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## Editorial

# Making Sense of Digital Portraits of Clinical Data

Amid the COVID-19 pandemic, Musée du Louvre has 'dust off its treasures, even the least-known', as put forward by its President-Director, and released digital versions of its entire collections online.<sup>1</sup> The collections, amounting to more than 480,000 pieces of artwork, include near Eastern antiquities, Egyptian antiquities, Greek, Etruscan and Roman antiquities, Islamic art, paintings, medieval, renaissance and modern sculpture, prints and drawings, medieval, renaissance and modern decorative arts. This tour de force online platform provides yet another example of how digitalisation has reshaped the experience of art through removal of barriers of cost and accessibility. In medicine, digitalisation of health information has created opportunities and resources that our predecessors had never been able to dream of.

The articles included in this issue of the Journal describe common and less common paediatric conditions and can be envisaged as portraits of paediatric clinical data based on conventional analogue review of clinical notes, which are on the other hand increasingly documented in the form of electronic health records. Cheung et al reported the pattern of distribution of various functional headaches, pain characteristics, interventions and psychosocial impacts on the child and family,<sup>2</sup> Huang et al described the features and risks for acute kidney injury in children with IgA nephropathy,<sup>3</sup> Zhang et al described clinical features of Kawasaki disease in children with an atypical age of onset,<sup>4</sup> To et al reviewed the prevalence of different thyroid disorders and co-morbidities in children and adolescents with Down syndrome,<sup>5</sup> and finally, Chan et al performed a 20-year retrospective review of the clinical characteristics and outcomes of paediatric non-tuberculous mycobacterial infection.<sup>6</sup> While these sets of clinical data do convey important messages that would enhance understanding of the medical problems and clinical management of our patients, one begs to ask how we could make further sense of clinical information that is mostly stored nowadays in an electronic format.

In Hong Kong, the Hospital Authority has taken the lead to establish a territory-wide web-based electronic patient health record system that allows the integration in a real-time fashion of patient-based information to be shared among clinics, public hospitals and private hospitals.<sup>7</sup> At its core, the electronic health record is a digitised version of the medical notes, diagnostic reports, laboratory results, and images. A recent study has found that paediatricians spent an average of 16 minutes per encounter using the electronic health record, with chart review, documentation, and ordering functions accounting for most of the time.<sup>8</sup> While the distribution of time spent by each of the paediatricians was highly variable within subspecialty, it was similar across subspecialties. The time is probably well spent.

Widespread adoption of electronic health records in Hong Kong and elsewhere in the world has created a framework and a platform for not only the purpose of collection and sharing, but when combined with data analytics and interpretation, may further enhance patient management, health care efficiency, clinical decision making, prognostication, and clinical research beyond conventional trials.<sup>9</sup> Visualisation tools have been created to integrate and

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manage the abundant and heterogeneous sets of electronic health data.<sup>10</sup> The increasing application of machine learning and artificial intelligence in the medical arena would no doubt further facilitate the exploitation of digital data as captured by the electronic health records for research. Indeed, in the field of paediatrics, machine learning has found increasing utilisation in neonatology, childhood psychiatry, and paediatric neurology.<sup>11</sup>

Extraction of relevant data from the electronic health records for analysis and research can be a daunting task. Different types of data are included in electronic medical records. Structured data include information as birth date, sex gender, physical growth measurements, vital parameters, and drug use. On the other hand, unstructured text, which is narrative in nature, includes admission and progress notes, discharge records, operation records, and radiology and pathology reports. The lack of structural frameworks renders digitisation of these texts difficult. The use of abbreviations and acronyms and the presence of spelling and grammatical errors further complicate the processing and analysis of these texts. Nonetheless, text mining enables the conversion of implicit knowledge hidden in the unstructured text into structured data that can be read by computers using natural language processing technologies.<sup>12</sup> Interestingly, a recent study revealed that while people are in general in favour of sharing medical data and agree that this would benefit health research, they are more cautious about sharing free-text than structured data.<sup>13</sup>

Bringing structure to the unstructured text in digital portraits of our patients is a challenging endeavour, but one that would reshape paediatric care and research through making greater sense of the ocean of implicit knowledge.

**YF CHEUNG**  
**Chief Editor**

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## Original Article

# Childhood Chronic Recurrent Headache in Hong Kong: A Case Control Study

KL CHEUNG, WW CHENG, KY Y NG, CH KO

### Abstract

Childhood headache is commonly encountered in paediatric practice and can lead to significant morbidities. Local research and management consensus is lacking. This is a case control study conducted on children with primary functional headaches from a specialist outpatient clinic utilising a structured questionnaire. Headaches were classified as migraine, tension headache and nonspecific headache, according to the International Headache Society criteria. We ascertained the pattern of distribution of various functional headaches, pain characteristics, interventions and psychosocial impacts on the child and family. Subjects with migraine were compared with those with tension and nonspecific headaches, which were grouped into non-migrainous headache. The findings were appraised with reference to local and overseas literatures from adult and paediatric practices. Forty-eight consecutive subjects were recruited, in which 58.3% were diagnosed to have migraine and 41.7% with non-migrainous headache. Characteristics of childhood headaches manifest differently in children compared to adults. A high incidence of unnecessary neuroimaging and psychosocial impairment warrants overhaul of local practice in refractory headaches. Impairment in social function was found to be common in both groups.

### Key words

*Childhood headaches; Migraine; Neuroimaging; Psychosocial impairment*

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### Introduction

Chronic recurrent headache is a common problem in office paediatric practice, but research in local population is lacking. Spontaneous remissions of childhood onset headaches were uncommon; 80% of subjects still had headaches three years later.<sup>1</sup> Headache in adolescence was significantly associated with report of pain and other comorbidities in early adulthood.<sup>2,3</sup> An 18-year follow-up identified a three-fold increase in migraine incidence in a cohort who already had migraine at age 7.<sup>4</sup> Longitudinal study revealed 50% of individuals with childhood migraine continued to experience the problem 30 years later.<sup>5</sup>

In 2001, Kong et al<sup>6</sup> conducted an epidemiological study on childhood headache in primary-level school children, and established a local prevalence of 2.8%. This

is a follow-up control study on a cohort of children who were actively followed up in the same specialised centre. We aim to ascertain the pattern of distribution of various functional headaches, pain characteristics, interventions and psychosocial impacts on the child and family. Subjects with migraine were compared with those with tension and nonspecific headaches, which were grouped into non-migrainous headache. The findings were subsequently appraised with reference to local and overseas literature from adult and paediatric practices.

## Methods

### *Questionnaire Development*

The questionnaire was designed to cover domains including characteristics, intervention and outcome measures of childhood primary functional headaches.<sup>7,8</sup> The items for performance variables were formulated with reference to Paediatric Migraine Disability Assessment Scores (PedMIDAS).<sup>9,10</sup> The number of questions and items were modified after input from clinical psychologist. Answers containing nominal and ordinal information were standardised into choices. Choices were arranged in a Likert scale manner as appropriate to quantify the respondent's attitude.

### *Data Collection*

Data was collected through questionnaire interview in a single tertiary specialist referral centre. Study subjects included children and adolescents aged 6 to 18 years old with primary functional headaches actively followed up in a paediatric neurology clinic from 1st November 2018 to 31st January 2019. The primary recurrent functional headaches were classified as migraine, tension headache and unclassified recurrent headache by the two paediatric neurologists in charge of the service, according to diagnostic criteria adapted from the International Headache Society (Table 1). Isolated headache attack and secondary headaches associated with sinusitis, intracranial lesions, head injury, psychiatric disorders and epilepsy were not recruited. Subjects with intellectual disability and ethnic minorities who could not communicate in English or Chinese were excluded.

Convenient consecutive samples were recruited during follow-up consultation. The principal investigator obtained written informed consent from the parents or guardians of eligible subjects. The same principal investigator conducted the questionnaire to the subject without any

suggestions to the choice of answer. While the questions were standardised, the verbal content was adjusted according to the child's developmental age, and answers were only interpreted and entered by the principal investigator. If the patient did not understand the content of any particular enquiry item, that item was explained to the parents or guardians to assist explanation to the child, but any suggestions to the choice of answer was disallowed. Failure to complete the items on headache characteristics would preclude further interview, and the incomplete questionnaire would not be included for subsequent analysis. Supplementary information was obtained from the case file and electronic patient record.

Information obtained included the type of functional headache, demographic information, headache characteristics (frequency, duration, intensity, location, quality, precipitating factors, associated symptoms), interventions and effectiveness of treatments, and degree of impairment on social function.

### *Data Analysis and Ethics Approval*

Subjects with migraine were compared with those with non-migrainous headache. In bivariate analysis, categorical data were compared using Chi-square and Fisher's exact tests. Normally distributed data were analysed by independent sample t-test. Non-normally distributed data were analysed by Mann-Whitney *U* test. Statistical significance was defined as two-tailed probability below 0.05. All statistical analyses were performed using the Statistical Package for the Social Sciences (Windows version 9.0; SPSS Inc, Chicago [IL], US).

This study did not involve any intervention that might harm study subjects. There was no financial incentive. The study was compliant with International Council for Harmonization - Good Clinical Practice (ICH-GCP). The questionnaire sheets and the data were only handled by the Principal Investigator. Personal identification information was omitted in the questionnaire sheet to protect privacy and minimise bias. The study protocol was approved by the Ethics Committee of Kowloon West Cluster of Hospital Authority, Hong Kong. Informed consent was obtained from respective parents.

## Results

The study was conducted from 1st November 2018 to 31st January 2019. Among the 52 consecutive subjects who fulfilled the inclusion criteria, we obtained informed

consents in 48 subjects, giving a response rate of 92.3%. The reasons to decline participation included limitation of time for interview, failure in understanding the purpose of the study and parental worries of adverse effects of participation on subsequent headache management. Twenty-eight children (58.3%) were diagnosed to have migraine, and 20 children (41.7%) with non-migrainous headache, including 7 (14.5%) tension-type headache and 13 (27.2%) unclassified recurrent headache.

Table 2 shows the demographic data of the two comparison groups. The mean age of onset of migrainous headache was  $11.57 \pm 3.44$  years, which was significantly higher ( $P=0.012$ ) than that in the non-migrainous group ( $9.05 \pm 3.12$  years). Eighty-nine percent (25/28) of migrainous patients had onset after age 9, while the onset was before age 9 in 55% (11/20) of non-migrainous patients. There was no significant gender difference between the two groups ( $P=0.558$ ).

**Table 1** Diagnostic criteria of migraine and tension headache adapted from the International Headache Society

<b>Migraine</b>	<b>Tension type headache</b>	<b>#Unclassified recurrent headache</b>
At least 5 attacks fulfilling criteria below	At least 10 previous attacks fulfilling criteria below:	Recurrent functional headache that do not fulfil diagnostic criteria for either migraine or tension type headache, or contain overlapping features from either condition at the time of classification
1. Headache duration 4 to 72 hours (2 to 48 hours in children)	1. Headache duration 30 minutes to 7 days	
2. Headache characterised by at least 2 of the followings:	2. Headache characterised by at least 2 of the followings:	
A. Unilateral location	A. Pressing (non-pulsating) nature	
B. Pulsating quality	B. Mild or moderate intensity (may inhibit, but not prohibit activity)	
C. Moderate or severe intensity (inhibits or prohibits daily activity)	C. Bilateral location	
D. Aggravated by climbing stairs or similar routine physical activity	D. No aggravation by walking stairs or similar physical activity	
3. At least one of the followings	3. Both of the followings:	
A. Nausea and / or vomiting	A. No nausea or vomiting	
B. Photophobia and phonophobia	B. Photophobia and phonophobia are absent, or only one is present	

# This entity is arbitrarily defined by the authors to facilitate analysis in the present study. The underlying pathology may be heterogeneous and does not represent a well-defined clinical diagnostic entity.

**Table 2** Demographics of migraine and non-migrainous headache

	<b>Migraine (n=28)</b>	<b>Non-migrainous headache (n=20)</b>	<b>P-value</b>
<b>Age (year)</b>			
5-8	3	11	
9-11	10	5	
12-14	7	4	
15-17	8	0	
<b>Gender</b>			
Female	15	9	0.558
Male	13	11	
<b>Mean onset age (SD) in year</b>	11.57 (3.44)	9.05 (3.12)	0.012
<b>Family history (1st degree relatives)</b>			
Yes	16	10	0.624
No	12	10	

Table 3 shows the characteristics of headache in the two study groups. Majority of children from the migrainous group (53.5%) and non-migrainous group (70%) experienced two or more attacks per month ( $P=0.251$ ). Nearly 70% of children with migraine reported headache duration longer than two hours, compared to only 30% in the non-migrainous group ( $P=0.001$ ). Children in the migrainous group reported higher average headache intensity score than the comparison group (6.7 vs 5.4,  $P=0.007$ ). No significant difference was found between the two groups in reporting lateralisation of pain ( $P=0.558$ ). Sixty percent of migrainous children had throbbing ache, compared to 15% in the comparison group ( $P=0.003$ ). Symptoms that were significantly more common in the migrainous group than the non-migrainous group included nausea (71% vs 30%,  $P=0.005$ ), photophobia (71% vs 30%,  $P=0.005$ ), phonophobia (50% vs 5%,  $P=0.001$ ), and preceding aura (57% vs 15%,  $P=0.003$ ). No significant difference was found between the two groups with reference to vomiting ( $P=0.111$ ) and dizziness ( $P=0.430$ ). No significance between group differences was identified in common aggravating factors, namely tiredness, sleep deprivation, physical activity, caffeine, negative mood and stress.

Table 4 summarises the investigations and interventions. Neuroimaging (CT or MRI) had been performed in 60% of subjects in either group ( $P=0.960$ ). All but one child from either group were relieved from headache by rest or sleep ( $P=0.807$ ). Significant higher proportion of children with migraine required abortive medications in comparison to non-migrainous patients (96% vs 65%,  $P=0.004$ ). For both migraine and non-migrainous headache, more than half of children only took abortive medication once in a month or less. The most commonly used abortive treatment was paracetamol in both groups (68% vs 55%,  $P=0.691$ ). Naproxen was used as abortive medication at significantly higher rate in migrainous patients (54% vs 15%,  $P=0.005$ ). With respect to preventive therapy, over 60% of children with migraine had been put on prophylactic medications, compared to none in the comparison group ( $P<0.001$ ). The most commonly used preventive medication was pizotifen. Second line prophylaxis included amitriptyline, propranolol, topiramate and acetazolamide. Four children with refractory migraine were referred to clinical psychology and their clinical details were given in Appendix. None from the non-migrainous group received psychotherapy.

Table 5 summarises the effect on performance and functioning. Most children with migraine (71%) or non-migrainous headaches (75%) did not take sick leaves in

last 6 months ( $P=0.698$ ). However, impairment in function was common in both groups, with a trend for migrainous children to report more negative effects on school-work (96% vs 75%,  $P=0.067$ ), mood (75% vs 55%,  $P=0.070$ ) and participation in social activities (50% vs 30%,  $P=0.081$ ).

## Discussion

Headache is common in adults and children, but local studies are scarce. Yu et al<sup>11</sup> surveyed the health status of teenagers in Kwai Tsing district of Hong Kong and revealed headache to be one of the commonest problems in medical consultations in preceding 3 months among 55% of studied subjects. Kong et al<sup>6</sup> conducted a questionnaire survey in 2120 primary school pupils, revealing chronic headache in 2.8% respondents, with tension-type headache 1.2%, migraine 0.5%, probable migraine 0.7%, and unclassified headache 0.5%. A community based study which was conducted in Hong Kong adolescents aged 15 years and older estimated that the prevalence of migraine, tension-type headache and nonspecific headache were 3%, 1.5%, and 0.4% respectively.<sup>12</sup> Ng et al<sup>13</sup> conducted a telephone interview on 1051 Cantonese speaking adults. Chronic pain was identified in 113 respondents, with headache (21%) following back pain (34%) as the second commonest problem.

Surveys in children via mails or telephone may be confounded by poor response rate, misinterpretation, leading question bias and recall bias.<sup>14-16</sup> In the present study, direct structured interview in a specialist clinic setting helped to minimise bias and allowed in-depth exploration on the impacts on the child and family. Chan et al<sup>17</sup> conducted a retrospective review on 66 adult migrainous patients managed in specialist neurology clinic. Eighty percent were females with mean age of onset before 30; 12% had positive family history and 42% had migraine aura. Aggravating factors included menstruation in 26%, stress in 18%, and sleep deprivation in 13%. That was compared to the present study conducted in similar setting on migrainous children, showing less female preponderance (54%), more familial predisposition (57%) and higher incidence of aura (57%). Aggravation by stress (57%) and sleep deprivation (57%) appeared more common than adults, though not significantly different from that in non-migrainous children. The difference between local adults and children may represent the complex interplay between genetic and environmental factors in migraine manifestation across the age spectrum.

**Table 3** Characteristics of pain and accompanying symptoms in migraine and non-migrainous headache

Pain characteristics and symptoms		Migraine (n=28) (%)	Non-migrainous headache (n=20) (%)	P-value
<b>Frequency of attacks in previous 6 months / month</b>				
>=2/month		15 (53.5)	14 (70.0)	0.251
<=1/month		13 (46.4)	6 (30.0)	
<b>Pain duration</b>				
<1 hour		5 (17.9)	11 (55.0)	0.001
1-2 hours		4 (14.2)	5 (25.0)	
2-4 hours		11 (39.3)	3 (15.0)	
>=4 hours		8 (28.6)	1 (5.0)	
<b>Location</b>				
Unilateral (either side / always same side)		15 (53.5)	9 (45.0)	0.558
Others (bilateral / occiput / face)		13 (46.4)	11 (55.0)	
<b>Pain quality</b>				
Throbbing / pulsating		17 (60.7)	3 (15.0)	0.003
Others (dull / constricting / tingling)		11 (39.3)	17 (85.0)	
<b>Pain intensity (Numerical rating ranging from 0 [no pain] to 10 [worst pain] )</b>				
Mild (1-4)		2 (7.1)	5 (25.0)	
Moderate (5-10)		26 (92.9)	15 (75.0)	
Average pain score		6.71	5.4	0.007
<b>Symptoms</b>				
Nausea	Yes	20 (71.4)	6 (30.0)	0.005
	No	8 (28.6)	14 (70.0)	
Vomiting	Yes	10 (35.7)	3 (15.0)	0.111
	No	18 (64.3)	17 (85.0)	
Nausea and vomiting	Yes	10 (35.7)	3 (15.0)	0.111
	No	18 (64.3)	17 (85.0)	
Photophobia	Yes	20 (71.4)	6 (30.0)	0.005
	No	8 (28.6)	14 (70.0)	
Phonophobia	Yes	14 (50.0)	1 (5.0)	0.001
	No	14 (50.0)	19 (95.0)	
Dizziness	Yes	18 (64.3)	15 (75.0)	0.43
	No	10 (35.7)	5 (25.0)	
<b>Aggravation</b>				
Physical activity	Yes	3 (10.7)	2 (10.0)	0.936
	No	25 (89.3)	18 (90.0)	
Tiredness / sleep deprivation	Yes	16 (57.1)	13 (65.0)	0.583
	No	12 (42.9)	7 (35.0)	
Caffeine	Yes	3 (10.7)	1 (5.0)	0.48
	No	25 (89.3)	19 (95.0)	
Negative mood (e.g. anxious, depressed)	Yes	13 (46.4)	7 (35.0)	0.428
	No	15 (53.5)	13 (65.0)	
Stress (e.g. study)	Yes	16 (57.1)	8 (40.0)	0.242
	No	12 (42.9)	12 (60.0)	
<b>Aura</b>	Yes	16 (57.1)	3 (15.0)	0.003
	No	12 (42.9)	17 (85.0)	

**Table 4** Investigations and interventions for migraine and non-migrainous headache

	Migraine (n=28) (%)	Non-migrainous headache (n=20) (%)	P-value
<b>Investigation</b>			
Ever had CT / MRI scan for headache			
Yes	17 (60.7)	12 (60.0)	0.96
	(13 for CT; 4 for MRI)	(12 for CT; 0 for MRI)	
No	11 (39.2)	8 (40.0)	
<b>Interventions</b>			
Relief after rest / sleep			
Yes	27 (96.4)	19 (95.0)	0.807
No	1 (3.6)	1 (5.0)	
Abortive therapy			
Yes	27 (96.4)	13 (65.0)	0.004
No	1 (3.6)	7 (35.0)	
Number of days in one month with medications taken to relieve headache			
0-1	16 (57.1)	13 (65.0)	0.606
2-4	8 (28.6)	5 (25.0)	
5-7	3 (10.7)	2 (10.0)	
>=8	1 (3.6)	0	
Medications taken most often and their effectiveness			
Paracetamol	19 (67.9)	11 (55.0)	0.691
Naproxen	15 (53.5)	3 (15.0)	0.005
Ibuprofen	2 (7.1)	2 (10.0)	0.663
Preventive therapy			
Yes	18 (64.3)	0	<0.001
No	10 (35.7)	20 (100.0)	
Medications taken most often and their effectiveness			
Pizotifen	14 (50.0)	0	
Amitriptyline	5 (17.8)	0	
Propranolol	4 (14.2)	0	
Topiramate	3 (16.7)	0	
Acetazolamide	2 (11.1)	0	
<b>Clinical psychology</b>	4 (14.2)	0	0.081

**Table 5** Performance variables in children with migraine and non-migrainous headache

Variables	Migraine (n=28) (%)	Non-migrainous headache (n=20) (%)	P-value
School days missed in last 6 months			
0	20 (71.4)	15 (75.0)	0.698
1-2	5 (17.9)	3 (15.0)	
3-4	3 (10.7)	2 (10.0)	
Difficulty to do schoolwork	27 (96.4)	15 (75.0)	0.067
Mood affected	21 (75.0)	11 (55.0)	0.07
Difficulty to maintain social activities	14 (50.0)	6 (30.0)	0.081
Interpersonal relationship affected	8 (28.5)	4 (20.0)	0.551

In the present study, migraine onset was less common in the first decade of life and became more prevalent during adolescence (Table 2). This is consistent with findings in previous epidemiological studies.<sup>6,15,18</sup> According to the International Headache Society (IHS) criteria, migraine readily differentiates from other functional headaches by characteristics, duration, location, quality, intensity, aggravating factors and associated symptoms (Table 1). We found that pulsating quality, nausea, photophobia and phonophobia had higher differentiating values for childhood migraine. However, classic migraine features such as lateralising ache, longer duration and worst intensity were also present in non-migrainous headaches, while common aggravating factors were prevalent in both groups (Table 3). In contrast, Anttila et al<sup>14</sup> found that unilaterality, pulsating quality, photophobia and aggravation by physical activity had doubtful predictive values for childhood migraine. These contrasting findings illustrate the difficulty to apply strict IHS criteria in the diagnosis of childhood migraine, particularly during the early stage of disease. Paediatricians should take into consideration the contexture of symptoms, behavioural changes, evolutions over time and parental information to arrive at the correct diagnosis.<sup>19</sup>

Sixty percent of subjects from either group had undergone neuroimaging in this study. That was significantly higher than the imaging rate of 16.7% from overseas reports on migrainous children.<sup>20</sup> Kan et al<sup>21</sup> reviewed the appropriateness of 88 CT brain in 82 paediatric headache patients from Tuen Mun Hospital of Hong Kong within a six-month audit period. Isolated headache or migraine, classified as low level of appropriateness according to the American College of Radiology Appropriateness criteria,<sup>22</sup> accounted for 22% of the brain scans performed. The high incidence of unnecessary neuroimaging for functional headache across the territory may reflect social and cultural misconceptions and that warrants enhanced education and development of clinical practice guidelines.<sup>21</sup>

Ninety-six percent of migrainous children in the present cohort had regular use of common analgesics or nonsteroidal anti-inflammatory drugs (NSAIDs). Chan et al<sup>17</sup> reported that triptans, paracetamol, NSAIDs and ergots were effective abortive treatments in their local series of 66 migrainous adults. Triptans is a group of selective serotonin receptor agonists at the 5-HT<sub>1B</sub> and 1D receptor sites.<sup>23</sup> It is recommended for moderate to severe headache unresponsive to analgesics or NSAIDs.<sup>24</sup> The US Food and Drug Administration (FDA) and the European Medicines

Agency (EMA) approved four triptans for use in migrainous children, namely almotriptan, rizatriptan, sumatriptan and zolmitriptan. Oral rizatriptan and almotriptan are recommended in children  $\geq 6$  years and in adolescents  $\geq 12$  years respectively. EMA approved nasal sumatriptan in children  $\geq 5$  years old and zolmitriptan nasal spray in adolescents  $\geq 12$  years old. Contraindications to use of triptans include vascular conditions (e.g. stroke, hypertension, Raynaud syndrome), current intake of monoamine oxidate inhibitors or ergotamines, impaired renal or liver function and pregnancy. It cannot be repeated more than once within 2 hours of first dose ingestion and cannot be taken more than two times per week and six times per month.<sup>25,26</sup> Side effects include warm sensation, fatigue, dizziness, tingling, chest tightness and somnolence.<sup>27</sup> In the present study, there were no migrainous children taking triptans as abortive treatment and the proposed reasons included the less availability, higher costs and less experience in use of triptans among local paediatric neurologists. Multi-centre survey is worth to ascertain the role of triptans in the treatment algorithm for local children.

Preventive medications were used in 64% of migrainous children in the current study. In general, incapacitating headache attacks over 3-4 times a month warrant prophylaxis.<sup>27</sup> Pizotifen, amitriptyline and propranolol were the most common preventive medications. The choice was similar to local adult series, with propranolol (59%), pizotifen (55%) and tricyclic antidepressants (43%) achieving  $\geq 40\%$  reduction in attacks.<sup>17</sup> Evidence-based guidance to the selection of medications is lacking. No significant difference in efficacy had been demonstrated in amitriptyline and topiramate compared to placebo.<sup>28</sup> Similarly, flunarizine, pizotifen, propranolol and valproate were shown to be ineffective in episodic migraine.<sup>29</sup> The choice of medications in children still relies largely on experience and personal preference.

Secular increase in chronic childhood headache over the past two decades has been correlated to factors such as increase in time demands, pressures from school, peers and family, and reduction in physical activities.<sup>1,4,15,30</sup> The psychosocial impacts could be immense. School absences, academic problems and social dysfunction impaired psychosocial development and self-esteem.<sup>31</sup> Co-morbid depressive, anxiety, and somatization disorders were common.<sup>14,32,33</sup> Significant impacts were also demonstrated in non-migrainous children.<sup>34</sup> In the present study, impairment of daily functioning was equally prevalent in migrainous and non-migrainous children (Table 5), with

over half of the subjects from either group having mood disturbances and difficulties in schoolwork. Kernick et al reported an average of 6 days of missing school per year.<sup>35</sup> In contrast, over 70% of the present cohort did not miss school. The discrepancy between the high incidence of mood disturbance and low rate of school absence might reflect enthrallment with academic performance and fear of stigmatisation in society. Further studies may explore the role of parental expectation in this paradox between school attendance and mood disturbance.

Behavioural treatment had become standard intervention for adult migraine and tension-type headache. Emerging studies and meta-analyses also demonstrated efficacy of psychotherapy in childhood headache.<sup>36-38</sup> A randomised controlled trial demonstrated cognitive behavioural therapy (CBT) plus amitriptyline resulted in greater reductions in headache days and migraine-related disability compared with headache education plus amitriptyline.<sup>39</sup> CBT might also augment the efficacy of standard medications in childhood migraine.<sup>38</sup> In the current study, despite the high incidence of psychosocial impairment, only 14% of migrainous children received psychotherapy, compared to none from the non-migrainous group (Table 5 and Appendix). The under-utilisation of psychotherapy may be related to lack of physician awareness of this intervention to children with severe refractory headaches. The confined availability of clinical psychological service in our locality also limits its use. Further studies are required to ascertain the role of psychotherapy and the underlying factors hindering timely referral, with overhaul of practice guidelines accordingly to improve care in refractory headaches.

The small sample size limited the power of this study. Children with unclassified headache might evolve into migraine, resulting in crossover bias. Recall bias with reference to the timing and intensity might be present in interviewing younger children and children with longstanding diseases. Informant might under-report medication overuse, which was prevalent in chronic headaches.<sup>40</sup> Findings from a single specialist centre might not be generalised to other services in the territory. Territory-wide multi-centre research is warranted to guide future management and helps to establish a standard practice guideline for local children.

### Declaration of Interest

The authors declare that they have no financial or other conflicts of interest in relation to this publication.

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## **Appendix.** Clinical information of patients with migraine and their clinical psychological intervention

### **Case 1**

YLS, 17-year-old female adolescent, was referred from Accident and Emergency Department to paediatric neurology clinic for chronic headache since 9 years of age. For initial presentation, she suffered from frontal headache with frequency of three times a week and duration of lasting 1 hour. She could not describe pain nature at that time. The headache was associated with dizziness, vertigo and vomiting. There was no aura or photophobia. She had no family history of migraine or headache. The headache persisted more than a year before seeking medical help. Physical examination was unremarkable. Computed tomography of brain was arranged and the result was unremarkable. The working diagnosis was tension-type headache. Abortive treatment with NSAIDs was offered initially. On subsequent follow-up, the headache symptoms did not improve much with abortive medications. Prophylaxis with amitriptyline was initiated but only mild improvement was noted. Subsequently, she also started to have episodes of shortness of breath, increase in severity of dizziness and numbness of limbs without weakness. Corresponding investigations including blood investigations, lung function test and nerve conduction study were performed and unremarkable. She also started to develop photophobia during headache attacks. Diagnosis of headache was amended to migraine. Multiple prophylactic medications including amitriptyline, pizotifen, topamax and diamox were tried but minimal improvement was noted. She relied on abortive treatments with nearly daily consumption of analgesics and NSAIDs. On enquiry to psychological components, she admitted there was increased stress from school and severe headache attack was usually preceded by school examination. She also disclosed her worries on her father's illness who was diagnosed with nasopharyngeal carcinoma. Referral to clinical psychologist was made and she started to attend clinical psychologist since age of 16 years. The patient's mood, adjustment to headaches and coping methods towards stress were reviewed. She was facilitated to weigh the pros and cons of consuming analgesics by herself. Psychoeducation on cognitive behavioural therapy (CBT) (e.g. relationship between thoughts, emotions, physical sensations, behaviours) and diaphragmatic breathing relaxation exercise were introduced, demonstrated and practised. For progress, she reported that she continued to experience headaches every day with moderate intensity; however, she had developed acceptance towards headaches already. There was no marked distress or mood disturbances related to her headaches. The effect of headache on activity of daily living became less significant. She was currently followed up by paediatric neurologists with prophylactic treatment and clinical psychologist for psychological intervention.

