OPathPaed service model for expanded newborn screening in Hong Kong SAR, China

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Prevention, if available and feasible, is always the better way to practise medicine. Newborn screening for genetic diseases is a successful example of preventive medicine in action, with specific focus on phenylketonuria. Early dietary treatment prevents devastating mental retardation, provided that the condition is detected in the presymptomatic neonatal period. In recent decades, the advent of tandem mass spectrometry enables cost-effective, accurate and simultaneous detection of more than 20 genetic diseases on a single dried blood spot.

Tandem mass spectrometry is a routine, state-of-the-art technology found commonly in most clinical laboratories, enabling screening with sensitivity and specificity of 99% and 99.99%, respectively, for most amino acid disorders, organic acidaemias and fatty acid oxidation defects.[1–5] The overall recall rate ranges from 0.07% to 0.33% with positive predictive values of 8% to 18%.[6–15]

The target population is mainly healthy newborns and the objective is to identify affected babies before the onset of symptoms to allow upstream intervention. Hence, the programme success relies heavily on the technology application and data interpretation.

Expanded newborn screening saves lives. Early identification and treatment of these disorders can help individuals live a normal life. Newborn screening is more than a test; it consists of parent education, consent, sample collection, analysis, results interpretation, reporting, counselling and case tracking.

In 2006, the American College of Medical Genetics recommended 29 disorders as the core panel for screening, and 25 secondary targets including disorders of amino acids, organic acids, fatty acid oxidations and haemoglobinopathies.[16] Expanded newborn screening has been widely accepted and implemented. For instance, newborn screening for hyperphenylalaninaemia has been mandatory by law in China since 2000, and expanded newborn screening that covers many more conditions has been implemented in many areas.[17]

However, in the Hong Kong Special Administrative Region (SAR) of China, the newborn screening covers only congenital hypothyroidism, glucose-6-phosphate dehydrogenase deficiency, and congenital hearing loss, but not hyperphenylalaninaemia. Reasons and difficulties are multifaceted.

First, the importance of expanded newborn screening has not been given a high enough priority. There is a general lack of public education and understanding of the cost-effectiveness and necessity of upstream identification and treatment of rare metabolic diseases. For instance, a survey of parental knowledge about expanded newborn screening[18] showed that 172 parents (87.8%) had not heard of expanded newborn screening and 137 parents scored their knowledge about metabolic diseases as zero. However, almost all parents (98.8%) agreed that Hong Kong SAR should follow the mainland policy on expanded newborn screening.

Second, comprehensive data on the local disease spectrum and incidence were not reported until recently.[19] The overall incidence of amino acid disorders, organic acidaemias and fatty acid oxidation defects was one in 4122 live births, one in 29,542 for hyperphenylalaninaemia. The incidences are similar to most parts of the world and thus support the introduction of a similar programme for Hong Kong babies.

Third, without expanded newborn screening, patients present downstream with clinical diseases or complications. As a result, experience in the diagnosis and management of metabolic diseases accumulates in hospital paediatricians and pathologists in acute hospitals. It is essential that there should be free flow of information and the sharing of experience between colleagues working in the acute hospitals and in the public health sector.

Fourth, more emphasis should be given to other important areas such as an update on the healthcare policy on newborn screening, the development of better confirmatory investigation services, and improvement in specific treatment for the diseases involved.

Last, but by no means least, the use of umbilical cord blood samples in the existing programme is not suitable for the detection of metabolic diseases, with false-negative rates seen to be unacceptably high.[22] Post-natal blood samples should be collected at least 24 hours after birth.[16]

This study proposes a hospital-based OPathPaed service model for the implementation of expanded newborn screening in Hong Kong SAR and seeks to evaluate its feasibility. OPathPaed integrates input from obstetricians, pathologists and paediatricians. As all babies born in Hong Kong are normally delivered in public or private hospitals, such an approach can achieve full coverage. Similar success of hospital-based population screening has been documented in local prenatal Down's syndrome screening[23] and congenital hearing loss newborn screening programmes.[24] In addition, local reference intervals of dried blood spot amino acids and acylcarnitines have been established from 310 healthy Chinese newborns.

