGA
   e. None of the above

2. Which is the first choice for treating ICPP?
   a. FSH
   b. LH
   c. GnRH
   d. GnRHa
   e. None of the above

3. Which is not the change after treating ICPP?
   a. The breast glands become softer and smaller
   b. Menstruation disappeared
   c. Vaginal secretion decrease or disappear
   d. Height growth rate is greater
   e. BMI is significantly decreased

4. Which is the change in ovaries after treating ICPP?
   a. The longitudinal ovarian diameter increases
   b. The transverse ovarian diameter increases
   c. The anteroposterior ovarian diameter increases
   d. The volume of the ovaries shrink
   e. The anteroposterior ovarian diameter decreases

5. Which of the following is not true for ICPP treatment?
   a. The transverse diameter of the uterus decreases during treatment
   b. The volume of the uterus decreases during treatment
   c. There is no significant change in the longitudinal uterine diameter, anteroposterior uterine diameter, and uterine FCR before and after treatment
   d. There is significant change in the thickness of the vaginal wall before and after treatment
   e. There is no significant difference in the anteroposterior diameter and transverse diameter of the cervix before and after treatment

(D) Perinatal and Developmental Outcomes of Teenage Pregnancy: An Analysis of a 10-year Period in a Local Region in Hong Kong

1. Which of the following perinatal outcomes is teenage pregnancy associated with?
   a. Preterm delivery
   b. Small for gestational age babies
   c. Babies with low birth weight
   d. Babies with congenital anomalies
   e. a, b & c

2. Teenage mothers have higher chances of giving birth to...
   a. Babies who are large for gestational age
   b. Babies with Apgar score <7 at 5 minutes of life
   c. Babies who are born at <37 weeks of gestation
   d. Babies who have congenital anomalies
   e. Babies who have very low birth weight

3. What is the risk factor found in this study that is related to developmental delay in children of teenage mothers?
   a. Maternal smoker
   b. Family on CSSA support
   c. History of child abuse
   d. Prior CCDS follow-up
   e. Childcare assistance
4. What other factors may influence a child's developmental progress?
   a. Parents' intelligent quotient
   b. History of breastfeeding
   c. Co-parenting conflicts
   d. None of the above
   e. All of the above

5. Which of the following statements is true?
   a. Teenage mothers tend to give birth to babies who are large for gestational age
   b. Babies born to adult mothers have lower rates of NICU admissions
   c. Maternal smoking does not affect a child's developmental progress
   d. Teenage mothers have higher odds of giving birth to preterm babies than adult mothers
   e. Babies born to teenage mothers have more chance of sustaining birth trauma

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**Answers of October issue 2021**

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Our Fond Memory
of the Late Dr. CHIU Man Chun (趙孟準醫生)

BBS 1974, MRCP (UK) 1979, DCH (Lond) 1979,
FRCP (Edin) 1990, FRCP (Glasg) 1991, FHKCPaed 1991,
FHKAM (Paediatrics) 1993, FRCP (Lond) 1995, FRCPCH 1997

Honorary Life Member of the Hong Kong Paediatric Society (2009)
Member of the Accreditation Committee and the Committee of Subspecialty Board,
Chairman of the Examination Committee of the Hong Kong College of Paediatricians
Chief of Service of the Department of Paediatrics at the Princess Margaret Hospital (1992-2010)

Dr. CHIU Man Chun was graduated from the Faculty of Medicine, the University of Hong Kong in 1974. After graduation, he was trained as paediatrician at the Queen Elizabeth Hospital and worked as Senior Medical Officer from 1981-1988. He was professionally trained in Paediatric Nephrology at the Great Ormond Street Hospital and Guy's Hospital in the United Kingdom. Upon his return from training, Dr. Chiu joined the new paediatric unit at the Princess Margaret Hospital as Consultant Paediatrician in 1988 and became the Chief of Service since 1992 till his retirement in 2010.

Dr. CHIU had great contributions to the field of paediatrics and child health throughout his professional life. He was one of the pioneers to establish paediatric nephrology in Hong Kong in terms of service development, training as well as patient and family support. He had set up the Paediatric Nephrology Centre at the Princess Margaret Hospital to provide holistic care to patients and families in particularly taking care of their psychological wellbeing through the unique clinical psychologist service provided at the department level for renal patients and children with other chronic illnesses. At the community level, he was the founder of the Children's Kidney Fund which was established in 1996 to support paediatric renal patients and their families.