### **Case 2**

AST, 15-year-old female adolescent, was referred from private paediatrician to paediatric neurology clinic for continual management of migraine since 12 years of age. She presented with headache localised to parietal region with aura of scintillation. The pain was dull and lasted more than an hour. It was associated with vomiting but not photophobia or phonophobia. The headache attack was infrequent and occurred once every few months. Physical examination was unremarkable and no brain imaging was performed. Because of infrequent attacks, abortive treatment with paracetamol was suggested without indication for prophylaxis. When promoting to Form 1 in secondary school, she reported recurrent abdominal pain apart from headache. The symptoms occurred more frequently during school days and became exaggerated in school examination period. She was symptoms free during school holidays. Psychological component was suspected and clinical psychologist referral was made. Clinical psychological assessment identified her stressor was related to high maternal expectation on her academic performance. Relaxation training and promotion of self-understanding were offered. She understood better for mind-body relationship. She foresaw possible academic stress and claimed she would strive to acquire newly learned skills including relaxation skills for coping. On follow-up, she reported she had no more migraine attacks and no recurrences of abdominal pain. No more clinical psychological intervention was required and she was currently followed up in paediatric neurology clinic without abortive treatment.

### **Case 3**

NLL, 17-year-old female adolescent, was referred from private general practitioner to paediatric neurology clinic for suspected tension type headache since 14 years of age. She presented with headache localised to occipital region with gripping in nature. The pain occurred in the morning and lasted 1-2 hours. It was associated with back pain and precipitated by stress and sleep deprivation. She did not complain of vomiting, photophobia or phonophobia. Physical examination was unremarkable. Computed tomography of brain was subsequently arranged and the result was unremarkable. She was started with abortive treatment and later added on prophylactic treatment (amitriptyline) because of increasing frequency and severity of headaches. Diagnosis was for review because of increasing severity of headache and evolving symptoms of phonophobia. Migraine was the diagnosis instead of tension type headache. Several medications for prophylaxis including pizotifen, topamax and amitriptyline were tried but she could not tolerate the side effects such as sleepiness and slow mentality. In view of intolerance to prophylactic drugs, clinical psychological intervention was recommended. Clinical psychological assessment revealed anxiety proneness in social situations, e.g. at school and with strangers on street, and low self-esteem. CBT for social anxiety and mood management were offered. She was guided to differentiate thoughts from reality and offered cognitive restructuring for her catastrophic thoughts. Subsequently no more clinical psychological intervention was needed. She was currently followed up in paediatric neurology clinic with use of abortive treatment for headache.

### **Case 4**

TWH, 13-year-old male adolescent, was referred for consultation in paediatric neurology clinic after repeated hospital admissions for non-specific dizziness and headache since age of 11 years. The headache was located to bilateral temporal area, throbbing in nature and in severe intensity. It could last from 30 minutes up to whole day. It was associated with dizziness and palpitations but no aura, phonophobia nor photophobia reported. Physical examination was unremarkable. Subsequent investigations for palpitation and dizziness and magnetic resonance imaging of brain were normal. Migraine was diagnosed later due to increasing severity of symptoms. Prophylaxis with pizotifen and abortive treatment with NSAIDs were offered. In view of the presence of somatic symptoms (palpitation and dizziness), clinical psychological intervention was recommended. Psychological assessment revealed academic stress related to promotion to secondary school and psychoeducation on mind-body relationship was briefly explained. However, the patient's father declined further clinical psychological intervention after first assessment when the child's bullying issue was disclosed. The patient was currently followed up in paediatric neurology clinic with pizotifen prophylaxis and headache's condition was stable.

## Original Article

# IgA Nephropathy Associated with Acute Kidney Injury in Young Patients: The Clinicopathological Features and Risk Factors Analysis

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### Abstract

**Objective:** Little is known about the clinicopathological markers of IgA nephropathy (IgAN) to identify the acute kidney injury (AKI) among young patients. This work aimed to explore the possible risk factors of AKI. **Methods:** From 2012 to 2017, 110 patients aging from 2.5 to 16 with biopsy-proven primary IgAN were studied in our medical centre. The patients were divided into the AKI group (n=13) and the non-AKI group (n=97). **Results:** The occurrence of AKI among young patients with IgAN was 11.82% (13/110). Most AKI patients showed more proteinuria higher proneness to hypertension and higher content of uric acid. The proportion of glomeruli with crescents to the normal glomeruli was higher in the AKI group. The multivariate logistic regression analysis suggested that the elevated levels of proteinuria and uric acid might be the risk factors of AKI. **Conclusion:** AKI was common in young IgAN patients (age 2.5 - 16), who showed more severe clinicopathological symptoms than those without AKI. Some symptoms might be helpful in terms of determining the risk factors of AKI.

### Key words

Acute kidney injury; Heavy proteinuria; IgA nephropathy; Risk factor; Uric acid

### Introduction

IgA nephropathy (IgAN) is one of the most common glomerulonephritis worldwide, especially among the Asian population. It is also the leading cause of the end-stage renal disease (ESRD) of patients with primary glomerular diseases.<sup>1,2</sup> Acute kidney injury (AKI) occurred in all age groups.<sup>3</sup> It has been reported that about 60% of the AKI patients could be fully cured during the post-acute stage, while 13.5% could be partially cured and 30% could not recover at all. The unrecoverable patients will gradually develop chronic kidney disease (CKD) and finally ESRD.<sup>4</sup>

It normally takes 10 to 20 years for 20-30% IgAN patients to develop ESRD;<sup>5-7</sup> IgAN patients with AKI are more likely to develop CKD and ESRD.

The clinical and pathological symptoms of IgAN patients with AKI have not been fully studied, especially those of young patients. Previous studies of IgAN patients with AKI mostly focused on macroscopic haematuria.<sup>8</sup> Little is known about the determinative symptoms of AKI-IgAN and its risk factors. In order to explore this aspect in depth, 110 patients aging from 2.5 to 16 with biopsy-proven primary IgAN were studied in the Children's Hospital of Zhejiang University School of Medicine from 2012 to 2017, with both the clinical and pathological characteristics of IgAN associated with AKI recorded.

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### Materials and Methods

#### Patients

The retrospective study data was recorded between January 2012 and January 2017 from 110 patients aging from 2.5 to 16 diagnosed with IgAN in the Nephrology Department of the Children's Hospital Zhejiang University

School of Medicine. Patients who were diagnosed with IgAN in other hospitals or with secondary IgAN (such as HSP, SLE and hepatitis B) were excluded from the study.

AKI was diagnosed upon the 2012 Kidney Disease: KDIGO criteria:<sup>9</sup> increase in SCr by 0.3 mg/dl (26.5  $\mu$ mol/l) within 48 h, or increase in SCr to 1.5 times baseline, which was known or presumed to have occurred within the prior 7 days, or urine volume <0.5 ml/kg/h for 6h; serum creatinine (SCr) was used as the standard parameter in this study for determining the occurrence of AKI. First, the glomerular filtration rate (GFR) is widely accepted as the best overall index of kidney function. But it is difficult to measure and is commonly estimated from the serum level of endogenous filtration markers, such as creatinine. Creatinine is mainly excreted by glomerular filtration. When the intake of meat is stable and there is no significant change in muscle metabolism the creatinine production will be relatively constant;<sup>9</sup> second, according to 2012 Kidney Disease: KDIGO criteria, the definition of AKI is mainly determined by increase in SCr and urine volume. But young patients' urine volume is difficult to record and in this study these patients lacked relevant urine volume data. So SCr was used as the standard parameter here. We set the lowest value recorded between 3 months before the admission and the discharge date as baseline. If the SCr levels were elevated all the time mean SCr levels of healthy people in this age group were used as baseline. Venous blood samples of all the patients were taken to measure SCr immediately after admission. SCr of all patients was monitored at least once every week during hospitalisation. SCr was measured in micromoles per litre. Stratification of AKI also referred to the 2012 KDIGO guideline for clinical practice. Table 1 shows the staging of AKI.<sup>9</sup> In the present study there were 8 patients (61.54%) in the stage I, 4 (30.77%) in stage II and 1 (7.69%) in stage III.

These 110 patients underwent renal biopsy for the following reasons: (1) Unexplained AKI was found at admission or during hospitalisation, possibly accompanied by proteinuria or haematuria; (2) Gross haematuria (possibly accompanied by proteinuria) lasted for more than 2 weeks, excluding UTI; (3) Proteinuria lasted (>150 mg/d and <50 mg/kg/d) for more than 3 months without haematuria, excluding postural proteinuria. Patients with heavy proteinuria and decreased serum albumin were excluded from the data in the beginning. Each sample contained more than 10 glomeruli in renal specimen. The diagnosis of IgAN was based on the presence of IgA as the only or main immunoglobulin in the glomerular mesangial and the absence of systemic disease.

### **Clinical Data**

Among the 110 patients studied, 13 matched the AKI criteria, making up the cumulative incidence of AKI 11.82%. The mean time taken from kidney biopsy to AKI occurrence was  $4.46 \pm 2.03$  days. Clinical data obtained from the original medical records of the patients included information on gender, age, levels of peak serum creatinine, uric acid, triglycerides, cholesterol, proteinuria (>50 mg/kg/24h) at the time of biopsy as well as the status of gross haematuria, anaemia and hypertension. Anaemia of patients in this study (2.5 years - 16 years) was defined by the following criteria:<sup>10</sup> (1) Children 6-59 months of age: Hb <110 g/l; (2) Children 5-11 years of age: Hb <115 g/l; (3) Children 12-14 years of age: Hb <120 g/l; (4) Non-pregnant women (15 years of age and above): Hb <120 g/l. Men (15 years of age and above): Hb <120 g/l. Hypertension was defined according to the sex-age-height adjusted reference tables from Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents.<sup>11</sup> Some patients had incomplete medical information, such as urine volume and medication history before admission (especially the history of taking traditional Chinese medicine). So, we didn't have these statistics.

One of the 13 young patients with IgAN terminated his treatment and hence no further data were available. The remaining 12 patients were followed up for up to 72 months. All of the 12 patients recovered from the AKI within 3 months. No renal replacement treatment (RRT) was applied.

### **Pathological Data**

Renal biopsy specimens were examined by light microscopy, electron microscopy and immunofluorescence and were graded according to the Oxford classification system and update<sup>12-15</sup> including mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental glomerulosclerosis (S), tubular atrophy/interstitial fibrosis (T) and cellular/fibrocellular crescents (C). Table 2 shows the recommendations for the interpretation of renal biopsy in IgA nephropathy.<sup>15</sup> Figure 1 shows different pathological images of patients in the AKI group and the non-AKI group.

### **Statistical Methods**

Data was analysed using the SPSS 18.0 software (SPSS Inc., Chicago, IL, USA). For continuous parameters, measurement results are reported as mean  $\pm$  standard deviation (SD) for normal distribution or median with first and third quartiles for skewed distribution. For categorical

parameters, results were reported as frequency or percentage. Continuous data were compared by means of Student's t test; proportions were compared with chi-square test. Univariate logistic regression and multivariate logistic regression were used to determine probabilities of the occurrence. All p values were two-tailed, and p<0.05 was considered statistically significant.

**Results**

**Clinical Features of Patients Between AKI Group and Non-AKI Group**

Table 3 describes the clinical parameters of patients with and without AKI. Thirteen out of 110 patients (11.81%) were diagnosed with AKI. The 13 patients were made up

of 10 male and 3 female patients with a mean age of 10.29±2.67. Compared with non-AKI group, AKI group showed higher occurrence of heavy proteinuria (76.92% versus 24.74%, p<0.001) and hypertension (15.38% versus 0, p=0.013). The mean value of uric acid was also higher in AKI group than in non-AKI group (365.47±109.98 umol/L versus 273.33±73.67 umol/L, p=0.011). No significant differences were observed in other parameters.

**Histopathological Features of Patients Between AKI Group and Non-AKI Group**

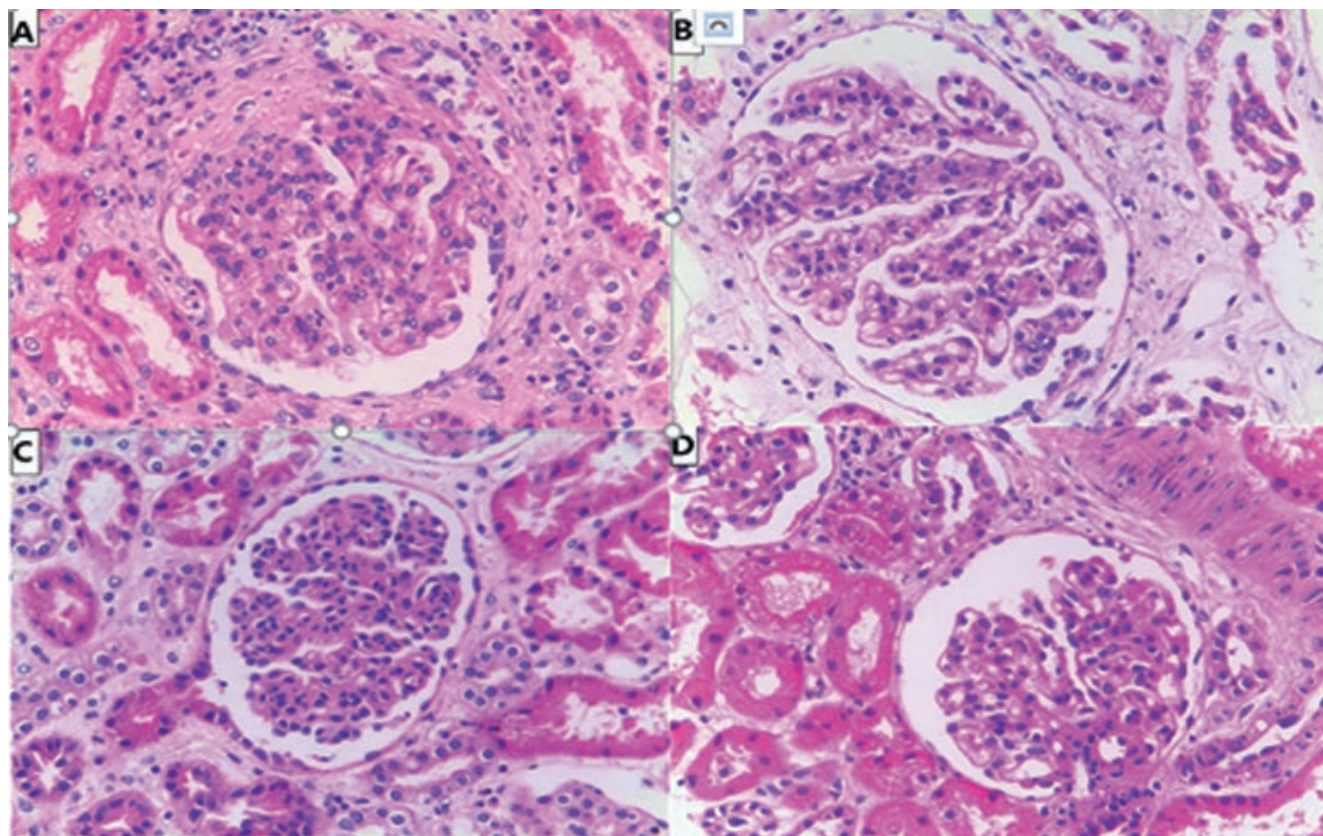
Table 4 describes the histopathological parameters of patients with and without AKI. Compared with non-AKI group, more glomeruli with crescents were observed in AKI group (p=0.022). No significant differences were observed in other parameters.

**Table 1** Staging of AKI

Stage	Serum creatinine	Urine output
1	1.5-1.9 times baseline OR ≥0.3 mg/dl (≥26.5 umol/l) increase	<0.5 ml/kg/h for 6-12 hours
2	2.0-2.9 times baseline	<0.5 ml/kg/h for ≥12 hours
3	3.0 times baseline OR Increase in serum creatinine to ≥4.0 mg/dl (≥353.6 umol/l) OR Initiation of renal replacement therapy OR, in patients <18 years, decrease in eGFR to <35 ml/min per 1.73 m <sup>2</sup>	<0.3 ml/kg/h for ≥24 hours OR Anuria for ≥12 hours

**Table 2** Recommendations for the interpretation of renal biopsy in IgA nephropathy

Detailed description of the features present on: Light microscopy Immunohistochemistry or immunofluorescence Electron microscopy
Summary of 5 key pathologic features Mesangial score <0.5 (M0) or >0.5 (M1) Endocapillary hypercellularity absent (E0) or present (E1) Segmental glomerulosclerosis absent (S0) or present (S1); presence or absence of podocyte hypertrophy / tip lesions in biopsy specimens with S1 Tubular atrophy / interstitial fibrosis 25% (T0), 26%-50% (T1), or >50% (T2) Cellular / fibrocellular crescents absent (C0), present in at least 1 glomerulus (C1), in >25% of glomeruli (C2)
Quantitative data Total number of glomeruli Number of glomeruli with endocapillary hypercellularity, necrosis, extra capillary hypercellularity (cellular / fibrocellular crescents), global glomerulosclerosis, and segmental glomerulosclerosis



**Figure 1** Different pathological images of patients in the AKI group and the non-AKI group. (A) A seven-year-old male patient with a high level of proteinuria and AKI (200x). (B) A thirteen-year-old male patient with a low level of proteinuria and AKI (200x). (C) A five-year-old female patient with a high level of proteinuria but without AKI (200x). (D) An eleven-year-old female patient with a low level of proteinuria and without AKI (200x).

**Table 3** Comparison of clinical features between AKI and non-AKI group at the time of biopsy

Characteristics	AKI group (13)	Non-AKI group (97)	P values
Male gender (n, %)	10 (76.92)	58 (59.79)	0.363
Age (year)	10.29±2.67	9.57±2.97	0.404
Gross haematuria (n, %)	10 (76.92)	74 (76.29)	1.000
Heavy proteinuria (n, %)	10 (76.92)	24 (24.74)	<0.001
Hypertension (n, %)	2 (15.38)	0	0.013
Anaemia (n, %)	2 (15.38)	3 (3.09)	0.105
Peak SCr when AKI attack (umol/L)	115 (98.5, 113.95)	NA	NA
UA (umol/L)	365.47±109.98	273.33±73.67	0.011
TG (mmol/L)	1.62 (0.85, 1.94)	1.29 (0.95, 2.12)	0.435
CHOL (mmol/L)	4.59 (3.80, 7.68)	4.45 (3.88, 5.64)	0.787

Notes: SCr: serum creatinine; UA: uric acid; CHOL: cholesterol; TG: triglycerides; NA: not applicable; heavy proteinuria: 24-hour proteinuria greater than 50 mg per body weight per day. Data were reported as mean ± SD or median; categorical variables were reported as percentage.

### The Associated Risk Factors With AKI

Table 5 shows the parameters associated with AKI among young patients with IgAN, analysed by the logistic regression. Heavy proteinuria (OR 16.867, 95% CI 2.144-132.725,  $p=0.007$ ) and the content of uric acid (OR 1.016, 95% CI 1.006-1.027,  $p=0.002$ ) were the most relevant parameters associated with AKI among young patients with IgAN.

## Discussion

The definition of AKI has not been clearly defined until the release of 2012 KDIGO criteria. IgAN is the most diagnosed primary glomerular disease. IgAN patients with AKI are more likely to develop CKD and ESRD. In order to take precautions of AKI, clinicopathological symptoms and possible risk factors need to be learned. In this study, the occurrence of AKI among young patients with IgAN was 11.82%; the clinical and pathological information were also provided, availing an insightful understanding of the

young IgAN patients with AKI. In this study it was found that AKI patients showed more notable clinical changes than non-AKI patients. Multivariate logistic regression analysis showed that the percentage of patients with heavy proteinuria and the level of uric acid differed the most between the two groups. The first conclusion is consistent with the previous study.<sup>16</sup> While hyperuricemia (HUA) caused by elevated uric acid levels (serum uric acid  $>420$   $\mu\text{mol/L}$  for men and  $>350$   $\mu\text{mol/L}$  for women) is a metabolic disease which could cause uric acid nephrolithiasis and gouty nephropathy. From the study of Hamid Nasri, uric acid played an important role in the pathological type and long-term prognosis of IgAN and it is an independent risk factor.<sup>17</sup> Xu et al conducted a systematic review and meta-analysis on HUA's risk of AKI, and conducted a randomised effect meta-analysis on a total of 75200 patients in 18 cohort studies. It was found that the high uric acid group had a higher risk of AKI than the control group (OR=2.24, 95% CI: 1.76~2.86,  $P<0.01$ ), and the increased uric acid content was one of the risk factors for AKI.<sup>18</sup> Lapsia et al considered that with the increase of

**Table 4** Comparison of pathological features between the AKI and the non-AKI group

Characteristics	AKI group (13)	Non-AKI group (97)	P values
Glomeruli with GS (n, %)	0	0	$>0.05$
Glomeruli with crescents (n, %)	6 (46.25)	16 (16.49)	0.022
M1 (n, %)	11 (84.61)	69 (71.13)	$>0.05$
E1 (n, %)	3 (23.07)	13 (13.4)	$>0.05$
S1 (n, %)	5 (38.46)	40 (41.23)	$>0.05$
T1 (n, %)	1 (7.69)	0	$>0.05$
T2 (n, %)	0	0	$>0.05$
C1 (0-25% crescents n, %)	5 (38.46)	16 (16.49)	$>0.05$
C2 ( $\geq 25\%$ crescents n, %)	1 (7.69)	0	$>0.05$

Notes: GS: global sclerosis. Data were reported as percentage.

**Table 5** Risk factors of childhood AKI of the IgAN patients with univariate and multivariate analysis

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	P	OR	95% CI	P
Heavy proteinuria (n, %)	10.139	(2.576, 39.906)	0.001	16.867	(2.144, 132.725)	0.007
Uric acid ( $\mu\text{mol/L}$ ) mean $\pm$ SD	1.013	(1.005, 1.020)	0.001	1.016	(1.006, 1.027)	0.002
Glomeruli with crescents (n, %)	4.339	(1.287, 14.627)	0.018	0.465	(0.065, 3.325)	0.446

Notes: Parameters with  $p<0.05$  in univariate analysis for a relationship with AKI were entered into multivariate analysis as covariates.

uric acid content, the risk of AKI would also increase. A J-shaped relationship appears to exist between serum uric acid and AKI.<sup>19</sup> However, there is no uniform conclusion on the uric acid critical value for children and adolescents. Heavy proteinuria and hyperuricemia could help us assess the risk of AKI in IgAN patients, but they could not help us diagnose AKI.

There are three common causes of AKI: prerenal, renal and postrenal. Prerenal acute AKI is mainly caused by hypoperfusion injury, such as severe dehydration, shock, congestive heart failure, etc. Renal AKI could be caused by various primary and secondary kidney diseases, nephrotoxic drugs, poisons and renal vascular diseases. Postrenal AKI is mainly caused by obstruction. Besides, congenital malformation of the urinary system could also cause AKI. In this study, no congenital malformation of the urinary system was found; The patient's parents were unable to provide some accurate information about the patients, such as the premorbid medication history (especially traditional Chinese medicine) and urine output. So, we don't know exactly the causes of AKI of these patients.

It was reported in the previous study that age, gender, malignant hypertension and certain pathological characteristics such as glomerulosclerosis and cellular crescents were risk factors of AKI in IgAN patients.<sup>20</sup> However, there was no such relationship observed in this study. Some limitations might affect the results of this work: first, the retrospective study was single-centre and the sample size was small; second, SCr content was the only criterium for determining AKI, due to the lack of urine volume data; third, the pathological symptoms of young IgAN patients were relatively mild compared with adult IgAN patients (only one IgAN patient with AKI had over 25% crescents observed and no glomeruli with global sclerosis observed in this study).

Wald and co-workers followed up AKI patients and non-AKI patients for 3 years and found the risk for AKI patients to develop ESRD was 72 times higher than that for non-AKI patients.<sup>21</sup> In this study, none of the AKI-IgAN patients progressed to ESRD, possibly because the patients in this study were not seriously ill, thus not showing strong pathological symptoms.

At present, the pathogenesis of primary IgAN is not completely clear, and there is no specific treatment. Due to the diversity, recurrence, chronic progression and non-parallel clinicopathology of the clinical manifestations of this disease, there are few high-quality, multi-centre, randomised controlled clinical trials which have been ideal

for clinical and renal pathological characteristics so far. Treatment options are mainly based on the main clinical manifestations and severity of renal disease. And the principles of multi-drug combination, low toxicity and long course of treatment are adopted. The main clinical drugs include adrenal glucocorticoids and various immunosuppressants, angiotensin converting enzyme inhibitors and angiotensin receptor antagonists, fish oil and anticoagulants.<sup>22</sup> On the basis of referring to relevant clinical guidelines, our hospital has been learning and accumulating clinical experience in the treatment of IgAN in recent years. Therefore, treatment is not the focus of this study.

## Conclusion

In this study, the overall occurrence of AKI in young IgAN patients was 11.81% (13/110). Heavy proteinuria and the uric acid content could be markers to help us diagnose AKI. When the 24-hour proteinuria of young patient is greater than 50 mg per body weight per day, the patient is more likely to have AKI; The higher the patient's uric acid level, the more likely the patient is to develop AKI.

## Declaration of Interest

None

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## Original Article

# Clinical Features of Kawasaki Disease in Children with an Atypical Age of Onset

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### Abstract

To evaluate the frequency of patients younger than six months and older than five years in a large cohort of patients with Kawasaki disease (KD), and to determine the clinical characteristics and outcomes of patients with an age of onset outside the typical age distribution. We performed retrospective chart review of KD patients treated at our hospital during a six-year period. Data of patients were record from discharge database. Patients were divided into three groups according to age of onset of illness. The typical age group (6 months to 5 years) was used as a reference, and the clinical features of KD patients  $\leq 6$  months old and  $>5$  years of age were analysed. A total of 2,318 cases were enrolled in this study population consisting of 1,432 boys and 886 girls. Cases  $\leq 6$  months of age and  $>5$  years of age accounted for 14.7% (340) and 14.0% (325) of the overall sample. Compared with the typical age group, the younger age group had longer of hospital stay, higher proportion of incomplete KD (iKD) cases, fewer illness days at admission, and fewer number of major criteria. Compared with the typical age group, the older age group had longer illness days at admission, longer total fever duration, and higher rate of delayed diagnosis. There were no significant difference between two groups in term of the rates of iKD, intravenous immunoglobulin resistance, and coronary artery lesion. Patients with KD  $\leq 6$  months of age tend to manifests incomplete symptoms with more pronounced systemic inflammation, while increased awareness contributed to improvement of diagnoses and outcomes. Patients with KD  $>5$  years of age have relatively low levels of systemic inflammation without worse treatment and outcome, but were prone to delayed diagnoses.

**Key words** Age; Clinical features; Kawasaki disease

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### Introduction

Kawasaki disease (KD), also known as mucocutaneous lymph node syndrome, is a pediatric systemic vasculitis of unknown origin. Now, it becomes globally common cause of acquired heart disease in children.<sup>1</sup> Intravenous immunoglobulin (IVIG) administration at acute onset of illness could reduce the incidence of coronary artery lesions from 15-25% of untreated patients to less than 5%.<sup>2</sup>

KD largely occurred in children within six months to five years of age. This may be associated with an immature immune system, because younger infants were protected by passive acquired maternal antibodies and older children were protected by acquired immunity.<sup>3</sup> The diagnosis and timely treatment of KD may also have improved over time, but early identification of patients at atypical age of onset

are challenge, especially for those who presenting atypical manifestations, due to no specific diagnostic markers for KD. Several study<sup>4-9</sup> have been reported the clinical features of younger and/or older patients with KD, but the small number of these studies weaken the power of the analysis and might resulted in instable results. More information of patients with KD at atypical age is still needed.

The goals of the present study were to evaluate the frequency of patients younger than six months and older than five years in a large cohort of patients with KD, and to determine the clinical characteristics and outcomes of patients with an age of onset outside the typical age distribution.

## Methods

### Study Population

We performed retrospective chart review of KD patients treated at our hospital during a six-year period (2009.1-2014.12). Data of patients were record from discharge database including three categories: (1) demographic and clinical indicators including gender, age, illness days admission, the numbers of main criteria, total fever duration, days of hospitalisation, effectiveness of the IVIG administration, echocardiographic results during hospitalisation; (2) pre- and post-IVIG complete blood count indicators including erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), white blood cell (WBC), percentages and absolute counts of neutrophils (NE), lymphocytes (LY), eosionphils (EO), monocytes (MO), haemoglobin, platelet; and (3) blood biochemical indicators, including indicators of liver function (alanine aminotransferase (ALT), aspartate transaminase (AST), albumin, total bilirubin (TBil) and gamma-glutamyl transferase (GGT), and serum electrolytes (sodium, potassium, chloride and calcium), measured before IVIG therapy. This retrospective study was approved by the Institutional Review Board of our university hospital and performed in accordance with the Declaration of Helsinki. All participants were given informed consent.

### Definitions

The diagnostic symptoms and signs for KD included fever, skin rash, bilateral nonexudative conjunctivitis, erythem of oral and pharyngeal mucosa, swollen extremities and/or palm and sole erythema, and acute non-suppurative cervical lymphadenopathy that is usually unilateral with a size of 1.5 cm or greater in diameter.

Patients who meet 5 of the 6 above criteria can be diagnosed with complete (cKD).<sup>10</sup> Patients who meet 4 criteria or fewer can be diagnosed as incomplete KD (iKD) in the presence or absence of coronary artery lesions (CAL), without other explanations for the febrile disease.<sup>11,12</sup> Both cKD and iKD were enrolled in our study population. Delayed-diagnosis KD was defined as initial IVIG being administrated 10 days post-onset of illness.<sup>13</sup> We defined IVIG resistance (IVIGR) as patients who had a continued fever or recurrence of fever  $>37.3^{\circ}\text{C}$  48 hours to two weeks after initial infusion of IVIG accompanied by at least one of the principal diagnostic criteria.<sup>14</sup> CAL were diagnosed based on two-dimensional echocardiography and defined as the previously reported criteria<sup>15</sup> either when (1) a lumen diameter of  $\geq 2.5$  mm in patients  $<3$  years old,  $\geq 3.0$  mm in patients within 3-9 years old, and  $\geq 3.5$  mm in patients  $>9$  years old, (2) the internal diameter of a segment measures 1.5 times that of an adjacent segment, or (3) the lumen was clearly irregular.

### Statistics

Data were listed as median (P25-P75) or the number of cases (%), as appropriately. Two-group comparisons were performed using nonparametric rank sum test for the continuous data, and using chi-square test for the count data. All analyses were carried out with SPSS 16.0 for Windows. Statistical significance was set as  $p$  less than 0.05.

## Results

### Data Collection

A total of 2,318 cases were enrolled in this study population consisting of 1,432 boys and 886 girls. Cases  $\leq 6$  months of age and  $>5$  years of age accounted for 14.7% (340) and 14.0% (325) of the overall sample.

### Comparison Between the Younger Age ( $\leq 6$ -month-old) Group and the Typical Age (6-month-old to 5-year-old) Group

As shown in Table 1, longer hospital stay, higher proportion of iKD cases, fewer illness days at admission, and fewer number of major criteria were observed in the younger age group compared with the typical age group. There were no significant difference between two groups with regard to the delayed diagnosis rate, the IVIGR rate, and the CAL rate. Comparisons of pre- and post-IVIG CBC between groups were listed in Tables 2 and 3. As shown in

Table 4, higher levels of TBil, GGT, potassium, and calcium, and lower levels of albumin and serum sodium were seen in the younger age group compared with the typical age group.

