Editorial
Birth Defects: Clinical Management and Beyond
Cheung

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ISSN 2309-5393 (online)
ISSN 1013-9923 (print)
Indexed in EMBASE/Excerpta Medica, Science Citation Index Expanded (SCIE) and Scopus
Full text online at www.hkjpaed.org
Birth defects include structural or functional anomalies with measurable effects on physical, intellectual, and social well-being. While it is intuitive in present view that they represent inborn errors of development, birth defects have been perceived historically as omens, portents, or punishments of supernatural origin. 'Malformed animal or human, creature afflicted with a birth defect' had been referred to as monster, the word that came into English use in the fourteenth century. This word comes from the Latin măstrum that harbours the meanings of omen, portent, an abnormal shape, and unnatural growth. It was not until the seventeenth century that William Harvey appreciated monstrosities from the perspective of abnormalities in embryonic development and disorders of conception as described in Exercitationes de generatione animalium. It was not until then that Harvey described the possible embryological perturbation that results in cleft lip in humans and animals, the oral aperture without lips and cheeks is seen stretching from ear to ear, and this is the reason, unless I make much mistake, why so many are born with the upper lips divided as it is in the hare and camel...... In the development of the human foetus, the upper lip only coalesces in the middle line at a very late period. The scientific appreciation of what had been regarded as monstrosities has evolved into the study of embryological development and its arrest and other perturbations.

In this issue of the Journal, several articles reported on the diagnosis, surgical management, and outcomes of congenital anomalies. Tovani-Palone et al shared their experience on centralisation of surgeries for the treatment of cleft lip and/or the palate and decentralisation of outpatient services in Brazil. Chee et al described the associated anatomic and genetic anomalies commonly encountered in newborns with omphalocele, their postnatal workup and prognosis over a 10-year period. Of importance to note is the high prevalence of associated congenital anomalies, in particular congenital heart defect. Interestingly, the authors also found that two of the 19 patients had the uncommon condition of alveolar capillary dysplasia. Xie et al reported on the diagnosis and the surgical management of infants with double aortic arch. As one reads through these articles, one could very much appreciate the excellent outcomes of surgical management of congenital anomalies in this era.

Notwithstanding, birth defects still constitute a significant clinical and public health challenge. Available data suggest that the occurrence of birth defects has not decreased over decades, and may in fact show a slight increase worldwide. The emerging Zika epidemic represents a new threat to further increasing their occurrence. The success to primary prevention of congenital anomalies depends on identification of the root causes. Disappointingly, hospital-based and public health surveillance studies have similarly concluded that a specific cause cannot

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Hong Kong Journal of Paediatrics is published by Medcom Ltd, Flat E8, 10/F, Ka Ming Court, 688-690 Castle Peak Road, Kowloon, Hong Kong SAR. Tel: (852) 2578 3833, Fax: (852) 2578 3929, Email: mcl@medcom.com.hk

Indexed in EMBASE/Excerpta Medica, Science Citation Index Expanded (SCIE) and Scopus

Website: www.hkjpaed.org

ISSN 1013-9923

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yet be determined for the majority of birth defects, identified important current gaps in the knowledge, and cautioned on the challenges of primary prevention. In a population-based cohort study, Feldkam et al could only assigned definite causes of birth defects in about 20% of their cases, 94% of these being related to chromosomal and genetic conditions, 4% attributable to teratogens mostly poorly controlled diabetes, and about 1% related to twinning.7

There is no doubt that further studies are required to define the unknown aetiology, which probably involves complex interaction between genetic and environmental factors during the period of conception and early gestation. Congenital heart defects provide an example of how understanding of genetic components of birth defects may impact on clinical outcomes. The major categories of genetic determinants of congenital heart disease including chromosomal abnormalities, copy number variation, and single gene disorders have been related not only to the cardiac phenotypes, but also to survival, neurodevelopmental outcome, and ventricular function.11 At a more mechanistic level, Wang et al have identified two negative autophagy regulators, protein kinase C-α and micro RNA-129-2, which mediate the teratogenicity of hyperglycaemia leading to neural tube defects and that deletion of the Prkca gene, which encodes protein kinase C-α, reverses diabetes-induced autophagy impairment, cellular organelle stress and apoptosis, and leads to reduction of neural tube defect in a rodent model.12 This first demonstration of a gene that plays a role in this birth defect may pave way for new preventive strategies.

We are what we are, we are what we were. The outcome of a newborn is the legacy of what happens to the fetus. The prenatal journey of a fetus is a sequel and destiny of the genetic regulatory pathways, the developmental biology of pluripotent stem cells, and other unknown factors, environmental or otherwise, since the very first moment of life. It is evident from this perspective than the distinction between scientific studies of the gene pathway, developmental biology, and clinical studies of children with birth defects become blurred. Only with the blurring of these boundaries that one could appreciate in the most comprehensive manner how the genetic, developmental, and clinical aspects intertwine and that one can capitalise on the bench discoveries for human use. It is with the blurring of the boundaries between research laboratories and institutions that one can further foster collaborations and enhance synergisms between developmental biologists, geneticists, toxicologists, epidemiologists, infectious disease experts, paediatric surgeons, and paediatricians to tackle the important clinical and public health challenges of birth defects.

YF Cheung
Chief Editor

References
Are There Regionalisation of High Complexity Surgeries and Decentralisation of Outpatient Treatment Services for Cleft Lip and/or Palate in the State of São Paulo, Brazil?

MR Tovani-Palone, A Formenton, SR Bertolini

Abstract

Objective: To investigate the existence of regionalisation of high complexity surgeries and decentralisation of outpatient treatment services for cleft lip and/or palate linked to the Brazilian Unified Health System (Sistema Único de Saúde - SUS) and/or of philanthropic nature in the state of São Paulo, Brazil, during the period between 2000 and 2015. Methods: This was a descriptive and comparative study, comprising searches on the National Register of Health Establishments, National Register of Associations of the PROFIS Network, free access sites and documents on the Internet. Further data were obtained from the Department of Informatics of SUS, by searching with the corresponding codes for surgical treatments of cleft lip and/or palate. Results: According to the National Register of Health Establishments, there are nine centres accredited as specialised in the high complexity treatment for cleft lip and/or palate throughout the state of São Paulo, located in eight cities. Six new centres have been accredited since 2000. Overall, there are 13 associations in the state, and two associations were created in the last 15 years. There is only one nucleus directed to cleft lip and/or palate. Among accredited establishments, a much larger number of Authorisations of Hospital Internment approved for performing high complexity surgeries was observed to the Hospital for Rehabilitation of Craniofacial Anomalies, University of São Paulo. Conclusion: There are indications of centralisation of high complexity surgeries for the treatment of cleft lip and/or palate, while a trend toward decentralisation was observed for outpatient services.

Key words  Cleft lip; Cleft palate; Organisational Policy; Public Health Practice; Regional Health Planning

Introduction

Cleft lip and/or palate (CL/P) are the most common craniofacial malformations affecting humans, with a prevalence of approximately 1:650 live births in Brazil.\(^1\) They present a multifactorial aetiology\(^2,3\) and occur during the embryonic and early fetal periods, due to failures of fusion among facial processes.\(^4\)

The anatomic deformities more frequent are the discontinuity of the lip, alveolar ridge and palate, which require an appropriate rehabilitation program with surgeries and outpatient assistance.\(^1\)

Although there are several treatment protocols for CL/P, the vast majority of them are complex\(^5\) and very expensive.\(^6\) The treatments are often long, that is, from childhood to adulthood, requiring specialised centres with interdisciplinary teams.\(^5\)

At present, Brazil has 28 establishments accredited by the Ministry of Health as specialised in the high complexity treatment for CL/P.\(^7\) Notwithstanding, this treatment remains a great challenge in less developed regions of the country, whether by shortage of centres for craniofacial rehabilitation\(^8\) or unpreparedness of health teams.\(^9\)

Surprisingly, in the state of São Paulo, Brazil, where there are various rehabilitation centres\(^7\) and formation of qualified manpower for the treatment of CL/P, these patients
also face difficulties in obtaining adequate access to health care services.9

The explanation for this may lie in the fact that the professional formation aimed at the treatment for CL/P is restricted to a few professionals. Thus, non-specialised health professionals and those specialised in other fields have little or no knowledge on this matter.9,10

This, in turn, may be related to recurrent failures in health assistance by the Brazilian Unified Health System (Sistema Único de Saúde – SUS) in establishments of medium complexity that are non-specialised for CL/P, and in basic health units located in the cities of residence.9

Moreover, São Paulo is the most populous Brazilian state. It has a population estimated at 44 million people11 and around 68,000 individuals with CL/P.

It is worth mentioning that there are two principles of SUS, regionalisation and decentralisation, which regulate the political-territorial organisation processes of this health system.12

Regionalisation is a political process, which occurs by relationships established among different social actors (governments, organisations, citizens) in a geographic space without restrictions to its administrative limits, with a very significant intergovernmental interdependence. It considers the geographic concentration of high complexity services, differences in population size and political-institutional conditions of different Brazilian states for the development of regional arrangements for health care. Other objectives include the development of strategies and planning tools, integration, management, regulation, and financing of a network of activities and services in the territory.12

Decentralisation is related to the transfer of elements concentrated at the federal level, including the decision-making power, management driven by providers, and financial resources to the states and especially the municipalities. This principle redefines the responsibilities among government entities, highlighting the relevance of subnational executives in the conduct of the health policy.12

From these considerations, it is clear that regionalisation and decentralisation can be very important to improve quality of health services for CL/P. However, there are very few information can be found in the literature about the political-territorial organisation of the treatment services for CL/P offered by SUS and/or free of charge in the state of São Paulo.

Thereby, this study aimed to investigate the existence of regionalisation of high complexity surgeries and decentralisation of outpatient treatment services for CL/P linked to SUS and/or of philanthropic nature in the state of São Paulo, during the period between 2000 and 2015.

Methods

This descriptive and comparative study comprised the identification, location and date of initial accreditation/starting year of existing establishments for the treatment of CL/P in the year 2015 by searches on the National Register of Health Establishments (Cadastro Nacional de Estabelecimentos de Saúde - CNES),7 National Register of Associations of the PROFIS Network,13 free access sites and documents on the Internet. To achieve some data on the starting year of establishments, informational contacts were additionally conducted by phone. The mapping of cities was carried out by searches in the IBGE-Cities database.14

To compare the specialised centres accredited by CNES and to verify the comprehensiveness of these institutions for surgical procedures of high complexity, secondary data extracted from the Department of Informatics of SUS (Departamento de Informática do SUS – DATASUS) were used.15

The surgical procedures chosen were based on the main primary and secondary surgeries performed routinely by the Hospital for Rehabilitation of Craniofacial Anomalies, University of São Paulo, Brazil (Hospital de Reabilitação de Anomalias Craniofaciais da Universidade de São Paulo, Brasil – HRAC/USP). These procedures were correlated with the codes of the Management System of the Table of Procedures, Drugs and OPM of SUS (Sistema de Gerenciamento da Tabela de Procedimentos, Medicamentos e OPM do SUS - Sigtap).16

Surgical routine – HRAC/USP:
• Primary cheiloplasty – 3 months of age;1
• Primary palatoplasty – 12 months of age;1
• Secondary palatoplasty and cheiloplasty – 6 years of age;1
• Secondary alveolar grafting – between 9 and 12 years of age.6,17,18

Surgical procedures and codes of the Sigtap:16
• Unilateral Labiaplasty in two stages: 0404030076;
• Total reconstruction of lip in patient with skull and maxillofacial anomaly: 0404030157;
• Secondary Labiaplasty in patient with skull and maxillofacial anomaly: 0404030122;
• Primary Palatoplasty in patient with skull and maxillofacial anomaly: 0404030106;
• Secondary Palatoplasty in patient with skull and maxillofacial anomaly: 0404030262;
• Alveoloplasty with bone grafting in patients with craniofacial anomaly: 0404030084.

From this, with these procedure codes were performed searches in the periods from January to December 2008
and January to December 2015, based on the number of Authorizations of Hospital Internment (Autorizações de Internação Hospitalar – AIHs) approved for each surgical procedure. The data were tabulated using the TabNet program.15

Moreover, institutions not accredited by CNES as specialised centres for the treatment of CL/P were not included in comparisons regarding AIHs approved for performed surgeries, and in mappings.

This study was approved by the Human Research Ethics Committee of the Federal University of São Paulo (Universidade Federal de São Paulo) (Nº 1481507).

Results

According to the CNES database (Table 1) there are nine centres accredited as specialised in the high complexity treatment for CL/P in the state of São Paulo, located in eight cities. A greater concentration of these institutions was observed in cities located between and along the central region and capital, which have more than half the state’s population.14 Furthermore, the absence of these services in the western, southwest, far south and coast of the state of São Paulo was also verified (Figure 1).

Until the year 2000 there were only three accredited centres. From then on there has been the incorporation of six new centres. The most recent is that of São José do Rio Preto (Table 1).

In view of the total of AIHs approved for performing primary and secondary surgeries for rehabilitation of CL/P in accredited centres, it was verified in 2008 and 2015 a much larger number of approved AIHs to HRAC/USP, followed respectively by the Sobrapar Skull and Face Hospital (Hospital Sobrapar Crânio e Face - SOBRAPAR) and the Clinical Hospital of the Faculty of Medicine of the University of São Paulo (Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo - HCFMUSP). The values found to other institutions were quite low, or even null (Table 2).

In order to assist the shortage of specialised services for CL/P, private non-profit organisations such as associations were created, offering technical assistance directly related to rehabilitation in some specialties, as well as social assistance. The so-called regional nuclei have also been created to provide support for the treatment of CL/P through the provision of outpatient services in the fields of medicine, dentistry, speech therapy, psychology and social work, and thus function as support centres to the rehabilitation process.9

A higher number and better distribution of parents and friends associations compared to accredited centres was verified (Table 3; Figure 2).

Table 1  Specialised treatment centres for CL/P in the state of São Paulo to the year 2015

<table>
<thead>
<tr>
<th>Accredited centres</th>
<th>Cities</th>
<th>Date of initial accreditation</th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNCRAF - Fundação para Estudo e Tratamento das Deformidades Craniofaciais</td>
<td>São Bernardo do Campo</td>
<td>06/2001</td>
</tr>
<tr>
<td>FUNCRAF</td>
<td>Itapetininga</td>
<td>06/2001</td>
</tr>
<tr>
<td>HCFMUSP - Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo</td>
<td>São Paulo</td>
<td>09/2003</td>
</tr>
<tr>
<td>Hospital de Base de São José do Rio Preto</td>
<td>São José do Rio Preto</td>
<td>12/2013</td>
</tr>
<tr>
<td>HRAC/USP- Hospital de Reabilitação de Anomalias Craniofaciais da Universidade de São Paulo</td>
<td>Bauru</td>
<td>09/1993</td>
</tr>
<tr>
<td>Hospital São Paulo - Hospital de Ensino Unifesp</td>
<td>São Paulo</td>
<td>01/1997</td>
</tr>
<tr>
<td>Santa Casa de Araraquara</td>
<td>Araraquara</td>
<td>11/2007</td>
</tr>
<tr>
<td>Santa Casa de Piracicaba</td>
<td>Piracicaba</td>
<td>12/2001</td>
</tr>
<tr>
<td>SOBRAPAR- Hospital Sobrapar Crânio e Face</td>
<td>Campinas</td>
<td>09/1993</td>
</tr>
<tr>
<td><strong>Total: 9</strong></td>
<td><strong>Total: 8</strong></td>
<td></td>
</tr>
</tbody>
</table>

Source: Adapted from CNES - Habilitations 0401.7
Over the past 15 years there has been the creation of two new associations in the state. However, there is only one nucleus directed to CL/P, located in Ribeirão Preto (Table 3).

There are also other institutions for the treatment of CL/P in the state of São Paulo, such as Hospital Municipal Infantil Menino Jesus and Hospital Guilherme Álvaro, located respectively in the cities of São Paulo e Santos. They are not accredited by CNES as specialised centres for the treatment of CL/P, but offer medium and/or high complexity treatments.29,30

Discussion

The interdisciplinary teams that work in the rehabilitation of CL/P continuously face the psychological, aesthetic and functional implications inherent in this type of malformation. The treatment is highly specialised, requiring teams with professionals from different health fields and integral care for achieving success.31 Moreover, serious problems for integral care of individuals with CL/P are the geographical distance and the long duration of treatment for most of the cases, with a very expensive cost especially for the lower social class individuals.32

According to the results of this study, from 2000 there was a significant increase in the number of high complexity specialised centres for the treatment of CL/P in the state of São Paulo, with geographic distribution mainly in regions with high population density. Thus, it is worth mentioning that there were initiatives aiming at the regionalisation of these centres, what is in principle of eminent importance, taking as base the large area of this state, equivalent to 95,839,190 mi².33

In addition, another data evaluated in this research was the number of AIHS approved for performing of high complexity surgeries for the treatment of CL/P in 2008 and 2015. In this item, HRAC/USP presented a much larger number, compared to the other accredited institutions. Also, it should be noted that, this treatment centre is located in Bauru, where there is a lower population concentration than in other regions, such as in Campinas and the state capital itself.14 Consequently, a greater centralisation of high complexity surgeries in HRAC/USP is suggested.

This can be related to the fact that HRAC/USP is the largest treatment centre for craniofacial anomalies in South America and a world class reference in the treatment of CL/P. It performs all the surgical and outpatient care required for full rehabilitation of individuals with CL/P, especially in the high and medium complexity care levels.