Dr. CHIU demonstrated his capable leadership in the development of novel services. He was the Co-chairman of Central Coordinating Committee (COC Paediatrics) of the Hospital Authority from 2002 to 2005. He helped the Hospital Authority to draft the service model of the Centre of Excellence in Paediatrics in 2007 which had laid the foundation to the development of the current Hong Kong Children's Hospital.

Dr. CHIU had remarkable visions in professional development and nurturing of new generations. The Paediatric Manual he published with 5 subsequent editions has not just benefited paediatricians in Hong Kong but also in other Asian countries. He was also the co-author of Paediatric Nephrology Handbook, Neonatal Manual and many other professional publications. Dr. CHIU had enormous contributions in professional bodies both locally and internationally. He was the Chairman of the Travelling Funding of the Hong Kong Paediatric
Society to encourage members to advance professional knowledge through participation in international meetings. He was awarded the Honorary Life Member of the Hong Kong Paediatric Society in 2009. He also served the Hong Kong College of Paediatricians on the Accreditation Committee, the Examination Committee, the Task Force for Higher Training of Paediatric Subspecialties and subsequently the Committee for Subspecialty Boards. He was the founding members of many regional and international societies. Through his international connections, he had enhanced the local training of paediatric nephrology to meet the world standard.

Besides the eminent achievements in the medical profession, Dr. CHIU was also gifted with special talent in music and writing. He was a well-known musician, lyricist, and writer in the local community with numerous masterpieces. He had inspired and healed many souls through the Chinese hymns he wrote for the Christian music ministry.

We are so sad that Dr. CHIU has left us. To the medical profession, we have lost a phenomenal leader, a respectable teacher, a close friend and a multi-talented colleague. To the children and families, they will forever miss this dedicated and passionate doctor who has devoted his lifetime to work for the betterment of children and support the families with all his possible capacities. He had indeed established a strong foundation for his successors and the young generation to develop quality services for children in Hong Kong and demonstrated clear directions for colleagues to follow. He will be eternally remembered by all of us in the field.

Dr. CHIU passed away peacefully on 29th September 2021 in Hong Kong. Memorial Service would be held at the Methodist Church in Wanchai on 13th November 2021. To his family, we would like to convey our most sincere and deepest condolences.

Dr. Chok-wan CHAN  
President of International Pediatric Association (IPA) (2007-2010)  
Honorary President of Asia-Pacific Pediatric Association (APPA)  
President of the Hong Kong Paediatric Society (1982-1985)  
On behalf of the Council of the Hong Kong Paediatric Society  
29th October 2021, Hong Kong
CLINICAL QUIZ (p85-86) ANSWER

What is the diagnosis?

The boy presented with macrocephaly, short stature, bowlegs, radial and ulnar metaphseal spraying and hypophosphatemia. The clinical features were compatible with hypophosphatemic rickets. In view of maternal history of short stature, X-linked dominant hypophosphatemic rickets / X-linked hypophosphatemia (XLH) (OMIM#307800) and autosomal dominant hypophosphatemic rickets / autosomal dominant hypophosphatemia (ADH) (OMIM#193100) were our top differentials.

Sequence analysis for coding exons of the PHEX (OMIM*300550) gene showed a hemizygous nonsense c.1104G>A (p.Trp368*) mutation in exon 10 of the PHEX gene. The variant was not detected in maternal blood. It was a de novo condition. The diagnosis of XLH (OMIM#307800) was substantiated.

The phenotypic spectrum of XLH varies from isolated hypophosphatemia to severe lower limbs bowing. It frequently manifests in the first two years of life, when weight bearing period starts, as bowing of lower limbs, delayed walking, abnormal gait or growth stunting. Our patient had the height centile drifting away from birth to below third at around 2.5 years old. He experienced mild leg bowing at 2 years old. The disease may be initially misdiagnosed for vitamin D deficiency, but biochemical investigations revealing lack of response to vitamin D supplements (vitamin D resistant) usually allows the diagnosis. X-ray demonstrates typical features of rickets without significant bone resorption (as opposed to vitamin D deficiency rickets).

The prevalence of XLH is estimated between 1.2-3.0/60,000. The clinical manifestation is variable. Thus under-diagnosis is not uncommon. Despite a wide degree of clinical variability, penetrance is approaching 100% by age one year. There is no known difference between penetrance in males and females.