### Comparison Between the Older Age (>5-year-old) Group and the Typical Age Group

As shown in Table 1, longer illness days at admission, longer total fever duration, and higher rate of delayed

diagnosis were observed in older age group compared with the typical age group. There were no significant difference between two groups in term of the rates of iKD, IVIGR, and CAL. Comparisons of pre- and post-IVIG CBC between groups were listed in Tables 2 and 3. As shown in Table 4, higher levels of albumin, TBil and serum sodium, and lower levels of ALT, AST, GGT, serum chloride, serum potassium, serum calcium were in the older age group compared with the typical age group.

**Table 1** Comparisons of clinical characteristics between groups

Variables	≤6 months (A)		>5 years (B)		6 months - 5 years (C)	
	n	median (p25-p75)/n(%)	n	median (p25-p75)/n(%)	n	median (p25-p75)/n(%)
Male-to-female ratio	340	1.68:1	325	1.71:1	1653	1.59:1
Illness days at admission, days	340	5 (4-7)**	325	6 (5-9)##	1653	6 (5-7)
Number of major diagnostic criteria	340	3 (2-4)**	325	4 (3-5)	1653	4 (3-5)
Total fever duration, days	338	7 (6-9)	322	8 (6-10)##	1650	7 (6-9)
Length of hospitalisation, days	340	7 (5-9)**	325	6 (5-8)	1653	7 (5-8)
Incomplete KD, %	340	272 (80.0)**	325	183 (56.3)	1653	909 (55.0)
Delayed diagnosis, %	326	32 (9.8)	300	33 (11.0)#	1568	103 (6.6)
IVIGR, %	318	43 (13.5)	291	52 (17.9)	1517	285 (18.8)
CAL, %	338	95 (28.1)	322	70 (21.7)	1645	391 (23.8)

\*\*p<0.01 vs group C, #p<0.05 vs group C, ##p<0.01 vs group C.

IVIGR: intravenous immunoglobulin resistance; CAL: coronary artery lesions

**Table 2** Comparisons of pre-IVIG CBC between groups

Variables	≤6 months (A)		>5 years (B)		6 months - 5 years (C)	
	n	median (p25-p75)	n	median (p25-p75)	n	median (p25-p75)
ESR, mm/h	299	59 (42-84)**	301	58 (34-86)##	1511	69 (45-92)
CRP, mg/L	313	90 (49-141)**	299	55 (17-113)##	1508	71 (32-123)
WBC, x 10 <sup>9</sup> /L	314	14.1 (10.5-18.8)**	301	11.0 (7.2-15.3)##	1522	12.4 (9.0-16.4)
NE, %	314	55.0 (40.9-67.0)**	301	73.1 (58.4-83.4)##	1522	61.2 (46.6-73.8)
Absolute NE, x 10 <sup>9</sup> /L	314	7.9 (4.7-11.1)	301	7.7 (4.2-12.2)	1522	7.4 (4.4-11.2)
LY, %	314	33.8 (24.6-44.8)**	301	17.4 (10.4-30.6)##	1522	28.5 (18.3-41.1)
Absolute LY, x 10 <sup>9</sup> /L	314	4.7 (3.3-6.2)**	301	1.9 (1.1-2.5)##	1522	3.3 (2.3-4.7)
EO, %	313	3.1 (1.3-5.4)**	301	1.5 (0.8-3.1)##	1518	2.1 (0.9-4.2)
Absolute EO, x 10 <sup>9</sup> /L	313	0.42 (0.19-0.73)**	301	0.17 (0.07-0.32)##	1518	0.26 (0.11-0.49)
MO, %	313	6.2 (3.8-8.9)*	301	5.9 (3.4-8.3)	1518	5.6 (3.3-8.1)
Absolute MO, x 10 <sup>9</sup> /L	313	0.8 (0.46-1.36)**	301	0.57 (0.35-0.92)##	1518	0.66 (0.40-1.00)
Haemoglobin, g/L	314	97 (90-102)**	301	115 (109-121)##	1520	108 (101-114)
Platelet, x 10 <sup>9</sup> /L	314	450 (352-567)**	301	317 (236-406)##	1520	364 (291-459)

\*p<0.05 vs group C, \*\*p<0.01 vs group C, ##p<0.01 vs group C.

CBC: complete blood cell count; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; WBC: white blood cell count; NE: neutrophils; LY: lymphocytes; EO: eosinophils; MO: monocytes

## Discussions

Several investigations about age-related KD have been conducted in the past decades. Chuang et al<sup>4</sup> reported 25 cases of KD in patients  $\leq 3$  months of age from 1994-2004; the incidences of changes in the lips and tongue, conjunctivitis, rash, swollen lymph nodes, changes in the

extremities and CAL were 84%, 80%, 68%, 28%, 24% and 80%, respectively. Liu et al<sup>5</sup> reported 30 cases of KD in patients  $< 6$  months old and also found that swollen cervical lymph nodes were rare and more frequent CAL were seen in these patients, with lower haemoglobin and albumin and higher platelet. Moreno et al<sup>6</sup> reported 25 infants with typical KD in Spain from 1992-2006 and showed

**Table 3** Comparisons of post-IVIG CBC between groups

Variables	$\leq 6$ months (A)		$> 5$ years (B)		6 months - 5 years (C)	
	n	median (p25-p75)	n	median (p25-p75)	n	median (p25-p75)
ESR, mm/h	207	67 (43-88)**	220	75 (53-92)	1139	77 (52-96)
CRP, mg/L	315	6 (3-13)	288	7 (3-16)	1522	6 (2-14)
WBC, $\times 10^9/L$	321	9.4 (7.3-12.1)**	292	6.9 (5.5-8.9)##	1540	7.9 (6.2-10.4)
NE, %	321	25.2 (17.4-34.0)**	292	50.1 (41.9-60.9)##	1540	35.4 (26.0-47.5)
Absolute NE, $\times 10^9/L$	321	2.3 (1.4-3.7)**	292	3.6 (2.3-5.2)##	1540	2.6 (1.8-4.3)
LY, %	321	61.3 (53.7-70.2)**	292	39.7 (30.1-48.6)##	1539	52.9 (41.8-62.3)
Absolute LY, $\times 10^9/L$	321	5.5 (4.5-7.1)**	292	2.6 (2.1-3.2)##	1539	3.9 (2.9-5.2)
EO, %	321	3.4 (1.9-5.7)**	291	2.1 (1.1-3.6)##	1538	2.7 (1.4-4.5)
Absolute EO, $\times 10^9/L$	321	0.33 (0.18-0.50)**	291	0.15 (0.08-0.25)##	1538	0.20 (0.11-0.35)
MO, %	321	7.5 (4.7-10.2)**	291	6.1 (4.3-8.1)#	1538	6.6 (4.3-9.4)
Absolute MO, $\times 10^9/L$	321	0.65 (0.42-0.98)**	291	0.45 (0.28-0.6)##	1538	0.52 (0.33-0.77)
Haemoglobin, g/L	321	96 (89-103)**	292	115 (108-121)##	1540	108 (101-114)
Platelet, $\times 10^9/L$	321	708 (573-830)**	291	439 (349-533)##	1540	532 (426-648)

\*\*p<0.01 vs group C, #p<0.05 vs group C, ##p<0.01 vs group C.

CBC: complete blood cell count; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; WBC: white blood cell count; NE: neutrophils; LY: lymphocytes; EO: eosinophils; MO: monocytes

**Table 4** Comparisons of blood biochemical indicators between groups

Variables	$\leq 6$ months (A)		$> 5$ years (B)		6 months - 5 years (C)	
	n	median (p25-p75)	n	median (p25-p75)	n	median (p25-p75)
ALT, U/L	331	24 (15-42)	313	15 (11-37)##	1609	22 (13-53)
AST, U/L	331	33 (24-46)	313	26 (20-37)##	1609	31 (24-46)
Albumin, g/L	331	35.0 (32.0-37.4)**	313	36.9 (34.0-39.8)#	1609	36.4 (33.4-39.1)
TBil, $\mu\text{mol/L}$	331	5.2 (3.4-8.5)**	312	4.6 (3.1-6.9)#	1609	4.2 (2.8-6.6)
GGT, U/L	331	46 (23-109)**	312	12 (9-36)##	1609	21 (10-71)
Sodium, mmol/L	311	136 (134-138)*	283	137 (134-140)#	1508	137 (134-139)
Chloride, mmol/L	311	105 (103-108)	283	104 (101-107)##	1506	105 (103-108)
Potassium, mmol/L	311	3.9 (3.7-4.3)**	283	3.5 (3.2-3.7)##	1508	3.7 (3.4-4.1)
Calcium, mmol/L	311	1.16 (1.10-1.22)**	283	1.09 (1.03-1.15)##	1504	1.13 (1.07-1.19)

\*p<0.05 group A vs group C, \*\*p<0.01 group A vs group C, #p<0.05 group B vs group C, ##p<0.01 group B vs group C

ALT: alanine aminotransferase; AST: aspartate transaminase; TBil: total bilirubin; GGT: gamma-glutamyl transferase

of the cases were nonresponsive to IVIG infusion and 24% of the cases were complicated with CAL. Tseng et al<sup>7</sup> analysed 48 infants with KD over a 10-year span and showed that patients were more likely to be atypical forms and that echocardiography was helpful for early diagnosis. One hospital in northern India reported<sup>8</sup> 97 cases with KD between Jan. 1994 and Apr. 2006, of which 38 patients were >5 years of age; they found that the peeling of extremities and arthritis were more common in the older age group, whereas swelling of hands and feet was infrequent. Stockheim et al<sup>9</sup> reported 28 KD cases  $\geq$ 8 years of age and showed that the clinical features were mostly male, Caucasian, and difficult to timely diagnosis, accompanied by other atypical signs and symptoms and with a CAL incidence of 21%. These studies indicated that KD at extreme age of onset had their own unique features, facing the challenge of early recognitions and having poor treatment and outcomes. However, most of these studies including small sample led to instable and inconsistent findings. In this study, the clinical features of KD patients  $\leq$ 6 months old and >5 years of age were reviewed.

After comparing the younger age and the typical age groups, it was found that the number of main criteria of the younger age group was lower but that the proportion of iKD was higher, indicating that younger patients often exhibited atypical symptoms. It was also found that illness days at admission were shorter in younger age group, and that fever duration and the incidences of delayed diagnosis, IVIGR and CAL were not significantly different between the two groups, suggesting increased awareness in younger infants with KD for their parents or guardians reduced the delaying visit, and for healthcare providers reduced the delaying of diagnosis, both of which resulted in improvement of the treatment and outcomes and were consistent with previous report by Lee et al.<sup>16</sup> Comparisons of complete blood count indicators showed that before and after treatment, WBC, LY, absolute LY, EO, absolute EO, MO, absolute MO, and platelet were all elevated in the younger age group, whereas ESR and NE were decreased. The difference in inflammatory cell components in the younger age group, coupled with the physiological characteristics of varying proportions of blood cells (i.e., the percentages of NE and LY from 4-6 days of age to 4-6 years of age were inverted and approached the normal levels found in adults by 4-6 years), indicated that systemic inflammation was more pronounced in the younger age group. Comparisons of blood biochemical indicators revealed that TBil and GGT in the younger age group were elevated, whereas albumin and serum sodium were

lowered; these indicators can be used as auxiliary inflammation indicators in younger patients with KD. In addition, pre- and post-IVIG decreased levels of haemoglobin in the younger age group were likely related to age.

When the older age and typical age groups were compared, it was found that the former had a longer illness day at admission and a higher proportion delayed diagnosis in the older age group suggesting that the understanding of older patients with KD needs improvement for both their parents and clinicians. The longer duration in older age group were related to delayed visit and treatment. It was also found that the gender ratio, the number of the main criteria, the proportion of iKD cases, the rate of IVIGR and the incidence of CAL were not significantly different between two groups. Comparison of complete blood count indicators indicated that before and after treatment, NE of the older age group were elevated, whereas WBC, LY, absolute LY, EO, absolute EO, MO, absolute MO, and platelet were decreased; before treatment, CRP and ESR were decreased. Coupled with the aforementioned physiological characteristics of varying proportions of blood cells, the extent of inflammation in the older age group was relatively low. The comparison of blood biochemical indicators showed that albumin, TBil and serum sodium were elevated in the older age group, whereas ALT, AST and GGT were decreased, which were also responses to low severity of systemic inflammation. Additionally, pre- and post-IVIG elevated haemoglobin in the older age group might be related to age.

A number of studies about age-related KD showed similarity with and discrepancies from our findings. A group from Taiwan<sup>17</sup> reported 120 KD cases (20 cases in patients <6 months old) from 1994-2003 and showed that in the younger age group, WBC and platelet were elevated, haemoglobin was decreased and iKD was common, which were similar to our findings, although more frequent CAL and delayed KD diagnosis showed differences from ours. Lee et al<sup>16</sup> analysed the characteristics of three age groups in 136 KD cases from 1999-2003 and showed that the rate of CALs in the older age group, the younger age group and the typical age group were 42%, 20% and 17%, respectively, indicating that coronary artery damage was frequent in the older age group but that there was no difference between the levels in the younger age group and the typical age group, which is partly different from the findings in this study. Kim et al<sup>18</sup> reported the characteristics of three age groups in 185 KD cases from

2006-2007 and found that the overall incidence of CAL was 9% and that the incidence of CAL was not different among the groups, which is similar to the findings in this study but different from our findings on similar iKD proportions among the groups. Manlhiot et al<sup>19</sup> reported a large sample study with 1,374 cases of KD and divided the cases into different groups based on age; they showed that the <1-year-old and >9-year-old groups had elevated incidences of CAL and that the >9-year-old group had frequent delayed diagnoses, indicating that the age of onset was associated with coronary artery outcomes, which is different from our findings. However, the frequent delayed diagnoses in the older age group were consistent with our findings. A group from Wuhan in China reported<sup>20</sup> 113 cases of KD (20 patients >5 years old) from 2004-2010 and found that the older age group had longer fever durations and a long duration of fever process before and after IVIG treatment, which is consistent with our findings; however, the ESR, IVIGR and CAL incidences were high, which is inconsistent with our findings. The characteristics of different age groups reported in different regions may be related to differences such as knowledge about KD, sample size and inclusion criteria of KD patients.

Our retrospective study has some limitations. Some items of the data were missing, which could have led to biases in statistical analyses; therefore, we have listed the number of cases for each group and each item. A minority of cases (22 cases in younger group, 34 case in older group and 136 cases, because these patients were all diagnosed after 10 day of onset of KD and the temperature and inflammation marker came back to normal) did not receive IVIG therapy, having an influence on accurate evaluation of IVIG resistance. Because the data were collected over 6 consecutive years, the cases with large sample sizes were able to enhance the stability of the data, which compensates for these weaknesses to a certain extent.

## Conclusions

Patients with KD ≤6 month of age tend to manifests incomplete symptoms with more pronounced systemic inflammation, while increased awareness contributed to improvement of diagnoses and outcomes. Patients with KD >5 years of age have relatively low levels of systemic inflammation without worse treatment and outcome, but were prone to delayed diagnoses.

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## Conflict of Interest

No authors' financial ties to products in the study or potential/perceived conflicts of interest

## Ethical Standards

Not applicable

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## Original Article

# Portrayal of Thyroid Abnormalities and Their Management in a Local Cohort of Children and Adolescents with Down Syndrome: An Update

SWY To, ACC Fu, CC SHEK

### Abstract

**Objective:** Evaluation of the prevalence of different thyroid disorders and co-morbidities in children and adolescents with Down syndrome (DS). **Methodology:** Retrospective review of medical records from a tertiary referral centre in Hong Kong from 2002 to 2017. Prevalence of different thyroid disorders and associations with co-morbidities were calculated. **Results:** Among the 157 patients enrolled in analysis, impaired thyroid function was found in 58 (36.9%) patients. The most common form of thyroid-related disorder was subclinical hypothyroidism. Of note, 4.5% of them had oscillating thyroid diseases. Anti-thyroid antibody testing was done in 19% of the patients. Haematological malignancies were significantly associated with development of any thyroid diseases ( $p=0.026$ ). Fifty percent of DS patients were shown to be affected by thyroid abnormalities by 22.9 years. **Conclusion:** Thyroid abnormalities are very common among children with DS. Anti-thyroid antibody testing is indicated in older children to delineate the risk of development or persistence of thyroid diseases. Consensus is needed to standardise the time points of thyroid function evaluation especially during early stages of life.

### Key words

Down syndrome; Hypothyroidism; Hypothyroidism; Thyroid disorders

### Background

Down syndrome (DS) is one of the commonest survivable autosomal aneuploidy,<sup>1</sup> occurring in one of 600 to 800 live births. Thyroid dysfunction is a well-recognised endocrinopathy experienced by patients with DS, with a lifetime prevalence ranging from 13 to 63%.<sup>2</sup>

Being a treatable cause of mental retardation, timely detection and treatment of hypothyroidism are pivotal to optimise the cognitive capacities and improve the quality of life in this already impaired population, especially when

the onset of hypothyroidism may be associated with symptoms and clinical findings that are subtle (e.g. macroglossia, developmental delay, feeding difficulties and constipation) and easily attributed to the underlying disorder.

In the last retrospective epidemiological study on DS in Hong Kong published in year 2006, covering 1986 to 2001, it has revealed thyroid dysfunctions were very prevalent (28.8%) in DS population in our locality. Among which, the majority was subclinical hypothyroidism (22.5%).<sup>3</sup>

There have been disparities in opinions with regard to the association between congenital hypothyroidism and DS. Although Fort et al found congenital hypothyroidism to be more common among infants with DS than in the general population, some other references challenged this observation. There have also been debates on optimal timepoints for screening thyroid function in DS children especially during the first year of life. The American Academy of Pediatrics (AAP) recommends that thyroid functions in DS children should be monitored at birth, at 6 and 12 months of age then annually.<sup>2,4-6</sup> However, recent studies adding extra timepoints between birth and six

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months of life revealed significant cases of hypothyroidism requiring thyroxine supplementation.

The correlation of acquired thyroid diseases and DS in older children, mostly autoimmune in origin, is otherwise better established and accepted over the years.<sup>7</sup> Furthermore, thyroxine therapy in DS children with subclinical hypothyroidism, or termed isolated hyperthyrotropinemia or compensated hypothyroidism has remained the object of debate. Some authors concluded that thyroxine replacement was seldom required in subclinical hypothyroidism in children with DS, as in those of the general population. A recent meta-analysis in adult non-pregnant subclinical hypothyroid patients concluded thyroxine replacement did not improve the general quality of life or thyroid-related symptoms.<sup>8</sup> On the contrary, other authors suggested that therapy should be forthcoming, even in mild cases, because such treatment prevents the development of more severe hypothyroidism.

More than one decade after our last local study, it is therefore about time to revisit the prevalence of the thyroid status and pattern of clinical management in this needed population in our locality and to compare with the disputable observations in other countries.

## Objectives

The primary objective of this study was to determine the prevalence of thyroid disorders among children and adolescents with DS in our locality; while the secondary objectives were to investigate the co-existence of congenital anomalies and/or co-morbidities, the incidence of autoantibodies, as well as their relationship with thyroid dysfunctions. Clinical management on the thyroid disorders, particularly the threshold of commencing thyroxine replacement in subclinical hypothyroidism was also evaluated.

## Methodology

### *Study Design and Subjects*

This was a retrospective cohort study of all children and adolescents with DS (ICD-10 code 758.0) who were admitted to the paediatric units or attended the specialist out-patient clinics of Princess Margaret Hospital from 1st January 2002 to 31st December 2017. Subjects were excluded when their hard and electronic data could not be retrieved. This study was approved by the Institutional

Review Board or Research Ethics Committee of Kowloon West Cluster.

### *Data Collection*

The hospital records were retrieved using the Clinical Data Analysis and Reporting System (CDARS) with the following data reviewed: demographics, growth parameters, karyotypes, co-existence of congenital anomalies and/or co-morbidities, thyroid stimulating hormone (TSH), free thyroxine (FT4) and thyroid antibodies (anti-thyroglobulin and anti-thyroid peroxidase levels) at the time of diagnosis of a thyroid disorder or at their latest presentation if their thyroid status has remained normal, investigations including thyroid scan and ultrasound scan of the thyroid gland. Age at the beginning of therapy, thyroxine and anti-thyroid medication dose at initiation and last visit were also recorded. The record tracing would be limited to the period when the patients have been managed by paediatricians if they have already reached the adult age range and followed up by the adult medical counterpart.

Thyroid disease was characterised as congenital hypothyroidism, acquired hypothyroidism, subclinical hypothyroidism and hyperthyroidism as per the criteria defined by the American Thyroid Association (ATA),<sup>9</sup> or as stated in the medical record, with the additional taxonomies of unspecified hypothyroidism, oscillating thyroid disease, transient hypothyroidism and transient hyperthyroidism for more prudent categorisations (Table 1). Cases of subclinical hypothyroidism were further separated into those TSH 5-10 mIU/L and those with TSH greater than 10 mIU/L. If the diagnostic data was not available, classification would be based on the available abnormal thyroid functions within six months before starting treatment.

### *Statistical Analysis*

Data were presented in count with percentage, mean with standard deviation (SD) or median with interquartile range (IQR). Prevalence of thyroid disease with 95% confidence interval (CI) was calculated. Chi-squared tests or Fisher's exact tests were used to compare categorical variables. Continuous variables were compared by Kruskal Wallis test among different thyroid disease status. Proportion of patients affected by thyroid disease with age was illustrated with Kaplan-Meier curve. All statistical data was analysed by Statistical Package for Social Sciences (SPSS) software (version 22). P-value of less than 0.05 was considered as statistical significant.

## Results

A total of 157 patients were enrolled in the study after excluding 11 patients with data not retrievable. There were 99 males (63.1%) and 58 females (36.9%). The majority was Chinese (97.4%), with one Japanese, one Korean and two Pakistani. The most common co-morbidity in the cohort was congenital cardiac disease (43.3%). Among the cohort, 99 patients had normal thyroid function throughout the course of paediatric follow-ups. The thyroid disease prevalence was 36.9% (95% CI 29.79% to 44.72%). The comparison of karyotyping information, congenital anomalies and co-morbidities in patients with and without thyroid diseases were described in Table 2. There was no association found between developing any thyroid diseases and gender, ethnicity, karyotype or different co-morbidities, except leukemia or myeloproliferative disorders ( $p=0.026$ ). There were six patients (3.8%) with leukemia or myeloproliferative disorders, five of whom had developed thyroid diseases.

Table 3 shows the details of different thyroid diseases. Among 58 patients with a thyroid-related diagnosis, three (1.9%) had congenital hypothyroidism, six (3.8%) had acquired hypothyroidism, 18 (11.5%) had subclinical hypothyroidism, three (1.9%) had unspecified hypothyroidism, seven (4.5%) had hyperthyroidism, seven (4.5%) had oscillating thyroid disease, 14 (8.9%) had transient hypo/hyperthyroidism. The TSH and FT4 levels were statistically significantly different among the thyroid

disease groups ( $p<0.001$  and  $p=0.007$ , respectively). The anti-thyroid antibody positivity was statistically significant between the disease groups ( $p=0.007$ ), but only 30 (19%) patients were tested with 12 of them having one or both antibodies positive. For those with normal thyroid function, only one was tested for anti-thyroid antibodies which were negative.

Among seven patients with congenital or subclinical hypothyroidism diagnosed below the age of one, five were diagnosed between newborn and six months of age, i.e. between the first and second time points for thyroid function evaluation in DS children as per AAP recommendation.<sup>4</sup> For the five patients diagnosed between newborn and six months of age, three of them were congenital hypothyroidism and two were subclinical hypothyroidism. All of the five patients were started on thyroxine supplement.

Seven patients had pure hyperthyroidism with the mean age of diagnosis at 13.01 years. For the seven patients with oscillating thyroid disease, most of them developed hypothyroidism first, then gradually moved to have hyperthyroidism. Their thyroid perturbations all developed in their adolescence. It did not see a gender predominance. Antibody positivity was remarkably higher in patients with hyperthyroidism (four out of five tested) and oscillating thyroid disease (six out of seven tested).

Thyroid scan was done in 10 patients, three were congenital hypothyroidism, two acquired hypothyroidism, three subclinical hypothyroidism and two transient

**Table 1** Diagnostic criteria for different types of thyroid diseases

Thyroid disease	Diagnostic criteria*
Congenital hypothyroidism	High TSH with low FT4 diagnosed within the first month of life, or as stated in the medical record
Acquired hypothyroidism	High TSH with low FT4 after first month of life, or as stated in the medical record
Subclinical hypothyroidism	High TSH with normal FT4 at diagnosis, or as stated in the medical record
Unspecified hypothyroidism	High TSH with low FT4 with unspecified time point at diagnosis, or when FT4 level was not available
Hyperthyroidism	Low TSH with high FT4 at diagnosis, or as stated in the medical record
Oscillating conditions	The change of hypothyroidism to hyperthyroidism, or in the opposite sequence, during the study period
Transient hypothyroidism	Transient high TSH with low or normal FT4, which later reverted to normal, which may or may not require replacement therapy
Transient hyperthyroidism	Transient low TSH and/or elevated FT4, which later reverted to normal, which may or may not require anti-thyroid therapy

Abbreviations: TSH, thyroid stimulating hormone; FT4, free thyroxine

\*High and low were assessed as per the reference ranges of the individual laboratories

**Table 2** Demographics and co-morbid diagnoses in the cohort\*

	Thyroid related diseases			<i>p</i> value <sup>†</sup>
	Total (n=157)	No (n=99)	Yes (n=58)	
Age at diagnosis (year) - median [IQR]	–	–	8.2 [1.5 - 16.2]	–
Gender				0.884
Male	99 (63.1)	62 (62.6)	37 (63.8)	
Female	58 (36.9)	37 (37.4)	21 (36.2)	
Ethnicity <sup>‡</sup>				0.130
Chinese	150 (97.4)	98 (99.0)	52 (94.5)	
Non-Chinese	4 (2.6)	1 (1.0)	3 (5.5)	
Karyotype <sup>‡</sup>				1.000
Trisomy 21	64 (94.1)	31 (93.9)	32 (91.4)	
Mosaicism	3 (4.4)	2 (6.1)	1 (2.9)	
Robertsonian translocation	1 (1.5)	0	1 (2.9)	
Congenital cardiac disease				0.430
No	89 (56.7)	60 (60.6)	29 (50)	
Yes without operation	45 (28.7)	26 (26.3)	19 (32.8)	
Yes with operation	23 (14.6)	13 (13.1)	10 (17.2)	
Visual impairment <sup>§</sup>	50 (31.8)	34 (34.3)	16 (27.6)	0.380
Hearing impairment	36 (22.9)	19 (19.2)	17 (29.3)	0.145
Sleep apnoea	15 (9.6)	9 (9.1)	6 (10.3)	0.796
Gastrointestinal disease				0.728
No	129 (82.2)	81 (81.8)	48 (82.8)	
Duodenal atresia / Hirschsprung disease / Imperforate anus	14 (8.9)	10 (10.1)	4 (6.9)	
Others <sup>§</sup>	14 (8.9)	8 (8.1)	6 (10.3)	
Leukaemia / myeloproliferative disorders	6 (3.8)	1 (1.0)	5 (8.6)	0.026
Orthopaedics				0.622
No	131 (83.4)	84 (84.8)	47 (81.0)	
C1/2 subluxation	14 (8.9)	9 (9.1)	5 (8.6)	
Others <sup>§</sup>	12 (7.6)	6 (6.1)	6 (10.3)	
Undescended testes (for male only)	9 (9.1)	5 (8.1)	4 (10.8)	0.724
Diabetes	1 (0.6)	0	1 (1.7)	0.369
Obesity	14 (8.9)	8 (8.1)	6 (10.3)	0.631
Psychological disturbance	6 (3.8)	2 (2.0)	4 (6.9)	0.194
Seizures	5 (3.2)	3 (3.0)	2 (3.4)	1.000
Renal abnormalities <sup>§</sup>	12 (7.6)	5 (5.1)	7 (12.1)	0.128

\*Values are presented as count (%), except where noted

<sup>†</sup>Pearson's chi-square test or Fisher's exact test<sup>‡</sup>With missing data<sup>§</sup>Visual impairment include astigmatism, strabismus, cataract, myopia and hypermetropia; other gastrointestinal diseases include gastroesophageal reflux, irritable bowel syndrome, constipation, inguinal hernia, umbilical hernia, gallstone; other orthopaedics include hallux valgus, flat foot; renal abnormalities include renal parenchymal disease, nephrocalcinosis, dilated renal collecting system

hypothyroidism. Thyroxine had been started in eight out of these 10 patients. Ultrasound thyroid was only performed in three patients.

Thyroxine replacement was required in 22 patients with the mean age of thyroxine commencement at  $6.98 \pm 7.68$  years (range: 0.01 to 22.62 years), dependent on the indications of treatment. The mean TSH of thyroxine commencement was  $64.0 \pm 119.5$  mIU/L (range: 2.6 to 500 mIU/L). Seven (31.8%) of them were replaced with thyroxine when their TSH was less than 10 mIU/L. Thirteen patients were treated with anti-thyroid drugs (ATD). All of the ATDs were carbimazole. The mean age of carbimazole commencement was  $16.2 \pm 5.49$  years (range: 2.92 to 22.93 years), which is much older than that for thyroxine.

## Discussion

This study confirmed the previously reported high prevalence of thyroid problems in DS patients in the defined study period. In line with the findings by Mak et al, subclinical hypothyroidism was the most prevalent thyroid abnormality in DS children, the mean age of diagnosis of hyperthyroidism was the oldest among all categories of

thyroid abnormalities.<sup>3</sup>

We acknowledged and addressed the findings in the previous local cohort study. We intended that the features distinguishing the current study from the previous publication would be (a) discussion of the inadequacy of AAP recommendations on thyroid screening in DS children, (b) occurrence and discussion of oscillating thyroid disease, (c) address on the variability of TSH thresholds at the commencement of thyroxine for treatment of hypothyroidism.