Figure 1  Mapping of cities with centres accredited for the treatment of CL/P in the state of São Paulo.
Source: Adapted from IBGE- Cities14 and Wikipedia.19
Other important characteristics are its humanistic philosophy, vast experience and the development of relevant researches in the field of CL/P.\(^1,34\) In addition, HRAC/USP serves patients from all regions of Brazil and others arising from abroad,\(^1\) so that such amount of performed surgical procedures does not reflect in the attendance only of patients from the state of São Paulo.

SOBRAPAR and HCFMUSP, in turn, presented considerably smaller numbers of approved AIHs compared to HRAC/USP. However, they also acts as important centres for performing of these surgeries in the state of São Paulo.

With the exception of HRAC/USP, SOBRAPAR and the accredited centres of the Foundation for Study and Treatment of Craniofacial Deformities (Fundação para Estudo e Tratamento das Deformidades Craniofaciais - FUNCRAF), the other accredited centres provide assistance for the treatment of several other diseases.\(^35\) Three of these institutions performed these surgeries in much smaller scale. Furthermore, some institutions not accredited by CNES as specialised centres for the treatment of CL/P also offer surgical treatments for CL/P,\(^29,30\) and may contribute to performing of these surgeries in the state of São Paulo.\(^15\)

In view of the above, it should be emphasized that, there may be benefits associated when the regionalisation of surgeries for craniofacial treatment involve only centres of excellence, such as HRAC/USP.\(^34,36\) In localities as this, there is probably better surgical results, reduction of operative and postsurgical mortality, reduction of the time

### Table 2  AIHs approved for surgical procedures performed by specialised treatment centres for CL/P in the state of São Paulo from January to December 2008 and January to December 2015

<table>
<thead>
<tr>
<th>Accredited centres - 2008</th>
<th>Cheiloplasty</th>
<th>Palatoplasty</th>
<th>Alveolar Grafting</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNCRAF - São Bernardo do Campo</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>FUNCRAF - Itapetininga</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>HCFMUSP</td>
<td>9</td>
<td>-</td>
<td>15</td>
<td>31</td>
</tr>
<tr>
<td>HRAC/USP</td>
<td>-</td>
<td>115</td>
<td>364</td>
<td>862</td>
</tr>
<tr>
<td>Hospital São Paulo - Hospital de Ensino Unifesp</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Santa Casa de Araraquara</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Santa Casa de Piracicaba</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>SOBRAPAR</td>
<td>27</td>
<td>-</td>
<td>57</td>
<td>104</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Accredited Centres - 2015</th>
<th>Cheiloplasty</th>
<th>Palatoplasty</th>
<th>Alveolar Grafting</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNCRAF - São Bernardo do Campo</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>FUNCRAF - Itapetininga</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>HCFMUSP</td>
<td>4</td>
<td>3</td>
<td>5</td>
<td>31</td>
</tr>
<tr>
<td>São José do Rio Preto - Hospital de Ensino Unifesp</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>HRAC/USP</td>
<td>55</td>
<td>106</td>
<td>82</td>
<td>427</td>
</tr>
<tr>
<td>Hospital São Paulo - Hospital de Ensino Unifesp</td>
<td>2</td>
<td>-</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Santa Casa de Araraquara</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Santa Casa de Piracicaba</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>SOBRAPAR</td>
<td>52</td>
<td>-</td>
<td>29</td>
<td>42</td>
</tr>
</tbody>
</table>

ULTS=Unilateral Labiaplasty in two stages; TRL=Total reconstruction of lip; SL=Secondary Labiaplasty; PP=Primary Palatoplasty; SP=Secondary Palatoplasty.

Source: DATASUS.\(^{15}\)
of stay in hospitals and greater access to provide more comprehensive care, due to the multidisciplinarity and interdisciplinarity character of the teams working for this purpose.\textsuperscript{36} This is quite relevant because work performed well does not generate further work, readmissions and so many other unnecessary procedures.

Another point is that, there are also problems in the work process and organisation of the reference and counter-reference system that impede the continuation of the treatment of individuals with CL/P. The treatment is frequently fragmented, with focuses on healing practices and restricted to specialised centres in the field.\textsuperscript{32}

Thus, ideally, insofar as specialised professionals are not required in all locations, but all individuals with CL/P should have access to the specialists and equipment when needed; the patients should, then, be forwarded from a service that performs certain healthcare to another more complex when required (reference), that is, in treatments requiring different levels of attention as in the case of CL/P. When the requested treatment has been performed, the patient should then be redirected back to the health service of origin (counter-reference) with a lower complexity.\textsuperscript{32}

A further problem is that there is unpreparedness of the public health services or even total ignorance of professionals regarding the care of monitoring and maintenance, even if basic, for these individuals in primary and secondary attention, not specific for CL/P.\textsuperscript{9} The cause may be directly related to the absence of this theme in the curriculums of undergraduate and postgraduate courses in health across the country. It is worth highlighting that, at postgraduate level, only HRAC/USP offers effective and humanised courses about CL/P, whether as an improvement, specialisation, master's, doctoral or postdoctoral.\textsuperscript{1}

In this context, associations and nuclei for the treatment of CL/P are very important, because in addition to providing knowledge of the peculiarities of CL/P and of the

### Table 3

<table>
<thead>
<tr>
<th>Associations</th>
<th>Cities</th>
<th>Starting year</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFIPP - Associação de Apoio ao Fissurado Lábio Palatal de Presidente Prudente e Região</td>
<td>Presidente Prudente</td>
<td>2000</td>
</tr>
<tr>
<td>AAFLAP - Associação de Apoio aos Fissurados Lábio Palatais</td>
<td>São José dos Campos</td>
<td>1987</td>
</tr>
<tr>
<td>AFISC- Associação de Apoio aos Fissurados Lábio Palatais de São Carlos</td>
<td>São Carlos</td>
<td>1984</td>
</tr>
<tr>
<td>APAFI-MC - Associação de Pais e Amigos dos Portadores de Fissuras Lábio Palatais de Mogi das Cruzes</td>
<td>Mogi das Cruzes</td>
<td>1993</td>
</tr>
<tr>
<td>PROFIS - Associação de Promoção do Fissurado Lábio Palatal</td>
<td>Catanduva</td>
<td>1992</td>
</tr>
<tr>
<td>ADAF - Associação dos Deficientes Auditivos e Fissurados</td>
<td>Ribeirão Preto</td>
<td>1995</td>
</tr>
<tr>
<td>ADAP - Associação dos Deficientes Auditivos, Pais, Amigos e Usuários de Implante Coclear</td>
<td>Bauru</td>
<td>1998</td>
</tr>
<tr>
<td>AFISSORE - Associação dos Fissurados Lábio-Palatais de Sorocaba e Região</td>
<td>Sorocaba</td>
<td>1989</td>
</tr>
<tr>
<td>AFISFRAN - Associação dos Fissurados de Franca</td>
<td>Franca</td>
<td>1993</td>
</tr>
<tr>
<td>CAI - Centro de Amparo e Proteção à Infância São Francisco de Assis</td>
<td>São Paulo</td>
<td>1986</td>
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<td>Bauru</td>
<td>1975</td>
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<tr>
<td>Recém Sorrindo</td>
<td>Pindamonhangaba</td>
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</table>

**Total: 13**

<table>
<thead>
<tr>
<th>Nucleus</th>
<th>City</th>
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</thead>
<tbody>
<tr>
<td>NADEF - Núcleo de Assistência à Pessoa com Deficiência</td>
<td>Ribeirão Preto</td>
<td>1994</td>
</tr>
</tbody>
</table>

**Total: 1**

Source: PROFIS Network,\textsuperscript{13} Metamorfis,\textsuperscript{20} AFIPP,\textsuperscript{21} AAFLAP,\textsuperscript{22} Municipal Prefecture of São Carlos,\textsuperscript{23} APAFI-MC,\textsuperscript{24} ADAP,\textsuperscript{25} AFISSORE,\textsuperscript{26} PROFIS-Bauru,\textsuperscript{27} Recém Sorrindo,\textsuperscript{28} contacts by telephone.
rehabilitation process to patients and families, many of them have their own supplementary assistance services in 11 cities spread in several regions of the state. However, there is not the availability of all ancillary services for primary and medium complexity care in all units, not even a broad coverage to the demand for treatment. Moreover, the state of São Paulo has one regional nucleus, which together with the associations and other institutions not accredited by CNES as specialised centres for the treatment of CL/P may contribute to the decentralisation of outpatient treatment services for CL/P in this state.

It should be noted also that the accredited centres of FUNCRAF do not perform high complexity surgical procedures, such as primary and secondary surgeries for CL/P. They correspond to outpatient units of high and medium complexity care and primary care under the responsibility of FUNCRAF, which are designed to minimise the problem of displacement and long trips of patients and contribute to the continuity of the treatment. Their current locations in the state of São Paulo are in the cities of Itapetininga and São Bernardo do Campo.

Furthermore, decentralisation to health units of SUS including both the basic and the specialised assistance that are non-specific for CL/P, as is the case of the Medical Ambulatories of Specialties (Ambulatórios Médicos de Especialidades) and Centres of Dental Specialties (Centros de Especialidades Odontológicas) existing in the state of São Paulo, would be possible to be carried out, since improvements were incorporated into the reference and counter-reference system, as well as to the expansion of theoretical/practical basic training courses on additional peculiarities of these anomalies for health teams.

**Limitations of the Study**

The accredited centres can have used other procedures codes for cheiloplasty, palatoplasty and alveolar grafting performed, which were not included in this research. We therefore can not make any kind of statement about the exact total number of surgeries performed in each institution, limiting us only at inform the number of AIHs approved available on the DATASUS database for performed surgeries whose procedure codes were used in our searches.

Further studies should be carried out to verify the feasibility or not to the current political-territorial organisation of the surgical and outpatient services for CL/P in the state of São Paulo.
Conclusion

Despite the creation of new specialised centres for the treatment of CL/P in the state of São Paulo, there are still indications of the occurrence of centralisation of high complexity surgeries for the treatment of CL/P, which are performed mostly by the Hospital for Rehabilitation of Craniofacial Anomalies, University of São Paulo, while for outpatient services a trend toward decentralisation was observed.

The matter regarding CL/P should be incorporated in the curriculum of undergraduate health field courses. The training courses for SUS professionals need to be expanded to decentralise part of the activities of CL/P for basic health units and specialised health centres that are non-specific in this field. Thus, confirming the improvement in the quality of life of patients and their families with lower costs to them as well as the government.

Note

All words in italics are written in Portuguese.

Declaration of Interest

The authors report no declaration of interest.

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aaflap.org.br/


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Abstract

Objective: To examine the perinatal characteristics, associated anomalies and clinical outcomes of newborns with omphalocele admitted to Queen Mary Hospital (QMH), Hong Kong during a 10-year period. Methods: We identified all newborns with omphalocele who were admitted to the neonatal intensive care unit at QMH from 2005 to 2014. Maternal and patient demographic data, associated anomalies and outcome data were reviewed retrospectively. Results: A total of 19 infants with omphalocele were identified. Median gestational age at birth was 38 weeks with a median birth weight of 3140 g. Fifty-three percent (10/19) were diagnosed with at least 1 other anomaly, with congenital heart defect being the most common associated anomaly. Median age at first operation (either primary closure or application of silo) was on day 1 of life, with delayed closure in staged operations being carried out at a median age of 8 days. Infants with non-liver containing omphaloceles were more likely to have primary repair compared to those with liver-containing ones (7/8 [88%] vs. 4/11 [36%], p=0.03). Overall survival rate at discharge was 84% (16/19). Two out of 3 cases died of lethal congenital anomaly (alveolar capillary dysplasia) while the other one suffered from postoperative midgut volvulus. Postoperative complications occurred in 6 patients (6/17 [35%]), with ventral hernia being the most common complication. Long-term medical problems including failure to thrive (6/12 [50%]), gastroesophageal reflux (5/12 [42%]), developmental delay (3/12 [25%]) and recurrent lung infections (1/12 [8%]) were identified. Conclusions: Associated anatomic and genetic anomalies are common in omphalocele. Postnatal workup should include screening of these anomalies. Prognoses for isolated omphaloceles with no major postoperative complications are good in the long-term.

Key words

Hong Kong; Omphaloceles; Outcome

Introduction

Omphalocele, a rare congenital abdominal wall defect (Figure 1), has an estimated prevalence of 1 per 3000-4000 live births. It has a high co-occurrence with other congenital anatomical or genetic anomalies. Survival rates of infants with omphalocele vary depending on the presence or absence of these associated anomalies. The purpose of our study is to review the perinatal characteristics, associated anomalies and clinical outcomes of omphalocele at a tertiary neonatal intensive care unit managing neonates with surgical problems in Hong Kong.
Methods

Study Cohort

All newborns diagnosed with omphalocele that were admitted to the neonatal intensive care unit at Queen Mary Hospital (QMH) were identified using the Clinical Data Analysis Reporting System (CDARS) from 1st January 2005 to 31st December 2014, using International Classification of Disease (ICD-9) coding number 756.7 for omphalocele. Cases included newborns that were born at our hospital or babies that were born at other hospitals and being transferred to us postnatally for further management. For cases with antenatal follow-up at our hospital, paediatric surgeon will be consulted and counselling will be given during antenatal follow-up. We collected both maternal and infant data including: gestational age (GA), birth weight, sex, mode of delivery, Apgar score (AS) at 5 minutes, concomitant diagnoses, age in days at first feeding, mechanical ventilation, any presence of pulmonary hypertension, total length of hospitalisation, and survival at discharge. Data were retrospectively collected and obtained from the medical records.

Definitions

Anomalies including omphalocele were diagnosed by the treating neonatologists. An omphalocele containing the liver is defined as a giant omphalocele. We classified anomalies as major congenital anomalies involving the cardiovascular, pulmonary, renal, gastrointestinal and genetic system. We defined first day of enteral feedings as the first day of life an infant received any type or amount of enteral nutrition. Duration of mechanical ventilation was defined as the total duration of mechanical ventilation (conventional or high-frequency) during the hospitalisation. Pulmonary hypertension was diagnosed by echocardiogram. Pulmonary hypoplasia was defined by the presence of narrow elongated chest and caudal declination of ribs on chest radiograph. Diaphragmatic dysfunction was documented using ultrasonography of diaphragmatic movement.

Statistical Analysis

The Fisher’s exact test was used and a two-tailed p value of less than 0.05 was considered to be statistically significant.

Results

We identified 19 infants with omphalocele during the 10-year study period. Majority of cases (15/19 [80%]) were known antenatally. Median maternal age was 34 years. Infants were born with a median GA of 38 weeks with a median birth weight of 3140 g. There was a female predominance with male to female ratio of 1:1.7. Majority of cases (14/19 [74%]) were born via Caesarean section with a good AS at 5 min of life (all cases with AS ≥8). The decision for Caesarean section was dictated by obstetric indications only (independent on the presence of omphalocele). There was no rupture of omphalocele sac during spontaneous vaginal delivery. Twenty-one percent (4/19) required intubation at birth (Table 1).

Eleven out of 19 cases were giant omphalocoeles (vs 8 non-liver containing omphalocoeles). The mean diameter of the abdominal wall defect was 5 cm. Associated anomalies were documented in 10 out of 19 infants (53%), among which congenital heart disease were identified most frequently (Table 2). Only one infant was diagnosed with >1 anomaly (gastrointestinal and renal anomalies).

Surgery was done in 17 cases (89%). Two patients died before surgery due to respiratory failure as a result of alveolar capillary dysplasia (ACD). Primary closure was achieved in 11 cases, while staged procedures (application of silo to the abdominal wall defect followed by delayed closure [Figure 2]) were carried out in 6 cases (Table 3).
Median age at first operation (either primary closure or application of silo) was on day 1 of life, while delayed closure in staged operations was carried out at a median age of 8 days of life (range 7 to 9 days of life). Infants with non-liver containing omphaloceles were more likely to have primary repair compared to those with liver-containing ones (7/8 [88%] vs. 4/11 [36%], *p*=0.03). First feeds were started at a median postnatal age of 8 days.

A total of 4 infants were diagnosed with pulmonary hypertension, 2 cases received both inhaled nitric oxide and sildenafil as pulmonary vasodilating agents. These 2 cases were subsequently diagnosed to have ACD as post-mortem finding. Pulmonary hypoplasia and diaphragmatic dysfunction were diagnosed in 26% (5/19) and 11% (2/19) infants respectively. Giant omphaloceles were more likely to have pulmonary hypoplasia compared with non-giant types (*p*=0.04). Median duration of mechanical ventilation was 4 days (mean duration of mechanical ventilation for giant omphaloceles was 17.5 days vs 1 day for non-liver containing omphaloceles).

Overall survival rate at discharge was 84% (16/19). Survival rate at discharge was 100% for isolated omphalocele without other congenital anomalies. Mortality rate for giant omphalocele was 18% (2/11). Two cases died on day 1 and day 15 of life as a result of the lethal pulmonary condition of ACD. One case died on day 50 of life because of midgut volvulus due to intra-abdominal adhesion requiring massive small bowel resection. The median length of hospitalisation among survivors was 23 days (range 7 days to 1 year and 4 months). Majority of patients (12/16 [75%]) can be discharged within the first 60 days of life (range 7 days to 54 days).