Parents of babies born between July and November 2010 in the Department of Obstetrics and Gynaecology, Princess Margaret Hospital, Hong Kong SAR, were invited to take part in the study. Pretest counselling workshops for mothers were conducted before discharge and informed consent was obtained. Education pamphlets with an enquiry hotline telephone number were distributed to the parents. Only full-term babies of normal birth weight were recruited. Participation in this study did not affect routine newborn screening.

Dried blood spot samples on Whatman 903 filter paper

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were collected by heel prick from newborns aged between 24 hours and 10 days. An alternative laboratory appointment was made within 10 days of birth for those babies who were less than 24 hours old at the time of discharge from the post-natal ward. Samples were stored at –20°C (with silica desiccation) until analysis. The study was approved by the local ethics committee.

A 3-mm dried blood spot was analysed using a commercial assay kit (MassChrom amino acids and acylcarnitines, Chromsystems Instruments and Chemicals, Munich, Germany), following the manufacturer's instructions. The treated sample was injected directly into a tandem quadrupole mass spectrometer (Waters Quattro micro, Waters Corporation, Milford, USA). Simultaneous detection and semi-quantitative determination using multiple reaction monitoring were performed for alanine, arginine, citrulline, glycine, leucine, methionine, ornithine, phenylalanine, tyrosine, valine, free carnitine, C2-, C3-, C4-,C5-, C5DC-, C6-, C8-, C10-, C12-, C14-, C16- and C18-acylcarnitines. Data acquisition was conducted by QuanLynx Application Manager (Waters Corporation, Milford, USA). Diagnostic performance of the method was evaluated for precision and accuracy. Thirty-one replicates were performed on four different days. Mean, standard deviation and coefficient of variation (CV) for each analyte were calculated. Ten QC samples from the Centers for Disease Control and Prevention (CDC) Newborn Screening Quality Assurance Program 2010 were analysed. The disease profile included 21 metabolic disorders, including hyperphenylalaninaemias, tyrosinaemia types I and II, maple syrup urine disease, homocystinuria, ornithine transcarbamylase deficiency, citrullinaemia types I and II, argininaemia, methylmalonic acidaemia, propionic acidaemia, isovaleric acidaemia, glutaric aciduria type I, branched-chain ketothiolase deficiency, carnitine uptake defect, carnitine palmitoyltransferase deficiency types I and II, carnitine-acylcarnitine translocase deficiency, medium-chain acyl-coenzyme A dehydrogenase, very long-chain acyl-coenzyme A dehydrogenase deficiency, and multiple acyl-CoA dehydrogenase deficiency (glutaric aciduria type II). The choices were based on the local disease spectrum[19] and the recommendation of the American College of Medical Genetics.[16] Reference intervals of all analytes were established using Analyze-it software version 2.14.

Babies with normal results were regarded as having a normal risk and were not notified. Pathologists were responsible for contacting the parents of babies showing abnormal results for post-test counselling and arranging referral to the metabolic clinic. Confirmatory testing was performed by measuring functional metabolites and/or genetic diagnosis by direct DNA sequencing wherever appropriate. One-year hospital records were reviewed to identify any hospital admission of any of the newborns screened. Figure 1 depicts the workflow of the OPathPaed service model.

Sixty education workshops were organised and 310 babies were recruited with informed parental consent. Some participants introduced the study to their relatives and friends and they also requested to have their older children tested. In addition, parents were selected at random for telephone interview and over 97% expressed their satisfaction and did not perceive any adverse effect on the mother-child relationship.

Within-run and between-run precision was satisfactory with mean coefficient of variation (CV) of 2.8–10.1% except for arginine and ornithine. Results on all external quality assessment samples were correct (data not shown). Apart from delivery history, no additional hospital admission information was found for any of the babies taking part in the study. Subsequently, the results were used to establish local reference intervals. Table 1 summarises the reference intervals and precision data.

This study reports a pilot investigation of expanded newborn screening for inborn errors of metabolism in Hong Kong SAR. It demonstrates the feasibility and success of a hospital-based service model for expanded newborn screening that is suited to the Hong Kong healthcare system. The merit of this model is its ability to integrate the screening programme with the newborn delivery model and existing expertise. Similar success has been established in the prenatal Down's syndrome screening and congenital hearing loss newborn screening programmes.