The incidence of congenital hypothyroidism (CH), which comprised of three DS patients (1.9%) in the cohort over the study period of 15 years was the same in our local population over another 15 years prior to our study period.<sup>3</sup> CH was therefore not the most accountable aetiology of thyroid abnormalities in DS children and adolescents. It could be explained by the observation that congenital hypothyroidism diagnosed at newborn, and after newborn and before six months is of non-immune aetiology, whereas the prevalence of thyroid problems in DS is associated with autoimmunity.<sup>10</sup> A previous study showed no cases of autoimmune positivity before the age of eight.<sup>11</sup> In our cohort, the mean age with positive antibodies was 13.17 years. None of the cases diagnosed during infancy was

**Table 3** Prevalence of different thyroid diseases and the presence of anti-thyroid antibodies\*

Thyroid disease	Total	Male	Age at diagnosis (years)	TSH (mIU/L)	FT4 (pmol/L)	Anti-thyroid antibody Tested	
						Total	Positive
Congenital hypothyroidism	3 (1.9)	2 (66.7)	0.07±0.04	37.42±18.36	14.70±5.66	2 (66.7)	0
Acquired hypothyroidism	6 (3.8)	5 (83.3)	9.23±8.47	90.25±200.79	9.55±3.31	6 (100)	1 (16.7)
Subclinical hypothyroidism	18 (11.5)	11 (61.1)	6.14±5.92	7.64±3.34	12.89±3.23	7 (38.9)	1 (14.3)
TSH 5 - 10 mIU/L	13 (8.3)	6 (46.2)	6.51±5.84	5.83±1.32	13.28±3.45	3 (23.1)	1 (33.3)
TSH > 10 mIU/L	5 (3.2)	5 (100)	5.17±6.72	12.32±2.05	11.96±2.7	4 (80)	0
Unspecified hypothyroidism <sup>†</sup>	3 (1.9)	1 (33.3)	2.99	8.20	–	0	–
Hyperthyroidism	7 (4.5)	2 (28.6)	13.01±5.73	0.05±0.06	39.15±17.75	5 (71.4)	4 (80)
Oscillating conditions	7 (4.5)	4 (57.1)	18.33±4.82	30.28±71.42	26.87±21.49	7 (100)	6 (85.7)
Transient hypothyroidism	13 (8.3)	11 (84.6)	7.91±8.17	7.74±3.7	13.44±2.64	2 (15.4)	0
Transient hyperthyroidism	1 (0.6)	1 (100)	19.09	1.35	26.60	0	–
Normal thyroid function	99 (63.1)	62 (62.6)	–	2.06±0.89	12.53±2.82	1 (1)	0
p value <sup>‡</sup>	–	0.214	0.003	<0.001	0.007	–	0.007

Abbreviations: TSH, thyroid stimulating hormone; FT4, free thyroxine

\*Values are presented as count (%) or mean ± SD

<sup>†</sup>With missing data

<sup>‡</sup>Comparison among disease groups using Fisher's exact test or Kruskal Wallis test

associated with positive antibodies.

With the advent of medical technology, it was realised that the biochemical evidence of hypothyroidism often supersedes clinical symptoms. And when worst comes to worst, DS features and hypothyroidism overlap and both contribute to developmental delay. In our cohort, five patients were diagnosed before the six-month thyroid function screening recommended by the AAP.<sup>4</sup> Their recommendations, largely based on expert opinions, had produced a hot debate among the endocrinologists on the diagnosis and treatment decisions. Although we have universal newborn screening for thyroid function, the screening might still have the problem of false negativity.<sup>12</sup> A cohort study done in a university-based birthing hospital rescreened a total 122 neonates with DS before four months of age who had normal newborn thyroid screening and found 17.4% with hypothyroidism requiring thyroxine replacement.<sup>6</sup> Adding more time points for screening before six months of age may detect early cases of hypothyroidism who passed their newborn screen and might improve their developmental trajectory by timely intervention, when there is no doubt that congenital hypothyroidism is the most treatable cause of mental retardation. Delaying thyroxine replacement after three months poses higher risk of mental retardation.<sup>13</sup> The additional screening, with the test itself not burdening much extra cost, could be done without additional paediatrician visits.

Seven patients in our cohort demonstrated oscillating thyroid disease, i.e. development of hypothyroidism then progressed to hyperthyroidism, or in the converse. For patients developing hyperthyroidism first, two of them progressed to hypothyroidism and then developed hyperthyroidism again. Six out of seven had positive anti-thyroid antibodies. This is a very peculiar feature in DS, with Graves' disease (GD) often preceded by Hashimoto thyroiditis (HT).<sup>14</sup> While there exists a continuum between HT and GD within the spectrum of autoimmune thyroid disorders (AITDs),<sup>15</sup> DS patients are at higher risk of progression from HT to GD, irrespective of other concomitant risk factors.<sup>14,16</sup> In our latest local study of juvenile GD in Hong Kong, the female to male ratio in our local study was up to 9.7.<sup>17</sup> There were five females and two males diagnosed hyperthyroidism in our cohort, in contrast to three females and four males in the group of oscillating thyroid disease. The loss of gender predominance is in concordance with the literature findings.<sup>16</sup>

Among those medicated with thyroxine, 31.8% of them were started on replacement when their TSH was less than 10 mIU/L. The benefit of thyroxine replacement in

subclinical hypothyroidism is debatable. The general perception is biased towards treatment which is beneficial and doing little harm. Yet newer studies have proven that early thyroxine treatment in DS children with hyperthyrotropinemia (TSH  $\geq 5$  mIU/L) did not improve mental or motor developmental achievement in their later life despite there was measurable positive effect on growth.<sup>18</sup> A large retrospective study also showed a 73.6% normalisation rate in five years follow-up if TSH was between 5 and 10 mIU/L in a cohort of over 120,000 paediatric patients.<sup>19</sup>

Meanwhile, some authors opined DS patients have a non-pathological shift in the normal range of TSH and may lead to overdiagnosis of subclinical hypothyroidism.<sup>20</sup> Another observational study also revealed that DS newborns had a lower total T4 concentration in combination with a higher TSH concentration compared with non-DS newborns.<sup>21</sup> Hyperthyrotropinemia is an inherent attribute of chromosomopathy in DS that alters the hypothalamic-pituitary-thyroid axis.<sup>22</sup>

On the other hand, Aversa et al revealed higher risk of deterioration of thyroid status in Hashimoto thyroiditis related subclinical hypothyroidism (SH) compared with idiopathic SH.<sup>21,23</sup> This emphasizes the importance of antibody testing in SH patients. Only 19% of our cohort had the antibody screening done.

The authors believed the normalisation of thyroid status in the group of transient hypothyroidism may be associated with negative antibody if screening had been performed. In our cohort, only two patients (15.4%) among the group of transient hypothyroidism were screened for anti-thyroid antibodies, with none of them being positive. The mean age of normalisation of thyroid function in the transient groups was 12.4 years. Nonetheless, there have been diversifying opinions with regard to the time course and natural history of hypothyroidism.<sup>5,24</sup>

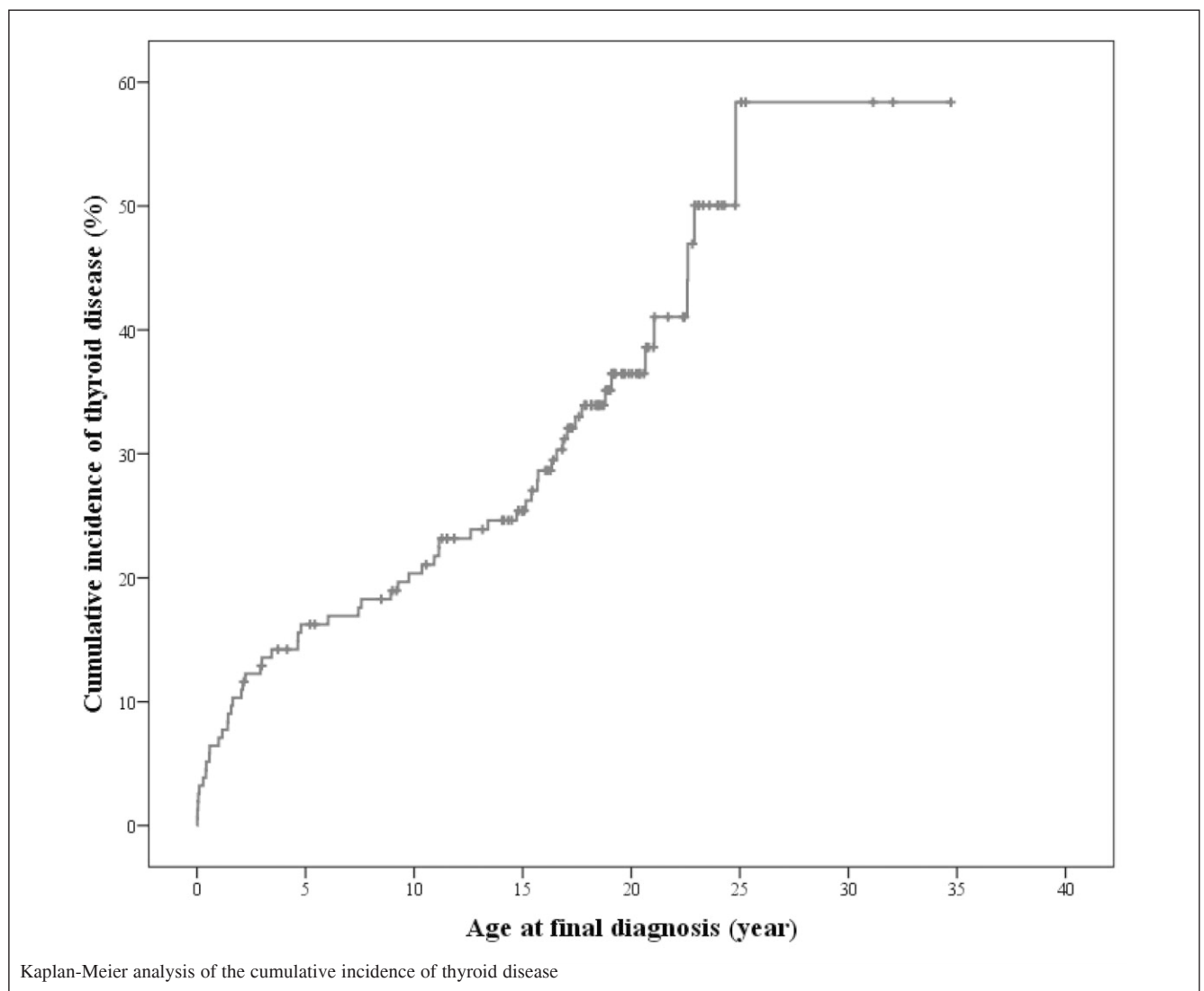
Owing to the high lifetime prevalence of thyroid diseases in DS patients (Figure 1) and the association between autoimmunity and development of persistent thyroid diseases, anti-thyroid antibody screening could shed light on selecting DS patients who are more probable to develop overt hypothyroidism and hence closer follow up.

Concerning the co-morbidities of DS, previous studies concluded that there were no association between congenital heart diseases and thyroid abnormalities.<sup>25</sup> However, congenital hypothyroidism is noted to occur more commonly in DS patients with congenital gastrointestinal anomalies,<sup>26</sup> though this was not observed in our cohort. The only significant association we found was between haematological malignancies and thyroid

diseases ( $p=0.026$ ). Although not widely reported, there were postulations between the two given the immunological abnormalities in DS patients.

There are a few limitations in this study. Firstly, the sample size is small from our single centre, with many missing data when the electronic and hard copies of the case notes could not be retrieved. The registrants in the cohort are not considered to represent the full population of DS children. There is heterogenous distribution of ethnicities in this metropolitan city. Our cluster might be skewed to be Chinese in majority but not the others. Secondly, small number of patients were screened for thyroid antibodies, especially those with

transient hypothyroidism and registrants not labelled having a thyroid-related disorder. Thirdly, the definition of subclinical or overt hypothyroidism (congenital, acquired or unspecified) in some cases might be ambiguous owing to early commencement of thyroxine when the hormonal manifestation had not yet been full-blown. This would affect our data analysis and comparison. Finally, the hormonal and antibody analyses came from different laboratories over the 15-year study period when the assay methodologies might have been updated. The same analyte would be reported by different reference ranges that might pose difficulties on our interpretations.



**Figure 1** Demonstrated the Kaplan-Meier cumulative lifetime prevalence curve, illustrating the development of thyroid diseases with age. There were 25% of DS patients with a diagnosis of thyroid dysfunction at 14.7 years and 50% at the age 22.9 (95% CI 21 to 24.9 years). Therefore one in two DS patients would be affected by thyroid disease when they reach adulthood.

## Conclusion

Thyroid abnormalities are common in children and adolescents with DS. More frequent thyroid function evaluations on top of the AAP recommendations could enhance earlier detection and intervention. However, despite the treatment is usually safe, there is debate on the TSH threshold of thyroxine contemplation in SH which might not produce the expected favourable outcomes as previously reported. Anti-thyroid antibody testing allows closer follow up and timely treatment especially when they have SH. Future studies may consider developing age-specific reference ranges for TSH and FT4 specific to DS patients. Consensus is needed to establish the working definition of euthyroidism and hypothyroidism, standardise the screening and management of thyroid abnormalities in children and adolescents with DS.

## Declaration

I declare that this dissertation represents my own work and this paper has not been published before. There is no conflict of interest concerning this study.

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## Original Article

# Clinical Characteristics and Outcomes of Paediatric Non-tuberculous Mycobacterial Infection: Single Institution Retrospective Review Over Past 20 Years

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### Abstract

Non-tuberculous mycobacterial (NTM) infection is uncommon yet clinically significant as it could cause severe morbidity and mortality. This study reviewed all paediatric patients under 20 years of age diagnosed to have NTM infection in Queen Mary Hospital during 1 January 1999 to 30 June 2018. Total 7 patients were identified with median age of diagnosis at 6 years old and median duration of follow up for 30 months. Majority (86%) have underlying comorbidities such as haemic malignancies or history of stem cell transplantation. Clinical manifestations varied from lymphadenitis, pulmonary infection, osteomyelitis, arthritis to systemic bacteraemia. Infective agents include *Mycobacterium fortuitum*, *M. abscessus* and *M. chelonae*. Mortality rate was high (29%). High index of suspicion and early recognition of NTM infection is important especially in immunocompromised and at-risk individuals. Prompt administration of appropriate therapy improves patient outcomes. Multidisciplinary collaboration is crucial. Treatment could be difficult and prolonged. Drug-related toxicities are common.

### Key words

*Diagnosis; Morbidity; Nontuberculous mycobacteria; Therapeutics*

### Introduction

Non-tuberculous mycobacteria (NTM) are ubiquitous in the environment such as water, soil, dust, animals, and birds. By far, more than 190 species of NTM have been

identified, and approximately 60 of which are suspected or known to be pathogenic in humans. Despite of their low virulence and indolent clinical course of infection, NTM infection could cause severe morbidity and mortality. Clinicians should not overlook this group of relatively less common yet clinically significant infection, especially in oncology and transplant settings. Retrospective review on clinical data helps summarise experience and remind physicians not to overlook this possibility especially in susceptible group of patients.

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### Methods

#### Study Design

A single-centre retrospective study was conducted in the University Department of Paediatrics and Adolescent Medicine of Queen Mary Hospital (QMH), a university-affiliated hospital offering tertiary and quaternary clinical services with encounter of highly complex patients in daily practice. All patients under 20 years of age and diagnosed to have NTM infection in QMH during 1st January 1999 to 30th June 2018 were retrieved through Clinical Data

Analysis and Reporting System using the diagnostic code (ICD-9) for "non-tuberculous mycobacterial infection" (031.9). Information on patient demographics, presence of underlying co-morbidities, clinical manifestations of infection, duration between symptom onset and confirmation of laboratory diagnosis, infective agent identified, sensitivity pattern, treatment given and duration, presence of complications as well as final outcome were collected and studied from written and electronic medical records through the Clinical Management System. All clinical isolates were sent to the Department of Health Public Health Laboratory Service Branch Centre for Health Protection for identification and susceptibility testing under standard broth dilution method and interpreted according to the Clinical and Laboratory Standards Institute. Patients without definitive diagnosis of NTM infection were excluded from the study. BCGiosis and immune reconstitution inflammatory syndrome (IRIS) due to Bacille Calmette-Guérin (BCG) strain of *Mycobacterium bovis* were excluded as *M. bovis* is considered part of *M. tuberculosis* complex (MTBC). MPT64 antigen detection in culture isolates were performed to exclude MTBC from genuine NTM infections.

### Statistical Analyses

This study was primarily descriptive in nature.

Continuous variables were expressed as median and range. Duration of follow up was defined from the date of first clinical presentation or diagnosis to date of last follow up (censorship) or death.

### Ethical Considerations

This study complies with the Declaration of Helsinki and approval from Institutional Review Board of the University of Hong Kong / Hospital Authority Hong Kong West Cluster had been obtained (UW 18-597 / HKUCTR-2581).

## Results

### Patient Demographics (see Table 1)

Total 7 patients with genuine NTM infection were identified (3 males, 4 females) with median age at diagnosis of 6 years old (range 4-20 years old) and median duration of follow up of 30 months (range 3 days up to 120 months). Majority (86%, 6 out of 7) have underlying comorbidities, such as haemic malignancies or post-stem cell transplantation (n=4), autoimmune diseases or immunodeficiency (n=1) and chronic respiratory disease (n=1). Clinical manifestations include systemic bacteraemia (n=3), lymphadenitis (n=2), osteomyelitis or

**Table 1** Case series of paediatric non-tuberculous mycobacterial infection in Queen Mary Hospital over past 20 years (1999-2018)

No	Agent	Sex	Age at diagnosis	Time from symptom onset to confirmed	Co-morbid laboratory disease diagnosis	Site of infection	Status	Duration of follow up
1	<i>M. fortuitum</i>	F	5 years	3 months	APECED	Lymphadenitis	Dead	18 months
2	<i>M. chelonae</i>	M	20 years	2 months	AML M2 t(6;9) MUD PBSCT gut GVHD, BO	Pneumonia and bacteraemia	Dead	2 months
3	<i>M. chelonae</i>	M	4 years	1 month	JMML, NF-1	Central line infection and arthritis	Alive	120 months
4	<i>M. fortuitum</i>	F	17 years	1 month	Beta-thal major post MUD PBSCT severe GVHD	Pneumonia and bacteraemia	Dead	5 months
5	<i>M. abscessus</i> <i>subsp. massiliense</i>	M	6 years	1 month	Cystic fibrosis	Pneumonia	Alive	82 months
6	<i>M. abscessus</i> <i>subsp. abscessus</i>	F	4 years	1 month	AML t(8;21)	Right groin, popliteal, ankle osteomyelitis and subcutaneous abscesses	Alive	30 months
7	<i>M. abscessus</i> <i>subsp. abscessus</i>	F	11 years	1 month	Nil	Left submandibular lymphadenitis	Alive	30 months

AML: acute myeloid leukaemia; APECED: autoimmune polyendocrinopathy with candidiasis and ectodermal dysplasia; BO: bronchiolitis obliterans; F: female; GVHD: graft-versus-host disease; HLA: human leukocyte antigen; JIA: juvenile idiopathic arthritis; JMML: juvenile myelomonocytic leukaemia; M: male; M.: mycobacterium; MUD: matched unrelated donor; NA: not applicable; NF: neurofibromatosis; PBSCT: peripheral blood stem cell transplant; t: translocation, thal: thalassaemia

arthritis (n=2), and pulmonary infection (n=2). Median time from symptom onset to confirmation of laboratory diagnosis is 1 month.

### Microbiology (see Table 2)

Infective agents identified including *M. abscessus complex* (n=3) (*M. abscessus subsp. abscessus* =2, *M. abscessus subsp. massiliense* =1), *M. fortuitum* (n=2), and *M. chelonae* (n=2). In general, the mycobacteria identified were sensitive to amikacin, showing intermediate sensitivity to ceftazidime, linezolid and meropenem; variable sensitivity to clarithromycin, levofloxacin, linezolid and cotrimoxazole; and resistant to ciprofloxacin, doxycycline and moxifloxacin. Mortality rate was up to 29% (2 out of 7 died).

### Treatment and Related Toxicities (see Table 3)

For the 2 patients with pneumonia and systemic bacteraemia due to mycobacteria, both died before treatments were completed, the one with *M. chelonae* infection (Case 2) was treated with intravenous (IV) imipenem-cilastatin with oral clarithromycin while the other with *M. fortuitum* infection (Case 4) was treated with IV imipenem-cilastatin with amikacin for 3 weeks during intensive phase followed by oral levofloxacin as continuation therapy (planned for 6 months but was given for around 5 months then patient died of progressive respiratory failure).

For the 2 patients with lymphadenitis, the one with *M. fortuitum* lymphadenitis (Case 1) was cured with 6 months of IV meropenem and amikacin while the other patient with *M. abscessus* lymphadenitis (Case 7) was treated with IV amikacin and ceftazidime/tigecycline for 4

weeks as initial treatment followed by oral clarithromycin for 4 months in total as maintenance therapy.

For the patient with central line infection due to *M. chelonae* (Case 3), prompt removal of central line followed by treatment with triple agents (IV imipenem-cilastatin, IV amikacin and oral clarithromycin) suffices to eradicate the catheter-related mycobacterial infection.

The patient with cystic fibrosis with pneumonia due to *M. massiliense* (Case 5) was treated according to United Kingdom Royal Brompton Hospital clinical guideline for the care of children with cystic fibrosis 2011 with 3-week intensive phase of IV amikacin, IV meropenem, IV ceftazidime and oral clarithromycin followed by prolonged continuation phase with nebulised amikacin and oral azithromycin daily for 1 year then continued with oral azithromycin 3 day per week for 2 more years for anti-inflammatory effect.

For the remaining patient with right groin, popliteal, ankle osteomyelitis and subcutaneous abscesses (Case 6), initial treatment was failed with 2-month course of oral clarithromycin, three 2-week courses of IV amikacin, 2 weeks of IV levofloxacin, 1 month of IV imipenem-cilastatin, 2 weeks of IV ceftazidime, and 1-month course of interferon-gamma (3 days per week). The patient was successfully salvaged with 2 re-purposed drugs (oral bedaquiline and clofazimine) together with cotrimoxazole.

Drug-related toxicities were encountered in 3 out of the 7 patients treated (Cases 5-7), and all manifested as drug fever and fixed drug eruptions - 2 due to the beta-lactam ceftazidime (Cases 5, 6) while 1 due to cotrimoxazole (Case 7). One also developed hepatitis (Case 6) with alanine transaminase and aspartate transaminase elevated above 1,000 requiring discontinuation of all anti-mycobacterial

**Table 2** Sensitivity patterns of non-tuberculous mycobacteria cultured from affected paediatric patients in Queen Mary Hospital (1999-2018)

No	Amikacin	Ceftazidime	Ciprofloxacin	Clarithromycin	Doxycycline	Levofloxacin	Moxifloxacin	Linezolid	Cotrimoxazole	Imipenem
<i>M. fortuitum</i>										
1	S	I		I	R	S				S
4	S	I		R	R	S				
<i>M. chelonae</i>										
2	S				R					
3	S	S		S	R	R	R	S		
<i>M. abscessus complex (including subsp. abscessus and massiliense)</i>										
5	S	I	R	S	R		R	I	R	I
6	S	I	R	R	R		R	S	S	I
7	S	I	R	S	R		R	I	S	R

I: intermediate; R: resistant; S: sensitive

**Table 3** Treatment regime, duration and related toxicities

No	Agent	Site(s) of infection	Initial treatment (intensive phase)	Maintenance treatment (prolonged continuation phase)	Treatment-related toxicities and final outcome
1	<i>M. fortuitum</i>	Lymphadenitis	(1) IV meropenem 350 mg q12h (20 mg/kg/dose) for 6 months (2) IV amikacin 250 mg q24h (15 mg/kg/dose) for 6 months	Nil	Cured (patient died 18 months later due to sepsis and multi-organ failure unrelated to episode of mycobacterial infection)
2	<i>M. chelonae</i> / <i>abscessus</i> complex	Pneumonia and bacteraemia	(1) IV imipenem-cilastatin 500 mg q6h (15 mg/kg/dose)* (2) Oral azithromycin 500mg daily (15 mg/kg/day) p.o.*	Not applicable	Died due to progressive respiratory failure
3	<i>M. chelonae</i> / <i>abscessus</i> complex	Central line related infection and arthritis	<b>Removal of central line</b> (1) IV imipenem-cilastatin q6h (15 mg/kg/dose) for 3 weeks (2) IV amikacin (15 mg/kg/day) q24h for 3 weeks (3) Oral clarithromycin 500 mg BD p.o. for 3 weeks	Nil	Cured
4	<i>M. fortuitum</i>	Pneumonia and bacteraemia	(1) IV imipenem-cilastatin 500 mg q6h (15 mg/kg/dose) for 3 weeks (2) IV amikacin 500 mg (15 mg/kg/day) q24h for 3 weeks	Levofloxacin 250 mg daily p.o. (8 mg/kg/day) (plan for 6 months, given for around 5 months then patient died)	Died due to progressive respiratory failure
5	<i>M. abscessus</i> complex ( <i>subsp. Massiliense</i> )	Pneumonia	(1) Amikacin 7.5 mg/kg b.d. for 3 weeks (2) Meropenem 40 mg/kg max. 2 gm t.d.s. IV for 3 weeks (3) Cefoxitin 200 mg/kg/day IV in 3-4 divided doses for 3 weeks (4) Clarithromycin 500 mg b.d. p.o. for 3 weeks	(1) Nebulised amikacin 250 mg b.d. given for 1 year (2) Azithromycin 175 mg (10 mg/kg) daily for 1 year then switched to 3 times per week for anti-inflammatory effect, continued for 2 more years then self-stopped	Cured Developed drug fever and fixed drug eruptions (likely due to cefoxitin or meropenem), also developed hepatitis

(continued on page 223)

**Table 3** Treatment regime, duration and related toxicities (cont'd)

No	Agent	Site(s) of infection	Initial treatment (intensive phase)	Maintenance treatment (prolonged continuation phase)	Treatment-related toxicities and final outcome
6 <sup>28</sup>	<i>M. abscessus</i>	Right groin, popliteal and ankle osteomyelitis with subcutaneous abscesses	<b>Radical surgical debridement with insertion of antibiotics-infused cement</b> (1) Oral clarithromycin for 2 months (2) Cotrimoxazole 480 mg BD p.o. (trimethoprim 10 mg/kg/day) for 2 months (3) IV amikacin 15 mg/kg/day q24h for 2 weeks per cycle for 3 cycles in total (as prolonged amikacin would result in irreversible ototoxicity) (4) IV levofloxacin for 2 weeks then IV imipenem-cilastatin for 1 month then IV ceftioxin 200 mg/kg/day for 2 weeks, stopped due to drug rash and hepatitis (5) Interferon-gamma for 1 month (3 days per week)	(1) Bedaquiline 100 mg daily p.o. daily for 1 month then daily (3 days per week) (2) Clofazimine 50 mg daily p.o. for 1 month then daily (2 days per week) (3) Cotrimoxazole 480 mg BD p.o. (trimethoprim 10 mg/kg/day)	Developed drug rash and hepatitis likely due to ceftioxin, stopped IV ceftioxin (also oral clarithromycin and cotrimoxazole), rash subsided and liver function normalised in 1 week Given total 8 months of bedaquiline and clofazimine. Infection treated and limb function preserved.
7	<i>M. abscessus</i>	Left submandibular lymphadenitis	(1) Oral clarithromycin 375 mg b.d. for 4 weeks (2) Oral levofloxacin 375 mg daily p.o. (given for 4 days) Switched to IV ceftioxin 1.45 gm q6h (40 mg/kg/dose) based on sensitivity (given for 5 days), further switched to oral cotrimoxazole 480 mg b.d. (given for 12 days then developed fever, rash and leukopenia), then switched to IV tigecycline 50 mg q24h (1.5 mg/kg/day) and given for 2 weeks (3) IV amikacin 540 mg (15 mg/kg/day) q24h for 4 weeks - withheld for 3 days when developed side effects due to cotrimoxazole, switched to IV imipenem-cilastatin 500 mg q6h (15 mg/kg/dose)	Oral clarithromycin 375 mg BD for 4 months (counted from initiation of treatment)	Developed fever, rash and leukopenia after given oral cotrimoxazole for 12 days Cured

b.d.: bis die sumendum (two times a day); gm: gram(s); IV: intravenous; kg: kilogram(s); M.: mycobacterium; max.: maximum; mg: milligram(s); p.o.: per os (by mouth); q6/12/24h: every 6/12/24 hours; t.d.s.: ter die sumendum (three times a day)

\* Treatment not completed as patient died of progressive respiratory failure. Patient also on concurrent IV micafungin 100 mg q24h (3 mg/kg/day) and IV ambisome 100 mg q24h (3 mg/kg/day) for aspergillus pneumonia

^ Azithromycin was chosen instead of clarithromycin as less chance of macrolide resistance as compared to clarithromycin

agents for 1 week before resuming antimicrobials when liver function normalised.

## Discussion

### **Classification of Mycobacteria**

Mycobacteria are aerobic acid-fast bacilli under genus Actinobacteria. Over 190 species had been identified so far, and approximately 60 of which are suspected or known to be pathogenic in humans. NTM refer to mycobacteria apart from MTBC, *M. leprae* and *M. ulcerans*. Distinguishing NTM from MTBC is of clinical significance as rapidly-growing NTM are in general not susceptible in vitro to anti-TB drugs but susceptible to traditional bactericidal agents. Besides, TB is a notifiable disease requiring public health tracking while NTM is not on the contrary. NTM comprises mycobacteria in environment which are non-pathogenic and also NTM which may cause diseases in humans.<sup>1,2</sup> NTM could be categorised by Runyon's classification into photochromogens, scotochromogens, non-chromogens (such as Mycobacterium avium complex MAC) and rapid growers known as rapidly growing mycobacteria (RGM)<sup>3</sup> (such as *M. abscessus*, *M. fortuitum* and *M. chelonae*). RGM are environmental organisms found worldwide that typically grow within 1 week in suitable culture medium. Potential diagnostic limitations in distinguishing different species occur and different susceptibility patterns for different species.<sup>4</sup>

### **Clinical Manifestations of NTM Infections**

Clinical syndromes caused by NTM include pulmonary disease<sup>5,6</sup> (Cases 2, 4 and 5), lymphadenitis<sup>7,8</sup> (either localised cervical lymphadenitis or complicated disseminated lymphadenitis) (Cases 1 and 7), skin and soft tissue infections<sup>9</sup> (either superficial chronic cutaneous lesions or deep-seated infections involving tendons, synovium, bones and joints) (Case 6), intra-vascular catheter related infections<sup>10-13</sup> and/or systemic bacteraemia (Cases 2, 3 and 4) as well as continuous ambulatory peritoneal dialysis-related peritonitis.<sup>14</sup> For local case cohort, we encountered almost all different clinical manifestations as stated above.

### **Immunity Against Mycobacterial Infection**

Cell-mediated immunity is the major protective immune response against intracellular bacteria, with non-tuberculous mycobacteria being one of them.<sup>15,16</sup> Th1

lymphocytes can produce interferon-gamma (IFN- $\gamma$ ) which activates macrophage to kill phagocytised intracellular microbe. In local cohort, one of the cases (Case 6) had incorporated IFN- $\gamma$  as part of anti-mycobacterial treatment.

### **Risk Factors for Development of NTM Infections**

Steroid and cytotoxic therapy predispose to a wide combination of phagocytic, cell-mediated and even humoral defects.<sup>9,17</sup> From local case series, 6 out of 7 have underlying acquired or congenital immunodeficiency render them predispose to non-tuberculous mycobacterial infection, with underlying haemic malignancies or history of stem cell transplantation being the commonest group (n=4), reflecting usage of steroid and/or cytotoxic therapy being an important risk factor for development of NTM infections.