Table 1  Demographics

<table>
<thead>
<tr>
<th></th>
<th>N = 19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>7 (37%)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Chinese</td>
<td>15 (79%)</td>
</tr>
<tr>
<td>White</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (16%)</td>
</tr>
<tr>
<td>Inborn</td>
<td>16 (84%)</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>14 (74%)</td>
</tr>
<tr>
<td>5-minute Apgar</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>3 (16%)</td>
</tr>
<tr>
<td>9-10</td>
<td>16 (84%)</td>
</tr>
<tr>
<td>Intubation at birth</td>
<td>4 (21%)</td>
</tr>
</tbody>
</table>

Table 2  Associated anomalies

<table>
<thead>
<tr>
<th></th>
<th>N = 19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac</td>
<td>5 (26%)</td>
</tr>
<tr>
<td>Venticular septal defect (VSD)</td>
<td>2</td>
</tr>
<tr>
<td>Atrial septal defect (ASD)</td>
<td>1</td>
</tr>
<tr>
<td>Patent Ductus Arteriosus (+ VSD)</td>
<td>1</td>
</tr>
<tr>
<td>Double-outlet right ventricle (DORV)</td>
<td>1</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>Alveolar capillary dysplasia (ACD)</td>
<td>2</td>
</tr>
<tr>
<td>Renal</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>Duplex kidney</td>
<td>1</td>
</tr>
<tr>
<td>Vesicoureteric reflux</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Imperforate anus, common cloaca</td>
<td>1</td>
</tr>
<tr>
<td>Genetic</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Beckwith-Wiedemann syndrome (BWS)</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 3  Operation

<table>
<thead>
<tr>
<th>Type of omphalocele</th>
<th>N = 19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-liver containing</td>
<td>8 (42%)</td>
</tr>
<tr>
<td>Primary closure</td>
<td>7</td>
</tr>
<tr>
<td>Died before operation</td>
<td>1</td>
</tr>
<tr>
<td>Liver-containing</td>
<td>11 (58%)</td>
</tr>
<tr>
<td>Primary closure</td>
<td>4</td>
</tr>
<tr>
<td>Silo followed by delayed closure</td>
<td>6</td>
</tr>
<tr>
<td>Died before operation</td>
<td>1</td>
</tr>
</tbody>
</table>

Figure 2  Staged repair of omphalocele.
Postoperative complications occurred in 6 patients (6/17 [35%]), with ventral hernia being the most common complication (total 3 cases with ventral hernia, 2 out of 3 cases underwent primary repair, 1 out of 3 cases with staged operation) (Table 4). Among the 16 survivors, 4 patients were lost to long-term follow up. Median duration of follow up was 5 years and 4 months (range 10 months to 10 years and 2 months). Long-term medical problems including failure to thrive (6/12 [50%]), gastroesophageal reflux (5/12 [42%]), developmental delay (3/12 [25%]) and recurrent lung infections (1/12 [8%]) were identified (Table 5). Clinical characteristics and outcomes of our case series were summarised in Table 6.

### Table 6  Summary of case series with omphalocele

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Type of omphalocele</th>
<th>Associated anomalies</th>
<th>Type of operation</th>
<th>Postoperative complications</th>
<th>Long-term complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>Non-liver containing</td>
<td>No</td>
<td>Primary repair</td>
<td>Nil</td>
<td>No long-term follow-up</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>Non-liver containing</td>
<td>BWS</td>
<td>Primary repair</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>Giant</td>
<td>VSD</td>
<td>Staged</td>
<td>Hernia</td>
<td>GER, FTT, developmental delay</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>Giant</td>
<td>VSD, PDA</td>
<td>Staged</td>
<td>Nil</td>
<td>GER, FTT</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>Giant</td>
<td>VSD</td>
<td>Staged</td>
<td>Wound infection</td>
<td>GER, FTT</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>Non-liver containing</td>
<td>No</td>
<td>Primary repair</td>
<td>Hernia</td>
<td>Developmental delay</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>Non-liver containing</td>
<td>Imperforate anus, common cloaca, duplex kidney</td>
<td>Primary repair</td>
<td>Adhesion</td>
<td>No long-term follow-up</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>Giant</td>
<td>No</td>
<td>Staged</td>
<td>Nil</td>
<td>FTT</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>Non-liver containing</td>
<td>ACD</td>
<td>Passed away before operation</td>
<td>N/A</td>
<td>N/A (passed away)</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>Giant</td>
<td>ASD</td>
<td>Staged</td>
<td>Nil</td>
<td>GER, recurrent lung infections, FTT, developmental delay</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>Giant</td>
<td>No</td>
<td>Primary repair</td>
<td>Hernia</td>
<td>Nil</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>Giant</td>
<td>Vesicoureteric reflux</td>
<td>Primary repair</td>
<td>Nil</td>
<td>FTT</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>Giant</td>
<td>No</td>
<td>Primary repair</td>
<td>Nil</td>
<td>GER</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>Giant</td>
<td>No</td>
<td>Staged</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>Non-liver containing</td>
<td>No</td>
<td>Primary repair</td>
<td>Nil</td>
<td>No long-term follow-up</td>
</tr>
<tr>
<td>16</td>
<td>F</td>
<td>Giant</td>
<td>DORV</td>
<td>Primary repair</td>
<td>Adhesion, midgut volvulus</td>
<td>N/A (passed away)</td>
</tr>
<tr>
<td>17</td>
<td>F</td>
<td>Non-liver containing</td>
<td>No</td>
<td>Primary repair</td>
<td>Nil</td>
<td>No long-term follow-up</td>
</tr>
<tr>
<td>18</td>
<td>M</td>
<td>Non-liver containing</td>
<td>No</td>
<td>Primary repair</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>19</td>
<td>M</td>
<td>Giant</td>
<td>ACD</td>
<td>Passed away before operation</td>
<td>N/A</td>
<td>N/A (passed away)</td>
</tr>
</tbody>
</table>

BWS: Beckwith-Wiedemann syndrome; VSD: Ventricular septal defect; PDA: patent ductus arteriosus; ACD: alveolar capillary dysplasia; ASD: Atrial septal defect; GER: gastroesophageal reflux; FTT: failure to thrive; DORV: double-outlet right ventricle

### Table 4  Postoperative complications

<table>
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<tr>
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</thead>
<tbody>
<tr>
<td>Hernia</td>
<td>3 (18%)</td>
</tr>
<tr>
<td>Adhesion</td>
<td>2 (12%)</td>
</tr>
<tr>
<td>Wound infection</td>
<td>1 (6%)</td>
</tr>
</tbody>
</table>

### Table 5  Long-term complications

<table>
<thead>
<tr>
<th></th>
<th>N = 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure to thrive (FTT)</td>
<td>6 (50%)</td>
</tr>
<tr>
<td>Gastroesophageal reflux (GER)</td>
<td>5 (42%)</td>
</tr>
<tr>
<td>Developmental delay</td>
<td>3 (25%)</td>
</tr>
<tr>
<td>Recurrent lung infections</td>
<td>1 (8%)</td>
</tr>
</tbody>
</table>
**Discussion**

We described the perinatal characteristics, associated anomalies and outcomes of a cohort of infants with omphalocele from a 10-year period. In previously reported population-based studies, the occurrence of omphalocele appears to be more common in women at the extremes of reproductive age (<20 or >40 years of age).\(^2\) Such observation was not detected in our study. The incidence of omphalocele in Hong Kong is not available as we are only one of the neonatal surgical units receiving cases in Hong Kong, and we do not have the number of prenatal cases and deliveries in other referring hospitals. There were a total of 15 cases of termination of pregnancies (TOP) and 3 spontaneous miscarriages related to omphalocele (with or without other congenital anomalies) during the study period (unpublished data obtained from personal communication with Dr. A Kan, Tsang Yuk Hospital Prenatal Diagnostic Clinic).

The proportion of neonates with co-occurring anomalies in our study (53%) was in range of other studies.\(^3,4\) Our finding that ventricular septal defects, atrial septal defects and patent ductus arteriosus were the most common congenital heart defects associated with omphalocele is also consistent with others.\(^5\) However, in this study we find a higher incidence of ACD, which is not reported in other studies. The need for use of both inhaled nitric oxide and sildenafil to manage refractory pulmonary hypertension should raise the clinical suspicion of ACD. Only one case (1/19 [5%]) was confirmed to have genetic disease (Beckwith-Wiedemann syndrome) in our series, this proportion is lower than other studies in the existing literature (15-17%).\(^5,6\) A smaller proportion of cases with underlying genetic condition in our study population is probably related to the fact that more parents opted for TOP when genetic conditions were diagnosed antenatally. During the study period, 8 fetuses with omphalocele were diagnosed to have chromosomal abnormalities and subsequently underwent termination of pregnancy or spontaneous miscarriage (unpublished data obtained from personal communication with Dr. A Kan, Tsang Yuk Hospital Prenatal Diagnostic Clinic).

The overall survival rate at discharge in our study was 84%, with 100% survival rate among isolated cases, which is comparable to other international studies.\(^5,6\) Mortality in our series were mainly contributed to the presence of lethal associated congenital anomalies i.e. ACD and major postoperative complication i.e. midgut volvulus resulting in massive gut resection with short gut syndrome not compatible with life. Majority of patients (12/16 [75%]) can be discharged within the first 60 days of life. Causes of prolonged length of hospitalisation included chronic lung disease secondary to lung hypoplasia, heart failure due to underlying congenital heart condition or social reason (await placement). With absence of associated anatomic/chromosomal anomalies and major surgical complications, the prognosis of infants with omphaloceles is favourable in the long term.

The data obtained from this study provide an important local source of information for the antenatal and postnatal counselling of parents whose infants were diagnosed to have omphaloceles. However, the data were collected from one single centre in Hong Kong with a small number of subjects only, rather than from population-based data, making establishment of statistically significant results difficult. We also did not have comprehensive data on the antenatal finding of omphalocele especially on the measurement of ratios e.g. fetal head circumference or abdominal circumference to size of omphalocele defect, to correlate with postnatal outcomes. We could overcome the forementioned limitations by establishing a territory-based registry including all cases in Hong Kong and having more collaboration with our obstetricians on the antenatal evaluation of omphaloceles.

**Declaration of Interest**

None.

**References**

Risk Factors Associated with General Movement Quality in Infants

L MA, LD MENG, YH CHEN, MJ YI, JW WANG, AH CAO

Abstract

Background: The quality of general movements assessment, used to assess individual infant from birth to 20 weeks of age, has emerged as one of the most reliable and valid predictors of severe neurological impairments. Aim: To investigate the risk factors for the quality of general movements, which is a predictive value for brain dysfunction in infants. Method: 618 cases at the stage of writhing movements and 539 cases at the stage of fidgety movements were selected for assessment of the quality of general movements. The risk factors for the quality of general movements in infants were analysed by ANOVA, chi-square test, and multivariate logistic regression. Results: Multivariate logistic regression analysis showed that the factors that were significantly correlated with the quality of general movements at the stage of writhing movements included delivery gestational age (OR=0.762, P<0.001), birth weight (OR=0.264, P<0.001), severe asphyxia (OR=2.445, P=0.012), and intrauterine distress (OR=4.865, P<0.001). The factors that were significantly correlated with the quality of general movements at the stage of fidgety movements were delivery gestational age (OR=0.786, P=0.003), birth weight (OR=0.217, P<0.001), severe asphyxia (OR=3.765, P=0.001), and hyperbilirubinaemia (OR=2.640, P=0.028). Conclusions: Low delivery gestational age, low birth weight, severe asphyxia, hyperbilirubinaemia and intrauterine distress are risk factors and predictors for abnormal general movements in infants.

Key words
Fidgety movements; General movements; Infant; Risk factor; Writhing movements

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Received December 20, 2016
Introduction

Prechtl’s general movements (GMs) assessment, the best functional method to predict cerebral palsy (CP) in high-risk infants, can most reliably predict CP in high-risk infants with a reported sensitivity of 98% (95% confidence interval, CI 74-100%) and specificity of 91% (95% CI 83-93%). The presence of poor repertoire (PR) at 1 month post-term seemed to predict lower neurodevelopmental scores at two years, especially in the domain of eye and hand coordination. Abnormal fidgety (AF) movement is an early marker for complex minor neurological dysfunction at puberty. The presence of cramped synchronised (CS) general movements during preterm and term age and the absence of fidgety (F) movements are strong predictors for later CP diagnosis. A 2004 report concluded that 70 to 80% of CP cases are due to prenatal factors and that birth asphyxia plays a relatively minor role (<10%). The major risk factors for CP during pregnancy include advanced maternal age (≥35 years), multiple pregnancy, medicine use in early pregnancy, harmful environment, recurrent vaginal bleeding during pregnancy, pregnancy-induced hypertension, and intrauterine growth retardation. Kaandorp and Kieviet also found that premature delivery, low birth weight, and asphyxia of newborn are independent risk factors of CP. The risks correlated with preterm birth increase as delivery gestational age decreases, and vulnerability remains in preterm infants. The prevalence of developmental delay for preterm infants is two-fold compared with full term infants, and the cognitive outcomes are slightly lower in intelligence quotient (IQ) and poorer in neurodevelopmental, as well as psychomotor outcomes. Several studies have reported the effects of asphyxia on the quality of GMs. The infants with abnormal GMs can receive scientific, reasonable treatment at an early stage, which may promote healthy development of the children.

Methods

This was a prospective study, conducted at Qilu Hospital of Shandong University, the Affiliated Hospital of Qingdao University and Union Hospital of Fujian Medical University in China, aimed to investigate the risk factors that affect the quality of general movements. The inclusion criteria were as follows: all infants born in participating obstetrics clinics, ranging from 3 days after birth to 15 weeks of corrected age. The exclusion criteria were as follows: infants died from a disease during the study, had central nervous system infection, genetic and metabolic disease, chromosomal disease, congenital abnormality, brain malformation, tumours of the central nervous system, and whose mother could not recall when the last period took place.

A total of 618 infants born in obstetrics clinics between October 2011 and December 2014 and had follow-up visits in the clinic were studied. All 618 cases were evaluated at the stage of writhing movements among them, 539 out of 618 cases were evaluated at the stage of fidgety movements, and the rest of 79 cases lost contact at the fidgety movement stage. The minimum delivery gestational age was 28 weeks and 6 days, whereas the maximum was 41 weeks and 4 days. The lowest and highest birth weights were 970 g and 4110 g, respectively. Three hundred twenty-nine out of 618 cases at the writhing movement stage were boys and the rest of 289 were girls. The mean delivery gestational age was 34.23±2.7 weeks and the mean birth weight was 2.92±0.54 kg. At the fidgety movement stage, 281 boys and 258 girls were included. The mean delivery gestational age was 34.15±2.43 weeks and the mean birth weight was 2.90±0.57 kg. Based on the results of GMs, 618 cases were divided into normal writhing movement group (n=408), poor repertoire group (n=167), and cramped-synchronised group (n=43) at the writhing age. At the fidgety age, 539 cases were divided into the normal fidgety movement group (n=501), abnormal fidgety movements group (n=16), and absence of fidgety movement group (n=22).

The risk factors were investigated and registered. The database was established. Values were assigned to the variables, and the data were analysed using statistical software. Twenty perinatal factors that could be correlated with GMs were collected. Asphyxia, which refers to no spontaneous breathing or respiratory depression after birth, leading to hypoxaemia, hypercapnia and metabolic acidosis, is an important cause of neonatal death and disability in children. Severe asphyxia meets the diagnostic criteria: (1) Profound metabolic or mixed academia (PH<7.00) on an umbilical cord arterial blood sample, if obtained; (2) An Apgar score of 0 to 3 for longer than 5 minutes; (3) Neonatal neurologic manifestations, such as, seizures, coma, or hypotonia; (4) Multisystem organ dysfunctions, for example, cardiovascular, gastrointestinal, haematologic, pulmonary, or renal system. Fetal distress, life-threatening health syndrome due to hypoxia and acidosis of the fetus in utero, is an important cause of neonatal asphyxia and even death. The fetal distress can be displayed with two or more of the following factors.
symptoms: (1) abnormal fetal movement, for example first increased fetal movement, and then decreased movement; (2) fetal heart rate monitoring: no stress test (NST) is non-reactive type, frequently late decelerations or decreased variability in the fetal heart rate; (3) the fetal heart rate $\geq 160$ bpm or $\leq 120$ bpm; (4) too little amniotic fluid, with amniotic fluid index (AFI) $\leq 50$ mm. Hyperbilirubinaemia was defined as a total serum bilirubin level of $>220.6$ µmol/L in mature birth, TSB$>256.5$ µmol/L in premature delivery.

Birth weight of less than 2500 g was considered as low birth weight. Low gestational age was defined as less than 37 weeks. Hyperbilirubinaemia was defined as a total serum bilirubin level of $>220.6$ µmol/L in mature birth, TSB$>256.5$ µmol/L in premature delivery.

### Assessment of GMs

GMs can be observed in fetuses as young as 9 weeks of postmenstrual age. In infants without neurological dysfunction, GMs continue in a similar pattern until about the end of the second month postterm, which is then followed by a gradually emerging new GMs pattern.

Normal GMs are gross movements, involving the whole body. They may last from a few seconds to several minutes or longer. What is particular about them is the variable sequence of arm, leg, neck and trunk movements. Their intensity, force and speed increase and decrease, and they have a gradual beginning and end. The majority of sequences of extension and flexion movements of arms and legs is complex, with superimposed rotations and often slight changes in direction of the movement. These added components make the movements fluent and elegant and create the impression of complexity and variability.