What are the clinical features of XLH?

XLH affected individuals would experience a diverse range of medical problems. At the time of diagnosis, they may experience delayed and disproportionate growth, lower extremity bowing, rickets, and cranial abnormalities and delayed motor development / gait problem. Individuals appear disproportionate with leg length SD score being significantly lower than sitting height SD score. Genu varum or genu valgus can occur while torsion and rotation of lower extremity may occur sometimes. Rickets features, e.g. wrist swelling, rachitic rosary, swollen knees, craniotabes, Harrison's sulci and bone pain would be found in affected individuals. In children, X-ray would reveal widened / frayed / cupped metaphysis and sometimes beading of ribs suggesting poor skeletal mineralisation leading to overgrowth of costochondral joint cartilage. Cranial abnormalities, e.g. frontal bossing, craniosynostosis, and Chiari malformations were reported in some patients with XLH but the exact incidence is unknown. The delayed motor development and gait problem are mainly contributed by lower limb bowing.

When they grow older, they may experience dental abnormalities, joint pain and impairment mobility, muscle pain or weakness, osteomalacia and stress fracture and hearing difficulties. Individuals with XLH are prone to spontaneous dental abscesses which are due to change in the dentin component of teeth. In adults, enthesopathy (calcification of the tendons, ligaments, and joint capsules) associated with joint pain and impaired mobility are common complaints. Sensorineural hearing loss has been reported but the actual prevalence of hearing loss is not known. In some patients with affected hearing, radiological finding showed generalised osteosclerosis and thickening of the petrous bone. Adults with XLH have a significantly reduced final height with a standard deviation score (SDS) of -1.9 compared to reference standards. Female and male with XLH have with similar clinical presentation.
What are the biochemical defects and molecular diagnosis of XLH?

XLH is a rare disease caused by mutations in the Phosphate Regulating Endopeptidase Homolog, X-linked (PHEX) gene. The PHEX gene is located on chromosome Xp22.11. This endopeptidase is primarily expressed on the surface of osteoblast, osteocytes, odontoblasts and cementoblasts. This endopeptidase regulates osteogenic cell differentiation and bone mineralisation. The pathophysiology of XLH is complex and it involves different molecular pathways that variously contribute to different manifestations of the disease. One important molecular pathway is that the inactivating mutation in PHEX gene will result in elevated level of fibroblast growth factor 23 (FGF23). FGF23 elevation contributes to hypophosphatemia by limiting intestinal phosphate absorption through restricting active vitamin D (1,25 (OH)2 vitamin D) response to hypophosphatemia and increasing urinary phosphate excretion by downregulating renal sodium-phosphate transporters (Figure 2).

Thus, at the time of diagnosis, patients show low serum phosphate levels secondary to increased phosphaturia (reduced tubular resorption of phosphate corrected for glomerular filtration rate (TmP/GFR)). The normal physiologic response to hypophosphatemia of an elevation of 1,25 (OH)2 vitamin D is absent. Usually, serum calcium and 25-hydroxy vitamin D are within the normal range while parathyroid hormone is normal to slightly elevated. At childhood period, Alkaline phosphatase is characteristically elevated, especially during time of rapid growth, and would returns to normal in adulthood with or without treatment.

Among the individuals with genetically confirmed XLH, around 70% is related to sequence error in PHEX gene (small intragenic insertion / deletion, missense, nonsense and splice-site variant) detected by sequence analysis. The remaining 30% is related to (multi)exon or whole gene deletion detected by gene-targeted deletion / duplication analysis. Studies showed truncating variants or pathogenic variants in the C-terminal portion of PHEX would have
more severe bone disease (severe bowing of lower limbs and the need for surgery). Patients with clearly pathogenic variants (e.g. nonsense variants, splice-site variants and frameshift variants) presented with lower tubular resorption of phosphate and lower 1, 25 (OH)2 vitamin D level than those with possible deleterious variants (missense variants and in-frame deletion).

Genetic counseling and management of XLH individuals

XLH shows an X-linked dominant inheritance pattern. The mother of a proband may be affected (heterozygote) or the affected individual may have a de novo pathogenic variant. If the mother of the proband carries an PHEX pathogenic variant, the chance of transmitting it in each pregnancy is 50%. An affected male passes the pathogenic variant to all his daughters and none of his sons. The features of X-linked hypophosphatemia are similar in males and females. Due to great intrafamilial variation, severity cannot be predicted.