### **Consideration of Primary Immunodeficiency in Patients with NTM Infections**

Among the 7 cases in local cohort, one (Case 7) of them was with good past health and no underlying comorbidities, it is postulated that subtle immune defect could exist and investigations on Mendelian susceptibility to mycobacterial diseases (MSMD) are under way though not yet revealing at the time of publication.

## Diagnosis and Treatment

Despite knowing the importance in differentiating TB and NTM, as mentioned they are in practical not easily distinguishable from clinical history, Mantoux test result, radiological pattern and initial laboratory reports. They also share overlapping clinical features such as pulmonary disease and lymphadenopathies. Delayed in diagnosis is common. The disease burden of NTM is unknown in region such as Hong Kong where TB is endemic. As no mandatory reporting is required, epidemiology and clinical studies are scarce. NTM are often assumed to be TB and treated as such, but susceptibility to antimicrobials are in fact very different. Classical anti-TB drugs (streptomycin, isoniazid, rifampicin, pyrazinamide and ethambutol) (S, H, R, E, Z) are generally not useful because of intrinsic resistance.<sup>18,19</sup>

Treatment against NTM differs in different patients according to the clinical manifestations, type of mycobacteria identified, sensitivity pattern, underlying comorbidities and the presence of drug-related toxicities.<sup>20-22</sup> Surgical debridement<sup>23</sup> (Case 6) or removal of foreign body (such as central venous

catheter) (Case 3) are indicated in selected cases.<sup>20-22</sup> Anti-mycobacterial treatment is usually prolonged in terms of months or years with employment of multiple antimicrobial agents in an attempt to avoid development of drug resistance.<sup>20-22</sup> Amikacin, imipenem, cefoxitin, clarithromycin and azithromycin are the key drugs commonly used to treat NTM infections.<sup>20-22,24</sup> From the sensitivity patterns of local cohort, NTM isolated are generally sensitive to amikacin; demonstrated intermediate sensitivity to cefoxitin, linezolid and meropenem; variable sensitivity to clarithromycin, levofloxacin, linezolid and cotrimoxazole; and resistant to ciprofloxacin, doxycycline and moxifloxacin (see Table 3). Development of multiple-drug resistant (MDR) strains of mycobacteria as well as compliance and drug-related toxicities related to prolonged duration of treatment are the 2 major challenges faced by physicians in combating NTM infections.

### **Macrolide Resistance**

Macrolide resistance for NTM, in particular *M. abscessus* spp. *abscessus* and *bolletii* exists due to erm gene. Macrolide resistance is associated with delayed treatment response and possible treatment failure in patient with lung disease on macrolide-containing regimens.<sup>25</sup> However, including a macrolide (clarithromycin or azithromycin) in the multidrug regimen may still be considered in such situations as the choice of oral alternatives is limited. Thus, macrolide was incorporated as part of treatment regime for the 3 local cases with *M. abscessus* infection (Cases 5-7) (including Case 5 which later identified to be *M. massiliense*).

### **Drug-related Toxicities (see Supplementary Table 3)**

From literature review, around 7% patients would develop adverse drug reactions towards anti-TB/NTM treatment, with transaminitis/ hepatotoxicity being commonest (87%), followed by rash (8%), angioedema (5%) and gastrointestinal intolerance.<sup>26</sup> Combination therapy is associated with increased toxicity.<sup>26</sup> Treatment time is on average being prolonged by a median of 1 month due to ADR.<sup>26</sup> In our study, drug-related toxicities were encountered in 3 out of the 7 patients treated (43%) (Cases 5-7), and all manifested as drug fever and fixed drug eruptions. Hepatotoxicity is encountered in 1 patient only (Case 6) with anti-NTM treatment withheld for 1 week.

### **Novel Treatment Agents**

For Case 6 who was a 4-year old girl with translocation t (8;21) acute myeloid leukaemia who developed right

groin, popliteal, ankle osteomyelitis and subcutaneous abscesses due to *M. abscessus* after 2 courses of induction chemotherapy, 2 experimental drugs (bedaquiline and clofazimine) were used to salvage this patient as off-label use in view of treatment failure against traditional anti-NTM agents. Bedaquiline and clofazimine are agents to treat MDR-TB and leprosy in adults, with uncertain efficacy in paediatric population. Both are lipophilic agents and able to achieve high bactericidal concentrations in soft tissues. Disease control had been achieved in this patient.<sup>28</sup>

Besides antimicrobial agents, 2 agents were also considered in the same patient to enhance patient's own cellular immunity against NTM infection, namely pegylated granulocyte colony-stimulating factor (pegfilgrastim) and IFN- $\gamma$ . Pegfilgrastim administration was associated with a significant increase of the inducible IL-12p40 subunit in patient serum.<sup>27</sup> Whereas in patients given filgrastim with a much shorter half-life of around 3.5-3.8 hours as compared to 42 hours for pegfilgrastim, IL-12p40 slightly declined and returned to baseline values by day +11 from the commencement of cytokine treatment. It is tempting to speculate that immunoreactive IL-12 in patients given filgrastim may have been degraded as a result of sharp increases in circulating PMN capable of releasing proteolytic enzymes. Side effect profile of pegfilgrastim is similar to filgrastim.

### **Strengths and Limitations of Study**

This is the first study reporting patient characteristics, microbiology, treatment and outcomes of paediatric NTM infections in QMH over past 20 years. Despite the very small number of cases extracted from local cohort of a single paediatric department which makes it difficult to draw definitive conclusions or generalise the findings, this paper crystallises experience and serves as a timely reminder to paediatric oncologists and transplant physicians not to overlook possibility of NTM infections in their specific clinical settings with common encounter of immunocompromised children facing the conglomeration of all five local paediatric oncology centres into single paediatric oncology and transplant centre at Hong Kong Children's Hospital since 2019. In addition, it also enlightens general paediatricians, immunologists and infectious disease specialists to look for concealed immunodeficiencies for children presented with NTM infections without know underlying susceptibility conditions. In the future, a territory-wide study or international collaboration with inclusion of adult cases would be recommended.

## Conclusion

To conclude, anticipation and early recognition of NTM infections especially in immunocompromised patients is important to facilitate prompt provision of appropriate therapy to improve clinical outcomes. Concealed immunodeficiencies should be actively sought for in children presented with NTM infections without known underlying susceptibility conditions. Multidisciplinary collaboration is crucial. Treatment could be difficult and prolonged and drug-related toxicities are common.

## Declaration of Interest

None

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## Case Report

# Coexistence of Coffin-Siris Syndrome and Stercoral Colitis

İ KARA, U KOC

### Abstract

Coffin-Siris syndrome is a rare syndrome diagnosed by clinical features such as mental retardation, growth retardation, absence or hypoplasia of the fifth distal phalanx, different facial features and supported by genetic testing. Stercoral colitis is an inflammatory colitis, which is usually caused by an increase in intraluminal pressure in stool material stuck in colon segments, which is rarely seen in patients with chronic constipation and may result in perforation, shock and death. Our 11-year-old male patient was brought to the emergency department with the complaint of inability to walk and the patient was diagnosed with stercoral colitis with appropriate evaluation. This is the first case in the literature in which coexistence of Coffin-Siris syndrome and Stercoral colitis were seen.

### Key words

*Coffin-Siris syndrome; Paediatrics; Stercoral colitis*

### Introduction/Aim

Coffin-Siris syndrome (CSS) is a condition characterised by the aplasia or hypoplasia of the fifth distal phalanx or nail, developmental or cognitive delay, varying facial features, hypotonia, hirsutism/hypertrichosis, and sparse scalp hair.<sup>1,2</sup> It presents with congenital anomalies including malformations of the heart, gastrointestinal, genitourinary and/or central nervous systems.<sup>1,2</sup> Nutritional difficulties, slow growth, ophthalmological abnormalities, and impaired hearing can also be seen.<sup>1,2</sup>

Stercoral colitis (SC) is an inflammatory colitis that occurs due to increased intraluminal pressure caused by faecal material impacted in colon segments.<sup>3</sup> The most important complication of SC is colon perforation, and the mortality rate varies between 32 and 57%.<sup>3-6</sup>

In most patients with chronic constipation, stool becomes harder due to physical inactivity, making it even more difficult to pass through the intestinal system, and thus creating a vicious cycle. This condition is usually seen in the elderly. SC diagnosis may be delayed in patients with neurological and psychological problems.<sup>7-9</sup> Since clinical evidence in SC is not clear, imaging-based diagnosis is required. Late diagnosis of SC can lead to serious complications and even mortality.<sup>3,4</sup>

SC is infrequently seen in young adults and even rarer among children. In this paper, we present a case of a child having the coexistence of CSS and SC for the first time in the literature.

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### The Case

An 11-year-old male patient previously diagnosed with CSS in another health center presented to our clinic with the complaint of not being able to push his feet down and walk. In addition to tonsil hypertrophy and hyperemia, he

had coarse facial features characterised by thick eyebrows, marked eyelashes, flat nose bridge, short nose, and thick lips. He also presented with small nails on the fifth fingers and toes, hypertrichosis, low anterior hairline, sparse scalp hair, and low height and weight percentiles (Figure 1). Considering the indications of mental retardation and complaints of frequent constipation, the sweat test was undertaken with the suspicion of cystic fibrosis, but the findings and thyroid hormones were normal. The patient had scarred skin on his feet due to frequent rubbing of hands and feet against each other. It was not possible to perform an abdominal examination since he did not allow anyone to touch his abdomen. Considering that he was not able to push his feet down, the orthopaedic clinic was consulted to evaluate the joint graphy in terms of the

presence of arthritis or a fracture. There was no indication of orthopaedic emergency, but the white blood cell count was high ( $20 \times 10^3/\text{mm}^3$ ). Magnetic resonance imaging of the brain revealed two arachnoid cysts. The patient was hydrated and started on antibiotics but continued to exhibit agitation and agony, and he was unable to stand up. An abdominal ultrasonography was attempted, but the findings were not adequate due to the constant agitation. Due to the dilatation of intestines and faecal impaction at plain abdominal radiograph (Figure 2), an abdominal tomography was performed and revealed thickening of the colonic wall with large volume of feces findings compatible with SC (Figure 3). Once the feces impaction was relieved, the patient's complaints were reduced. He was started on an appropriate diet and was discharged in a few days after full recovery.

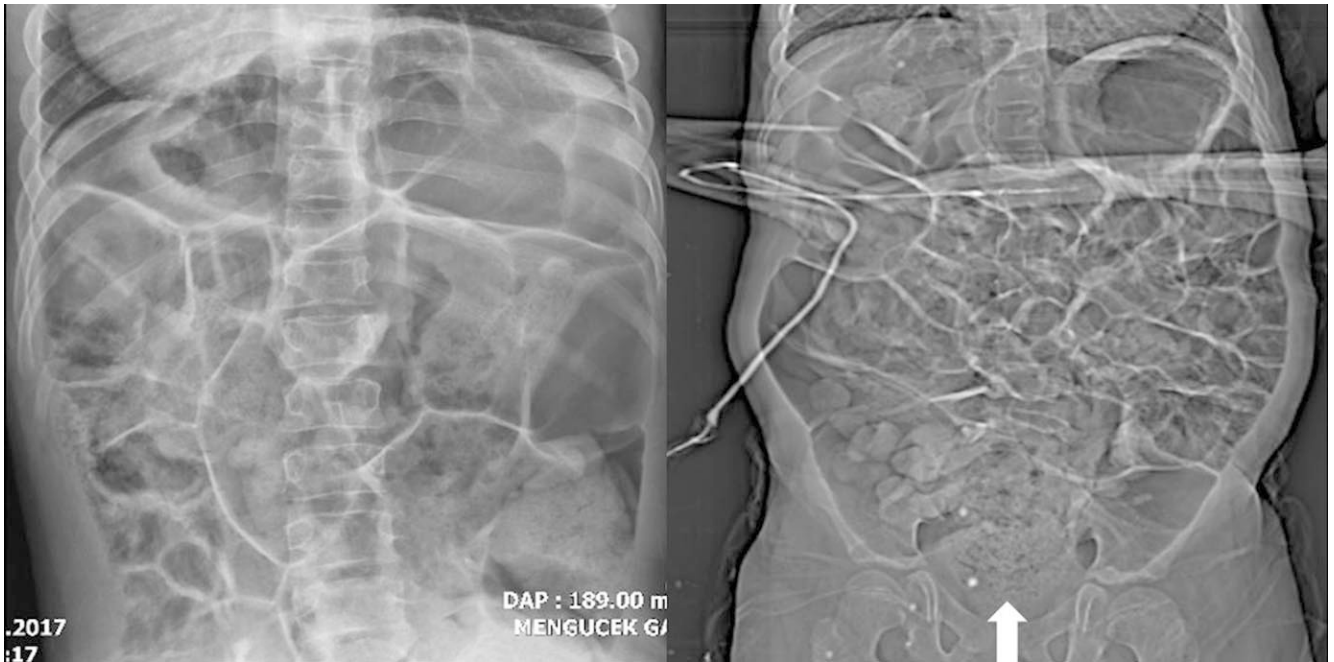


**Figure 1** An 11-year-old male patient previously diagnosed with Coffin-Siris syndrome had coarse facial features characterised by thick eyebrows, marked eyelashes, flat nose bridge, short nose, thick lips, small nails on the fifth fingers and toes, hypertrichosis, low anterior hairline, sparse scalp hair.

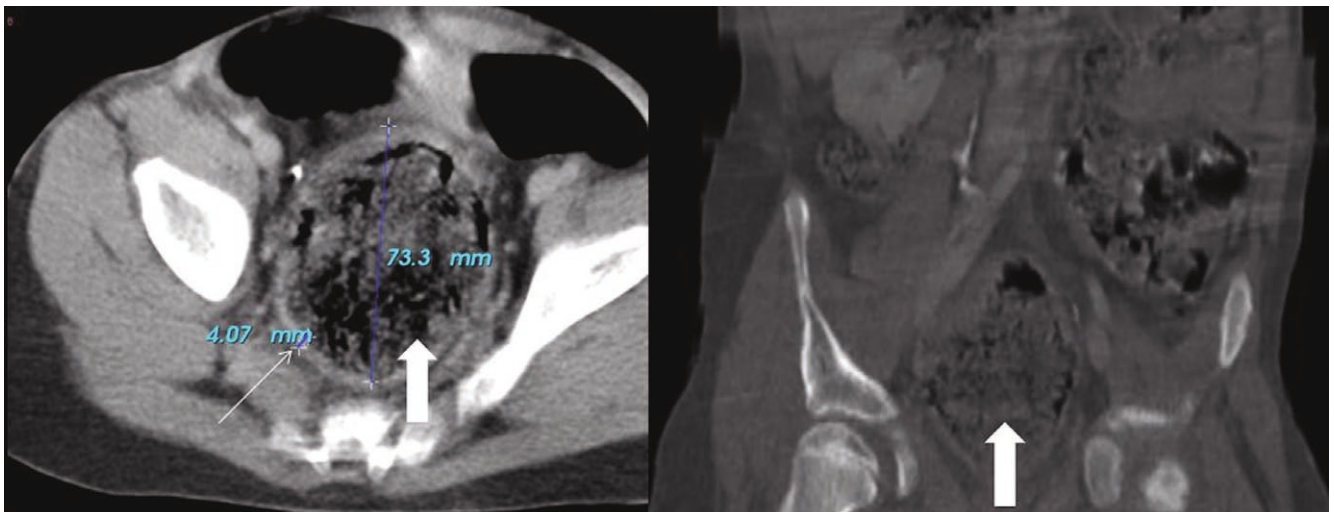
**Discussion**

CSS is a congenital anomaly characterised by shortness of the fifth distal phalanx (65%) or aplasia or hypoplasia of nail (80%), varying degrees of developmental or cognitive delay, different facial features, hypotonia, hirsutism/hypertrichosis (95%), sparse scalp hair (68%), dental anomalies (96%), intrauterine growth retardation

(67%), craniofacial anomalies, short stature (68%), spinal anomalies (66%), congenital heart disease (45%), coarse facial appearance, bushy eyebrows, and thick lips. Nutritional difficulties, slow growth, ophthalmological abnormalities, and hearing impairment can also be seen in patients with CSS.<sup>1,2,10</sup> The diagnosis of CSS is most commonly based on clinical features, and genetic assessment has a complementary role.<sup>11,12</sup>



**Figure 2** A plain X-ray studies of the abdomen revealed the dilatation of intestines and faecal impaction (arrow).



**Figure 3** Abdominal tomography revealed thickening of the colonic wall (thin arrow) with large volume of feces (thick arrows) findings compatible with stercoral colitis.

Our paediatric patient presented with coarse facial features, bushy eyebrows and thick lips, short fifth distal fingers, hypoplastic nails, and developmental and cognitive retardation. Hirsutism/hypertrichosis, sparse scalp hair, dental anomalies, and short stature were other clinically significant indications. He did not have a congenital heart disease, but his brain magnetic resonance image revealed two small arachnoid cysts. His clinical findings were consistent with the diagnosis of CSS. His genetic analysis had been performed 10 years earlier and the diagnosis had been confirmed. Since the patient continuously rubbed his feet against each other, there were scarred tissues and new lesions on the contact points.

The development of faecaloma or stercoroma due to the build up and impaction of dry feces causes colonic distention and applies pressure on the wall mucosa, reducing blood flow to the area and eventually leading to ischemia. If the pressure on the intestinal wall continues, necrosis or perforation develops,<sup>7,8</sup> which, if overlooked or untreated, may result in shock and death.<sup>9,13,14</sup>

SC has similar prevalence in both sexes and is seen at an average age of 59.<sup>8</sup> Almost all patients present with conditions and factors implicated in constipation, such as hypothyroidism, diabetes, cognitive disorders, and the use of anticholinergic, narcotic, antacid and tricyclic antidepressants.<sup>13,14</sup> Eighty-one percent of the SC cases have the complaint of constipation,<sup>4,12</sup> but diarrhea is rarely associated.<sup>8,14</sup>

Our patient was mentally retarded and had a previous diagnosis of CSS. He was not taking any medication and he was in constant motion. Since he was not able to explain the reason for his agony, he continuously cried and he was not able to stand on his feet. He also did not allow us to touch his abdomen.

The three most common localisations of stercoral ulceration are the anterior wall of the rectum, the antimesenteric border of the rectosigmoid juncture, and the apex of the sigmoid colon.<sup>14,15</sup> SC and stercoral ulcers are most frequently seen in the sigmoid colon<sup>4,14</sup> since it is the narrowest part of the colon with the lowest blood stream, and feces is also the driest in this area.<sup>4</sup> Our patient was found to have 73.3 mm dilatation of colon involving the rectosigmoid region and his feces were impacted.

Direct abdominal radiography can show faecal loading or calcified faecaloma. Direct graphy of our case revealed markedly dilated intestinal lumen. Abdominal CT facilitates the diagnosis and treatment. The CT findings of SC include build up of feces in the sigmoid colon,

pericolonic stranding, thick mucosa or discontinuous areas of of colonic mucosa (perfusion defect), thickening of the colonic wall of more than 3 mm, and proximal colon expansion.<sup>7-9,16</sup> The current patient had proximal colon expansion, thickening of the colonic wall of more than 3 mm, and feces accumulation in the colon.

In SC cases, abnormal gas, free fluid, and intense mucosal perfusion suggest perforation and is associated with increased mortality.<sup>9,14,17</sup> There was no evidence of perforation in our patient. Fifty-two percent of the patients with non-perforated SC are successfully treated with a bowel regimen.<sup>7</sup> During the follow-up period of the current case, we observed spontaneous faecal discharge and adjusted the patient's diet; therefore, there was no need for surgery.

In the literature, to date, only four paediatric cases of SC have been reported; a two-year-old child due to misuse of ibuprofen,<sup>18</sup> an incidentally diagnosed case presenting with a chronic cough,<sup>19</sup> a 17-year-old girl with an eating disorder,<sup>20</sup> and an 11-year-old with stercoral perforation associated with bezoar.<sup>21</sup> This is the first case report in the literature presenting the coexistence of a very rare CSS and an even rarer SC in a paediatric patient. In clinical practice, we encounter mentally retarded patients with varying complaints and appropriate patient management is of utmost importance in these cases. For the current patient, the careful attention of the radiology specialist concerning the walking difficulty complaint possibly saved the patient's life by preventing the development of a future perforation through the immediate initiation of a laxative diet.

## Conclusion

This is the first case of the coexistence of CSS and SC reported in the literature. In patients with mental retardation, chronic constipation, distention, and abdominal sensitivity despite the lack of a voiced abdominal complaint due communication difficulties, the possibility of SC should be considered, and these patients should be managed accordingly.

## Informed Consent

Informed consent was obtained from the patient's parents.

## Conflict of Interest

No conflict of interest was declared by the authors.

## Financial Disclosure

The authors declared that this study has received no financial support.

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## Case Report

# Retained Peripherally Inserted Central Venous Catheter in a Neonate: Consider Thrombosis

LY Siu, TL Ku

### Abstract

We report two neonates with stuck Premicath® being freed with topical and systemic thrombolytic respectively. One term baby with Premicath® inserted for hyperosmolar dextrose solution infusion. On removal after 13 days' use, difficulty was noted in pulling out the distal 3.5 cm part. Three thousand units of urokinase in 0.3 ml normal saline was instilled and aspirated after 14 hours, together with the intact Premicath® removed. Another extreme preterm baby had Premicath® inserted for paternal nutrition infusion. Removal of Premicath® was decided on day 23 of catheter use. However, great resistance was noted after pulling out 4 cm to 10 cm marking at entry site. Ultrasound study suggested thrombosis inside the lower end of IVC, with extension to the upper left common iliac vein. Six weeks course of subcutaneous enoxaparin was started and the intact Premicath® was successfully removed on day 12 of enoxaparin treatment.

### Key words

Neonate; Low molecular weight heparin; Stuck catheter; Thrombosis; Urokinase

### Introduction

The term "stuck catheter" was first mentioned as a unique problem of central venous catheter use in 1997.<sup>1</sup> Premicath®, Vygon, a 28-G polyurethane catheter was first reported to have this problem arising from calcified fibrinous tissue adherent to the venous endothelial surface in 2005.<sup>2</sup> We used Premicath® since 2012 and had encountered stuck Premicath® twice since 2017. We successfully freed the two stuck Premicath® in the following ways.

### Case 1

A 3-day-old Chinese girl, born at 39+2 weeks of gestation with a birth weight of 2.94 kg was transferred in Special Care Baby Unit (SCBU) from postnatal ward for symptomatic hypoglycaemia. There is no parental consanguinity, maternal diabetes nor risk factors for sepsis. On admission, she had 10% weight loss and the first blood glucose was undetectable. After bolus intravenous glucose infusion, her blood glucose normalised and hypoglycaemic symptoms resolved. She required high glucose infusion rate (GIR) to maintain normal blood glucose, necessitating hyperosmolar dextrose solution infusion. Therefore, on day 4 a Premicath® was inserted over her right cubital fossa with catheter tip inside superior vena cava for dextrose 15% infusion. Her GIR requirement peaked at 16.9 mg/kg/min and hypoglycaemic kit work up results showed low fatty acids with high insulin level consistent with hyperinsulinism. When the result of hyperinsulinism was available on day 10, Endocrine Team doctor started diazoxide. On that day, the Premicath® was blocked but fortunately, after instillation with urokinase 5000 units in 0.5 ml normal saline for 2 hours, patency was

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re-established. Gradually upon stepping up milk fortified with Polycal and weaned down of dextrose infusion, full enteral feeding was established on day 16.

Upon removal of Premicath® on day 16, day 13 of catheter insertion, difficulty was noted in pulling out the distal 3.5cm of Premicath® (Figure 1). Orthopaedic surgeon's opinion was sought; they offered surgical exploration to remove the Premicath® if conservative means for removal failed. With the belief that a small thrombus at the tip of the Premicath® causing catch up at the small peripheral vein, instillation of urokinase was tried. Three thousand units of urokinase in 0.3 ml normal saline was instilled and aspirated after 14 hours, together with the intact Premicath® removed.

## Case 2

A Chinese baby girl born at 24+6 weeks of gestation with a birth weight of 620 g had umbilical venous catheter changed to Premicath® for paternal nutrition infusion on day 14. The Premicath® was inserted via left long saphenous vein with tip reaching upper border of L2 and it functioned well all along. On day 35, clinical sepsis was suspected in view of increase ventilatory requirement and platelet dropped abruptly from 365 to 113x10<sup>9</sup>/L over two days but with normal coagulation. After sepsis work up, empirical course of Vancomycin and Cefotaxime was

started. Two days later, the platelet dropped further down to 70x10<sup>9</sup>/L despite antibiotics treatment. Uncontrolled catheter related sepsis was suspected and by then the baby nearly reached full enteral feed. Therefore, removal of Premicath® was decided on day 23 of catheter insertion, Friday. Upon removal of Premicath®, great resistance was noted after pulling out for 4 cm to 10 cm marking at entry site. Abdominal X-ray showed the Premicath® tip lied anteriorly to the 3rd and 4th lumbar spine. The position of the Premicath® tip corresponded to the inferior part of the inferior vena cava (IVC). Therefore, venous thrombosis was suspected and urgent ultrasound with Doppler study was arranged. After this attempt of Premicath® removal, the platelet count started to rise; to 126x10<sup>9</sup>/L on Saturday and to 128x10<sup>9</sup>/L on Sunday and back to 223x10<sup>9</sup>/L on Monday, day 40.

On day 40, day 26 of catheter insertion, USG study showed a focal echogenic lesion present inside the lower end of IVC, with extension to the upper left common iliac vein, most likely representing a thrombus. Haematologist's opinion was sought, after counselling parents on the pathogenesis of catheter related thrombosis, its potential complications like worsening of thrombo-embolism, residual thrombosis and post-thrombotic syndrome, benefit and risk with low molecular weight heparin treatment, parents showed understanding and agreed for treatment. Six weeks course of subcutaneous enoxaparin was started on day 40 at 1.5 mg/kg every 12 hourly, with anti-factor



**Figure 1** Distal 3.5 cm of Premicath® stuck.

Xa monitoring. The intact Premicath® was successfully removed on day 52, the 12th days of enoxaparin treatment. The 6 weeks course of enoxaparin was completed uneventfully and the platelet count was monitored during treatment which remained normal. Repeated USG IVC post enoxaparin treatment showed no thrombus.

## Discussion

Most of the typical strategies to facilitate Premicath® removal like repositioning of the arm in case 1 and the leg in case 2, application of heat and vessel massage was used unsuccessfully. Traction over time is one reported strategy for percutaneous inserted central catheters (PICC) removal in Neonatal Intensive Care Units and was reported to be successful in 44.4 percent of the cases in which they were performed.<sup>3</sup> However, the thin walls of the 28-G Premicath® with limited tensile strength make them prone to fracture and we dare not to try traction over time. Reinsertion of the stylet into the lumen of the catheter to facilitate PICC removal had been reported to be a novel technique for difficult removal of neonatal PICC.<sup>4</sup> However, the inner lumen of this Premicath® is 0.17x0.35 mm and the Premicath® is a catheter with stylet and split cannula introducer in one piece. This made finding of a suitable stylet impossible and this way to remove PICC is at risk for catheter puncture or breakage that can become an embolism. Therefore, we decided for systemic anticoagulation.

Our attempt to try intra-catheter instillation of urokinase in the first case echoed with adult report of using tissue plasminogen activator to free stuck PICC.<sup>5</sup> In adult report, their approach of using low dose thrombolytic therapy was based on the presumed pathophysiology that the adhesions prevent PICC removal, and the adhesion developed initially from fibrin sheaths. In our case, if adhesion had occurred, we should have faced difficulty in initial removal of the PICC, not till the final 3.5 cm. Anyway, thought different belief, both use of topical thrombolytic therapy were successful. While tissue-type plasminogen activator is largely responsible for initiating intravascular fibrinolysis, urokinase is the major activator of fibrinolysis in the extravascular compartment. If our conservative approach was unsuccessful, alternative option would be surgical exploration; therefore, this enzymatic approach is worth trying if the PICC is still patent.

The use of central venous catheter (CVC) is the most common cause of thrombosis in newborn infants, accounting for up to 89% cases.<sup>6</sup> Previous reports have indicated that, compared with adults and children, neonates are at greater risk for thrombosis owing to their immature haemostatic and coagulation systems, small blood vessel diameter, need for infusion of high-osmolar solutions, and low flow rate of infusate.<sup>7</sup> Haemostatic imbalance associated with infection and dehydration adds to the predisposition for CVC-related thrombi in neonates. In our second case, the catheter related blood stream infection was disproved by negative blood culture but she required fluid restriction for patent ductus arteriosus and bronchopulmonary dysplasia, putting her at high risk for developing catheter related thrombus on the 23rd day of Premicath® insertion. The majority of CVC-related thrombi are silent, but some are associated with line dysfunction, limb swelling, altered skin color or perfusion, and/or thrombocytopenia.<sup>8</sup> The resolution of her thrombocytopenia after 4 cm of Premicath® was pulled out in the absence of culture proven infection highly suggested that her thrombocytopenia was caused solely by the thrombus formation.

For neonates with asymptomatic catheter-thrombosis, guideline suggests supportive care and close monitoring of the size of the thrombus.<sup>9</sup> In our case, the need for treatment is obvious as the thrombus stuck the Premicath®. Among neonates requiring treatment for thrombosis, low molecular weight heparin (LMWH) is the treatment of choice. Enoxaparin is a LMWH with 100 units of anti-factor Xa activity per mg. LMWH has many advantages over unfractionated heparin. These include greater bioavailability when given by subcutaneous injection, longer duration of anticoagulant effect, and clearance that is independent of dose, which results in a more predictable response. They can be administered subcutaneously and require minimal laboratory monitoring and dose adjustment. Other potential advantages are the reduced risk of immune-mediated thrombocytopenia and osteoporosis.

In summary, stuck Premicath® seems unavoidable with the survival of smaller babies. In dealing with this problem, we propose imaging to rule out knots and adherent focus in preventing removal first. If nothing can be identified in preventing removal, for patent Premicath® stuck at limbs, topical urokinase instillation may be tried. For Premicath® stuck in major vessels, consider thrombosis and manage accordingly.

## Declaration of Interest

None

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## Case Report

# A Child with Unusually Severe Anaemia Paediatric Idiopathic Pulmonary Haemosiderosis: From Diagnosis to Treatment

JWCH CHENG, L LEE, YY LAM, WK CHIU

### Abstract

A 3-year-old boy YC presented with pallor after an episode of upper respiratory tract infection. Blood tests revealed iron deficiency anaemia and extensive workup for its causes were unremarkable. On identifying persistent pulmonary infiltrates on a contrast computerised tomography scan, workup went along the direction of diffuse alveolar haemorrhage and the ultimate diagnosis of idiopathic pulmonary haemosiderosis (IPH) was confirmed by bronchoalveolar lavage and thoroscopic lung biopsy. Although rare, IPH has a variety of presenting symptoms and should be considered as a differential diagnosis for unexplained anaemia. Physicians must be vigilant for complications from the disease itself and its treatment. Management options are variable but mainstay treatment consists of corticosteroid therapy with or without adjuvant immunosuppressants.