During term age and during the first postterm months, GMs are commonly referred to as writhing movements. The best observing time for writhing movements was from the 3rd day after birth to corrected age of 4 weeks (according to the expected date of delivery). GMs of a writhing pattern are characterised by small to moderate amplitude and by slow to moderate speed. Fast and large extensor movements may occasionally break through, particularly in the arms. Typically, such movements are elliptical in form; this component creates the impression of a writhing character of movement.

Types of abnormal GMs during preterm, term and early postterm ages are:

1. Poor repertoire of GMs (PR): A sequence of the successive movement components is monotonous and movements of the different body parts do not occur in the complex way as seen in normal GMs.
2. Cramped-synchronised GMs (CS): CS are atypical and lack fluency, variation, and complexity. CS are also stereotyped in nature (limb and trunk muscles contract and relax nearly simultaneously).
3. Chaotic general movements (Ch): Movements of all limbs are of large amplitude and occur in a chaotic order without any fluency nor smoothness. They consistently appear to be abrupt.

Between 2 and 5 months of age, fidgety movements (FMs) become apparent: these show smaller amplitudes of circular shape, lower speed, and a higher variability in acceleration.

FM were judged as abnormal if they were:

(a) Absent ($F^-$): FMs are never observed from corrected age of 9 to 15 weeks. Other movements can, however, be commonly observed.

(b) Abnormal (AF): They look like normal FMs but their amplitude, speed, and jerkiness are moderately or greatly exaggerated.

### Video-based Assessment

All infants were video recorded while partially dressed in active wakefulness. Each recording lasted for 30 minutes excluding periods of crying. Two digital video recordings were made of each infant: For term infants, the assessment of writhing movements was at 1 month, the assessment of fidgety movements was at 3 months. For preterm infants, the assessment of writhing movements was at 1 month corrected age, and the second at 3 months corrected age, the age at which fidgety movements should be present. If the result was abnormal (PR, CS, $F^-$, or AF), the infant should be recorded again after three days, until the results reach two consistent conclusions. If the infant had a fever, he or she should be recorded again after the temperature returns to normal. If the infant was hypoglycaemic, a rerecording was performed after blood sugar became stable. The latest recording time could not be more than 1 week after the prescribed time. The quality of GMs was assessed independently by two observers who were blinded to the group assignments of the participants. In cases of disagreement, the video recordings were reassessed and an agreement was reached after a discussion. All observers had successfully completed a 7-day basic course of Prechtl’s assessment of general movements.
Statistical Analysis

All statistical analyses were conducted using IBM SPSS statistical software Ver.21 (IBM Corp.). Multivariate logistic regression analysis was conducted to obtain the odds ratios (OR) for the result of GMs after adjusting the variables showed significant correlation in one-factor analysis of variance (ANOVA) or chi-square test. ANOVA was used in measurement data (the data is normally distributed). Chi-square test was used in enumeration data. Wilcoxon rank sum test was used for ranked data. P values <0.05 were considered statistically significant.

Results

Possible Perinatal Factors Correlated with GMs

The twenty perinatal factors (Table 1) that might be correlated with GMs included delivery gestational age, birth weight, fetal distress, prolonged labour, threatened abortion, cord entanglement, multiple birth or single birth, meconium-stained amniotic fluid, diabetic mother, placenta previa, cesarean section, early pregnancy (3 months) infection, intracranial haemorrhage, Apgar score (1 minute), severe asphyxia, pregnancy induced hypertension, Hypoglycaemia, hyperbilirubinaemia, convulsion of newborn and gender as the object of investigation that come from prenatal, natal, and postnatal.

Risk Factors of GMs at the Writhing Movements Stage

The twenty perinatal factors that might be correlated with GMs were collected and analysed using one-factor ANOVA and chi-square test. Among these factors, five factors that showed significant correlation in both tests, including delivery gestational age, birth weight, severe asphyxia, fetal distress, and Apgar score (1 minute) (Tables 1 & 2), were analysed using logistic regression. The differences among the three groups in delivery gestational age, birth weight, severe asphyxia, and hyperbilirubinaemia were statistically significant (Table 5).

Correlations of Writhing Movements with Birth Weight and Delivery Gestational Age

Delivery gestational age (r=-0.374) and birth weight (r=-0.281) were negatively correlated (P=0.01) with the GMs. The lower the birth weight or the younger the delivery gestational age, the more severe the degree of abnormal GMs at the writhing movement stage.

Correlations of Fidgety Movements with Birth Weight and Delivery Gestational Age

Delivery gestational age (r=-0.305) and birth weight (r=-0.180) were also negatively correlated (P=0.01) with the GMs. The lower the birth weight or the younger the delivery gestational age, the more severe the degree of abnormal GMs at the fidgety movement stage.

Risk Factors of GMs at the Fidgety Movements Stage

The twenty perinatal factors that might be correlated with GMs were collected and analysed using one-factor ANOVA or chi-square test. Among these factors, five factors which showed significant correlation in both tests, including delivery gestational age, birth weight, severe asphyxia, hyperbilirubinaemia and fetal distress (Table 4) were analysed using logistic regression. The differences among the three groups in delivery gestational age, birth weight, severe asphyxia, and hyperbilirubinaemia were statistically significant (Table 5).

Correlations of Fidgety Movements with Birth Weight and Delivery Gestational Age

Delivery gestational age (r=-0.305) and birth weight (r=-0.180) were also negatively correlated (P=0.01) with the GMs. The lower the birth weight or the younger the delivery gestational age, the more severe the degree of abnormal GMs at the fidgety movement stage.

Table 1 Valuation of the influential factor associated with the quality of GMs

<table>
<thead>
<tr>
<th>Variables</th>
<th>Risk factor</th>
<th>Valuation and description</th>
</tr>
</thead>
<tbody>
<tr>
<td>X1</td>
<td>Delivery gestational age</td>
<td>Numerical variables</td>
</tr>
<tr>
<td>X2</td>
<td>Birth weight</td>
<td>Numerical variables</td>
</tr>
<tr>
<td>X3</td>
<td>Fetal distress</td>
<td>No=0, Yes=1</td>
</tr>
<tr>
<td>X4</td>
<td>Hyperbilirubinaemia</td>
<td>No=0, Yes=1</td>
</tr>
<tr>
<td>X5</td>
<td>Severe asphyxia</td>
<td>No=0, Yes=1</td>
</tr>
<tr>
<td>X6</td>
<td>Cord entanglement</td>
<td>No=0, Yes=1</td>
</tr>
<tr>
<td>X7</td>
<td>Whether the newborns are twins</td>
<td>No=0, Yes=1</td>
</tr>
<tr>
<td>X8</td>
<td>Meconium-stained amniotic fluid</td>
<td>No=0, I grade =1, II grade =2, III grade =3</td>
</tr>
<tr>
<td>X9</td>
<td>Whether the mother is diabetic</td>
<td>No=0, Yes=1</td>
</tr>
<tr>
<td>X10</td>
<td>Placenta previa</td>
<td>No=0, Yes=1</td>
</tr>
<tr>
<td>X11</td>
<td>Cesarean section</td>
<td>No=0, Yes=1</td>
</tr>
<tr>
<td>X12</td>
<td>Early pregnancy (3 months) infection</td>
<td>No=0, Yes=1</td>
</tr>
<tr>
<td>X13</td>
<td>Intracranial haemorrhage</td>
<td>No=0, Yes=1</td>
</tr>
<tr>
<td>X14</td>
<td>Apgar score (1 minute)</td>
<td>Numerical variables</td>
</tr>
<tr>
<td>X15</td>
<td>Threatened abortion</td>
<td>No=0, Yes=1</td>
</tr>
<tr>
<td>X16</td>
<td>Pregnancy induced hypertension</td>
<td>No=0, Yes=1</td>
</tr>
<tr>
<td>X17</td>
<td>Hypoglycaemia</td>
<td>No=0, Yes=1</td>
</tr>
<tr>
<td>X18</td>
<td>Prolonged labour</td>
<td>No=0, Yes=1</td>
</tr>
<tr>
<td>X19</td>
<td>Convulsion of newborn</td>
<td>No=0, Yes=1</td>
</tr>
<tr>
<td>X20</td>
<td>Gender</td>
<td>Female=0, Male=1</td>
</tr>
</tbody>
</table>
Table 2  One factor ANOVA and chi-square test for GMs result at the writhing movement stage

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group</th>
<th></th>
<th></th>
<th>F(χ²)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delivery gestational age, weeks, mean (SD)</td>
<td>N</td>
<td>PR</td>
<td>CS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>34.73 (2.80)</td>
<td>33.50 (2.10)</td>
<td>32.27 (2.17)</td>
<td>26.415</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Birth weight, mean (SD)</td>
<td>3.05 (0.46)</td>
<td>2.73 (0.54)</td>
<td>2.39 (0.63)</td>
<td>49.932</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severe asphyxia, number (Yes/No)</td>
<td>38/370</td>
<td>77/90</td>
<td>22/21</td>
<td>(115.495)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fetal distress, number (Yes/No)</td>
<td>47/361</td>
<td>85/82</td>
<td>30/13</td>
<td>(140.326)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Apgar score (1 minute) mean (SD)</td>
<td>9.14 (1.42)</td>
<td>8.73 (1.55)</td>
<td>7.70 (2.40)</td>
<td>19.051</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 3  Odds ratio for GMs result at the writhing movement stage

<table>
<thead>
<tr>
<th>Variables</th>
<th>Regression coefficient</th>
<th>Standard error</th>
<th>Wald</th>
<th>df</th>
<th>P</th>
<th>OR</th>
<th>95% Confidence intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delivery gestational age</td>
<td>-0.272</td>
<td>0.048</td>
<td>32.657</td>
<td>1</td>
<td>0.000</td>
<td>0.762</td>
<td>0.694-0.836</td>
</tr>
<tr>
<td>Birth weight</td>
<td>-1.332</td>
<td>0.210</td>
<td>40.027</td>
<td>1</td>
<td>0.000</td>
<td>0.264</td>
<td>0.175-0.399</td>
</tr>
<tr>
<td>Severe asphyxia</td>
<td>0.894</td>
<td>0.354</td>
<td>6.378</td>
<td>1</td>
<td>0.012</td>
<td>2.445</td>
<td>1.222-4.895</td>
</tr>
<tr>
<td>Fetal distress</td>
<td>1.532</td>
<td>0.333</td>
<td>22.608</td>
<td>1</td>
<td>0.000</td>
<td>4.865</td>
<td>2.535-9.344</td>
</tr>
</tbody>
</table>

Table 4  One factor ANOVA and chi-square test for GMs result at the fidgety movement stage

<table>
<thead>
<tr>
<th>Variables</th>
<th>F</th>
<th>AF</th>
<th>Fχ²</th>
<th>F(χ²)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delivery gestational age, weeks, mean (SD)</td>
<td>34.46 (2.78)</td>
<td>34.43 (1.86)</td>
<td>31.73 (2.43)</td>
<td>10.626</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Birth weight, mean (SD)</td>
<td>2.99 (0.50)</td>
<td>2.79 (0.37)</td>
<td>2.15 (0.81)</td>
<td>28.950</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severe asphyxia, number (Yes/No)</td>
<td>97/404</td>
<td>12/4</td>
<td>9/13</td>
<td>(32.920)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hyperbilirubinaemia, number (Yes/No)</td>
<td>261/240</td>
<td>12/4</td>
<td>18/4</td>
<td>(10.425)</td>
<td>0.005</td>
</tr>
<tr>
<td>Fetal distress, number (Yes/No)</td>
<td>177/324</td>
<td>11/5</td>
<td>8/14</td>
<td>(7.484b)</td>
<td>0.024</td>
</tr>
</tbody>
</table>

Table 5  Odds ratio for GMs result at the fidgety movement stage

<table>
<thead>
<tr>
<th>Variables</th>
<th>Regression coefficient</th>
<th>Standard error</th>
<th>Wald</th>
<th>df</th>
<th>P</th>
<th>OR</th>
<th>95% Confidence intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delivery gestational age</td>
<td>-0.241</td>
<td>0.077</td>
<td>9.680</td>
<td>1</td>
<td>0.003</td>
<td>0.786</td>
<td>0.675-0.915</td>
</tr>
<tr>
<td>Birth weight</td>
<td>-1.527</td>
<td>0.309</td>
<td>24.344</td>
<td>1</td>
<td>0.000</td>
<td>0.217</td>
<td>0.118-0.398</td>
</tr>
<tr>
<td>Severe asphyxia</td>
<td>1.326</td>
<td>0.383</td>
<td>12.008</td>
<td>1</td>
<td>0.001</td>
<td>3.765</td>
<td>1.799-7.969</td>
</tr>
<tr>
<td>Hyperbilirubinaemia</td>
<td>0.971</td>
<td>0.441</td>
<td>4.843</td>
<td>1</td>
<td>0.028</td>
<td>2.640</td>
<td>1.112-6.266</td>
</tr>
</tbody>
</table>
Discussion

GMs at writhing age mainly correlated with asphyxia related illness. While perinatal asphyxia is an obstetric complication that strongly affects the central nervous system. In our study, a total of 618 cases at the writhing movement stage and 539 cases at the fidgety movement stage were selected for assessment of GMs. We found that low delivery gestational age, low birth weight, severe asphyxia, and intrauterine distress are high-risk factors and predictors of abnormal general movements at the stage of writhing movements. Low delivery gestational age, low birth weight, severe asphyxia, and hyperbilirubinaemia are high-risk factors and predictors of abnormal general movements at the stage of fidgety movements.

We also found that delivery gestational age and birth weight were negatively correlated with the GMs, indicating that, the lower the birth weight or the younger the delivery gestational age, the more severe the degree of abnormal GMs at the writhing movement stage. Delivery gestational age and birth weight were negatively correlated with the GMs, indicating that the lower birth weight or the younger delivery gestational age, the more severe the degree of abnormal GMs at the fidgety movement stage.

Based on the analysis above, low delivery gestational age, low birth weight, severe asphyxia, and fetal distress are related to PR and CS. Low delivery gestational age, low birth weight, severe asphyxia, hyperbilirubinaemia, and fetal distress are related to AF and F, which may lead to developmental disorders in children, such as dyskinesia or learning difficulties. The infants with risk factors of GMs should receive early intervention which may improve GMs quality.

What is the possible mechanism? Preterm birth and low birth weight carry a higher vulnerability to suffering brain insults compared to term infants. These babies can develop any kind of known brain lesions including those affecting the most premature babies (i.e. an intraventricular haemorrhage) and lesions affecting more typically term babies like asphyxia and stroke. They were at much higher risk for destructive brain lesions that resulted in cystic necrotic white matter injury and secondary cortical and subcortical gray matter degeneration. Essentially complete myelination failure occurs in relatively uncommon but clinically significant necrotic lesions as a consequence of the degeneration of all cellular elements. Several studies have identified that preterm survivors display significant reductions in the growth of the cerebral cortex and subcortical gray matter structures that include the basal ganglia, thalamus, hippocampus, and cerebellum.

Global Cerebral Ischemia occurs following neonatal asphyxia and leads to harmful neurological consequences. In most cases, patients develop severe cognitive and motor impairments. The study focused on learning and memory deficits that are correlated with brain neuroanatomical reorganisation that appears after Global Cerebral Ischemia. Lipid peroxidation has been implicated as a major mechanism of cellular membrane damage involved in asphyxia in the newborn piglet. Hyperbilirubinaemia often exposes the affected infants to an elevated risk of acute bilirubin encephalopathy or its chronic form, kernicterus. Bilirubin, a powerful antioxidant, also can act as a powerful but silent neurotoxin at the most vulnerable stage of preterm life. The impact is long-lasting with both functional and structural neurologic injury that alters the processing of afferent input and leads to disordered efferent function. Moreover, these perturbations can potentially arrest or retard the natural neural maturation and/or lead to disordered clinical extrapyramidal function, sensory processing of hearing, visual responses, and learning. Hyperbilirubinaemia is a risk factor for GMs at the fidgety movement stage, but not at the writhing movements stage. The possible reason is that the short duration of hyperbilirubinaemia at the writhing movement stage cannot cause severe brain damage.

GMs generated from central pattern generator located in the brainstem, which may be regulated by corticospinal tract or reticulospinal tract. The central pattern generator may be damaged in the process of brain injury above by these high risks. If the central pattern generator is damaged, the quality of GMs may be affected.

In summary, low delivery gestational age, low birth weight, severe asphyxia, hyperbilirubinaemia, and fetal distress are risk factors and predictors of abnormal GMs. The prevention of risk factors can prevent the occurrence of abnormal GMs, which can effectively predict and prevent neurological impairments of the newborns, especially premature infants.

Acknowledgment

This work was funded by the Special foundation for Taishan Scholars (Grant number 20110814), the National Natural Science Foundation of China (81401131), China Postdoctoral Science Foundation (2015M572049), China State Scholarship fund (201506225013).
Conflict of Interest

The authors declare no competing financial interests.

Ethical Consideration

This study was approved by the Ethics Committee of Qilu Hospital of Shandong University, the Affiliated Hospital of Qingdao University and Union Hospital of Fujian Medical University. The methods were carried out in accordance with the approved guidelines. Informed consent was obtained from the parents. Photographs were redacted to prevent human subjects from being identified.