The objectives and design of this study were in concordance with other published pilot studies of expanded newborn screening.[7–11] The major essential elements required in a pilot study of expanded newborn screening were included; for example, education and consent, sampling

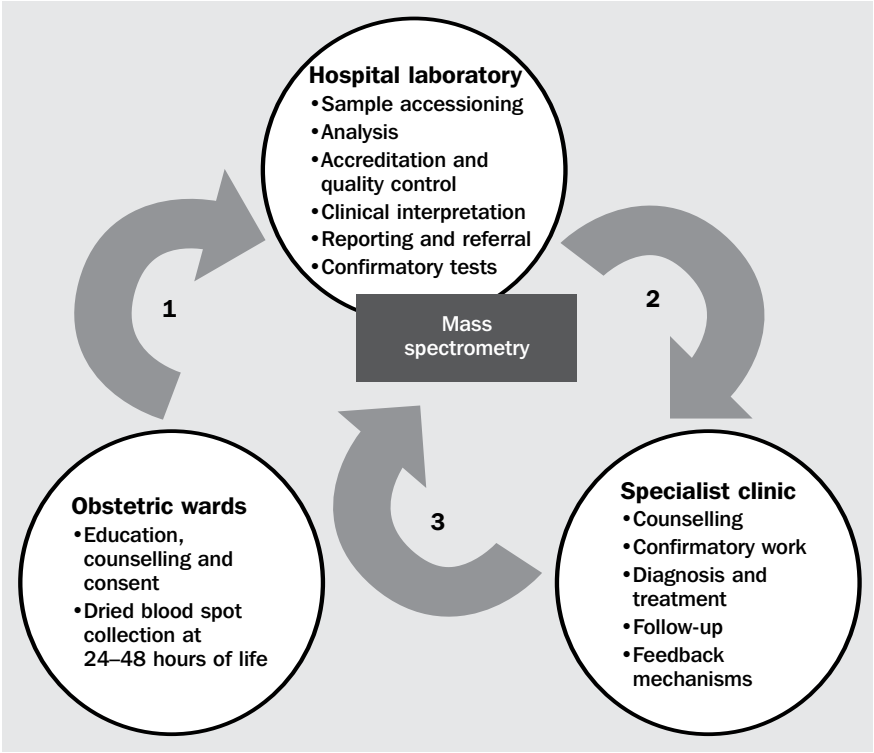

Fig. 1. Hospital-based OPathPaed service model of expanded newborn screening for Hong Kong SAR.

Table 1. Reference intervals and CV of the dried blood spot amino acids and acylcarnitines in Chinese full-term neonates.

Analyte	2.5th percentile (μmol/L)	97.5th percentile (μmol/L)	CDC cut-offs (μmol/L)	Mean CV (%)
Alanine	159	366	NA	2.9
Arginine	3.79	29	<50	21.9
Citrulline	11	31	<60	4.8
Glycine	206	607	NA	6.4
Leucine	70	234	<300	2.8
Methionine	4.8	19	<100	4.0
Ornithine	63	242	NA	22.1
Phenylalanine	43	92	<150	4.5
Tyrosine	45	163	<408	5.8
Valine	40	198	<300	4.9
C0-carnitine	16	53	>8.60	5.8
C2-carnitine	5.72	45	NA	3.8
C3-carnitine	0.62	3.50	<6.00	3.7
C4-carnitine	0.11	0.35	<1.40	3.7
C5-carnitine	0.07	0.33	<0.80	4.8
C5DC-carnitine	0.10	0.35	<0.35	10.1
C6-carnitine	0.03	0.09	<0.50	4.5
C8-carnitine	0.03	0.13	<0.50	3.2
C10-carnitine	0.04	0.21	<0.55	3.7
C12-carnitine	0.04	0.23	NA	3.8
C14-carnitine	0.08	0.30	<0.79	4.1
C16-carnitine	0.77	4.84	<7.50	4.7
C18-carnitine	0.26	1.24	<2.50	5.6

NA: not available.

strategy, specimen requirement, screening methods, quality assurance and laboratory accreditation, result analysis and interpretation, reporting, reference intervals and clinical decision cut-offs, follow-up and case-tracking actions, psychological assessment, confirmation of abnormal screening results, and appropriate referral.