### Key words

*Anaemia; Diffuse alveolar haemorrhage; Haemosiderin; Haemosiderosis; Hydroxychloroquine; IPH*

### Case Report

YC was born full term from non-consanguineous healthy parents. His developmental milestones, immunisation history and growth history were unremarkable.

YC presented with pallor after an episode of viral illness in May 2015 at the age of 21 months. He had no symptoms of anaemia or bleeding tendencies. Physical examination showed a child with body weight at 3rd to 10th percentile. He had pallor, but no petechiae. Abdominal examination was unremarkable. Chest examination revealed no deformity, symmetrical air entry with normal breath sounds. Per rectal examination yielded tarry stool. Other

systems were unremarkable. Chest X-ray (CXR) showed right lung haziness.

His haemoglobin level (Hb) was 4.6 g/dL. It was microcytic hypochromic anaemia with MCV, MCH and RBC at 64.9fL, 18.7 pg and  $2.3 \times 10^{12}/L$  respectively. Blood film showed aniso-poikilocytosis, microcytosis, hypochromasia, polychromasia, and target cells. Reticulocyte count was elevated at  $235 \times 10^9/L$  (4.93%). White blood cell count, platelet count, liver function test, renal function test, C-reactive protein and erythrocyte sedimentation rate were normal. Haemoglobin pattern was normal. He was iron deficient with iron level and total iron binding capacity of 2.8  $\mu\text{mol}/L$  and 84.7  $\mu\text{mol}/L$  respectively.

YC's severe iron deficiency anaemia was treated with blood transfusion. He was asked to increase dietary meat portions and supplemented with Ferrum Hausmann.

One month later YC's Hb dropped from 8.3 to 4.5 g/dL despite good drug compliance and being asymptomatic. Five blood transfusions were given between June to September 2015 due to repeated significant Hb drop. Extensive workup along the differential diagnoses of production problems, haemolysis, infective causes, autoimmune causes, and gastrointestinal blood loss however did not give any positive clue except for faecal

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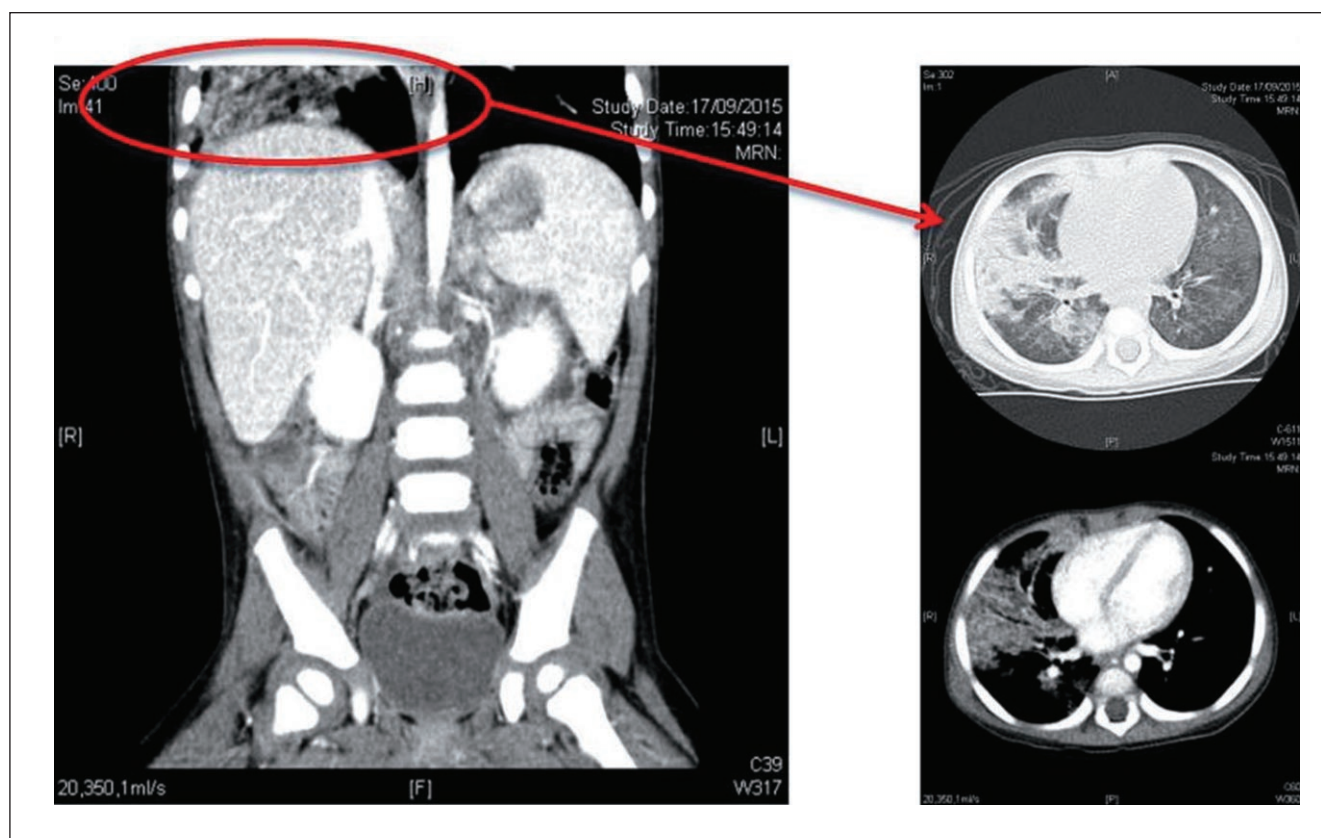
occult blood being positive. Otherwise Meckel's scan, oesophagealgastroduodenoscopy, laparoscopy, ultrasound abdomen and red cell scans were all unremarkable.

YC was admitted in September 2015 for wheezing. He was afebrile but tachypnoeic and tachycardic. Chest examination revealed bilateral expiratory wheezes. CXR demonstrated bilateral diffuse lung haziness which was not previously present. Hb was 7.4 g/dL with marked reticulocytosis. Because of the discrepancy between wheezing and CXR findings, an urgent contrast computerised tomography (CT) thorax and high resolution CT thorax was requested, showing bilateral diffuse pulmonary infiltrates which suggested pulmonary haemosiderosis (Figure 1).

To confirm the radiological suspicion, bronchoalveolar lavage was proceeded yielding pinkish bronchial aspirates, with histopathological analysis showing numerous haemosiderin laden macrophages (Figure 2). It was otherwise negative for bacterial, fungal and tuberculosis studies. Then YC underwent thorascopic lung biopsy which

showed no capillaritis indicative of other causes of diffuse alveolar haemorrhage. Further workup for related autoimmune diseases included radioallergosorbent test (RAST) for cow's milk protein allergy, anti-glomerular basement membrane (anti-GBM) antibody and cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA). The diagnosis of idiopathic pulmonary haemosiderosis (IPH) was made after ruling out other secondary causes of diffuse alveolar haemorrhage (DAH).

YC was offered a 3-day course of intravenous methylprednisolone 30 mg/kg/dose for acute flares which was gradually weaned down to maintenance oral prednisolone at 1 mg/kg on alternate days. Top up of maintenance oral prednisolone to 1 mg/kg/day daily with concurrent addition of oral hydroxychloroquine 4.5 mg/kg/day as a steroid-sparing agent and adjuvant therapy was needed (2 months after pulse methylprednisolone) before YC became free from bleeding episodes. He was also put on inhaled fluticasone at 200 mcg/kg/day. Henceforth YC remained asymptomatic with a stable Hb level since May

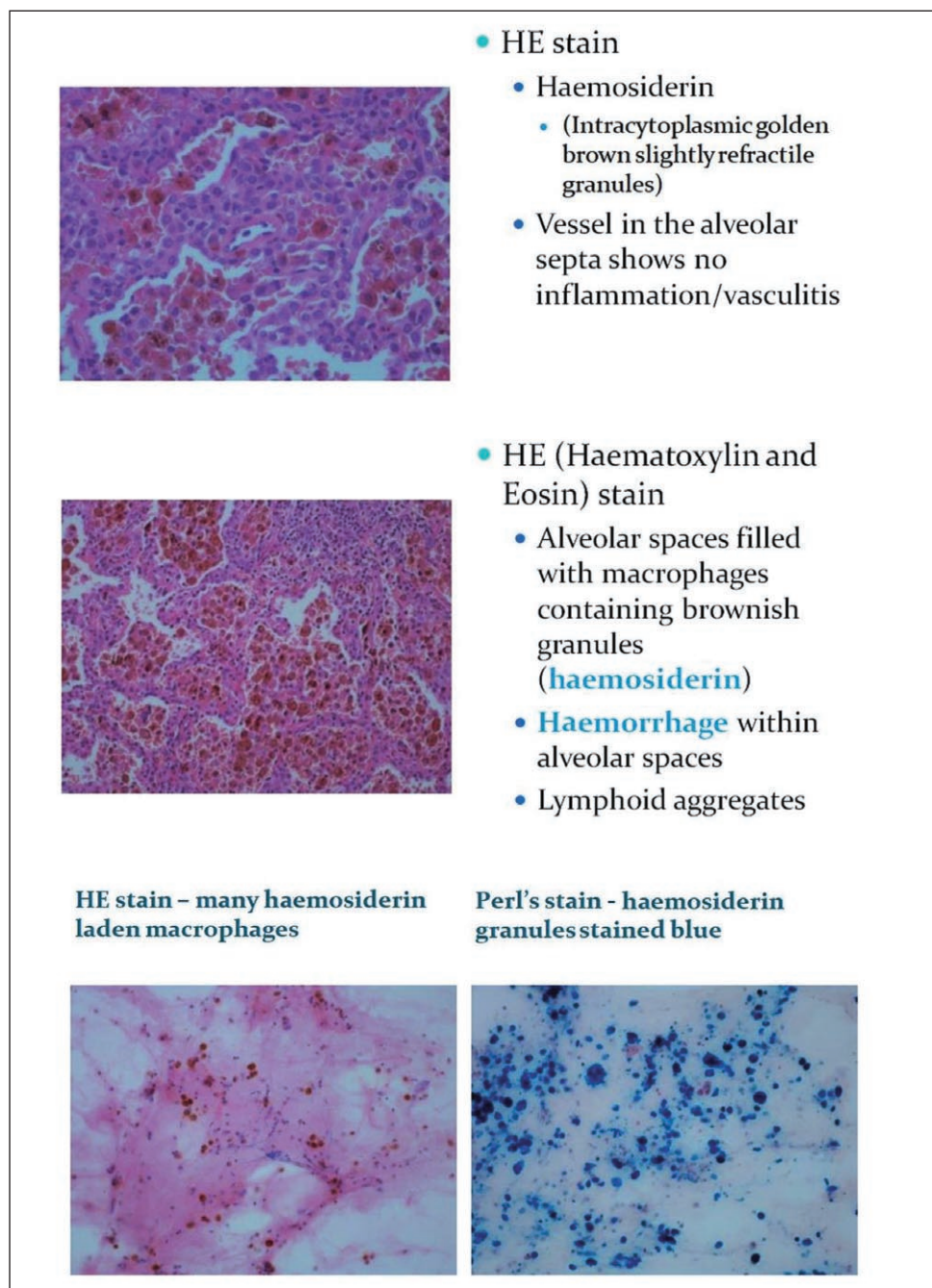


**Figure 1** Contrast CT thorax and high resolution CT thorax showing bilateral diffuse pulmonary infiltrates suggestive of pulmonary haemosiderosis.

2016. The daily dose of oral Prednisolone was tailed down to alternate days after 17 months. The inhaled Fluticasone was weaned in 8 months' period. Hydroxychloroquine has been continued up till present. He is regularly followed up for monitoring of growth, side effects of long term steroid use, lung function and any signs of autoimmune diseases.

## Discussion

IPH is a rare disease entity that mainly affects patients under 10 years of age.<sup>1-3</sup> Classically it is characterised by haemoptysis, anaemia and pulmonary infiltrates, and confirmed by alveolar haemosiderin laden macrophages in bronchoalveolar lavage.<sup>1,4,5</sup> Incidence of paediatric IPH



**Figure 2** Histopathological analysis of bronchoalveolar lavage using HE and Perl's stains showing numerous haemosiderin laden macrophages.

varies in different localities, with reports ranging from 0.24 patients/million people/year in Sweden<sup>4</sup> to 1.23/patients/million people/year in Japan.<sup>6</sup>

Clinically patients can present with anything between an insidious onset of mild respiratory symptoms, as with our patient, to acute life-threatening respiratory failure. The high variability of presentation makes diagnosis difficult, with delay in diagnosis ranging from 1 to 6.3 years.<sup>3</sup> A lack of respiratory symptoms does not preclude the diagnosis.<sup>5</sup> In our patient, the only clue was iron deficiency anaemia with exacerbation by viral illness. Diagnosis relies on high suspicions for unexplained iron deficiency anaemia, with radiological and histological confirmation.

Radiologically CXR or CT thorax typically shows bilateral diffuse pulmonary infiltrates. Bronchoalveolar lavage shows the pathognomonic haemosiderin-laden macrophages in bronchial wash-outs, and in gastric lavage samples due to swallowed pulmonary infiltrates. For the same reason, stool occult blood could be positive.

Lung biopsy is not necessary but highly recommended to differentiate between capillaritis and non-capillaritis. DAH syndromes with pulmonary capillaritis are mostly autoimmune causes including Wegener's granulomatosis, microscopic polyangiitis, Goodpasture's syndrome, etc., while those without pulmonary capillaritis include IPH, Heiner's disease, and certain non-inflammatory cardiovascular disorders. The non-capillaritis DAH syndromes can be further differentiated with blood tests for c-ANCA, RAST tests, and anti-GBM antibodies.<sup>1,3,4</sup>

Supportive treatment in terms of blood transfusion, oxygen and mechanical ventilation is warranted for children experiencing symptomatic anaemia and/or respiratory distress due to significant acute pulmonary bleeding. There are still debates over the most effective treatment for IPH, yet pulse steroid therapy is well-established for controlling severe life-threatening pulmonary bleeding.<sup>1,3,4</sup> Taytard et al suggested pulse methylprednisolone at 300 mg/m<sup>2</sup>/day for 3 days.<sup>3</sup> Susarla et al reported on use of intravenous methylprednisolone at 2–4 mg/kg/day every 6 hours or pulse intravenous methylprednisolone at 30 mg/kg (max 1 g) for 3 days.<sup>5</sup>

Upon remission and for disease maintenance, steroid therapy in a regular pulse or regular oral regimen with weaning after disease remission is commonly used for disease control,<sup>1–5,7</sup> with follow-on oral prednisolone at 1 mg/kg/day on daily<sup>3</sup> or alternate-day basis.<sup>5</sup> The largest review article<sup>3</sup> suggested monthly methylprednisolone

300 mg/m<sup>2</sup>/day for 3 days per month for initial treatment, with daily oral prednisone added (1 mg/kg/d) for severe situations. Duration of maintenance treatment remains debatable.<sup>3,5,7</sup> Inhaled corticosteroid is recommended by Nusslein et al as a supplementary treatment.<sup>1</sup>

Adjunctive treatment including hydroxychloroquine,<sup>3–5</sup> mycophenolate mofetil,<sup>3</sup> azathioprine,<sup>3–5</sup> methotrexate<sup>5</sup> and cyclophosphamide<sup>1,4,5</sup> are reported to be options for steroid-refractory IPH or patients who cannot tolerate the side effects of steroids. These agents can be administered alone or with steroid therapy. Intravenous immunoglobulin<sup>5</sup> is also a possible adjunct for refractory bleeding.<sup>1,4,5</sup> Evidence has shown that a more aggressive treatment approach allows better survival,<sup>4,5</sup> with improvement in 5-year survival up to 86%<sup>4</sup> as compared to the old figures of 3–5 years' median survival.<sup>1</sup>

In conclusion, IPH is a rare disorder with a variety of presenting symptoms but should be considered as a differential diagnosis for unexplained anaemia. Physicians must be vigilant for development of associated autoimmune diseases and long-term side effects of corticosteroids. Treatment options are variable but mainstay treatment consists of corticosteroid therapy with or without adjuvant immunosuppressants.

## Declaration of Interest

The authors report no conflicts of interest.

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## Case Report

# A Chinese Girl with ELANE-related Severe Congenital Neutropenia

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**Abstract** ELANE-related severe congenital neutropenia is a very rare genetic disorder characterised by very low absolute neutrophil count at early age. Affected individuals suffer from recurrent infections and have potential of malignant transformation. This paper describes a case report of a Chinese girl who had severe neutropenia since neonatal age with recurrent perianal and oral infection. Clinical features, diagnosis and management of ELANE-related severe congenital neutropenia are discussed. Clinicians are alerted how to differentiate severe congenital neutropenia from usually benign chronic neutropenia.

**Key words** Children; Congenital neutropenia; ELANE-related neutropenia; Neutropenia

### Case Report

A Chinese girl born to non-consanguineous parents was referred to haematology clinic for evaluation of persistent neutropenia at the age of 5 months. She was born with prematurity of 30 weeks and her birth weight was 1.54 kg. She was the first child in the family with unremarkable family history. During neonatal period, she had mild respiratory distress syndrome, grade 1 necrotising enterocolitis resolved by intravenous antibiotics and supportive management. She did not have omphalitis or delayed umbilical cord detachment. She was discharged

from the neonatal unit on day 59 of life. There was no syndromal feature or signs of exocrine pancreatic insufficiency.

Her total white cell count, haemoglobin and platelet counts were normal. The absolute neutrophil count (ANC) was  $9.22 \times 10^9/L$  (N:  $6-23.5 \times 10^9/L$ ) at birth and it dropped to  $1.4 \times 10^9/L$  on day 10 of life. Since 51-day-old, the ANCs were noted persistently less than  $0.2 \times 10^9/L$  (Figure 1). No cyclic pattern of ANC or abnormal cells was noted. IgA, IgG and IgM levels were unremarkable. The anti-neutrophil antibody was negative. The girl had repeated infections involving oral mucosa and skin since three months of age. Her infection history was summarised in Table 1.

At 13-month-old, bone marrow examination showed granulocytic hypoplasia with markedly reduced in granulopoiesis and neutrophilic series was virtually absent. Only monocytic and eosinophilic series were evident. Erythropoiesis was active and megakaryocytes were adequate. There was no cellular infiltration or overt dysplastic features. In view of persistent severe neutropenia and repeated infection, whole exome sequencing was performed and she was found to have a heterozygous nucleotide deletion in exon 5 causing frameshift and premature stop mutation in the *ELANE* gene ( $5:c.618_627del:p.L206fs$ ), which was confirmed by Sanger sequencing. Hence, the patient was diagnosed to have ELANE associated severe congenital neutropenia (SCN). Sanger sequencing of the *ELANE* gene was

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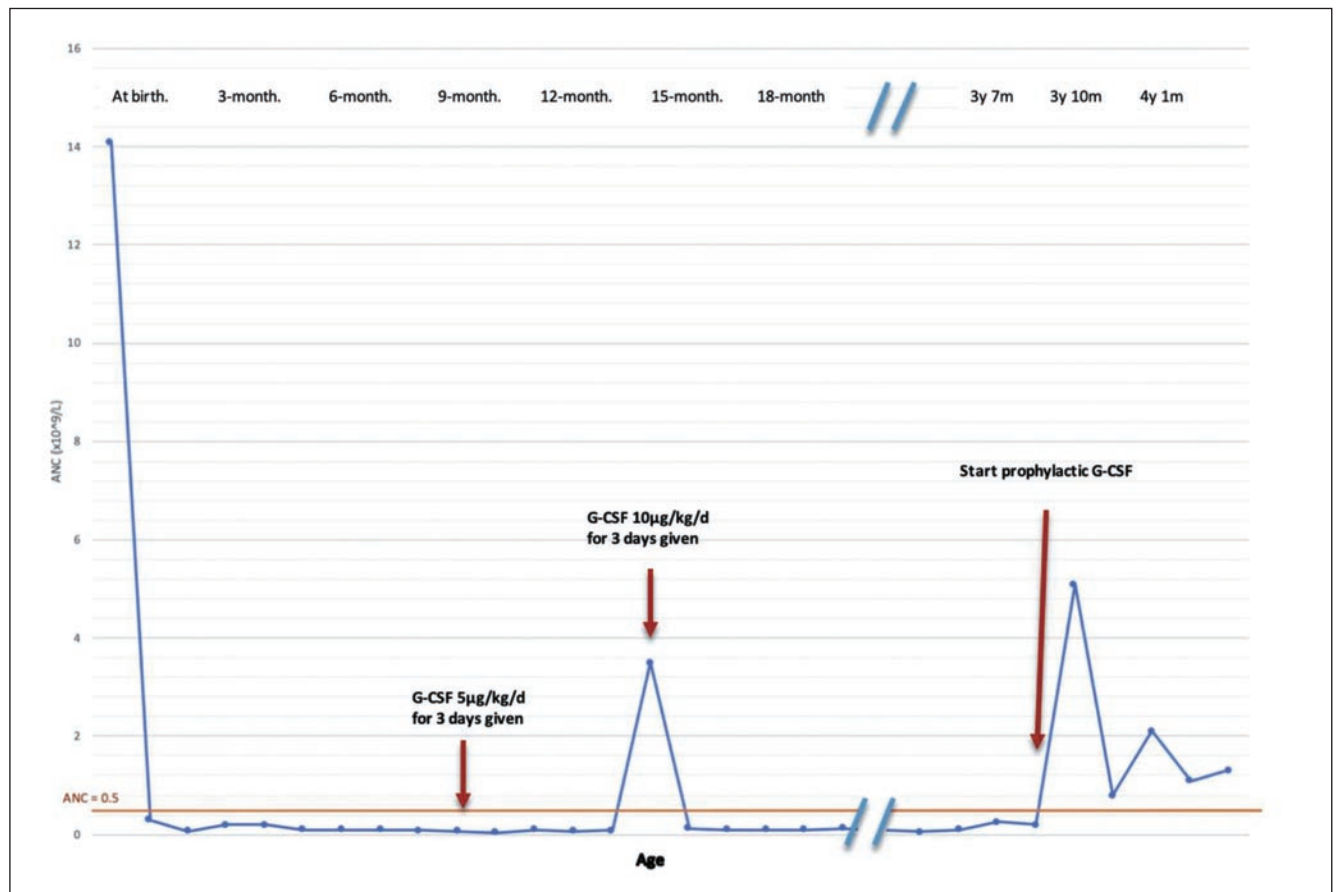
performed for her parents and both were not found to be carriers of the mutation.

Granulocyte colony stimulation factor (G-CSF) treatment (5 microgram/kg/day for 3 days) was tried when she was 9-month old during an episode of vulval abscess. However, there was no response with ANC remained  $0.07 - 0.09 \times 10^9/L$  after the treatment. During an episode of severe oral infection at 13-month old, she was given high dose of G-CSF treatment at 10 microgram/kg/day for three days. Her ANC responded and rose from  $0.06 \times 10^9/L$  to the peak of  $3.5 \times 10^9/L$ . Prophylactic G-CSF was initially declined by parent. At 3-year-old, the child still suffered from recurrent infection with repeated hospital admission once a month. The weight gain was not satisfactory and dropped to 10th percentile. After further discussion, parent agreed to start regular G-CSF 10 microgram/kg/day at cycle of three consecutive days and rest two days. Parents were educated and empowered to do subcutaneous G-CSF injection at home. The neutrophil could be maintained

above  $0.5 \times 10^9/L$  (Figure 1) with no more hospitalisation for infection. The family was referred to university center for consideration of haematopoietic stem cell transplantation. There was no suitable donor identified yet. Six months after starting regular G-CSF therapy, the patient showed catch-up in body weight back to 25th percentile and enjoyed normal development at the age of 4 years.

## Discussion

Neutropenia is a disorder of abnormally low absolute neutrophil count (ANC) in the blood. It is classified as severe when ANC is less than  $0.5 \times 10^9/L$ . Diagnosis of congenital neutropenia requires three episodes of ANCs lower than  $0.5 \times 10^9/L$  for at least three months after birth. Patients with SCN usually have ANC less than  $0.2 \times 10^9/L$  since infancy.<sup>1</sup>



**Figure 1** Absolute neutrophil count of the patient.

It is not uncommon for children to have acquired neutropenia after viral infection or intake of drugs such as sulfonamides, anticonvulsants, phenothiazines, chemotherapy agents, anti-thyroid drugs etc..<sup>2</sup> In such cases, the children have normal ANC before and their ANC level return to normal after the infection subsided or the causative drug is removed. In children with chronic neutropenia which defined as neutropenia on at least three occasions over 3 months, it is important to differentiate them from chronic benign neutropenia and severe congenital neutropenia. Chronic benign neutropenia includes two groups of disorder, autoimmune neutropenia (AIN) and chronic idiopathic neutropenia (CIN). AIN and CIN share a similar clinical course with the difference only in the presence of anti-neutrophil antibody in AIN but absent in CIN. The majority of children with chronic benign neutropenia do not have life threatening infection.<sup>3</sup>

SCN patients usually suffer from recurrent episodes of significant or life-threatening infections. The most frequent sites of infection are skin and mucosa, ear, nose and throat and the lungs. Diffuse mucosal lesion could involve digestive tract leading to abdominal pain and diarrhoea.<sup>1</sup> For our patient, she was found persist severe neutropenia (ANC < 0.2x10<sup>9</sup>/L) since 1 month of age, repeated episodes of febrile illness and infection over skin and oral mucosa

required multiple hospital admissions and antibiotic treatment.

Kostmann syndrome, first described by Rolf Kostmann in a Swedish publication in 1950 was considered as the paradigm of congenital neutropenia.<sup>4</sup> Kostmann reported on 6 children with severe neutropenia (ANC < 0.2x10<sup>9</sup>/L) at first week of life with arrest of granulocytic differentiation at the promyelocytic stage. Without treatment, affected children suffered from recurrent fever, skin infections, oral ulcers and even died from severe infections. Fifty years later, homozygous mutations in the gene encoding the mitochondrial protein HCLS1-associated X1 (HAX1) were identified in these patients.<sup>5</sup> With the advancement of molecular science, SCN is now deemed a genetically heterogenous group of related disorder. The discovery of most forms of autosomal-dominant SCN, and virtually all forms of cyclic neutropenia, are due to mutations in the coding region of ELANE (previously known as ELA2), the gene for neutrophil elastase.<sup>6</sup> Nowadays, many congenital syndromes with genetic mutations are also known to be associated with congenital neutropenia, e.g. Kostmann syndrome (HAX1), glycogen storage disease type 1b (SLC37A4), Shwachman-Diamond syndrome (SDBS gene), Chediak-Higashi syndrome (LYST), Barth syndrome (TAZ),

**Table 1** Summary of infection in the patient

Age	Presenting symptom	ANC (10 <sup>9</sup> /L)	Culture result	Treatment	Outcome
3 months	Fever and cough	0.2	No organism found	IV Cefotaxime	Full recovery
7 months	Chickenpox	0.1	Not done	IV Acyclovir	Full recovery
9 months	Vulval abscess	0.08	Abscess swab: Pseudomonas Aeruginosa, Acinetobacter species	IV Amoxicillin-Clavulanate G-GSF 5 microgram/kg/day for 3 days	Abscess resolved ANC after G-CSF: 0.09x10 <sup>9</sup> /L
11 months	Perianal ulcer and abscess	0.1	Abscess swab: Enterobacter, Citrobacter	IV Vancomycin & Timentin followed by oral Levofloxacin & Linezolid	Full recovery
12 months	Perianal abscess	0.07	Abscess swab: E. coli, Aeromonas Streptococcus oralis	IV Vancomycin & Timentin, followed by oral Augmentin & Linezolid plus topical fusidic acid	Abscess resolved
13 months	Lower lip ulcers and abscess	0.1	No organism found	IV Ceftriaxone & Meropenam IV Acyclovir IV & oral Fluconazole G-CSF 10 microgram/kg/day for 3 days	Full recovery ANC after G-CSF: 3.5x10 <sup>9</sup> /L
16 months	Fever, oral thrush and cellulitis of nose	0.0	No organism found	IV Tazocin & oral fluconazole, acyclovir	Full recovery

ANC=absolute neutrophil count; G-CSF=granulocyte colony stimulation factor

dyskeratosis congenita (various genes associated including *DKC1*, *TERC*, *TERT*, *CTCT*) etc.

ELANE-related neutropenia includes SCN and cyclic neutropenia (CyN). Mutations in *ELANE* were found in 80-100% of individuals with well-documented cyclic neutropenia and 35-63% of individuals with congenital neutropenia.<sup>6</sup> In a review by Markaryan et al. with the data from the Severe Chronic Neutropenia International Registry (SCNIR) on genotype-phenotype relationships of *ELANE* mutations, there were 187 SCN patients with 94 mutations and 120 CyN patients with 22 mutations. Twelve overlapping mutations were observed in both CyN and SCN patients. Although the distribution of mutations in CyN versus SCN was statistically significantly different in premutation tests of specific mutations, mutation class and mutation position, individual mutation may not be strictly correlating with the phenotype. However, in the cohort all frameshift *ELANE* gene mutations were associated with severe congenital neutropenia.<sup>7</sup> The genetic variant 5:c.618\_627del:p.L206fs in our case was not reported before in other literature.

Bone marrow examination is often helpful to confirm the diagnosis of SCN and to rule out other disorders such as myelodysplasia or leukaemia. Bone marrow in SCN patients typically shows maturation arrest at the promyelocyte stage of neutrophil formation and cytogenetic analysis is normal.<sup>1</sup>

CyN is distinguished from SCN by regular oscillation of neutrophil counts. In most cases of CyN, neutropenia recurs on an average of every 21 days while SCN patients shows no cyclic pattern. Infectious complications in CyN patients are generally milder and it is not associated with an increased risk of malignancy or conversion to leukaemia.<sup>6</sup>

Individuals diagnosed with *ELANE*-related SCN, regular dental examination for gingival and periodontal disease, prompt treatment of fever and infection with antibiotics, and careful evaluation by an otolaryngologist and pulmonologist for chronic sinopulmonary inflammation and deep abscess are recommended. The administration of prophylactic antibiotics e.g. Cotrimoxazole was commonly used. Treatment with granulocyte colony-stimulating factor (G-CSF) is effective in preventing infections, alleviating symptoms in almost all affected individuals by raising blood ANC and reducing mortality from sepsis. The required doses are usually daily or alternate-day injections of 5-10 microgram/kg/day.<sup>8</sup> Our patient only responded to high dose G-CSF (10 microgram/kg/day). Regular evaluation for evidence of myelodysplasia (MDS) or acute myelogenous leukaemia

(AML) is recommended. Individuals with congenital neutropenia with or without an *ELANE* variant have cumulative incidences of 21% for MDS or AML, after 10 years of started treatment with G-CSF.<sup>9</sup>

Haematopoietic stem cell transplantation (HSCT) is the curative treatment for *ELANE*-related congenital neutropenia.<sup>10</sup> For individuals with SCN who are refractory to high-dose G-CSF or who undergo malignant transformation, HSCT is the only alternative treatment.