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32. Nossin-Manor R, Chung AD, Whyte HE, Shroff MM, Taylor MJ,


Abstract

**Background:** This study aimed to report the diagnosis, treatment, outcome and variable anomalies of the children with double aortic arch (DAA). **Methods:** The medical records of the patients with DAA treated at Children’s Hospital, Zhejiang University School of Medicine were reviewed for the following information: demographic information, clinical characteristics, imaging results, treatment and outcome. **Results:** Eleven patients with DAA were included into the study. Age of diagnosis raged from 5 days to 6.6 years with a mean of 26 months; age of onset ranged from 3 days to 8 months. 81.8% patients (9/11) had initial respiratory symptoms including cough, tachypnoea and wheezing; five patients had feeding difficulty or dysphagia. Seven patients had heart murmur and 3 had cyanosis. Primary diagnosis was asthma or respiratory infections in six patients, congenital heart anomalies in 4 and double aortic arch only in 1. All patients were indicated for surgery corrections for DAA or associated heart anomalies. Five out of the 11 patients underwent surgery timely after diagnosis; five parents refused surgery treatment for their children and one delayed surgery for their child because of economical problems. Outcome was favorable for the patients who underwent surgery at early age and associated with minor heart anomalies; and they were symptom-free at six months after surgery. **Conclusion:** For the children with recurrent respiratory symptoms, vascular rings should be considered in differential diagnosis. Symptomatic patients with DAA should be subjected to surgeries timely. Medical insurance policies should be improved for those families with low income and immigrant populations.

**Key words** DAA; Echocardiography; Vascular rings

Background

Vascular rings (VR) are a group of rare congenital vascular anomalies, which accounts for 1-2% of congenital heart disease.1 Double aortic arch (DAA) is the most common form of vascular rings in clinic. DAA is an anomaly of the aortic arch in which two aortic arches form a complete vascular ring that can compress the trachea and/or esophagus.2 Patients with DAA may present with respiratory symptoms such as recurrent cough, tachypnoea, wheezing or gastrointestinal symptoms. Therefore, patients maybe misdiagnosed with respiratory diseases such as asthma or gastro-oesophageal reflux because of similar clinical presentations.3

A high proportion of DAA patients had a delayed diagnosis in our Pediatric Cardiology Center. And for those patients combined with other heart anomalies, parents may be more likely to refuse surgery treatment for them. Delays in diagnosis, and parents’ refusing treatment lead to poor outcome of patients with DAA. In the present report, we described the diagnosis, management and outcome of 11 patients with DAA in a children’s hospital.
Methods

This study was approved by Ethical Committee of Children’s Hospital, Zhejiang University School of Medicine (Rf.2016-33). We retrospectively reviewed the clinical records of all the patients diagnosed with DAA in our hospital. All the clinical information, diagnosis, treatment and outcome were retrieved from the clinical records.

Imaging examinations included chest X-ray and echocardiography for all patients, and a computed tomography angiogram or magnetic resonance angiogram or cardiac catheterisation when required. Bronchoscopy was used to check the tracheal compression; esophagogram was done to for patients with oesophageal compression. Surgical correction was suggested for all symptomatic patients. For the patients with associated other heart anomalies, division of the vascular ring was done under cardiopulmonary bypass support; for those with isolated DAA, surgical correction was done without cardiopulmonary bypass. Non-surgical treatment included infection control, airway management and nutrition support.

Results

Clinical Characteristics

Eleven patients were diagnosed with DAA in the Pediatric Cardiology Center, Children’s Hospital, Zhejiang University School of Medicine from 2008 to 2014. Basic demographic information and clinical characteristics of the patients are shown in the Table 1. Age of diagnosis raged from 5 days to 6.6 years with a mean of 26 months; age of disease onset ranged from 3 days to 8 months. Seven patients were males and four females. 81.8% patients (9/11) had initial respiratory symptoms including cough, tachypnoea and wheezing; five patients presented feeding difficulty or dysphagia. Seven patients had heart murmur and 3 had cyanosis. Primary diagnosis was asthma or respiratory infections in six patients, congenital heart anomalies in 4 and double aortic arch only in 1. Associated heart anomalies included atrial septal defect (ASD) in 3, patent ductus arteriosus in 4, ventricular septal defect in 2, tetralogy of fallot in 1, pulmonary atresia (PA) in 1.

Imaging Results

Chest X-ray, electrocardiogram, echocardiography were performed for all patients after admission; seven patients were subjected to computed tomography (CT) examination, one magnetic resonance angiography (MRA); Figure 1 shows a DAA encircling the trachea and tracheal compression of case 7 by CT; Figure 2 shows the double aortic arch by CT. Esophagogram revealed oesophageal compression in three patients; and three patients were diagnosed by cardiac catheterisation and selective angiocardiography.

Management and Outcome

All patients were indicated for surgery corrections for DAA or associated heart anomalies. Five out of the 11 patients underwent surgery timely after diagnosis; five parents refused surgery treatment for their children (cased 2, 5, 9, 11) and one delayed surgery for their child (case 3). The medical records showed that the main reasons for refusal were economical problems; and all the parents who refused or delayed treatment were at a low social economical level, and 4 were migrant workers. For the other 5 patients, surgery for repairing DAA and other associated congenital heart anomalies was done after diagnosis. The median age at surgery was 25 months. For the patients who underwent at early age (Cases 1, 6, 10) and associated with minor heart anomalies, outcome was favourable; these three patients were symptom-free six months after surgery. For cases 4 and 8, respiratory symptoms including wheezing and tachypnoea persisted for one year after surgery, and improved after one year.

Discussion

VR are a group of anomalies caused by abnormal embryologic development of the brachial arch system characterised by an anomalous branching pattern of the vessels originating from the aortic arch, abnormal positioning of the aortic arch itself, interrupted or supernumerary arches, or anomalous origin of the pulmonary artery from the contralateral pulmonary artery or ascending aorta. Vascular rings may lead to variable degrees of respiratory problems or feeding difficulties by forming a complete or partial ring compressing the trachea, the bronchi, and the esophagus. DAA is the most common form of vascular rings. General pediatricians who are not familiar with this condition may misdiagnose or missed diagnose DAA.
<table>
<thead>
<tr>
<th>No.</th>
<th>Age at diagnosis</th>
<th>Age at disease onset</th>
<th>Sex</th>
<th>Weight (kg)</th>
<th>Clinical presentations</th>
<th>Combined heart anomalies</th>
<th>Management</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6 months</td>
<td>5 months</td>
<td>Female</td>
<td>6.5</td>
<td>Recurrent cough, wheezing</td>
<td>ASD</td>
<td>Surgery repair of DAA</td>
<td>12 months at the last follow-up, Good without remarkable symptoms, normal growth and development</td>
</tr>
<tr>
<td>2</td>
<td>12 months</td>
<td>7 months</td>
<td>Male</td>
<td>8.5</td>
<td>Cough and wheezing, tracheal compression</td>
<td>--</td>
<td>Parents refused surgery treatment</td>
<td>No surgery until the last follow-up. The patient has recurrent asthma-like respiratory symptoms.</td>
</tr>
<tr>
<td>3</td>
<td>5 days</td>
<td>3 days</td>
<td>Female</td>
<td>3.3</td>
<td>Feeding difficulty, oesophageal compression</td>
<td>--</td>
<td>Parents delayed surgery</td>
<td>No surgery until the last follow-up at 11 months of age and with remarkable gastrointestinal symptoms like feeding choking</td>
</tr>
<tr>
<td>4</td>
<td>6 years 7 months</td>
<td>2 years</td>
<td>Female</td>
<td>15</td>
<td>Heart murmur, cyanosis, oesophageal compression</td>
<td>TOF</td>
<td>Surgery for TOF at 4 years, Delayed surgery repair of DAA at 6 years 7 months</td>
<td>Good with mild respiratory symptoms</td>
</tr>
<tr>
<td>5</td>
<td>3 years 6 months</td>
<td>1 month</td>
<td>Male</td>
<td>12.5</td>
<td>Cough and wheezing, heart murmur, cyanosis tracheal compression</td>
<td>PA, VSD, PDA, ASD</td>
<td>Parents refused surgery treatment</td>
<td>N/A</td>
</tr>
<tr>
<td>6</td>
<td>7 months</td>
<td>10 days</td>
<td>Male</td>
<td>10</td>
<td>Heart murmur, tracheal compression</td>
<td>PS</td>
<td>Surgical repair of PS and DAA</td>
<td>Good, free of symptoms</td>
</tr>
<tr>
<td>7</td>
<td>8 months 4 days</td>
<td>3 months</td>
<td>Male</td>
<td>9</td>
<td>Cough and wheezing, heart murmur</td>
<td>--</td>
<td>Surgical repair of DAA</td>
<td>Good, free of symptoms</td>
</tr>
<tr>
<td>8</td>
<td>3 years 5 months</td>
<td>5 months</td>
<td>Male</td>
<td>13</td>
<td>Cough and wheezing, Heart murmur, oesophageal compression</td>
<td>PDA</td>
<td>Surgical repair of PDA and DAA</td>
<td>With respiratory symptoms during the six month after surgery, improved at the last follow-up at the age of 5 years</td>
</tr>
<tr>
<td>9</td>
<td>5 years 4 months</td>
<td>8 months</td>
<td>Male</td>
<td>16</td>
<td>Cough and wheezing, heart murmur, cyanosis</td>
<td>VSD</td>
<td>Parents refused surgery treatment</td>
<td>No surgery until the last follow-up. The patient has been admitted to hospital because of recurrent respiratory symptoms</td>
</tr>
<tr>
<td>10</td>
<td>10 months</td>
<td>1 month</td>
<td>Female</td>
<td>8</td>
<td>Feeding difficulty, wheezing, tracheal compression</td>
<td>--</td>
<td>Surgical repair of DAA</td>
<td>Good and free of symptoms</td>
</tr>
<tr>
<td>11</td>
<td>18 months</td>
<td>2 months</td>
<td>Male</td>
<td>10</td>
<td>Cough and wheezing, heart murmur, cyanosis</td>
<td>PDA, ASD</td>
<td>Parents refused surgery treatment</td>
<td>No surgery until the last follow-up. Recurrent wheezing and cough</td>
</tr>
</tbody>
</table>

DAA: double aortic arch; ASD: atrial septal defect; TOF: Tetralogy of Fallot; PA: pulmonary atresia; VSD: ventricular septal defect; PDA: patent ductus arteriosus; PS: pulmonary stenosis
Figure 1  CT showing a DAA encircling the trachea and tracheal compression of case 7.

Figure 2  CT Scan illustrating the double aortic arch.
The patients with a DAA may present with cough, tachypnoea, wheezing, dyspnoea, and recurrent respiratory tract infections, especially for the infants and young children less than 2 years of age; these patients are often misdiagnosed as pneumonia and asthmatic bronchitis. All the patients in this series had respiratory tract symptoms, and about half of the patients were misdiagnosed and admitted to the Pulmonology Department after initial diagnosis. Only one newborn was diagnosed timely who was suspected with DAA prenatally. The asymptomatic patients may be delayed to be diagnosed until symptoms such as dysphagia occurred in adulthood. Alsenaidi et al⁸ made a retrospective review on 81 children with a DAA; they found that initial diagnosis can be made by chest X-ray with the major characteristics including pulmonary hyperinflation, lowering hilum of the left lung, right arch or DAA by anteroposterior position or lateral position. Chest X-ray showed no remarkable changes except pneumonia or lung markings changes. Six cases were misdiagnosed as respiratory tract infections at the first admissions to the hospital.

All the patients with DAA in this cohort had symptoms, in contrast of the previous reports that most patients were asymptomatic at diagnosis.⁷,⁹ The reason maybe that our hospital is the only tertiary children’s hospital in this province, and patients with severe diseases were transferred from local hospitals. Our concern is that there are many asymptomatic patients with DAA maybe not diagnosed; and symptomatic patients have been delayed in diagnosis due to lack of knowledge on DAA in many local hospitals. Pediatricians should be alert when managing those patients with recurrent pneumonia, wheezing, dysphagia, and particularly those without improvement after administering bronchodilators; vascular rings should be suspected and multi-modality imaging exams should be performed for these patients. In our series, 91% of the patients were combined with heart anomalies, and 36.1% had tracheal compression; for the patients with presentations which cannot be explained with heart anomalies, vascular rings should be considered. The diagnosis of vascular rings is relying on imaging examinations. Multi-detector row CT with three-dimensional reconstruction can clearly reveal the anatomy of blood vessels, compression and extent of narrowness, which is the first choice for diagnosis of DAA.¹⁰ Echocardiography is an indispensable assisting diagnostic modality, which can detect combined heart anomalies in DAA. For patients with tracheal compression, bronchoscopy can be performed for determining the extent of narrowness, which will be valuable for designing surgery procedures and outcome evaluation. Esophagogram is also a reliable method for initial diagnosis, however cannot be considered as the first choice because of its limitations in evaluating tracheal compression and disease classification. MRI and angiography is still not widely used in clinic because of its high cost.

For the patients with symptoms, early surgery treatment should be performed. For those patients with tracheal compression, airway stenosis may occur and symptoms such as wheezing or recurrent respiratory infections may persist until one year after surgery. However, in our series, more than half of the patients refused treatment after diagnosis, including those patients with severe tracheal compression; all the patients were associated with other heart anomalies. The reasons were due to high cost and the parents were in low social economical level. The low reimbursement rate of new rural medical insurance lead to refusal for treatment in the families with very low income. The local government should be called to increase the reimburse rate of those children with complicated anomalies; and immigrant families with low income should be focused.

In conclusion, for the children with recurrent respiratory symptoms, vascular rings should be considered in differential diagnosis. Symptomatic patients with DAA should be subjected to surgeries as soon as possible. Medical insurance policies should be improved for those families with low income and immigrant populations.

Disclosures

No competing interest exists in this study.

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**Seton Placement for Fistula-in-ano in Children**

**Z TURKYILMAZ, R KARABULUT, K SONMEZ, S ERYILMAZ, V TAIROV**

**Abstract**

Fistula-in-ano (FIA) is a common condition in infancy, often accompanied by perianal abscess (PA). Primary treatment approach is conservative whether it is PA or FIA. The most frequently performed surgeries in non-healing FIA are fistolotomy and fistulectomy, in which the recurrence rate is between 0 to 68%. Seton placement used in adult patients especially in intersphincteric fistulae in the treatment of FIA has been used in a limited number of studies conducted in children. It was our aim with this study to present our experience in three patients on whom seton placement was carried out in FIA by using the wristband part of the surgical glove. Recurrence was not seen in seton placements conducted in our patients. Operation time is usually limited to 20 minutes. Moreover, the material used as seton in our study was the wristband of the surgical glove, which is both cheap and easy to use. Seton placement used quickly and cheaply for FIA in children should be preferred due to no recurrence and incontinence.

**Key words**

Children; Fistula-in-ano; Seton placement; Treatment

**Introduction**

Fistula-in-ano (FIA) is a common condition in infancy, often accompanied by perianal abscess. Perianal abscess (PA) in children is associated with a 20 to 85% overall rate of progression to FIA. Primary treatment approach is conservative whether it is PA or FIA. FIA can spontaneously heal. The most frequently performed surgeries in non-healing FIA are fistolotomy and fistulectomy, in which the recurrence rate is between 0 to 68%. Seton placement used in adult patients especially in intersphincteric fistulae in the treatment of FIA has been used in a limited number of studies conducted in children. It was our aim with this study to present our experience in three patients on whom seton placement was carried out in FIA by using the wristband part of the surgical glove.

**Case Reports**

**Case 1**

A 2-year-old boy received drainage and antibiotic treatment for perianal abscess located 2.5 cm away from the anus at the 9 o’clock position in the lithotomy position, which developed after he was 7 months old. However, an external opening emerged after the second relapse and continuous discharge was noted, suggesting the diagnosis of FIA.
Case 2
A 13-year-old patient developed perianal fistula with discharge, approximately 3 cm away from the anus in 10-11 o'clock position in the lithotomy position, which persisted for one year despite receiving treatment for perianal abscess several times.

Case 3
The 1.5-year-old boy received drainage and antibiotic treatment for perianal abscess located 3 cm away from the anus in the 3 o'clock position in the lithotomy position since 11 months of age. However, an external opening emerged after the second relapse and continuous discharge was noted, and therefore the patient received FIA diagnosis (Figure 1).

When these three patients applied to our clinic for treatment, seton placement was decided to be performed after having received necessary consents. The patients did not report latex allergy and there were no predisposing factors in our patients and their families. Patients were put in lithotomy position after being anaesthetised. The fistula was revealed by pushing the 17-gauge blunt needle from the external opening of the FIA to the internal opening at the level of the anal crypt. Following this, the skin between the internal and external openings of the FIA was incised above the blunt needle. On the next stage, the thin, hard, flexible ring in the wristband part of the surgical, sterile glove was cut and used as seton, and it was passed through the fistula with the guidance of the needle. In both cases, two tips of this modified seton were connected in a way to not cut over the fistula. The tightness of the seton was adjusted in a way to leave half of the distance between the internal and external openings of the FIA (Figure 2). These operations lasted twenty minutes including anaesthesia procedures. The patients were given oral antibiotics and sitz bath with batticon. While the seton dropped spontaneously on day 15 in the younger patients and 19 on the older patient, it was seen that the FIA healed. Allergy to rubber latex of the surgical glove was not seen in our patients during this procedure. While relapse was not encountered on the third and sixth months’ follow-up of the patients, it was seen that the operation was also satisfying cosmetically. Incontinence was not seen in the patients, and none of the patients had additional diseases such as Crohn’s disease.