According to the latest Clinical Laboratory Standards Institute guidelines (LA4-A4 Blood Collection on Filter Paper for Newborn Screening Programs), blood samples collected after 24 hours of age are adequate for detecting hyperphenylalaninaemia, while allowing earlier screening of organic acidaemias and fatty acid oxidation defects. In Hong Kong, all deliveries are normally conducted in hospital and the babies usually stay with their mothers in the post-natal ward for 24-48 hours. Thus, it is convenient to collect dried blood spots prior to discharge and ensure maximal service coverage.

In many expanded newborn screening programmes, the majority of the responsibity for the service rests with the laboratory.[14,25,26] In the authors' experience, pathologists specialised in biochemical genetics are able to provide the pivotal function throughout the screening programme. Pretest counselling is a very important process to ensure that parents or legal guardians have adequate understanding of the screening purpose, advantages and disadvantages, as well as patients' rights. The roles and responsibilities of laboratory genetic counsellors were advocated recently, and covered issues such as test options, testing strategy, methodology, test sensitivity, limitations and results implications.[27]

It is understood that metabolic disease patients may present with late-onset or atypical conditions, who may escape detection by expanded newborn screening. However, most false-negative cases would be expected to present within the same hospital catchment area, and it is logical to suppose that the same team conducting the screening programme will continue to provide support to these patients, resulting in efficient long-term feedback.

The multidisciplinary service should include consultation services, provision of emergency metabolic investigation, regular reviews and conferences. Close collaboration between obstetricians, chemical pathologists and paediatricians has been established in most regional hospitals in Hong Kong SAR, resulting in an effective multidisciplinary approach to screening.

The field of newborn screening is expanding rapidly. For example, in addition to disorders of amino acids, organic acids and fatty acids oxidation, the potential of tandem mass spectrometry has been extended to cover conditions such as lysosomal disorders,[28–31] congenital adrenal hyperplasia,[32–35] and T-cell receptor excision circles for the diagnosis of severe combined immunodeficiency.[36–39]

In 2008, an inquest was called into the death of a 14-year-old Hong Kong Chinese boy who died of glutaric aciduria type II (multiple acyl-CoA dehydrogenase deficiency).[40] Permission was obtained from the Coroner's Court for the following information abstracted from the response to the jury's recommendation. In the rider, it was recommended that a multidisciplinary task force comprising chemical pathologists, paediatricians, geneticists and obstetricians be established urgently and should seriously consider the implementation of expanded newborn screening in Hong Kong.

The report commented that randomised clinical trial of clinical value and cost-effectiveness was not feasible because of the rarity of inborn errors of metabolism. Moreover, results of cost-effectiveness studies indicate that most newborn screening programmes improve outcomes and reduce overall costs.

Some 29 conditions are considered appropriate for newborn screening because there is an appropriate test, an efficacious treatment, and there is adequate knowledge of the disease's natural history.[16] Availability of curative treatment is not a prerequisite for implementation.

The example of an emergency investigation, 'The Right to be Impatient', undertaken by the Ontario Ombudsman into whether the Ontario Health Ministry had failed to administer newborn screening properly, was quoted in the rider to the coroner's report, in order to illustrate the

seriousness of potential medicolegal negligence as a result of deferring the implementation of expanded newborn screening (www.ombudsman.on.ca/Files/sitemedia/Documents/Investigations/SORT%20Investigations/the_right_to_be_impatient_20050927.pdf).

The current lack of progress is underlined by several examples: a 12-month-old girl with hyperphenylalaninaemia diagnosed as cerebral palsy,[41] a 14-day-old baby suffering from respiratory failure and cerebellar haemorrhage due to isovaleric acidaemia,[42] and a fatal case of a two-month-old boy with very long-chain acyl-CoA dehydrogenase deficiency.[27]

Without an expanded newborn screening programme in Hong Kong, patients will continue to suffer from delayed diagnosis and treatment. Although the major limitation of this study is the small sample size, it is the first pilot investigation in expanded newborn screening that addresses specific needs in Hong Kong SAR. It should prove useful to the future territory-wide programme. □

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