In summary, we report a case of *ELANE*-related congenital neutropenia in a Chinese girl. The severe neutropenia may result in life-threatening pyogenic infections, acute or chronic gingivostomatitis, sinusitis or skin infection. It can be differentiated from benign chronic neutropenia by its more serious clinical course with repeated significant infections. Clinicians should be alerted and further investigated with bone marrow and genetic tests. Aggressive antibiotic treatment for infections, use of G-CSF and HSCT have significantly improved the outcome of this group of patients.

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## Declaration of Interest

None

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# Contemporary Practice in Paediatrics

## Recommendations in the Prevention and Management of Hepatitis B Reactivation in Paediatric Patients Receiving Immunosuppressive Therapy in Hong Kong Special Administrative Region, China

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**Abstract**

Hepatitis B reactivation can be a fatal complication of paediatric hepatitis B patients receiving immunosuppressive therapy. However, there is no specific recommendation in paediatric patient group. This article aims to summarize the paediatric recommendations from international guidelines with reference to Hong Kong SAR paediatric data. Hepatitis B reactivation risk is stratified into "high risk group", "moderate risk group" and "low risk group". All paediatric patients who will receive immunosuppressive therapy in moderate and high risk groups should be tested for hepatitis B surface antigen and antibody to hepatitis B core antigen prior to receiving treatment. Hepatitis B deoxyribonucleic acid (HBV DNA) level should be checked if the patients' either test is positive. Antiviral prophylaxis should be given in high risk group patients. Antiviral prophylaxis should be considered in moderate risk group patients. Hepatitis B screening tests and antiviral prophylaxis are not recommended in low risk group. Entecavir and Tenofovir disoproxil fumarate are drugs of choice.

**Key words**

*HBV reactivation; Immunosuppressive therapy; Paediatric*

**Introduction**

As medicine advances, more intensive or wider indications of immunosuppressive therapy are now offered to various paediatric patients (e.g. high dose corticosteroids; intensive systemic chemotherapy for haematological malignancies and solid tumours; potent immunosuppressive or immunomodulating therapy including biologics for refractory autoimmune diseases).

In Hong Kong, hepatitis B virus (HBV) infection is still endemic in the overall population. It is expected that the risk of HBV reactivation in paediatric patients receiving immunosuppressive treatment and with prior HBV infection will be significant. The consequence of such hepatitis flare may be fatal. On the other hand, Hong Kong has commenced universal HBV vaccination program since 1988. The vaccine coverage rate is over 99%.<sup>1</sup> Hence, the majority of local born mothers of child bearing age under the age of 30 had received HBV vaccine.

However, there is still mother-to-child transmission (MTCT) despite very effective universal vaccination program and post-natal immunoprophylaxis with HBV immune globulin (HBIG) in babies born from hepatitis B surface antigen positive (HBsAg+) mothers.<sup>2</sup> These MTCT transmitted cases together with postnatal acquired cases will thus be subjected to the potential risk of HBV reactivation during their immunosuppressive therapy.

The Coordinating Committee (COC) (Paediatrics) under Hong Kong Hospital Authority (HA) endorsed this recommendation. This recommendation is produced by the Working Group (WG) of prevention and management of hepatitis B reactivation in paediatric patients receiving immunosuppressive therapy in Hong Kong SAR. The WG was launched and formed by COC (Paediatrics) under Hong Kong HA.

**Rationales for a Different Paediatric Guideline for Paediatric Patients Undergoing Immunosuppressive Therapy**

There is number of reasons to set up a paediatric guideline in this special patient group: (1) paediatric population has much lower HBsAg+; and HBsAg negative and antibody to hepatitis B core antigen positive (HBsAg-/anti-HBc+) prevalence; (2) some diseases only occur in children like neuroblastoma and retinoblastoma while others are more common in paediatric population such as minimal change glomerulonephritis, acute leukaemia, brain tumour or lymphoma; (3) the treatment response in paediatric patients to the therapy is different. Treatment success rate of haematologic malignancies such as acute leukaemia and lymphoma are better in paediatric population; (4) there is significant differences in treatment regimen – intensity of chemotherapy for haematologic and solid tumour malignancies is usually much higher resulting in more profound immunosuppression; and (5) the recommended dose used in paediatric patients is based on body weight or body surface area.

**HBV Serology Status in Paediatric Population**

The presence of anti-HBc indicates past history of or resolved HBV infection with or without HBsAg and antibody to HBsAg (anti-HBs) positivity. Knowledge of the patient's anti-HBc status is useful as HBV reactivation can happen if the patient undergoes immunosuppressive treatment even when HBsAg is negative.

The exact prevalence of anti-HBc in Hong Kong population is not known. In East Asia region, it is estimated the anti-HBc+ prevalence is ranging from 13.5% to 40.9%

in adult population.<sup>3-5</sup>

Since there is no local paediatric seroprevalence data on HBsAg and anti-HBc status, the WG estimated (1) the HBsAg+; and (2) HBsAg-/anti-HBc+ paediatric seroprevalence from local MTCT data.<sup>6</sup> In this 30-year cohort study in Hong Kong, the MTCT rate was 3.5% among HBsAg+ mothers and the majority of MTCT occurred before age of 2.<sup>6</sup> As the latest overall expectant mothers' HBsAg+ prevalence is around 5%,<sup>1</sup> the estimated paediatric HBsAg+ prevalence is estimated to be about 0.17% at age of 2 due to MTCT. The prevalence is expected to increase after adolescent age because of subsequent horizontal transmission, notably from sexual contact. The data shows that HBsAg+ prevalence is around 1% which is the prevalence in expectant mothers with age less than 20.<sup>1</sup>

In the same 30-year cohort study, anti-HBc seroconversion rate with HBsAg- status in children born from HBsAg+ mothers was 9%. Around half of anti-HBc seroconversion occurred before age of 2 while the other half occurred over the next 20 years.<sup>6</sup> Therefore, the HBsAg-/anti-HBc+ prevalence in general paediatric population is estimated to be 0.45% in toddler age and up to 0.8% in early adulthood. Nearby regions with similar HBV prevalence has reported HBsAg-/anti-HBc+ paediatric prevalence up to 2.4%.<sup>7</sup>

### **Caseload Estimation on Paediatric Patients Requiring Immunosuppressive Therapy with Prior HBV Infection**

Searching the Clinical Data Analysis and Reporting System (CDARS) for all paediatric patients under the HA service and have used various immunosuppressive therapy over 2 years period from 1st April 2015 to 31st March 2017, there are total 2081 patients retrieved, i.e. 1040 patients receiving immunosuppressive therapy each year.

This number correlates well with the summation of estimated number of new cases requiring immunosuppressive therapy (around 1000 per year) from various subspecialties (oncology, nephrology, rheumatology, gastroenterology and hepatology, respiratory, infectious diseases, cardiology, neurology and endocrinology).

As the estimated local paediatric HBsAg+ prevalence ranges from 0.17% to 1% and HBsAg-/anti-HBc+ prevalence ranges from 0.45% to 2.4%, it is expected the annual number of paediatric patients requiring

immunosuppressive therapy with HBsAg+ or anti-HBc+ is about  $1000 \times (1\% + 2.4\%) = 34$ .

### **Immunosuppressive Therapy with Profound or Significant Immunosuppression**

The most significant therapy that can cause profound immunosuppression is B-cell depleting agents, e.g. rituximab and afatumumab; B-cell and T-cell depleting agent, e.g. alemtuzumab; and haematopoietic stem cell transplant (HSCT) therapy.

The less profound but still very significant immunosuppression is systemic chemotherapy (e.g. oncologic or nephrology conditions). The systemic chemotherapy include alkylating agents (e.g. cyclophosphamide, ifosfamide, temozolamide, cisplatin, carboplatin); plant alkaloids (e.g. vincristine, vinblastine); anti-tumour antibiotics (e.g. doxorubicin, daunorubicin, idarubicin, actinomycin, bleomycin); antimetabolites (e.g. methotrexate, cytarabine, fludarabine, clofarabine); topoisomerase inhibitor (e.g. irinotecan, topotecan, etoposide); and enzymes such as asparaginase.

Other immunosuppressive therapy can cause significant immunosuppression include moderate to high dose corticosteroids, tumour necrosis factor (TNF) alpha inhibitor (e.g. etanercept, adalimumab, certolizumab, infliximab, golimumab), cytokine or integrin inhibitor (e.g. abatacept, ustekinumab, natalizumab, vedolizumab), tyrosine kinase inhibitors (e.g. imatinib, nilotinib), and others immunosuppressive agents (e.g. mycophenolate mofetil (MMF), 6-thioguanine, cyclosporine, tacrolimus, sirolimus etc.).

Traditional immunosuppressive agents include azathioprine, 6-mercaptopurine and methotrexate monotherapy cause less immunosuppression as compared with the above agents and therapy.<sup>8</sup>

### **Paediatric Systemic Corticosteroid Dosing for Risk Stratification**

The exact dosing for low, moderate or high dose and duration of corticosteroids that can cause substantial immunosuppression is uncertain. Advisory Committee of Immunization Practices (ACIP)<sup>9</sup> and American Academy of Pediatrics (AAP)<sup>10</sup> recommend 20 mg or more prednisolone daily or equivalent for longer than 2 weeks is generally considered clinically significant to induce immunosuppression.<sup>11</sup> A recent report shows that high

dose (more than 40 mg daily) corticosteroid less than 7 days can cause significant hepatitis flare in HBsAg+ adult patients.<sup>12</sup> Therefore, the WG categorises steroid dosing into (a) low dose and (b) moderate to high dose group. The duration of significant exposure is beyond 2 weeks.

**a. Low Dose Steroid Group:**

- i. Any doses of systemic corticosteroid given daily or on alternate day for less than 2 weeks.
- ii. Topical therapy, local injection, intra-articular or aerosol use of corticosteroids, or physiological maintenance doses of corticosteroids.

**b. Moderate to High Dose Steroid Group:**

- i. Moderate or high doses of systemic corticosteroids given daily or on alternate day beyond 2 weeks.
- ii. Steroid dosing: receiving  $\geq 1$  mg/kg per day up to  $\geq 40$  mg per day (irrespective of body weight) of prednisolone or its equivalent, or  $\geq 10$  mg/day if they weigh more than 10 kg.

## Risk of HBV Reactivation

The risk stratification is based on the anticipated incidence of reactivation reported from literatures. In general, the risk would be related to the premorbid HBV status and the degree of immunosuppression (treatment risk). The following combined risk stratification may not be comprehensive. Clinical judgement is required, especially when patients are given combination of multiple immunosuppressive therapies.<sup>13</sup>

**a. High Risk Group (Anticipated Incidence of Reactivation >10%)**

- i. HBsAg+ or HBsAg-/anti-HBc+ patients treated with B cell-depleting agents, B-cell and T-cell depleting agents or HSCT recipient;
- ii. HBsAg+ patients treated with systemic chemotherapy for oncologic conditions;
- iii. HBsAg+ patients treated with  $\geq 1$  mg/kg per day up to  $\geq 40$  mg per day (irrespective of body weight) of prednisolone or its equivalent, or  $\geq 10$  mg/day if they weigh more than 10 kg, of systemic corticosteroids given daily or on alternate day beyond 2 weeks.<sup>9-11</sup>
- iv. HBsAg+ patients treated with anti-rheumatic therapy such as anti-TNF agents or disease modifying anti-rheumatic drugs (DMARDs).<sup>14</sup>

**b. Moderate Risk Group (Anticipated Incidence of Reactivation 1-10%)**

- i. HBsAg-/anti-HBc+ patients treated with systemic chemotherapy for oncologic conditions;

- ii. HBsAg-/anti-HBc+ patients treated with TNF alpha inhibitors, cytokine or integrin inhibitors, tyrosine kinase inhibitors or DMARDs;

- iii. HBsAg-/anti-HBc+ patients treated with  $\geq 1$  mg/kg per day up to  $\geq 40$  mg per day (irrespective of body weight) of prednisolone or its equivalent, or  $\geq 10$  mg/day if they weigh more than 10 kg, of systemic corticosteroids given daily or on alternate day beyond 2 weeks.<sup>9-11</sup>

**c. Low Risk Group (Anticipated Incidence of Reactivation < 1%)**

- i. HBsAg+ or HBsAg-/anti-HBc+ patients treated with traditional immunosuppressive agents monotherapy, e.g. azathioprine (AZA), 6-mercaptopurine (6-MP) and methotrexate (MTX);
- ii. HBsAg+ or HBsAg-/anti-HBc+ patients treated with any doses of systemic corticosteroid given daily or on alternate day for less than 2 weeks;
- iii. HBsAg+ or HBsAg-/anti-HBc+ patients receiving topical corticosteroid therapy;
- iv. Local injection, intra-articular or aerosol use of corticosteroids, or physiological maintenance doses of corticosteroids.

In patients receive low dose corticosteroid or traditional immunosuppressive monotherapy, if their conditions deteriorate and immunosuppressive therapy need to be stepped up or changed to combination immunosuppressive therapy, these patients' risk of HBV reactivation will increase to moderate or high risk according to patients' HBV status. Therefore, HBsAg and anti-HBc should be checked during screening. In new immunosuppressive therapy with an uncertain risk of HBV reactivation, it is suggested to manage these patients as moderate to high risk group according HBV status.

## Proposal on HBV Infection Screening Strategy in Patients Receiving Immunosuppressive Therapy

There is no need to check HBsAg and anti-HBc in low treatment risk group for HBV reactivation such as using short term, low dose or physiological systemic corticosteroid therapy; topical, or local corticosteroid therapy. Though some traditional immunosuppressive agent monotherapy e.g. AZA, 6-MP alone have low treatment risk of HBV reactivation, these patients may have underlying condition which may subsequently deteriorate and need to step up of immunosuppressive therapy with higher treatment risk. Therefore, HBsAg and anti-HBc

should also be checked during screening in patients requiring single traditional immunosuppressive agent if potential escalation of immunosuppression therapy is anticipated.

All paediatric patients who will receive immunosuppressive therapy in moderate and high treatment risk groups for HBV reactivation should be tested for HBsAg **and** anti-HBc prior to receive treatment as there is a significant risk of HBV reactivation in HBsAg+ or HBsAg-/anti-HBc+ patients.<sup>15</sup>

If a patient is found to be HBsAg+ or anti-HBc+, HBV deoxyribonucleic acid (DNA) level should be checked. For HBsAg-/anti-HBc+ patients with detectable HBV DNA level, the risk of HBV reactivation is similar as in HBsAg+ patients and their management should be the same.<sup>16,17</sup>

There is no role in using anti-HBs to detect HBV reactivation. Individual consideration can be made on the need of HBV revaccination in those found to be non-immune (both anti-HBs negative and anti-HBc negative, anti-HBs-/anti-HBc-), especially in those patients with ongoing exposure to blood products and risk of HBV exposure.

Laboratory test for HBsAg may be positive within 1 month after HBV vaccination. Anti-HBc result may be affected by recent blood or blood products transfusions as the prevalence of anti-HBc can be high in local adult population. The interpretation of serology results thus needs to be correlated with any recent HBV vaccination and blood products transfusion. Anti-HBc should be repeated 1 month later if required.

If HBV is not the cause for liver derangement in patients receiving immunosuppressive therapy, investigation for other hepatitis should be performed including hepatitis A (HAV), hepatitis C (HCV), hepatitis E (HEV) and or even rat HEV if HEV immunoglobulin (IgM) positive but HEV nucleic acid not detected.<sup>18</sup>

## Definition of HBV Reactivation and Hepatitis Flare

The American Association for the Study of Liver Diseases (AASLD) recommended using evidence of HBV reactivation AND a hepatitis flare to define HBV-associated hepatitis.<sup>15</sup>

### **The Definition of HBV Reactivation is as Follows:**

HBsAg+ patients:

1.  $\geq 2$  log (100-fold) increase in HBV DNA compared to the baseline level,

2. HBV DNA  $\geq 3$  log (1,000) IU/ml in a patient with previous undetectable level (since HBV DNA levels fluctuate), or
3. HBV DNA  $\geq 4$  log (10,000) IU/ml if the baseline level is not available

HBsAg-/anti-HBc+ patients:

1. HBV DNA is detectable OR
2. HBsAg seroreversion occurs (reappearance of HBsAg)

The definition of hepatitis flare is an alanine aminotransferase (ALT) increase to  $\geq 3$  times from baseline AND  $>100$  U/L.

## Clinical Recommendations on the Use of Antiviral Prophylaxis<sup>13</sup>

### **High Combined Patient and Treatment Risk Group**

The consensus of WG supports antiviral prophylaxis over no prophylaxis for high risk group as the risk of HBV reactivations in these patients receiving anti-cancer or anti-rheumatic therapy is high.

### **Moderate Combined Patient and Treatment Risk Group**

It is recommended to consider starting antiviral prophylaxis. For patients and or families who do not want starting long term antiviral therapy, serial monitoring of liver function test (LFT) and HBV DNA during immunosuppressive therapy should be done. For those HBsAg-/anti-HBc+ patients, monitor HBsAg to look for HBsAg seroreversion. The frequency of monitoring can range from 1 to 3 months depending on the type of immunosuppressive therapy. Antiviral therapy should be initiated upon confirmation of HBV reactivation before ALT elevation.

### **Low Combined Patient and Treatment Risk Group**

The consensus of WG does not support use of antiviral prophylaxis or preemptive therapy in low risk group patients as the HBV reactivation risk is low.

## Choice of Antiviral Medications

Both entecavir (ETV) and tenofovir can be used as special drug under the current Hospital Authority Drug Formulary (HADF).<sup>19</sup>

ETV is the drug of choice because of its high potency and high barrier to resistance (resistance rate is 1.2% in 6 years).<sup>17</sup> ETV is approved by United States Food and Drug Administration (US FDA) for treatment of chronic HBV

infection in paediatric patients with age  $\geq 2$  years of age. The dosage is according to body weight (Appendix 1).

Tenofovir disoproxil fumarate (TDF) is also of high potency with even lower resistance rate as compared with ETV as evidenced by no resistance development after up to seven years of TDF use.<sup>17</sup> However, renal function and serum phosphate level should be closely monitored as TDF has small risk of inducing proximal tubular dysfunction and renal insufficiency during treatment. US FDA has approved paediatric use for treatment of HBV infection in age  $>12$  years with body weight  $>35$  kg (Appendix 1).

Newer generation tenofovir alafenamide (TAF) has the benefit that lower dose of tenofovir can be used with similar efficacy and with much lower proximal tubule dysfunction and renal insufficiency side effects. However, TAF is not yet approved by US FDA for the treatment of HBV infection in the paediatric age group.

Both ETV and TDF need renal adjustment of dosage in patients with renal impairment (creatinine clearance less than 50 ml/minute) (Appendix 2).

### Treatment Monitoring and Duration<sup>15-17,20-22</sup>

Antiviral prophylaxis should be started as soon as possible and at least 1 week before or at the initiation of immunosuppressive therapy if feasible. It should be continued for at least 6 months after discontinuation of such therapy and at least 12 months after B cell depleting agents or HSCT. In emergency corticosteroid treatment, urgent HBsAg and anti-HBc should be checked and corticosteroid treatment should not be delayed till HBsAg and anti-HBc results are available.

If there is any uncertainty towards the clinical need of long-term antiviral therapy, it is advisable to refer these patients to specialists such as paediatric hepatologists, or paediatric infectious diseases specialists for further management.

While on antiviral prophylaxis therapy, initially LFT should be monitored every 3 months, or more frequent as clinically indicated. If TDF is used, renal function test (RFT) and serum phosphate should be monitored at the same time frame as LFT. Serum HBV DNA should be monitored every 3 to 6 months while on antiviral therapy. Patients and families should be reminded of the risk of HBV reactivation and hepatitis flare after discontinuation of antiviral prophylaxis.

For HBsAg+ patients after antiviral prophylaxis therapy discontinuation, LFT should be monitored at 1 and 3 months and then every 2 to 3 months. HBV DNA should be checked at 1 and 3 months after discontinuation of antiviral

prophylaxis therapy. For patients treated with B cell depleting agents and HSCT recipients, HBV DNA should be checked at 1, 3 and 6 months after discontinuation of antiviral prophylaxis. Antiviral therapy should be promptly resumed if evidence of HBV reactivation and patients can be referred to specialists for assessment.

For those moderate combined patient and treatment risk group patients who opt for no antiviral prophylaxis therapy, the frequency of monitoring of HBV DNA can range from 1 to 3 months depends on type of immunosuppressive therapy. Antiviral therapy should be initiated upon confirmation of HBV reactivation.

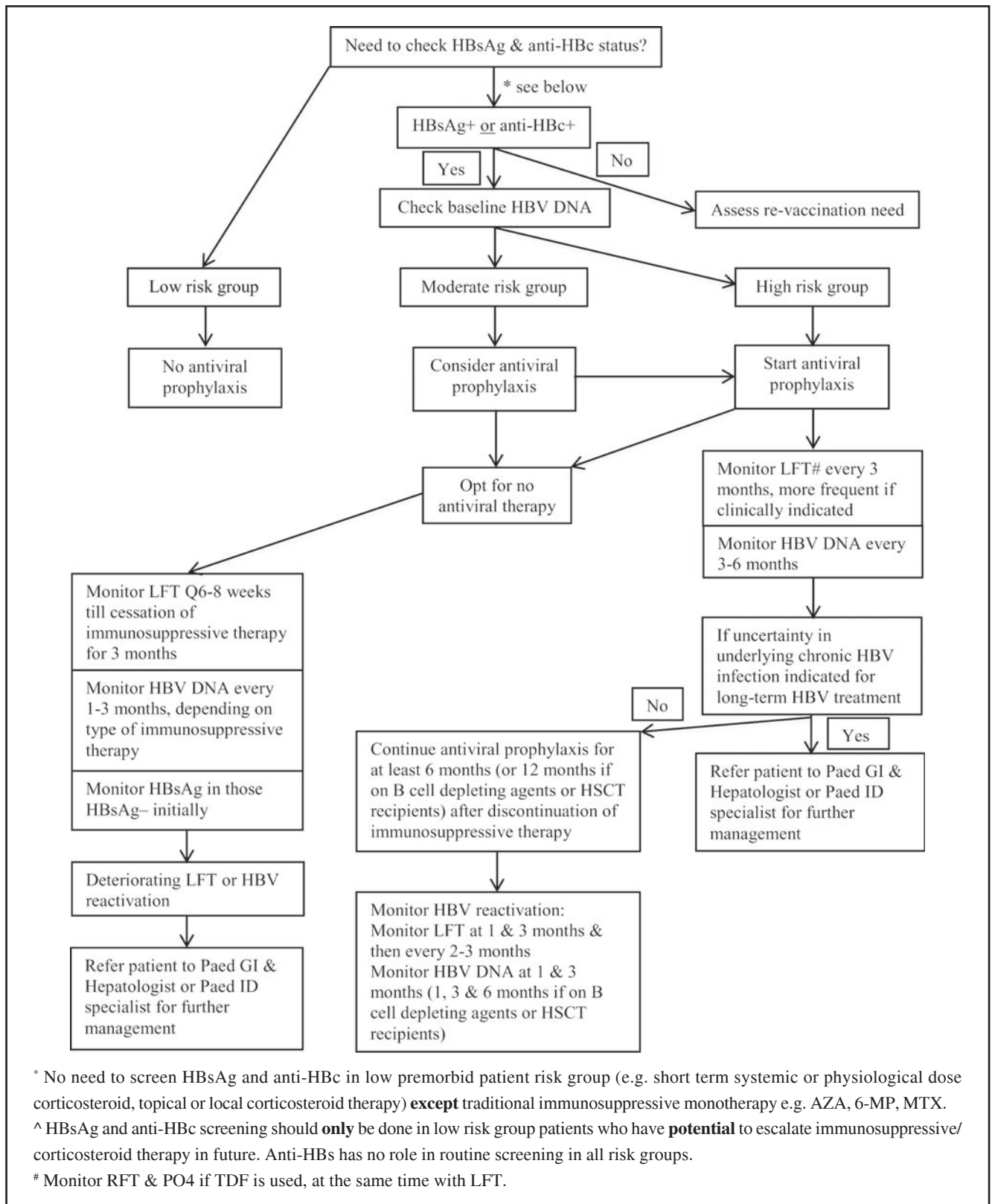
For HBsAg-/anti-HBc+ patients, HBsAg and LFT should be checked to look for HBsAg seroreversion, i.e. HBsAg reappearance. HBV DNA then should be checked when HBsAg turned positive or ALT goes up. The frequency of monitoring can range from 1 to 3 months depending on the type of immunosuppressive therapy. Antiviral therapy should be initiated upon confirmation of HBV reactivation.

### Special Patient Group – Non-liver Solid Organ Transplant Recipients<sup>15-17</sup>

The WG determined that paediatric liver transplant recipients' management is beyond the scope of this recommendation. The management of liver transplant recipients' HBV reactivation should be referred to the liver transplant center's practice guideline in Hong Kong.

The majority of non-liver solid organ transplant patients are renal transplant in Hong Kong. These patients require dialysis and are at risk of ongoing HBV infection due to frequent blood products exposure and they have impaired immune response to HBV vaccine before transplantation. It is suggested that they should be evaluated for HBV infection and immunity annually, i.e. HBsAg, anti-HBc and anti-HBs. HBsAg-, anti-HBc- and anti-HBs- recipients should receive HBV re-vaccination pre-transplant if HBsAg-. Organ transplant recipients with HBsAg+ should receive lifelong antiviral therapy to prevent or treat HBV reactivation after transplantation. ETV and TDF are the preferred antiviral drugs.

It is suggested to monitor HBV reactivation without antiviral prophylaxis in HBsAg-/anti-HBc+ patients, or consider treating these patients with antiviral therapy for the first 6 to 12 months during the maximal immunosuppression. It is recommended to monitor HBV reactivation by checking HBsAg (HBsAg seroreversion), ALT and HBV DNA every 3 months or more frequently for the first year post-transplant and after receipt of T-cell-



**Figure 1** Algorithm of prophylactic use of antiviral therapy for paediatric patients planned for immunosuppressive/corticosteroid therapy

depleting therapies e.g. anti-thymocyte globulin during maximal immunosuppression in untreated non-liver organ transplant recipients. Antiviral therapy should be started immediately if HBV reactivation.

## Declaration of Interest

Wai Hung CHAN, Mike Yat Wah KWAN, David Christopher LUNG, Winnie Kwai Yu CHAN, Mei Ching CHAN, Frankie Wai Tsoi CHENG, Chung Mo CHOW, Assunta Chi Hang HO, Tak Loi KU, Wai Ming LAI, Daniel Wai Yau MAK, Chi Hang NG, Freddie Man Hong POON, Shirley Man Yee WONG, Rosanna Ming Sum WONG, Sik Nin WONG, Eric Kin Cheong YAU, Mei-Hwei CHANG, Jia-Feng WU, Xinbao XIE, Yu Lung LAU, Kwok Chiu CHAN: None to declare

Henry LY CHAN: Independent non-executive director for Shanghai Henlius Biotech Inc.; advisor for AbbVie, Aligos, Arbutus, Gilead Sciences, Glaxo-Smith-Kline, Hepion, Janssen, Merck, Roche, Vaccitech, VenatoRx, Vir Biotechnology; speaker for Gilead Sciences, Mylan, Roche

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**Appendix 1.** Recommended antiviral therapy for paediatric patients**1. Entecavir (ETV)**

Recommended dosage in adult patients:

Treatment-naïve patients: ETV 0.5 mg daily

Lamivudine-experienced patients: ETV 1 mg daily

**Recommended dosage in paediatric patients:**

The following table describes the recommended dose of ETV for paediatric patients 2 years of age or older and weighing at least 10 kg. The tablet dissolves in plain water should be used for patients with body weight up to 30 kg. The current ETV formulations in HA are dispersible tablet or plain tablet. Both are readily soluble in water and dosage can be given according to body weight.

**Dosing schedule for paediatric patients**

Body Weight (kg)	Recommended Once-Daily Dose (mg)	
	Treatment-Naïve Patients	Lamivudine-Experienced Patients
10 to 11	0.15	0.3
>11 to 14	0.2	0.4
>4 to 17	0.25	0.5
>17 to 20	0.3	0.6
>20 to 23	0.35	0.7
>23 to 26	0.4	0.8
>26 to 30	0.45	0.9
>30	0.5	1

**2. Tenofovir disoproxil fumarate (TDF)**

Recommended dosage for age 12 years or older with body weight more than 35 kg:

Dosage: TDF 300 mg daily

**3. Tenofovir alafenamide (TAF)**

Recommended for adult only and not recommended for use if creatinine clearance less than 15 ml/minute

Dosage: TAF 25 mg daily

NB: Pharmaceutical companies do not update US FDA age limit approval in local drug insert, the WG suggested paediatricians should follow the most update US FDA approval.

US FDA approved TDF use in age from >2 years and beyond, however, TDF powder is not available in Hong Kong and hence, body weight based paediatric dosing is not included.

**Appendix 2.** Recommended dosage adjustment of antiviral therapy in renal impairment**Dosing schedule for paediatric patients**

Creatinine clearance (ml/minute)	Entecavir (Dose according to BW)	Tenofovir disoproxil fumarate (300 mg for $\geq 12$ y.o. & $\geq 35$ kg)
$\geq 50$	Daily	Daily
30 - 49	Q48H	Q48H
20 - 29	Q72H	Q72H
10 - 19	Q72H	Q96H
<10	Once weekly	Once weekly
CAPD	Once weekly	Once weekly
Haemodialysis (Administer after HD)	Once weekly	Once weekly

## Clinical Quiz

### What is the Diagnosis?

VRY FORMOSO, M LEÃO, CC CORREIA, M FONTOURA

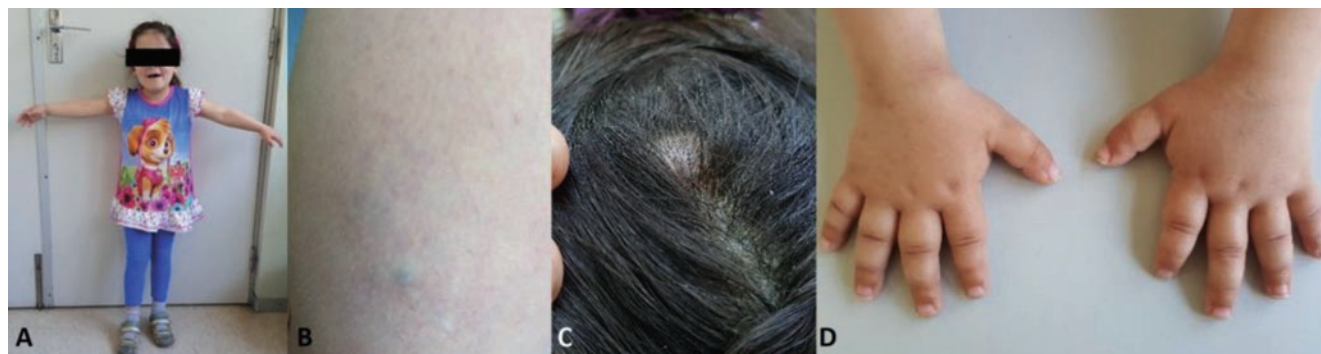
#### Case Report – Presentation

We present the case of a three-year-old female child, who underwent evaluation in our paediatric endocrinology outpatient clinic due to "congenital hypothyroidism" and short stature.