Discussion
FIA frequently develops after PA in children, and in cases that are not healed within 3 to 5-months of conservative treatment, fistolotomy or fistulectomy are recommended, with which the fistula tract is removed with the blocked anal crypt. However, recurrence rate is high in childhood FIA cases whether it is treated conservatively or surgically. Seton placement in children as has been used in the treatment of adults with FIA has been infrequently reported in the literature. Seton was used in addition to fistolotomy or fistulectomy in six out of 17 patients in the series of Carmona et al, and it was also used in the series of Charalampopoulos et al since intersphincteric fistula was seen in only three out of 52 children under the age of two with FIA. In the study by Inoue et al, which is considered the largest series of seton use in infants, FIA developed in thirty-six patients (40%) out of 90 with PA. Thirty-five out of the 36 patients (97.2%) recovered with seton use. While 12% fecal incontinence was detected with seton use in adult patients...
with FIA, such a complication was not encountered in the study by Inoue.\textsuperscript{1,5} But most cases of FIA in children tend to be superficial, low and very rarely trans- and intersphincteric. So incontinence problem is rare in FIA treatment in children.\textsuperscript{3} In the series by Charalampopoulos et al, where fistolotomy, fistulectomy and only 3 setons were performed, no recurrence was seen in fifty-two cases with FIA, but five (15.1\%) recurrences were seen in the series of Ezer et al with thirty-nine patients.\textsuperscript{2,3} In the series of Niyogi, where the same procedure was applied, nine recurrences (23\%) were seen in thirty-nine children under the age of 2 and seven recurrences (54\%) were seen in children over the age of 8.\textsuperscript{4} In two adult series, where seton was used, 0\% and 3.9\% recurrence rates were seen.\textsuperscript{7,8} Recurrence and incontinence were not seen in seton placements conducted in children and in our study. Operating time was usually limited to 20 minutes. Moreover, the material used as seton in our study was the wristband of a surgical glove, which is both cheap and easy to use.

**Conclusion**

According to short term results seton placement used quickly and cheaply for FIA in children should be preferred due to no recurrence and incontinence.

**Declaration of Interest**

None

**References**

Case Report

Lung Ultrasonography for Pulmonary Atelectasis in a Child

AK ÖZKAYA, HL YILMAZ, SS GÖKAY, ÖT KENDIR

Abstract

Pulmonary atelectasis in children is a pathological condition with no specific symptoms or findings that may be seen in the course of several pulmonary and thoracic diseases. Early and accurate diagnosis is essential in the treatment of pulmonary atelectasis. The first imaging method to be considered when a patient with pulmonary atelectasis is encountered is posterior-to-anterior chest X-ray. However, several pulmonary diseases can today be diagnosed and monitored using bedside ultrasonography. We describe a case of peripherally located radio-opacity in the right upper zone at posterior-to-anterior chest X-ray in a 9-year-old patient under monitoring due to asthma and presenting with cough and nasal discharge. Images compatible with atelectasis were obtained at pulmonary evaluation with bedside ultrasonography. No atelectatic areas were observed at control ultrasonography and posterior-to-anterior chest X-ray following appropriate treatment. Lung ultrasonography is an imaging technique that is especially promising in children and that may represent an alternative in the diagnosis and monitoring of pulmonary atelectasis.

Key words

Atelectasis; Lung ultrasound; Paediatric

Introduction

The identification of pulmonary opacities using chest X-ray may sometimes be problematic for clinicians. The two most common causes of pulmonary opacities are pneumonia and atelectasis.1 Atelectasis represents the loss of pulmonary volume in association with parenchymal compression (non-obstructive atelectasis) or partial or complete obstruction of the airway in the bronchial tree.2 Atelectasis compromises respiratory functions by affecting the ventilation-perfusion balance. It can increase the risk of pneumonia by reducing ventilated pulmonary tissue. Pulmonary atelectasis in children can develop in association with several pulmonary diseases and occurs through three main mechanisms; (i) air passage obstruction, (ii) defect in extrathoracic, intrathoracic or chest wall structures or pulmonary parenchymal compression due to neuromuscular disease, or (iii) surfactant insufficiency or dysfunction.3 No symptoms or findings specific to pulmonary atelectasis develop in many patients. Fever, cough, tachypnoea, wheezing, rhoncus and chest pain are commonly seen symptoms and findings in pulmonary atelectasis and in other respiratory conditions. So long as the atelectatic area is not extensive, the presence of pulmonary atelectasis does not alter the clinical condition.3 The primary imaging method in the diagnosis of pulmonary atelectasis is posterior-to-anterior chest X-ray. The extension of the atelectatic area can be determined with posterior-to-anterior and lateral X-rays, but it is difficult to make this distinction in some conditions, particularly pneumonia, and another
imaging technique is required for confirmation. Indeed, peripherally located manifestations can be confused with pneumonia or other space-occupying lesions. The use of assessment with bedside ultrasonography, and particularly lung ultrasonography, is increasing by the day in emergency and intensive care units. Lung ultrasonography can assist with the diagnosis of pleural effusion, pneumothorax, pulmonary consolidation, interstitial syndrome, interstitial lung disease, atelectasis and other causes of pulmonary and non-pulmonary dyspnoea. Biconcave structures with distinct margins can be seen by ultrasonography in non-obstructive atelectasis. The acoustic pattern is a moderate echogenic appearance with air trapping. The parenchyma generally appears hypoechoic. Atelectatic lung tissue may collapse during inspiration and expand again, and atelectasis may temporarily disappear. Simultaneous or secondary pneumonic consolidation may also be observed. A convex appearance on the atelectatic margin with an increase in lung tissue volume, or different appearances associated with respiration may be seen. Obstructive atelectasis frequently develops in association with obstruction in the distal part of the airway (bronchial carcinoma, mucus plug). Images are less dependent on respiration. Echogenic air contents and vascular structures may be seen depending on the duration of atelectasis. Hepatisation and typically fluid bronchograms are seen in the event of post-stenotic pneumonia.

Lung ultrasonography is becoming increasingly important in the diagnosis and monitoring of various diseases, particularly in children. We report the case of a 9.5-year-old girl under observation due to asthma in whom pulmonary atelectasis was confirmed with ultrasonography.

Case Report

A 9-year-old girl presented to hospital with respiratory difficulty and cough over the preceding 3 days. Nasal discharge and productive cough had begun 3 days previously. The symptoms had worsened over the preceding one day, and she was referred to our hospital when the physician to whom she initially presented identified opacity at chest X-ray. The patient had been diagnosed with asthma 3 years previously and had received various treatments due to occasional mild asthma attacks. Vital findings were stable at physical examination, both lungs were equally ventilated and mild wheezing was present in both. Complete blood count and biochemical tests were normal. Chest X-ray revealed a radio-opaque appearance with no air bronchograms in the region close to the midline in the right upper zone (Figure 1). Evaluation of pulmonary tissue extending vertically and horizontally between the right anterior 1st and 3rd intercostal spaces using bedside ultrasonography, revealed a hypoechoic area 7.98 cm² in size containing hyperechogenic components compatible with non-dynamic air bronchograms and occasionally increased B-lines (Figure 1). Ultrasonography was performed by the first author (AKÖ) using a SonoSite Edge portable ultrasound device with a 6-15 MHz linear probe (6 cm scan depth) in B-mode. The lesion was interpreted as atelectasis, and an inhaler bronchodilator and chest physiotherapy were prescribed. Hypoechoic area was no longer observed at repeat lung ultrasonography 2 days later and radio-opaque appearance was also no longer observed in the right upper zone at repeat posterior-anterior chest X-ray (Figure 2).

Discussion

Bedside ultrasonography is not only an imaging technique but also an alternative and descriptive diagnostic tool in several pulmonary diseases. Since it is economical, portable and simple to perform, permits patient transfer and does not involve exposure to radiation, it is becoming increasingly commonly used. In terms of determining atelectasis triggered by anaesthesia, Acosta et al determined atelectatic pulmonary areas using lung ultrasonography after thoracic MRI following the administration of anaesthesia to 15 children. Taking MRI as a reference, lung ultrasonography has been shown to possess high sensitivity (88% and 95%, CI 74% to 96%) and specificity (89% and 95%, CI 83% to 94%). In newborns, lung ultrasonography has been shown to exhibit 100% sensitivity for pulmonary atelectasis, compared to 75% for chest X-ray. It can be difficult to differentiate between pulmonary consolidation areas and atelectatic regions using ultrasonography or chest X-ray. It may be easier to distinguish air bronchograms in extensive consolidated areas. The reflection of bronchial structures in small lesions may not be capable of identification in atelectasis and pneumonia. The appearance of bronchial structures containing air in collapsed pulmonary tissue differs from that in consolidated regions. In atelectasis, the margins of hypoechoic lesions can be clearly distinguished, bronchograms are generally stable, no centrifugal movement is observed and they are located parallel to one another. In pneumonia, however, bronchograms are generally wider, dynamic and exhibit
Figure 1  (a) Radio-opacity extending to the apex in the right upper zone at posterior-anterior chest X-ray, (b) radio-opaque appearance originating from the hilar region and extending to the apex, (c) B-lines tending to coalescence and (d) a 7.98-cm² area compatible with atelectasis at lung ultrasonography evaluation.

Figure 2  The previous radio-opaque appearance is no longer visible at control posterior-anterior chest X-ray (a) and there is no area compatible with atelectasis at control lung ultrasonography evaluation (b).
centrifugal movement.\textsuperscript{1,4,6} Accompanying atelectasis with consolidation may sometimes be observed. Alveolar inflammation, increased fluid in the interstitial space, inflammation in the bronchial tree and oedema with secretion accumulation may occur in areas of pneumonia-related consolidation. In consequence, fluid accumulates inside the bronchial structures and sonographic reflections occur in the form of fluid bronchograms. Mucous plugs may forms as a result of increased fluid accumulation and debris in the bronchial structures, and obstructive atelectasis may develop together with pneumonic consolidations in association with this. Moreover, compressive atelectasis may be observed together with pleural effusion or empyema around pulmonary tissue.\textsuperscript{6}

While lung ultrasonography is very sensitive and specific in the diagnosis of atelectasis in children, superficial pulmonary parenchyma or those close to the surface can also be evaluated with ultrasonography. However, deep lesions may not be determined during evaluation with ultrasonography. One study revealing the usefulness of lung ultrasonography in patients with pneumonia confirmed this.\textsuperscript{7} In fact, evaluation in terms of atelectasis using ultrasonography may be advantageous due to the anatomical characteristics in children compared to adults. However, studies concerning determination of atelectasis in children using ultrasonography are insufficient in terms of numbers and quality.\textsuperscript{5,6} In addition, the visualisation not only of deep pulmonary parenchymal lesions, but also tumours and other space-occupying lesions in the posterior mediastinum and pulmonary areas is not generally possible, due to the restricted depth penetration of the ultrasound probe, and the super imposition of acoustic shadows of osseous and other structures.\textsuperscript{8}

In addition, lung ultrasonography can also be used in the monitoring of atelectasis as well as diagnosis. In a case report of pulmonary atelectasis confirmed by ultrasonography, Elia et al showed pulmonary re-expansion with ultrasonography following cleaning of the airways with bronchoscopy.\textsuperscript{2} Similarly, atelectasis in a patient with postoperative pulmonary atelectasis was confirmed with ultrasonography, and improved pulmonary tissue sonographic findings were reported after treatment.\textsuperscript{9} Lung ultrasonography appears to be useful in identifying collapsed alveoli in patients undergoing mechanical ventilation and in revealing resolution of the atelectasis.\textsuperscript{10}

In conclusion, we think that bedside ultrasonography can be used as a simple, easy to administer and useful tool that does not involve exposure to radiation in the diagnosis and monitoring of pulmonary atelectasis in children.

\textbf{Declaration of Interest}

There are no conflicts of interests to be declared.

\textbf{References}

Case Report

Marshall-Smith Syndrome in a Chinese Boy

MR Zhu, PP Liu, XF Liu, H Wu

Abstract

Marshall-Smith syndrome (MSS) is a malformation disorder that is characterised by accelerated bone maturation, developmental delay and facial deformation. The current medical literature describes more than 50 patients as having MSS, involving the nervous system, musculoskeletal system, respiratory system, connective tissues, eyes, and ears. Here, we report a new patient diagnosed with MSS with an additional finding – a perianal wart and a large scrotum.

Key words

Marshall-Smith syndrome

Introduction

Marshall-Smith syndrome (MSS), initially reported by Marshall in 1971, is a malformation disorder characterised by accelerated bone maturation, developmental delay and facial deformation.1 Six years ago, researchers reported that de novo mutations in the gene encoding transcription factor nuclear factor 1X (NFIX) was the cause of MSS.2 Upper airway obstruction is possibly due to craniofacial and laryngeal anomalies, and aspiration pneumonia results from epiglottis dysplasia and pharyngeal incoordination. The above two respiratory complications lead to the high mortality of the disease. In recent years, airway support and other supportive treatments have ensured a longer life in these patients. Here, we present a novel phenotype of MSS in a Chinese boy, including a perianal wart and a large scrotum.

Case Report

A 3.05-kg male infant was born at 39 weeks of gestational age to a 30-year-old G6P2 mother. She had a long history of cigarette smoking, including approximately 7-8 cigarettes per day on average during pregnancy, and turbid amniotic fluid at the time of delivery. The infant was delivered by selective cesarean section. At 18 days of age, the boy was admitted to the neonatal intensive care unit due to progressive dyspnoea. On admission, his weight was 2600 g (5-10th percentile), his length was 50 cm (50-90th percentile), and his head circumference was 31.5 cm (3rd percentile). He had reduced subcutaneous fat and suffered from malnutrition. Continuous positive airway pressure was performed due to inspiratory stridor and retraction. The typical appearance of malformations was as follows: a small anterior fontanel (0.3×0.2 cm), overlapping cranial sutures on his forehead, a low hairline, protruding eyes, blue sclera, megalocornea, corneal clouding (Figure 1A), a normal anterior chamber depth, a right intraocular pressure of 21 mmHg, a left intraocular pressure of 29 mmHg, normal eye movement, a flat midface, an upturned nose, a soft subcutaneous mass on the right side of the nose (Figure 1B), glossoptosis, deep palatine arches (Figure 1C), thin fingers and toes (Figures 1D and 1E), poor muscle tone and reflexes, a perianal wart and a large scrotum (Figure 1F). His complete blood cell count, arterial blood gas, and liver, thyroid and renal function test results were within normal ranges. Echocardiography indicated a patent foramen ovale.
ovale. Chest X-ray revealed increased pulmonary vascular markings and cardiomegaly. The patient did not pass the newborn hearing screening. Ultrasound of the eyes revealed deep cupping of the optic discs and horizontal corneal diameters of approximately 16.0 mm. No abnormalities were noted on head magnetic resonance imaging. Laryngoscopy indicated a thickening of the subglottic soft tissue, hypertrophy of the bilateral inferior nasal concha and rhinostenosis.

A molecular analysis was performed by Hangzhou Hi-tech Incubation Park consisting of whole-exome sequencing of the infant and his parents. No genetic anomalies were found in the parents. A frame shift mutation (c.1156_1160del:p.Q386fs) in exon 8 of the patient's NFIX gene was found. However, his parents did not carry this mutation, which indicated a novel mutation in the patient.

### Discussion

MSS is a malformation disorder characterised by accelerated bone maturation, growth retardation and facial

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**Figure 1** Typical appearance of malformations: (A) protruding eyes, blue sclera, megalocornea, and corneal clouding; (B) a flat midface, upturned nose, and a soft subcutaneous mass on the right side of the nose; (C) glossoptosis and deep palatine arches; (D) and (E) thin fingers and toes; (F) a perianal wart and a large scrotum.

### Table 1 Pathogenicity of gene mutations

<table>
<thead>
<tr>
<th>Gene</th>
<th>NM_ID*</th>
<th>Exon</th>
<th>cDNA</th>
<th>Protein</th>
<th>Heterozygosity</th>
<th>Mutation type</th>
<th>Mutation frequency</th>
<th>Pathogenicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>NFIX</td>
<td>NM_001271043</td>
<td>8</td>
<td>c.1156_1160del</td>
<td>p.Q386fs</td>
<td>Heterozygous</td>
<td>Frameshift</td>
<td>0</td>
<td>Pathogenic</td>
</tr>
</tbody>
</table>

*The mRNA serial number from the NCBI serialisation library
Malformation. Currently, more than 50 patients have been described as having MSS in the medical literature, with involvement of the nervous system, musculoskeletal system, respiratory system, connective tissues, eyes, and ears. Facial features include low-set ears, a high forehead, an upturned nose, a low nose bridge, a flat midface, eclubium, gingival hypertrophy, irregular tooth locations, an outstretched tongue, and a micromandible. Typical ophthalmic abnormalities consist of shallow orbits, bilateral proptosis, blue sclera, high myopia, glaucoma, visual hypoplasia, and keratoheolcosis. Severe dyspnoea results from a combination of aspiration pneumonia and upper respiratory tract obstruction (due to nasal stenosis, atretorrhinia, laryngomalacia, laryngeal stenosis, and a narrow glottis). Several patients have external ear malformations and sensorineural or conductive hearing loss. Regarding bone and connective tissue, we found dysosteogenesis, accelerated bone maturation, a short stature, scoliosis, non-traumatic fractures, osteopenia, and overlapping cranial sutures in the patient described herein. His proximal and middle fingers (toes) were wide, and his terminal fingers (toes) were short and narrow. Abnormal physical growth and behaviors are common in MSS and include the following: a happy disposition, a gregarious nature, palikinesia, hypophrenia, and linguistic and mental retardation. Some of these patients cannot talk or walk. MSS patients have truncal and peripheral hypertonia, active tendon reflexes, an open mouth caused by oral incoordination, quadriplegia due to cervical stenosis, callosal agenesis, ventricle enlargement, macrogyria, polymicrogyria, septum pellucidum dysplasia, and epilepsy (which is rare). Other prevalent features include hypertrophic pylorostenosis, craniosynostosis, and exomphalos.