Management of XLH syndrome takes multi-disciplinary approach involving pediatricians, endocrinologists, radiologists, orthopedic surgeons, dental surgeons, clinical geneticists, ENT surgeons ...etc. After the diagnosis is established, management mainly focus on three aspects: pharmacological and surgical treatment, prevention of secondary manifestations and surveillance.

Pharmacological treatment focuses on pain alleviation and correcting bone deformation. In children, treatment usually starts at the time of diagnosis and continues till long bone growth is completed. Treatment includes oral phosphates and high dose calcitriol (active form of vitamin D). Titration is needed to avoid gastrointestinal side effects like diarrhea. Doses are adjusted based on successful reduction of serum alkaline phosphatase, improvement in lower limbs bowing, radiological improvement e.g. resolution of rachitic changes and improved growth velocity while balancing the occurrence of secondary complications at the same time. In adults, treatment is generally reserved for individuals with symptoms like skeletal pain, upcoming orthopedic surgery, biochemical evidence of osteomalacia with an elevated alkaline phosphatase, or recurrent stress fractures.

Despite adequate pharmacologic therapy, some individuals with XLH would still have persistent lower-limb bowing and torsion, which may lead to misalignment of the lower extremity. In these individuals, surgical treatment is frequently pursued. Surgical options are age-dependent. For degenerative joint disease and enthesopathy, total hip and knee arthroplasty is sometimes required.

Individuals with XLH are prone to recurrent dental abscesses leading to premature loss of decidual and permanent teeth. Good oral hygiene with flossing and regular dental care and fluoride treatments are essential for prevention. A recent study has showed that treatment of adults with phosphate and calcitriol can improve the severity of dental disease.

For prevention of secondary complications, hyperparathyroidism is associated with treatment for XLH. Hyperparathyroidism most often occurs secondary to high phosphate doses and may proceed to tertiary hyperparathyroidism (hypertrophied and uncontrolled parathyroid gland). If secondary hyperparathyroidism is detected, either the calcitriol dose may be increased or the phosphate dose decreased. If tertiary hyperparathyroidism is identified, surgical evaluation is needed.

Hypercalcaemia and hypercalcuiuria are complications of long-term treatment for XLH. They are associated with high calcitriol doses. If hypercalcaemia or hypercalciuria is detected, the calcitriol dose should be decreased. Nephrocalcinosis is reported in persons medically treated for XLH. It can occur despite absence of laboratory detected hypercalcaemia and hypercalciuria. A baseline renal ultrasound examination is recommended before start of treatment. The frequency of renal ultrasound examination to monitor for the development of nephrocalcinosis is not established; one- to five-year intervals have been recommended [Carpenter et al 2011, Sabbagh et al 2014].

Surveillance would be indicated for disease progression, treatment response and therapeutic complication. In order to monitor for hyperparathyroidism, hypercalciuria and hypercalcaemia, intact parathyroid hormone, alkaline
phosphatase level, serum calcium concentrations, urinary calcium, phosphate and creatinine should be measured quarterly. Lower extremity X-ray is needed for assessing skeletal response to treatment while frequency is guided by physical examination and symptoms. Renal ultrasound examination is needed to monitor nephrocalcinosis. Dental follow up is recommended twice yearly for children or teenagers with XLH and at risk for caries.

Acknowledgement

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

References

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Categories of articles include the following:

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

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1. Use Arabic numerals for numbers above nine, for designators (e.g. case 5, day 2, etc.) and for units of measure; numbers should be spelled out if below 10, at the beginning and end of sentences, and for fractions below one.

2. Manuscripts should be submitted as a Word document in British English in the following format: Typed double-spaced, page size 22 cm. x 29 cm. (8 1/2 in. x 11 in.), page margins 2.54 cm (1 in), font size 12 pt.

3. Do not use abbreviations in the title or abstract and limit their use in the text. Standard abbreviations may be used and should be defined on first mention in the text unless it is a standard unit of measurement.

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

Ethical Consideration

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

The manuscript should usually be arranged as follows:

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

Abstract and Key words

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

Introduction

Methods

Results

Discussion

References

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

Examples of References:

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

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