Born at 37 weeks gestational age with low birthweight, she adapted poorly to extrauterine life, with constant groan and axial hypotonia, for which she was admitted to the neonatal intensive care unit. During her stay, endocrine studies showed progressively increasing high Thyroid-stimulating Hormone (TSH) levels (10 mIU/L; 14 mIU/L)

and decreasing low Free Thyroxine (FT4) levels (10.42 pmol/L; 9.14 pmol/L) - no anti-thyroid antibodies were detected and the thyroid ultra-sound was normal. Congenital hypothyroidism was diagnosed and, at 2 months of age, she began levothyroxine (LT4) therapy.

When evaluated at the age of three, even though short stature was not present (Height P25%) and growth was apparently not impaired (Growth Velocity P10-25%), the patient's physical examination unveiled several unique characteristics – obesity, brachydactyly, round facies and hard subcutaneous nodules (Figure 1). A complete family history revealed that all of these



**Figure 1** Index patient. (A) General habitus; (B and C) Subcutaneous nodules; (D) Hands – brachydactyly with evident shortening of the distal phalanx of the thumb.

The clinical quiz was prepared by:

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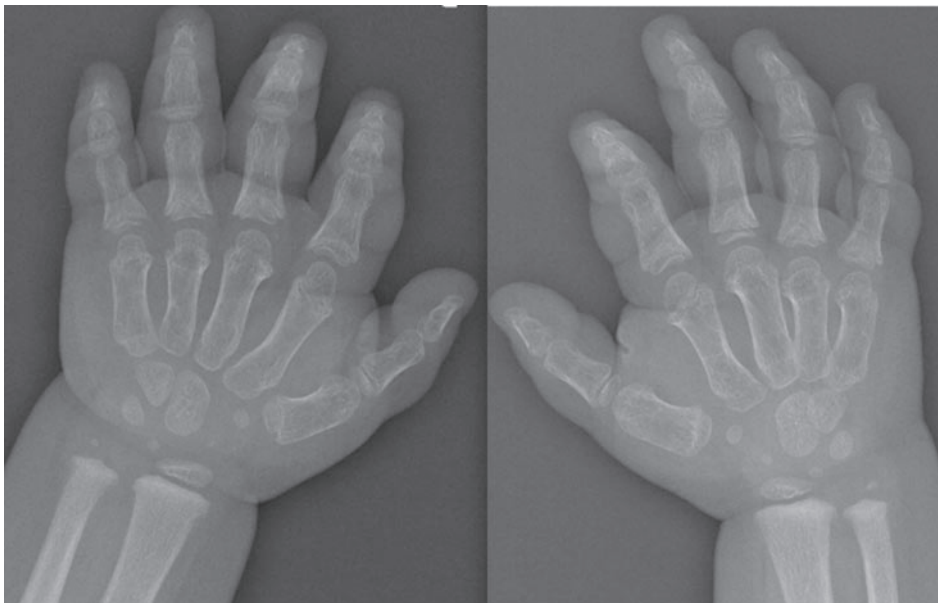
physical characteristics were also present on other family members, particularly her mother (Figure 2), one maternal uncle and her maternal grandfather.

The re-evaluation of previous lab results as well as new lab, histologic and radiologic studies revealed important information: Neonatal thyroid hormone studies suggested

an insensitivity to TSH's action; current high Parathormone (PTH), low vitamin-D and hypocalcemia suggested an insensitivity to PTH action; Ossifications were identified on the subcutaneous nodules' histology; a hand X-ray confirmed the clinical evidence of brachydactyly (Figure 3).



**Figure 2** Index patient and her mother. (A) General habitus; (B) Hands side-by-side – Brachydactyly with evident shortening of the distal phalanx of the thumb.



**Figure 3** The index patient's hand X-ray showing the characteristic brachydactyly.

Answer to "Clinical Quiz" on Pages 262-265

N.B. The Editors invite contributions of illustrative clinical cases or materials to this section of the journal.

## 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  $\geq 3$  of the 5 answers are correct. The total score of the 4 articles will be 4 CME points.

### (A) Childhood Chronic Recurrent Headache in Hong Kong: A Case Control Study

1. According to diagnostic criteria established by the International Headache Society, which of the following is NOT diagnostic criteria of migraine in children?
  - a. Headache duration 2 to 48 hours
  - b. Headache duration 48 to 96 hours
  - c. Photophobia and phonophobia
  - d. Unilateral location
  - e. Headache aggravated by climbing stairs or similar routine physical activity
2. Which of the following feature(s) is/are found to have higher differentiating values for childhood migraine in the present study?
  - a. Pulsating quality, nausea, photophobia and phonophobia
  - b. Lateralising ache, longer duration and worst intensity
  - c. Aggravation by physical activity
  - d. (a) and (c)
  - e. (b) and (c)
3. Which of the following is a true statement?
  - a. In the present study, migraine onset was less common in the first decade of life, and became more prevalent during adolescence.
  - b. Paediatricians should take into consideration the contexture of symptoms, behavioural changes, evolutions over time, and parental information to arrive at the correct diagnosis of childhood headaches.
  - c. Isolated headache or migraine was classified as high level of appropriateness for brain scans to be performed, according to the American College of Radiology Appropriateness criteria.
  - d. (a) and (b)
  - e. (a), (b) and (c)
4. Which of the following is the most common preventive medication in the present study?
  - a. Amitriptyline
  - b. Pizotifen
  - c. Propranolol
  - d. Topiramate
  - e. Acetazolamide
5. Which of the following is NOT a true statement?
  - a. Secular increase in chronic childhood headache over the past two decades has been correlated to factors such as increase in time demands, pressures from school, peers and family, and reduction in physical activities.
  - b. In the present study, impairment of daily functioning was equally prevalent in migrainous and non-migrainous children.
  - c. Cognitive behavioural therapy might augment the efficacy of standard medications in childhood migraine.
  - d. The under-utilisation of psychotherapy might be related to lack of physician awareness of this intervention to children with severe refractory headaches and the confined availability of clinical psychological service in our locality.
  - e. Co-morbid depressive, anxiety and somatisation disorders were uncommon in chronic childhood headaches.

**(B) IgA Nephropathy Associated with Acute Kidney Injury in Young Patients: The Clinicopathological Features and Risk Factors Analysis**

1. Which one is the leading cause of the ESRD of patients with primary glomerular diseases?
  - a. Poststreptococcal glomerulonephritis
  - b. Membranous nephropathy
  - c. IGA nephropathy
  - d. Diabetic kidney disease
  - e. None of the above
2. How many percent of the AKI patients could be fully cured during the post-acute stage?
  - a. 60%
  - b. 65%
  - c. 70%
  - d. 50%
  - e. 55%
3. Which of the following is not the basis of diagnosis of AKI according to the 2012 KDIGO criteria?
  - a. Increase in SCr by 0.3 mg/dl within 48 h,
  - b. Increase in SCr to 1.2 times baseline
  - c. Increase in SCr by 26.5  $\mu$ mol/l within 48 h,
  - d. Urine volume <0.5 ml/kg/h for 6h
  - e. None of the above
4. Which of the following is not part of the Oxford classification system?
  - a. Mesangial hypercellularity
  - b. Endocapillary hypercellularity
  - c. Segmental glomerulosclerosis
  - d. Tubular atrophy/interstitial fibrosis
  - e. Cytoclasia
5. According to this study, which two parameters are the most relevant ones associated with AKI among young patients with IgAN?
  - a. Heavy proteinuria and gender
  - b. Age and gender
  - c. Malignant hypertension and heavy proteinuria
  - d. Heavy proteinuria and the content of uric acid
  - e. Malignant hypertension and the content of uric acid

**(C) Portrayal of Thyroid Abnormalities and Their Management in a Local Cohort of Children and Adolescents with Down Syndrome: An Update**

1. What is the most common form of thyroid abnormalities in children with Down syndrome?
  - a. Congenital hypothyroidism
  - b. Transient hypothyroidism
  - c. Subclinical hypothyroidism
  - d. Acquired hypothyroidism
  - e. Hyperthyroidism
2. What is the current AAP recommendation for thyroid function evaluation in children with Down syndrome?
  - a. Thyroid function at birth then annually.
  - b. Thyroid function at birth then every 6 months.
  - c. Thyroid function at birth, at 6 months and 12 months then annually.
  - d. Thyroid function at birth, at 3 months, 6 months, 12 months then annually.
  - e. Thyroid function at birth, every 3 months till 12 months then annually.
3. What is the usual TSH cutoff for starting thyroxine supplement in cases of subclinical hypothyroidism?
  - a. 5 mIU/L
  - b. 10 mIU/L
  - c. 20 mIU/L
  - d. 40 mIU/L
  - e. 50 mIU/L
4. What are the possible causes of subclinical hypothyroidism in Down syndrome?
  - a. Non-pathological shift in normal range of TSH.
  - b. Chromosomopathy in Down syndrome attributes to alter in hypothalamic-pituitary-thyroid axis.
  - c. Autoimmunity in Hashimoto thyroiditis related subclinical hypothyroidism.
  - d. (a) and (b)
  - e. All of the above
5. What is special about oscillating thyroid disease in children and adolescents with Down syndrome?
  - a. It shows a continuum between Hashimoto thyroiditis and Graves' disease within the spectrum of autoimmune thyroid disorders.
  - b. Hashimoto thyroiditis is usually preceded by Graves' disease.
  - c. Children and adolescents with Down syndrome are more likely to progress from Hashimoto thyroiditis to Graves' disease.
  - d. (a) and (b)
  - e. (a) and (c)

**(D) Clinical Characteristics and Outcomes of Paediatric Non-tuberculous Mycobacterial Infection: Single Institution Retrospective Review Over Past 20 Years**

1. Which of the following mycobacterial infection is a notifiable disease in Hong Kong?
  - a. Mycobacterium abscessus
  - b. Mycobacterium avium complex
  - c. Mycobacterium chelonae
  - d. Mycobacterium fortuitum
  - e. Mycobacterium tuberculosis
2. Which of the following mycobacteria is not considered as non-tuberculous mycobacteria (NTM)?
  - a. Mycobacterium abscessus
  - b. Mycobacterium avium complex
  - c. Mycobacterium bovis
  - d. Mycobacterium chelonae
  - e. Mycobacterium fortuitum
3. Which of the following(s) is/are the clinical manifestation(s) of NTM infections?
  - a. Chest infection
  - b. Catheter-related bloodstream infection (CRBSI)
  - c. Lymphadenitis
  - d. Skin and soft tissue infection
  - e. All of the above
4. Which of the following(s) is/are the predisposing risk factor(s) to NTM infections?
  - a. Malignancy
  - b. Post-transplant
  - c. Primary immunodeficiency
  - d. Steroid use
  - e. All of the above
5. Which of the following antimicrobial agent is effective against NTM infection based on local sensitivity pattern?
  - a. Amikacin
  - b. Isoniazid
  - c. Pyrazinamide
  - d. Rifampicin
  - e. Moxifloxacin

***Answers of July issue 2021***

(A) 1. e; 2. a; 3. e; 4. c; 5. e

(C) 1. d; 2. e; 3. e; 4. a; 5. a

(B) 1. d; 2. e; 3. d; 4. e; 5. e

(D) 1. e; 2. a; 3. c; 4. e; 5. e

## Obituary of Dr CHIU Man Chun (1949-2021)



### *A Life Passionately Lived*

After graduating from the Medical Faculty of The University of Hong Kong in 1974, Dr Chiu Man Chun underwent general paediatrics training in Paediatric A Unit of Queen Elizabeth Hospital and received subspecialty training in paediatric nephrology in Great Ormond Street Hospital for Children and Guy's Hospital, London. Dr Chiu was a pioneer in paediatric intensive care service and brought in neonatal intensive care in the era without neonatal intensive care units. He piloted continuous ambulatory peritoneal dialysis and continuous arteriovenous haemofiltration in infants. Dr Chiu expanded and eventually consolidated paediatric nephrology subspecialty services when he took up the consultant post in Princess Margaret Hospital in 1988. He was Chief of Service from 1992 till his retirement in 2010. Dr Chiu was also Co-chairman of Central Co-ordinating Committee (COC Paediatrics) of the Hospital Authority from 2002 to 2005.

Dr Chiu had not only laid a solid foundation for the development of paediatric nephrology in Hong Kong. Through his vast international networks and leadership in the Asian Paediatric Nephrology Association and International Paediatric Nephrology Association, he had also crafted the substantial international presence of the Hong Kong Paediatric Nephrology community in academia, service development, training and fraternity. He was the key driver in the development of paediatric nephrology in many Chinese cities and the Guest Professor of several top Children Hospitals in Beijing and Shanghai. During his long and distinguished career, Dr Chiu was also a staunch supporter to developing the adolescent medicine services in Hong Kong.

Recounting Dr Chiu's dedicated service to Hong Kong College of Paediatricians is like writing a mini-history of the founding and growth of the College. Dr Chiu was one of the 30 Subscribers to the formation of Hong Kong College of Paediatricians in May 1991. He served as the Honorary Secretary from 1991 to 1997, and had remained on the College Council until 2005. During his terms, he was one of the first members of the Scientific and Postgraduate Committee (1991-1993), which was later reformed to become the Education Committee in 1993. A first member of the Examination Committee in 1993, Dr Chiu was also the Committee Chairman from 1999 to 2005. He also had a long service on the Accreditation Committee from 1997 to 2015. He was the College representative to the Part I Board of Examiners of the UK College, and was an examiner in the clinical examinations both in Hong Kong and the UK.

When the development of subspecialty training was eagerly awaited about a decade after our College's inauguration, Dr Chiu joined the Task Force for Higher Training of Paediatric Subspecialties when it was set up in 2001. He had been a pivotal member in the transformation of the Task Force into the Working Group on Accreditation of Paediatric Subspecialties in 2008, and ultimately in 2013 to the present-day Committee for Subspecialty Boards.

Dr Chiu was a visionary leader. He built arches for paediatrics and child health to reach high. Other than innovative in ward re-designs, he was especially masterful in constructing service models. He established the Paediatric Nephrology Centre and Centre for Paediatric Infectious Diseases in Princess Margaret Hospital. Working with Sir Cyril Chantler and the local stakeholders, Dr Chiu masterminded the service model of a Children's Hospital for Hong Kong in his report titled "For the Future Generation and Paediatrics" in 2007. It had become the blueprint of the Hong Kong Children's Hospital now towering on the South Apron of the old Kai Tak Airport.

Dr Chiu contributed immensely to the novel paediatric services at the HKU-Shenzhen Hospital. The department has become a model paediatric centre providing services and specialist training in general paediatrics, paediatric subspecialties and neonatology in Mainland China.

Being a devoted Christian, Dr Chiu had made good use of the creative gift from God. He wrote prolifically in a broad range of styles. He was a voluntary editor of Breakthrough Magazine. In his very busy days as a junior doctor, he was a popular columnist that shared many touching experiences and reflections in his patient encounters under the pen name "梓翔". These stories were compiled into "醫生札記" (1980). It was one of the 10 most recommended books for student readers in 1990-1991. About infectious diseases, there were "兒童及青少年SARS面面觀" (2003) and "流感、禽流感真貌" (2006). In "弦動人生" he wrote about his inspirations and testimony to God during a South American trip after he had retired from the Hospital Authority. Many generations of paediatricians have benefited from Dr Chiu's clinical vademecum and textbooks. These included five editions of Paediatric Manual, Paediatric Nephrology Handbook (co-authored with Dr YU Chau Leung) and Neonatal Manual (co-authored with Prof FOK Tai Fai). He also edited Practical Paediatric Nephrology - an Update of Current Practices with Professor Hui Kim YAP. It is his magnum opus and a classic must-read for paediatricians in Hong Kong, Singapore, Mainland China and beyond.

Dr Chiu was well known for his musical talents. He founded the HK Medical Association Choir to complement the HK Medical Association Orchestra, bringing many doctors, nurses and their families together to make music for charitable causes. Music was with him everywhere he worked and served: he had organized chamber music performances in his department at Princess Margaret Hospital; he put together large concerts to celebrate monumental events in the paediatric nephrology community. These concerts were often very successful fund-raisers, too. He wrote a total of 36 well-known Chinese hymns for the Christian music ministry. His healing power came not only from his medical expertise, but also by being a man for all men. He was loving, caring, committed, humorous and generous. Being a Wahyanite, he had put the welfare and happiness of all close to his heart. His benevolence had transformed the lives of many.

Our College mourns with a heavy heart the passing of Dr Chiu, a giant, a legend, and a paediatrician that we all look up to. We shall treasure the legacy he had bestowed upon us, and follow his footsteps to strive for excellence in Paediatrics.

We send our sincerest condolences to Dr Chiu's family. Our thoughts are with them.

*Dear Dr Chiu, we thank you with all our hearts. May you have eternal peace in God's love.*

The Council on behalf of Hong Kong College of Paediatricians

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## Corrections

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In the article "**Tolerability and Efficacy of Racecadotril in Acute Diarrhoea, A Prospective, Randomised, Parallel Study in an Indian Tertiary Care Teaching Hospital**" by Sarangi et al and appeared in the July 2021 issue of the journal [HK J Paediatr (new series) 2021;26:149-154], a correction was needed.

On page 149, the sixth sentence of the abstract reads, "Result: The mean stool volume in 48 hours ( $79.5 \pm 17.31$  g/kg body weight versus  $91.04 \pm 33.4$  g/kg body weight,  $p=0.0001$ )". The sentence has been updated to read, "The mean stool volume in 48 hours ( $179.5 \pm 17.31$  g/kg body weight versus  $191.04 \pm 33.4$  g/kg body weight,  $p=0.0001$ )".

This correction has been made to the current online version of the article, which is available at updated website:

<http://www.hkjpaed.org/details.asp?id=1345&show=1234>

<http://www.hkjpaed.org/pdf/2021;26;149-154.pdf>

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In the article "**Hong Kong Universal Newborn Hearing Screening (UNHS) Care Path Protocol under Joint Committee on UNHS**" by Ma et al and appeared in the July 2021 issue of the journal [HK J Paediatr (new series) 2021;26:168-174], a correction was needed.

On page 168, the last sentence in the abstract reads, "Meetings with multidisciplinary professionals had been conducted during the years of 2013 and 2014." The sentence has been updated to read, "Meetings with multidisciplinary professionals had been conducted during the years from 2013 to 2017." A sentence is added, "A consensus on a common care path for infants identified to have hearing impairment had been reached."

This correction has been made to the current online version of the article, which is available at updated website

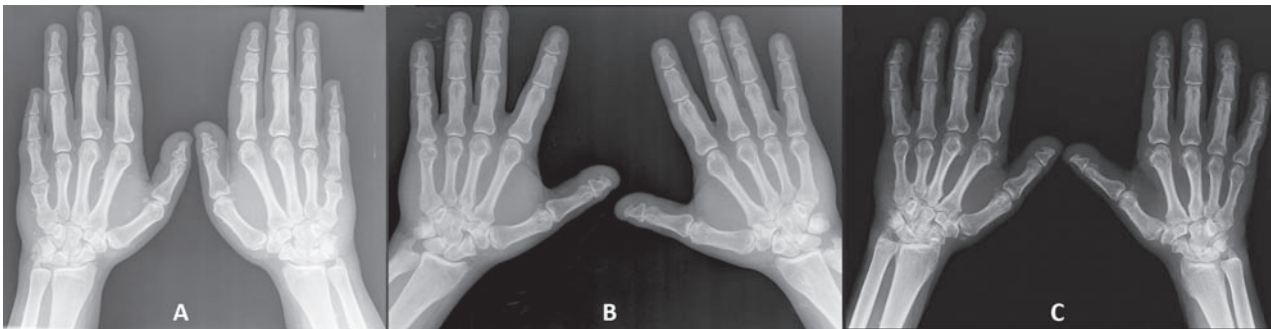
<http://www.hkjpaed.org/details.asp?id=1350&show=1234>

<http://www.hkjpaed.org/pdf/2021;26;168-174.pdf>

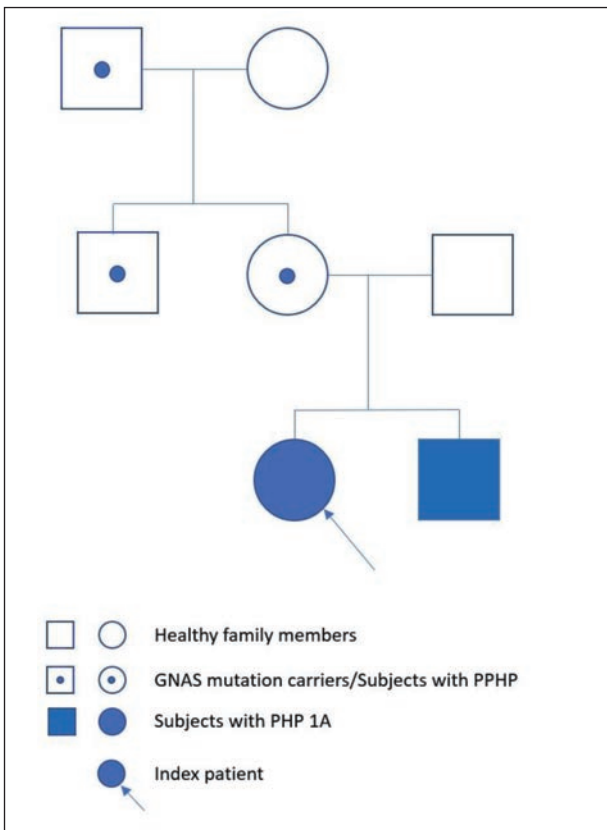
CLINICAL QUIZ (p254-255) ANSWER

After the new data was obtained, Pseudohypoparathyroidism (PHP)-Ia was suspected and later confirmed in the index patient, through the identification of a variant in the *GNAS* gene – c.1174G>A (p.E392K) in exon 13.

Molecular analysis was also requested for the family members who shared the same somatic features (Figure 4) (but whose posterior lab workup found no hormonal abnormalities) – they were found to also carry the same variant – in the case of her uncle and mother this was compatible with the hypothesis of a paternal-inherited variant – Pseudopseudohypoparathyroidism (PPHP) (Figure 5).



**Figure 4** Hand X-ray of other studied family members showing brachydactyly (including a shortening of the distal phalanx of the thumb) and the presence of small ectopic ossifications. (A) Mother - shortening of IV and V metacarpals; (B) Uncle - shortening of V metacarpals; (C) Grandfather - shortening of metacarpals IV and V.



**Figure 5** The subject's family chart/pedigree.

## Clinical Features and Findings – PHP-Ia and PPHP

PHP encompasses a heterogeneous group of disorders that differ in phenotype and aetiology but share end-organ resistance to PTH as their main characteristic.<sup>1,2</sup>

PHP-Ia, the most common subtype of PHP, is caused by pathogenic (inactivating) variants of the *GNAS* gene.<sup>1-6</sup> These variants are inherited in an autosomal dominant manner but, because of paternal imprinting, specific phenotypes are determined by the parental origin of the defective allele:<sup>1-4,6,7</sup>

- When subjects inherit the inactivating variant from their father, they only manifest somatic features (Albright's Hereditary Osteodystrophy (AHO)):<sup>1-4,8</sup> short stocky build, rounded face, brachydactyly and ectopic ossifications<sup>1,2,5,6</sup> – PPHP<sup>2-4\*</sup> (Table 1).
- On the other hand, when maternally inherited, in addition to AHO characteristics, obesity and intellectual disabilities<sup>#</sup>, an impairment of hormonal signaling through stimulatory G-proteins occurs.<sup>2-4,6,8</sup> This causes PTH resistance (usually manifesting through hypocalcemia, hyperphosphatemia and elevated circulating PTH, in the absence of magnesium and renal function imbalances or vitamin D deficiency) and a variable degree of insensitivity to other hormones dependent on that signaling mechanism – TSH, growth hormone – releasing hormone, Gonadotropin, Somatotropin<sup>1-8</sup> – PHP-Ia<sup>1,3,4,6,8</sup> (Table 1).

**Table 1** Disorders of *GNAS* inactivation - Phenotypes and genetic mechanisms

Phenotype	Endocrine defects	Clinical features	Parental origin of inactivated <i>GNAS</i> allele	Molecular defect
PHP- Ia	Multihormone resistance	AHO; early onset obesity	Maternal	Heterozygous <i>GNAS</i> pathogenic variant
PHP-Ic	Multihormone resistance	AHO	Maternal	Heterozygous <i>GNAS</i> pathogenic variant
PHP-Ib	PTH resistance; partial TSH resistance in some	Enhanced intrauterine growth; mild brachydactyly in some	Maternal	Heterozygous deletion of <i>STX16</i> or regulatory elements in <i>GNAS</i> complex locus (familial) Or Paternal 20q disomy or unknown epigenetic defect (sporadic)
PPHP	None	AHO; intrauterine growth restriction	Paternal	Heterozygous <i>GNAS</i> pathogenic variant
POH	None	Progressive heterotopic ossification extending to deep connective tissues	Paternal	Heterozygous <i>GNAS</i> pathogenic variant
Osteoma Cutis	None	Heterotopic ossification limited to dermis & subcutaneous tissues	Paternal	Heterozygous <i>GNAS</i> pathogenic variant

PHP - Pseudohypoparathyroidism; PPHP - Pseudopseudohypoparathyroidism; POH - Progressive Osseous Heteroplasia; AHO - Albright's Hereditary Osteodystrophy.

(Adapted from Haldeman-Englert CR, Hurst ACE, Levine MA. Disorders of *GNAS* Inactivation. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews®. [Internet] 2017).

\* Rarely, in some families, a paternally inherited *GNAS* mutation can lead to a different condition - Progressive Osseous Heteroplasia (POH) – that is characterised by dermal ossification beginning in infancy, followed by increasing and extensive bone formation in deep muscle and fascia, usually without other AHO manifestations<sup>2,6</sup> (Table 1).

# Some authors also describe the presence of obesity and intellectual disabilities in PPHP patients, considering them part of the AHO phenotype.<sup>2,4,6,7</sup>

In PHP-Ia, penetrance is complete but timing and severity vary significantly among affected individuals.<sup>3</sup> While evidence of TSH resistance is frequently present at birth (often detected on neonatal screenings) and can lead to the misdiagnosis of congenital hypothyroidism,<sup>1-4,8</sup> PTH resistance usually develops progressively during childhood.<sup>2-4,6</sup>

In comparison to the general population, higher rates of asthma,<sup>2,8</sup> sleep apnea (not only explained by obesity),<sup>2,8</sup> cataracts,<sup>2</sup> type-2 Diabetes Mellitus,<sup>5</sup> spinal stenosis,<sup>2,3,5,8</sup> carpal tunnel syndrome,<sup>2,3,5,8</sup> hearing loss,<sup>5,8</sup> decreased olfaction<sup>2,5</sup> and otitis media<sup>2,5</sup> have been reported in PHP-Ia patients.

A diagnosis based on clinical and biochemical findings should be confirmed by molecular genetic analysis.<sup>2,3,8</sup> The detection of a mutation in an index case allows a correct diagnosis and the possibility of predictive genetic testing in relatives.<sup>6</sup> It is appropriate to evaluate apparently asymptomatic first-degree relatives of an affected individual.<sup>3</sup>

### Management of PHP-Ia

Early diagnosis and intervention as well as the establishment of a multidisciplinary follow-up are extremely important.<sup>2</sup>

Radiologic evaluation for brachydactyly is part of the condition's initial assessment.<sup>1,3</sup>

Endocrine essays are mandatory but may be very misleading due to the high variability in onset timing and severity of endocrine abnormalities among individuals, even within the same family.<sup>1</sup> Generally, these patients should be regularly monitored for serum PTH, calcium, phosphate<sup>1,3</sup> and calcifediol<sup>2</sup> as well as urinary calcium excretion.<sup>1,3</sup> Routine screening for any associated endocrinopathies is recommended – particularly hypothyroidism and hypogonadism.<sup>1-3</sup> Shorter intervals between assessments are recommended during childhood.<sup>2,3</sup>

In children, growth and pubertal development should be closely monitored.<sup>1-3</sup> Treatment of GH-deficient PHP-Ia patients with GH is still controversial<sup>1</sup> but should be considered.<sup>3,8</sup> Weight and body mass index should be monitored regularly to prompt early nutritional intervention when required.<sup>1,2,8</sup> Neurocognitive/neurodevelopmental assessments should be considered at diagnosis or pre-school age.<sup>2</sup>

Normocalcemia should be maintained in these patients through adjusted treatment with vitamin D metabolites such as calcitriol and, if necessary, oral calcium supplementation.<sup>1,2</sup> PTH target values should be the upper limits of the reference range – while excessive levels may adversely affect bone mineralization and the growth plate, PTH suppression may lead to renal calcifications and hypercalciuria.<sup>1-3,8</sup> If PTH levels are excessive, treatment should be considered even in normocalcemic patients.<sup>1</sup>

Treatment of hypothyroidism and hypogonadism is similar to any other non-PHP-Ia related form.<sup>1-3</sup>

There are no specific treatments for AHO manifestations – subcutaneous ossifications may be surgically removed if particularly incommensurate.<sup>1,3,8</sup>

### Case Report – Follow-up

Currently, at the of age 7, the index patient remains euthyroid and has maintained normal phosphocalcium metabolism under LT4, calcitriol, calcium carbonate and vitamin-D supplementation. Formal cognitive assessment revealed a normal (but borderline low) IQ.

Recently, the subject's mother delivered a 2360g male newborn. Because of his family history, phosphocalcium metabolism and endocrine studies were requested on the sixth day of life – while the former were within normal range for his age, a free-T4 level of 8.62 pmol/L and a TSH concentration of 13 mIU/L were detected. Therefore, he presented PHP-Ia in a similar fashion to his sister with hypothyroidism/TSH insensitivity developing first (before any phosphocalcium imbalances occurred). The same GNAS variant was detected in this newborn's genetic study confirming the diagnosis (Figure 5). He has been asymptomatic under LT4 substitution after 4 months of follow-up.

## Take-home Messages

With this case report we aim at exemplifying the often-challenging diagnosis of PHP-Ia/PPHP – highlighting the importance of family history and of some particular clues found through physical and radiological exams. These findings support the request for endocrine assessments and, eventually, molecular analysis.

Knowledge of this disease's pathophysiology and intricate genetic patterns of inheritance along with careful study of the family's pedigree is therefore of paramount importance when managing these patients', their families' and their future offspring's conditions, allowing us to predict the phenotypes and therefore, future screening and therapeutic needs.

Early phosphocalcium metabolism and thyroid function assessments are recommended in these families' newborns.<sup>2</sup>

## Declaration of Interest

The authors declare there are no conflicts of interest to disclose.

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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.

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

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#### Results

#### Discussion

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

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1. *Standard journal article* Greenberg DL, Root RK. Decision making by analogy. N Engl J Med 1995;332:592-6.
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#### **Unpublished Material**

12. *In press* Lillywhite HD, Donald JA. Pulmonary blood flow regulation in an aquatic snake. Science. In press.
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