The typical clinical manifestations of MSS in the current patient included hypoelutism, upper airway obstruction, pneumonia, abnormal appearance, glaucoma, thin fingers and toes, encephalodysplasia, and hearing screening failure. Additionally, we found some novel phenotypes, e.g., a perianal wart and large scrotum. Shaw et al. reported a case with an anteriorly displaced anus and a case with hypospadias, and Gómez-Santos et al. reported a newly diagnosed MSS patient with additional findings of hypertrophy of the labia minora and the clitoris. With the exception of the above three cases, no cases of facial masses or malformed urethra, genitals, or anus have been reported.

![Figure 2](image_url)  
**Figure 2** Sequence diagram of the gene mutation sites; WH1_007 father, WH1_009 baby, WH1_008 mother.
According to our survey, this MSS case is the first to be reported in mainland China, demonstrating that Chinese individuals can also suffer from this disorder, i.e., MSS syndrome is a global disease. Moreover, the result revealed a novel mutation (c.1156_1160del) in exon 8 of the \textit{NFIX} gene, which cannot be found in five other SNP databases (dbSNP, ESP, ExAC, HTD and HGVD). However, we did not perform molecular function analysis of this novel mutation (c.1156_1160del); therefore, the pathogenic significance with this novel mutation in the \textit{NFIX} gene needs to be further studied.

\textbf{Declaration of Interests}

The authors declare that they have no conflicts of interest.

\textbf{Declaration of Informed Consent}

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

\textbf{References}

Case Report

18q-Deletion Syndrome: Characteristic MRI Features

WWC Tsui, EYL Kan, WS Mak, STH Fung

Abstract

We illustrate the MRI findings of a child confirmed with 18q-deletion syndrome. Neurologic manifestations of this condition frequently involve the white matter, which is likely a result of haploinsufficiency of myelin basic protein as it is a major contributor to the formation of central nervous system myelin. In our case report, MRI demonstrated bilateral symmetric white matter T2 hyperintense signal with diminished gray-white matter differentiation suggestive of a delayed myelination pattern. Follow-up imaging 5 years later showed minimal progression of myelination.

Key words 18q-deletion; Hypomyelination; Myelin basic protein

Introduction

The reported incidence of 18q-deletion syndrome is estimated to be 1 in 40,000 births. It is characterised by partial deletion of the long arm of chromosome 18. Majority of individuals with 18q-deletion syndrome are non-familial and is a result of a de novo random event occurrence during fertilisation. There is a wide spectrum of clinical presentations ranging from neurological deficits, musculoskeletal, genitourinary, endocrine, and immunological abnormalities.

The most often described neurological manifestation is hypomyelination of the central nervous system (CNS). The deleted segment of the long arm of chromosome 18 contains the gene for myelin basic protein (MBP), which plays an important role in myelin formation. We report a confirmed case of 18q-deletion syndrome with MRI showing abnormal myelination and minimal progression of myelination over time.

Case Report

A 7-year-old girl first presented at birth with multiple anomalies. She was born at 36 weeks gestation with low birth weight of 2150 grams and Apgar scores of 8 at one minute and 9 at five minutes. Multiple anomalies included dysmorphic facial features, hearing loss, hypoplastic first ribs, congenital vertical talus, sacral dimple, and ectopic anal opening. Non-paralytic hypotonia, microcephaly, delayed growth velocity with failure to thrive and short stature were evident soon after birth. Screening for congenital hypothyroidism was initially negative. A sigmoid colostomy and subsequent closure with posterior sagittal anorectoplasty were performed before 6 months old. Repair of tarsals and metatarsals with bilateral Achilles tenotomy were performed at age 1. Global developmental delay (GDD) with discrepant social and speech development with mild grade learning disability was noted.
since 18 months old requiring special needs education. Further endocrinological workup showed autoimmune hypothyroidism, requiring thyroxine supplement. Blood for IgA was normal. Diagnosis of 18q-deletion syndrome was made by karyotype analysis demonstrating partial deletion of the long arm of chromosome 18, del(18)(q21.3). To the best of our knowledge, this is the first case to be reported in Hong Kong with MRI correlation.

MRI brain was performed at 1 and 6 years of age. The initial scan revealed diminished myelination at the internal capsules and bilateral peripheral white matter (Figure 1). Abnormal and symmetrical T2-hyperintense signals were noted in the deep white matter bilaterally (Figure 1). Follow-up imaging performed 5 years later demonstrated lack of progression of myelination pattern with poor deep and subcortical white matter myelination on T2-weighted

Figure 1  MRI at 1-year of age. (A and B) T1-weighted inversion recovery (IR) and T2-weighted images of 1-year-old showing normal myelination, respectively. (C) T1-weighted IR sequence shows delayed myelination, notably at the anterior limb of internal capsule, frontal, and temporal central and occipital peripheral white matter. (D) T2-weighted axial image shows symmetric abnormal T2-hyperintensity involving peri-trigonal deep white matter (black arrows) as well as delayed myelination at the anterior limb of internal capsules (arrowheads).
images (Figure 2). There was also diffuse white matter reduction and thinning of the corpus callosum (Figure 2). Both MRI studies showed the cerebellum was not affected.

Discussion

18q-deletion syndrome results from a partial deletion of the long arm of chromosome 18. The deletion encompasses a number of genes, of which MBP is most notable and has been described as a major component of the CNS. Up to 40% of the CNS is composed of MBP. MBP is expressed in oligodendrocytes for the maintenance and formation of myelin. Expression of MBP in oligodendrocytes and not Schwann cells could explain the involvement of the CNS and possible sparing of the peripheral nervous system.

The phenotype varies greatly between individuals but generally includes mental retardation, hypotonia, short stature, flat midface, ear anomalies, abnormal genitalia, and foot deformities. It was proposed that the variability derives from the heterogeneity of the deletion size and content. Thyroid dysfunction is not uncommon in 18q-deletion patients, where 12% of cases are affected according to Schaub et al. They observed that thyroid status is not static in these patients and progress from euthyroid to hypothyroidism over time. Yet, the mechanism is not known. Initial neonatal hypothyroidism screening was negative in our case. However, further endocrinological investigation was prompted by the picture of GDD revealing autoimmune hypothyroidism.

18q-deletion syndrome is classified among the hypomyelination disorders. Loevner et al showed the most common MRI findings were diffuse symmetrical T2-hyperintense signals in bilateral deep white matter, with the posterior periventricular regions most severely affected. Our case showed a pattern of delayed myelination as evidenced by minimal grey-white matter differentiation on T2-weighted imaging. Minimal changes in the abnormal white matter remained largely the same over the follow-up period, which is consistent with previous observations of persistent abnormal white matter pattern despite long periods of time. Consistent with previously reported MRI findings, the cerebellum and brainstem were largely unaffected in our case.

It has been considered that the abnormal white matter on MRI signifies hypomyelination. However, Tada et al has studied magnetic resonance spectroscopic findings in a patient with 18q-deletion and found elevated choline levels suggestive of increased turnover of myelin as a dysfunction of oligodendrocytes or myelin fibres. This could correlate with our observed findings of minimal myelination despite a period of years, such that there may be an altered balance of myelination and demyelination rather than simply a process of hypomyelination.

Figure 2  The previous radio-opaque appearance is no longer visible at control posterior-anterior chest X-ray (A) and there is no area compatible with atelectasis at control lung ultrasonography evaluation (B).
Radiological differential diagnoses of 18q-deletion syndrome include Pelizaeus-Merzbacher disease (PMD), Pelizaeus-Merzbacher-like disease, leukodystrophies with trichothiodystrophy, sialuria, fucosidosis and hypomyelination with atrophy of the basal ganglia and cerebellum (HABC). In PMD, Pelizaeus-Merzbacher-like disease, sialuria, and HABC, the cerebellum may become markedly atrophic, while in fucosidosis basal ganglia involvement is common. Derivation of the diagnosis involves combining clinical phenotype with radiological features of hypomyelination. PMD is an X-linked disease and occurs mainly in males. Nystagmus is usually more prominent and with earlier onset in PMD and Pelizaeus Merzbacher-like disease and evolving spasticity is also a feature of them. Marked skin hypersensitivity to sunlight occurs in trichothiodystrophy while in sialuria and fucosidosis, coarse facial features with organomegaly are common characteristics of storage diseases to help differentiate them from 18q-deletion syndrome. Extrapyramidal signs are often seen earlier in HABC than other hypomyelinating disorders. The myelination in 18q-deletion syndrome is much more advanced than in other hypomyelinating disorders. 18q-deletion syndrome differs from other hypomyelinating disorders such that its myelin deficit in MRI appears milder and patchier than in other hypomyelinating disorders. The clinical phenotype in this case together with MRI findings of hypomyelination provided clues for paediatricians to consider hypomyelinating diseases. This subsequently guided definitive diagnosis of 18q-deletion via karyotype analysis.

Conclusion

Partial deletions of the long arm of chromosome 18 are associated with a variable phenotypic clinical presentation. With regards to the CNS, the most commonly seen neurological manifestation on MRI is a delayed myelination pattern, which may reflect an insufficiency of MBP. Together with clinical findings, MRI features can aid clinical diagnosis of 18q-deletion syndrome.

Declaration of Interest

We declare that we have no conflict of interests.

References

Letter to the Editor

Trauma-induced Paediatric Stroke in a Carrier of the Prothrombin G20210A Heterozygous Mutation

Dear Editor,

Stroke is rare in children with an incidence of 1.6 cases of ischaemic arterial strokes per 100 000 children per year. However, stroke is among the most important causes of morbidity and mortality in children.

We had a child patient who has had ischaemic brain pathology in the right middle cerebral artery area with no vascular abnormality or any signs of thrombosis and who has been tested and found to be heterozygous for the Prothrombin G20210A mutation.

The 16 month old girl fell from the sofa and the occipital part of the head was mildly injured without losing consciousness. A few hours later, parents noticed that their daughter was unable to move upper and lower extremities of left body side. After admission to Klaipeda Hospital (Lithuania), a computed tomography scan of the head was performed. Brain ischaemia was suspected, and the girl was transferred to the Hospital of Lithuanian University of Health Sciences "Kauno Klinikos" (Lithuania) for treatment. Magnetic resonance imaging showed brain ischaemia in the right middle cerebral artery with no vascular abnormality or any signs of thrombosis. During treatment of the acute ischaemic stroke, focal seizure episodes appeared – eyes were turning to the left and left hand convulsions occurred. The electroencephalogram (EEG) registered minimal and doubtfully clinically significant alterations characteristic to epilepsy in the occipital part of the brain. Phenobarbital was administered and convulsions ceased. A genetic test was performed in order to exclude the possibility of a prothrombotic genetic predisposition. Heterozygous G20210A mutation in the prothrombin gene was detected. Genetic analysis of the factor V Leiden R506Q mutation was negative.

After 6 months, patient was re-evaluated. No new complaints or seizure episodes during the 6 month period were reported. Her vital signs and physical exam results were normal except for the left hemiparesis symptoms. Magnetic resonance imaging showed a glial scar in the previous ischaemic brain area. EEG returned no clinically significant characteristics that would indicate epilepsy.

Increased paediatric stroke rates are observed in children with congenital metabolic diseases, congenital heart disease, prothrombotic states or infection, head and neck trauma or in non-atherosclerotic arteriopathies. These factors are usually found in combination in children with stroke. The presented patient had two factors: a rare genetic predisposition to thrombosis and head trauma. According to unpublished data, from all these patients (n=84), who had been hospitalised due to thrombotic complications at Hospital of Lithuanian University of Health Sciences "Kauno Klinikos" in Lithuania from 2014 until 2016, only 4 patients were carriers of G20210A mutation. Other authors have described ischaemic stroke cases but without head injury, or without genetic predisposition. In total 7 cases of patients with ischaemic stroke after mild head injury in children were presented by Rana and his colleagues. Attia and colleagues reported a 6-year-old boy with cerebral venous sinus thrombosis, who was a G20210A heterozygote.

In conclusion, our case shows that Prothrombin G20210A mutation might be related to the increased risk of young-onset stroke after head injury.

Declaration of Interest

The authors declare that there is no conflict of interests.

Ethical Conduct of Research

The authors state that they have obtained appropriate institutional review board approval. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.
References


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Dear Editor,

We would like to raise the following issues regarding the case report "Very Prolonged Breastfeeding Causing Nutritional Rickets in a 4-year-old Local Hong Kong Boy".1

We are absolutely appalled by the lack of scientific rigour of the report, which apparently only aimed to create sensation rather than to educate.

First, we have serious doubts about the diagnosis of rickets based on the superficial clinical information presented. The diagnosis of rickets was assumed in this 4-year-old boy presenting with short stature (height just below the 3rd percentile), genu valgum and bilateral costochondral swelling, which had apparently resolved after treatment with Vitamin D. In the first place, there had been no mention of a proper examination and measurement of the genu valgum as recommended.2 The clinical photo (Figure 1A)3 demonstrating the presence of genu valgum only depicted the child's lower limbs standing with legs apart on an apparently soft surface and poorly aligned to give an impression of an exaggerated valgus. The radiograph (Figure 1B)3 of the lower limbs did not show epiphyseal changes of rickets. The clinical signs of costochondral swelling mentioned could not be verified as relevant clinical photos or X-rays were not provided. Moreover, the biochemical results were not supportive of rickets as demonstrated by normal serum Alkaline Phosphatase and Parathyroid Hormone levels. The serum 25(OH)D level (48 nmol/L) was only borderline insufficient (normal range 50-250 nmol/L). A recent SACN4 report on Vitamin D and Health concluded that, despite the varied results of studies, serum 25(OH)D concentrations of children with rickets were below 25 nmol/L in the majority of studies examined.

Without proper examination and documentation of the clinical signs, as well as supporting radiological signs and biochemical markers of rickets,4 the gradual alignment of the child's lower limbs on subsequent follow-up, from maximal genu valgum at 4 years to the neutral position at 6½ years (Figure 2B),4 and possibly the modest movement of height percentile from just below the 3rd to the 10th could well have been explained by the natural history of a physiological genu valgum, instead of vitamin D treatment.

Second, we have grave concern about the incongruity of describing the child's unsatisfactory feeding pattern as "prolonged breastfeeding" only because he had been breastfeeding once daily at such an age, as well as attributing his Vitamin D insufficiency to the "prolonged breastfeeding". A detailed dietary history and sun exposure history should have been taken, analysed and reported, instead of giving only a few broad comments about his continued breastfeeding, small appetite for solids and little exposure to sunlight.

Notwithstanding the above, we concur that vitamin D is important for children. We should ensure all children, especially exclusively breastfed babies, have adequate vitamin D, given that breastmilk, by its nature, has a low level of vitamin D. It is important to educate parents that most of the vitamin D in our body is made by exposing the skin to sunlight. Having outdoor activities with exposure of limbs and face to sunlight for a short daily period enables children to produce vitamin D for optimal growth. For those with a history of insufficient or inconsistent sunlight exposure and intake of Vitamin D rich food (e.g. fatty fish, egg yolk, liver and fortified food), supplementation should be seriously considered.5

Declaration of Interest

None

References

Reply

Dear editor,

We would like to thank Dr. R Cheng and colleagues for their comments on our case report.

The aim of writing up the case report was to share with peers, our clinical findings of rickets in a "family with insufficient Vit D supplement/intake" because of poor knowledge in nutrition and dietary supplement of Vit D. The patient, his 2-year-old brother and the mother were all nutritionally deficient in Vit D. The history of dietary intake was small, Vit D was not supplemented and sun-exposure was limited. The patient, a 4-year-old boy, had the longest breast feeding history until presentation but we had noted that he was then actually breastfed only once a day and did start to have more other food but still had insufficient Vit D intake and sun exposure.

We agree with your observations that we did not have robust evidence for rickets. There were obvious knocked knees and rickety rosary. We agree with you that this is not a florid case most probably because they did not have sufficient sun exposure, all having solid food though of insufficient quantity and had reduced the amount of milk intake as they grow older.

We thank your comments and we want to reiterate that our aim is to advise parents that breast feeding is best for children for the first year and yet Vit D supplement, a variety of food sufficient in quantity, and sun exposure, are important.

References


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Clinical Quiz

What is the Diagnosis?

The proband is a 5 years old boy. He was born at full term in China to a non-consanguineous Chinese couple. Antenatal checkup was normal. Postnatally, he had long segment Hirschsprung’s disease with colectomy and ileocolic anastomosis performed at 1 year of age. He was referred to genetic clinic for multiple congenital anomalies. Physical examination at 19 month old of age showed microcephaly (44.7 cm, <3rd centile), bilateral low set and posteriorly rotated ears, hypertelorism, upturned nostrils, bilateral postaxial polydactyly, bilateral 2/3 syndactyly of toes (Figure 1). He had normal male genitalia. His body weight and body height were 9.2 kg (3-10th centile) and 77.5 cm (3-10th centile) respectively. He had borderline developmental delay. He had failure to thrive with body weight and body height centiles at 3rd centile in subsequent follow up.

Figure 1  (A) Post-axial polydactyly of right hand; (B) Facial profile; (C) 2/3 syndactyly of left toes. (Consent for publication has been obtained).

The clinical quiz was prepared by:
SSW Cheng
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Answer to "Clinical Quiz" on Pages 266-267
N.B. The Editors invite contributions of illustrative clinical cases or materials to this section of the journal.
Abstracts of Articles in Chinese

巴西聖保羅州的極複雜唇裂及／或齶裂手術是否區域化，而相關的門診服務則分散設立在不同地區？

MR Tovani-Palone, A Fomenton, SR Bertolini. Are There Regionalisation of High Complexity Surgeries and Decentralisation of Outpatient Treatment Services for Cleft Lip and/or Palate in the State of São Paulo, Brazil? HK J Paediatr (new series) 2018;23:211-219

目的：於2000年至2015年期間在巴西聯合健康系統或／和巴西聖保羅州立慈善機構登記的唇裂和／或齶裂，對進行高複雜性手術的區域化和門診病人治療服務分散設立在不同地區的情況進行調查。方法：本研究為分類和比較性，互聯網免費網址和記錄範圍包括國家健康基本登記系統、國家 PROFIS 網組織登記中心。其他資料來自 SUS 資料部門，以相應代碼查詢唇裂和齶裂手術治療情況。結果：根據國家基本健康登記系統，聖保羅州認證的專門進行唇裂和齶裂高難度手術中心有9個，位於8個城市中。2000年後認證的新中心有6個。州內組織共13個，其中2個成立於近15年。唇裂齶裂主導核心僅有1個。獲得認證的機構中，聖保羅大學頭面畸形康復醫院，得到醫院內部管理部門批准的高難度唇裂齶裂手術數量特別大。結論：資料顯示高難度的唇裂齶裂手術治療呈現中心化，而門診服務則分散設立在不同地區的趨勢。

關鍵詞：唇裂，齶裂，公共健康實施，管理政策，區域健康計畫

陳健良醫師

臍膨出嬰兒的相關異常和臨床療效：單一中心回顧


目的：對10年期間香港瑪麗醫院住院的臍膨出新生兒的圍產期特徵、相關異常、臨床療效進行研究。方法：作者查出2005至2014年瑪麗醫院新生兒重症監護室住院的所有臍膨出新生兒。對病人和母親的一般資料、相關異常、和臨床療效，進行回顧性綜述。結果：查出臍膨出嬰兒共19例。中位分娩孕週為38週，中位出生體重3140克。52%（10/19）的診斷併伴至少一項其他異常，先天性心臟異常為最常見的相關性異常。中位手術年齡（一期手術關閉或應用 Silo）為生後第一天，分段手術進行延遲關閉的中位年齡為8天。一期修復大多用於無肝臟內部的臍膨出的嬰兒，對比帶有肝臟內容的臍膨出，分別為（7/8 [88%] vs. 4/11 [36%], p=0.03）。出院時的生存率為84%（16/19）。3例中的2例死於致命性先天性畸形（嚴重肺泡毛細血管發育不良），另一例出現術後中腸轉轉。6例發生術後併發症（6/17 [35%]），以腹部疝最為常見。發現的遠期臨床問題包括體格發育停滯（6/12 [50%]）、胃食管反流（5/12 [42%]）、癲癇發作（3/12 [25%]）和反復肺部感染（1/12 [8%]）。結論：臍膨出常見有相關性異常和遺傳異常。新生兒檢查應包括對各種異常的篩查。無術後併發症的單純臍膨出的預後遠期良好。

關鍵詞：香港、臍膨出、療效
背景：嬰兒整體動作質量之相關高危因素


關鍵詞：煩躁不安動作、整體動作、嬰兒、風險因素、扭動動作

陳健良醫師

嬰兒及兒童的雙主動脈弓

CH Xie, FQ Gong, GP Jiang, SL Fu. Double Aortic Arch in Infants and Children. HK J Paediatr (new series) 2018; 23:233-238

關鍵詞：雙主動脈弓 (DAA)、心臟超聲、血管環

陳健良醫師
肛門兒童的掛線置入


掛線(FIA)常見於嬰兒，常併發肛周膿腫(PA)。對FIA或PA的治療都是保守性質。對不癒合的FIA所進行的手術處理，最常見的是縫管切除術或縫管切除術，其復發率為0-68%。掛線置入，原來用於成人肛門尤其是括約肌間腸治療，已在少數研究中用於兒童病人。本研究目的，在於報告作者的經驗，以外科手術手套的碗口部分進行掛線置入治療3例FIA病人。所進行的掛線置入的病人沒有復發。手術時間通常20分鐘內。此外，所用的掛線是外科手術手套的碗口部分，便宜而且容易使用。掛線置入可快速廉價治療兒童FIA，沒有復發和大便失禁，應該優先採用。

關鍵詞：兒童、肛門、掛線置入、治療

—例肺不張兒童的肺部超聲檢查

AK Özkaya, HL Yilmaz, SS Gökay, ÖT Kendir. Lung Ultrasonography for Pulmonary Atelectasis in a Child. HK J Paediatr (new series) 2018;23:242-245

兒童肺不張可見於數種肺部和胸腔疾病過程中的一個病理情況，無特徵性症狀或臨床表現。早期準確診斷對於治療至關重要。遇到肺不張病人的首選影像檢查是正位X線胸片。然而，目前使用床邊超聲檢查可對數種肺部疾病進行診斷和監測。作者報告一病例，9歲，因喘息、咳嗽、流涕進行檢查，正位X線胸片為外周分佈的右上區不透射影。床旁超聲檢查的肺部檢查影像符合肺不張。適當治療後，對照超聲檢查和正位X線胸片的肺不張影像消失。肺部超聲是一影像技術，尤其適用於兒童，可作為診斷和監測肺不張提供新的選擇。

關鍵詞：肺不張、肺部超聲、兒科

中國男童帶馬歇爾—史密斯綜合徵—例


馬歇爾—史密斯綜合徵（MSS）為一種畸形性疾病，特徵為加速成長骨關節成熟、發育遲緩和面部殘缺。目前醫學文獻描述MSS病人超過50例，累及神經系統、肌肉骨關節系統、呼吸系統、結締組織、眼睛和耳朵。在此，作者報告一例診斷為MSS，具有新的臨床表現——肛周贅肉和大陰囊。

關鍵詞：馬歇爾—史密斯綜合徵（Marshall-Smith）綜合徵
18-qt缺乏綜合徵—特徵性的核磁共振成像（MRI）表現

WWC Tsui, EYL Kan, WS Mak, STH Fung. 18q-Deletion Syndrome - Characteristic MRI Features. HK J Paediatr (new series) 2018;23:250-253

作者描述一例確診18q缺失綜合徵兒童的MRI情況。其神經學表現常累及白質，可能是由於中樞神經系統髓鞘形成的主要成分—髓鞘基本蛋白的單倍體不足造成。在本例報告中，MRI顯示雙側白質對稱性T2高信號，伴灰白質的區別消失，提示遲緩髓鞘化特徵。隨後5年追蹤影像顯示髓鞘化進展低下。

關鍵詞：18q缺失、髓鞘化、髓鞘基本蛋白
MCQs

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

(A) Are There Regionalisation of High Complexity Surgeries and Decentralisation of Outpatient Treatment Services for Cleft Lip and/or Palate in the State of São Paulo, Brazil?

1. Which of the following is related to regionalisation?
   a. Centralisation of high complexity services.
   b. Transfer of the decision-making power, management driven by providers and financial resources to the states and municipalities.
   c. Development of regional arrangements for health care.
   d. Transfer of elements concentrated at the federal level to the municipalities.
   e. Very little intergovernmental interdependence.

2. Which of the following is correct about the institutions for treatment of cleft lip and/or palate in the state of São Paulo, Brazil?
   a. The state of São Paulo has three regional nuclei.
   b. There is only one regional nucleus.
   c. The state of São Paulo has 20 associations.
   d. There are five associations.
   e. There are two specialised treatment centers.

3. Which of the following is NOT correct about the Hospital for Rehabilitation of Craniofacial Anomalies, University of São Paulo, Brazil?
   a. It serves patients from all regions of Brazil and others arising from abroad.
   b. It is linked to the Brazilian Unified Health System.
   c. It is a world class reference in the treatment of cleft lip and/or palate.
   d. It is a private hospital.
   e. It is the largest treatment center for craniofacial anomalies in South America.

4. Which of the following is (are) a problem (problems) for the treatment of cleft lip and/or palate in Brazil?
   a. Organisation of the reference and counter reference system.
   b. Unpreparedness of the public health services and geographical distance.
   c. Absence of this theme in the curricula of undergraduate and postgraduate courses.
   d. Total ignorance of many professionals about cleft lip and/or palate.
   e. All of the above.

5. Which of the following is NOT a characteristic of the treatment of cleft lip and/or palate?
   a. It is highly specialised.
   b. It requires a team with professionals from different health areas.
   c. It is often inexpensive.
   d. The treatment course is often long.
   e. It requires integral care.
(B) Associated Anomalies and Clinical Outcomes in Infants with Omphalocele: A Single-centre 10-year Review

1. Which of the following is the most common congenital anomaly associated with omphalocele?
   a. Alveolar capillary dysplasia
   b. Urinary tract anomaly
   c. Beckwith-Wiedemann syndrome
   d. Congenital heart disease
   e. Imperforate anus

2. Which of the following statement is NOT TRUE according to the article?
   a. Infants with non-liver containing omphaloceles were more likely to have primary repair compared to those with liver-containing ones.
   b. Giant omphaloceles were more likely to have pulmonary hypoplasia compared with non-giant types.
   c. In general, infants with giant omphaloceles were mechanically ventilated for a longer duration than those with non-liver containing ones.
   d. Congenital heart disease is the most common associated anomaly in infants with omphaloceles.
   e. Survival rate at discharge was low for isolated omphalocele without other congenital anomalies.

3. What is the median age of first feeding in this study?
   a. Day 6 of life
   b. Day 7 of life
   c. Day 8 of life
   d. Day 9 of life
   e. Day 10 of life

4. What is the most common postoperative complication identified in this study?
   a. Ventral hernia
   b. Adhesion
   c. Wound infection
   d. Gut volvulus
   e. Deep vein thrombosis

5. Which of the following is NOT a known medical long-term complication of omphalocele?
   a. Failure to thrive
   b. Gastroesophageal reflux
   c. Recurrent urinary tract infections
   d. Developmental delay
   e. Recurrent lung infections

(C) Risk Factors Associated with General Movement Quality in Infants

1. Which of the following is NOT risk factors and predictors for abnormal general movements in infants?
   a. Low delivery gestational age
   b. Low birth weight
   c. Severe asphyxia
   d. Hyperbilirubinaemia
   e. Whether the newborns are twins

2. Which of the following is an abnormal type of GMs during preterm, term and early post-term age?
   a. Normal GMs (N)
   b. Cramped-synchronised GMs (CS)
   c. Fidgety movements (F+)
   d. Absent (F−)
   e. Abnormal (AF)

3. Which of the following is an abnormal type of GMs at the stage of fidgety movements?
   a. Poor repertoire of GMs (PR)
   b. Cramped-synchronised GMs (CS)
   c. Chaotic general movements (CH)
   d. Absent (F−)
   e. Fidgety movements (F+)

4. Which of the following is the best observing time for writhing movements?
   a. From the third day after birth to corrected age of 4 weeks (according to the expected date of delivery)
   b. From the ninth day after birth to corrected age of 15 weeks (according to the expected date of delivery)
   c. From the third day after birth to age of 4 weeks
   d. From the ninth day after birth to age of 15 weeks
   e. Between 2 and 5 months of age

5. Which of the following is the best observing time for fidgety movements (FMs)?
   a. From the third day after birth to corrected age of 4 weeks (according to the expected date of delivery)
   b. From the ninth day after birth to corrected age of 15 weeks (according to the expected date of delivery)
   c. From the third day after birth to age of 4 weeks
   d. From the ninth day after birth to age of 15 weeks
   e. Between 1 and 2 months of age
(D) Double Aortic Arch in Infants and Children

1. Which is the correct description for double aortic arch?
   a. Anomalous left pulmonary artery
   b. Right aortic arch
   c. An anomaly of the aortic arch in which two aortic arches form a complete vascular ring
   d. Coarctation of aorta
   e. Vascular sling

2. Patients with double aortic arch may be misdiagnosed with many other diseases except:
   a. Asthma
   b. Diarrhoea
   c. Gastro-oesophageal reflux
   d. Feeding difficulties
   e. Recurrent cough

3. Which symptoms may occur if the vascular ring causes compression of the trachea and/or oesophagus?
   a. Cough
   b. Vomiting
   c. Tachypnoea
   d. Wheezing
   e. All of the above

4. Which modality should be considered first to confirm the diagnosis of double aortic arch:
   a. Bronchoscopy
   b. Chest X-ray
   c. Computed tomography
   d. Angiography
   e. Electrocardiogram

5. A vascular ring occurs when the aorta or its branches form a complete ring around the trachea and the esophagus. Which is the most common anomaly?
   a. Double aortic arch
   b. Right aortic arch
   c. Anomalous left pulmonary artery
   d. Anomalous left carotid artery arising further to the right than usual and passing anterior the trachea
   e. Anomalous innominate artery arising further to the left on the arch than usual

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**Answers of April issue 2018**

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CLINICAL QUIZ (p258) ANSWER

What is the diagnosis?

The clinical features of this child with history of Hirschsprung's disease, microcephaly, failure to thrive, developmental delay, postaxial polydactyly and bilateral 2/3 syndactyly of toes were compatible with Smith-Lemli-Opitz syndrome (SLOS). Therefore plasma sterol for investigation of cholesterol biosynthesis defects was performed. It showed normal plasma cholesterol level with markedly elevated 7-dehydrocholesterol and 8-dehydrocholesterol. Diagnosis of SLOS was biochemically confirmed and he was then put on cholesterol supplement and HMG CoA reductase inhibitor. His failure to thrive was gradually improved with latest body weight and height centile at 50th and 25th centile respectively. DHCR7 genetic analysis was then carried out which showed compound heterozygous pathogenic variants DHCR7 (NM_001360.2):c.[1A>G];[575C>T]. Both parents were asymptomatic heterozygous carriers.

SLOS (OMIM #270400) is an autosomal recessive disease resulted from deficiency of the final enzyme in the cholesterol synthesis pathway. It was first described in 1964 by Department of Pediatrics at the University of Wisconsin, Madison. The birth prevalence of SLOS is estimated to be approximately 1:20,000 to 1:40,000 live births in western population.

It is characterised by prenatal/postnatal growth retardation, microcephaly, moderate to severe intellectual disability and/or multiple malformations. The malformations included distinctive facial features, cleft lip/palate, cardiac defects, underdeveloped external genitalia in males, postaxial polydactyly and 2/3 syndactyly of toes (Y-shape). The clinical presentation is highly heterogeneous. Clinical diagnostic criteria have not been established. High index of suspicion is required. And this case is the first molecularly confirmed case in Chinese population.

Figure 2  The diagram showing the biosynthesis of cholesterol.
What are the Biochemical Defects in SLOS?

Children with SLOS have defect in the last step of biosynthesis of cholesterol. Deficiency in enzyme 7-dehydrocholesterol delta-7-reductase activities would lead to reduction of cholesterol and accumulation of the cholesterol precursors 7-DHC and 8-dehydrocholesterol (8-DHC) (Figure 2). This contributes to the unique sterol profile in SLOS.

How is the Diagnosis Established in SLOS?

The diagnosis of SLOS relies on clinical suspicion and detection of elevated serum concentration of 7-DHC. Serum concentration of cholesterol may be in the normal range in approximately 10% of affected individuals, making it an unreliable test for screening and diagnosis. In 1998, the gene 7-dehydrocholesterol reductase (DHCR7) encodes the enzyme 7-dehydrocholesterol delta-7-reductase that reduces 7-DHC to cholesterol was discovered to be the causative gene of SLOS. It is so far the only gene that causes SLOS. Sequence analysis of DHCR7 detects approximately 96% of cases. Carrier detection is possible if the pathogenic variants in the family are known. Carriers are asymptomatic. In the old day, prenatal testing for pregnancies at risk is only possible by using amniotic fluid or tissue from chorionic villus sampling for biochemical testing of elevated 7-DHC. Currently, prenatal diagnosis or even preimplantation genetic diagnosis can be offered to at risk couples if the known pathogenic variants have been identified in those families.

What Are the Management Issues for SLOS?

Management of SLOS required multi-disciplinary approach, which included pharmacological interventions, e.g. cholesterol supplementation and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (HMG CoA reductase inhibitors), physical/occupational/speech therapies and dietitian support. Neonatal cholestatic liver disease responds well with cholesterol and/or bile acid therapy.

HMG CoA reductase inhibits the cholesterol pathway proximal to the enzymatic defect in SLOS and increases the expression of hypomorphic DHCR7 alleles. It was relatively safe and improved the dehydrocholesterol-to-total sterol ratio biochemically in patients with SLOS.

Acknowledgement

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

References

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

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

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

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