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Original Article

Evaluation of the 18-month "Pilot Study of Newborn Screening for Inborn Errors of Metabolism" in Hong Kong

The Task Force on the Pilot Study of Newborn Screening for Inborn Errors of Metabolism

Abstract ***Introduction:*** After the release of the Chief Executive's 2015 Policy Address in Hong Kong, a pilot study was planned and implemented to study the feasibility of trying out in the public healthcare system a screening programme for newborn babies for inborn errors of metabolism (IEM). After six months of preparation, the "Pilot Study of Newborn Screening for Inborn Errors of Metabolism" was launched in October 2015 in two public birthing hospitals (Queen Elizabeth Hospital and Queen Mary Hospital). It lasted for 18 months in two phases: Phase I from October 2015 to March 2016 (covering 21 IEM diseases) and Phase II from April 2016 to March 2017 (covering totally 24 IEM diseases). ***Aim:*** This paper is to review the course of events and discuss about the clinical findings of the Pilot Study. ***Results and conclusion:*** The Pilot Study had been operated smoothly, in aspects of parental education, specimen collection, preparation and dispatch of specimens. There were effective communication and cooperation among different parties involved in baby recall, arrangement of further investigations and clinical management. 15,138 out of 15,361 (98.5%) eligible babies had parental written consents to join the Pilot Study and 9 IEM cases were confirmed (incidence of the Pilot Study was 1 in 1,682 (Confidence interval (CI): one in 909 to one in 3,333)). Two mothers were incidentally picked up with IEM of carnitine uptake deficiency (CUD) and classic phenylketonuria respectively, and two false negative cases of Citrullinaemia type II (CIT type II) were notified. Incidence was increased to 1 in 1,376 if the two false negative cases were also included and it is higher than those in other countries or regions. Collectively, IEM cannot be claimed to be rare in Hong Kong.

Key words Hong Kong; Inborn errors of metabolism; Newborn screening; Pilot study

Introduction

Screening is defined as the "systematic application of a test or enquiry to identify individuals at sufficient risk of a specific disorder to warrant further investigation or direct preventive action, amongst persons who have not sought medical attention on account of symptoms of that disorder."[1] Worldwide newborn screening programmes were started in 1960s. They can improve infants' health, through early identification and timely intervention of particular disorders which can be life-threatening or cause long-term disabilities to babies.[2]

With advancement of technology, tandem mass spectrometry (MS/MS) is the most commonly used technology for the newborn screening (NBS) of inborn errors of metabolism (IEM) because it is more effective than conventional screening method. It replaces the conventional testing method of one analysis of one metabolite for one specific disease with one analysis of many metabolites for different diseases.[3] Expanded newborn screening for IEM exists in most western European

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countries, Australia, New Zealand as well as neighbouring Asian countries – China, Japan, Singapore and other places like Taiwan.[4] Internationally, the screening programmes for IEM has been implemented at various pace for different panels of disorders, and even at various states of the same country.[5] The differences are mainly due to various factors, such as the prevalence of specific disorders and medical practice.[6]

In Hong Kong, the territory-wide Neonatal Screening Programme (NSP) was started in 1984 under the Clinical Genetic Service (CGS) of the Department of Health (DH) of the Hong Kong Special Administrative Region (HKSAR). It has a public health endeavor providing free-of-charge service to screen two relatively prevalent disorders, congenital hypothyroidism (CH) and glucose-6-phosphate dehydrogenase (G6PD) deficiency, among babies who are born in the eight public hospitals with obstetric services.[7] The Workgroup on Expansion of Neonatal Screening Programme in Hong Kong ("Workgroup") was set up in July 2013 to review the information and relevant evidence for the expansion of newborn screening (NBS) programme to cover IEM. It comprised of representatives from the Food and Health Bureau (FHB) of HKSAR, the DH, the Hospital Authority (HA) and included disciplines of Clinical Genetics, Paediatrics, Obstetrics, Pathology and Public Health. After the announcement of the Policy Address 2015, the Workgroup set up a Task Force (TF) to plan and prepare for the implementation of the pilot study to assess the feasibility of trying out the screening programme for newborn babies for IEM in the public healthcare system in our locality.

The pilot study was titled "Pilot Study of Newborn Screening for Inborn Errors of Metabolism" (Pilot Study). In this paper, we review the course of events and discuss about the findings of the Pilot Study.

Methods

The Pilot Study was conducted for a period of two years, including the first six months for preparatory works. The protocol was produced by the TF members for the implementation of the Pilot Study, which was launched in October 2015. Two public hospitals under the HA, namely, Queen Elizabeth Hospital (QEH) and Queen Mary Hospital (QMH) and the Newborn Screening Laboratory (NSL) of Princess Margaret Hospital (PMH) participated in the Pilot Study.

Apart from the existing healthcare professionals (HCPs) in QEH, QMH and NSL, additional medical staff of Advanced Practice Nurses (APN), registered nurses, laboratory technicians, phlebotomists and clerical staff were recruited for increased workload in the Pilot Study. They were equipped with education and training materials, including training sessions and competency assessments, resource books and training kit, before the launching of the Pilot Study.

Dried blood spots (DBS) from newborn babies for laboratory testing was taken for 18 months from October 2015 to March 2017. Courier services were arranged to collect the DBS from different hospitals and send to NSL. Such LC-MS/MS, Fluorometric-based auto-analyser as essential equipment in NSL were purchased for specimen processing, analytics and reporting. The NSL operated 5 days (From Monday to Friday) per week.

Among many different IEM, a total 24 (Table 1) were selected to be included in the Pilot Study. The four criteria that were agreed upon and adopted for selection of IEM included: 1) screening capability – availability of accurate, reliable screening, diagnostic testing and laboratory capability; 2) clinical significance – seriousness and number of cases encountered in our locality; 3) availability of treatment - efficacy and/or effectiveness of the treatment; and 4) favourable outcome after early treatment – adequacy of the understanding of the natural history of the condition and its long-term outcome with early treatment.

In consideration of technical readiness, the Pilot Study initially covered 21 IEM diseases in Phase I during the first six months (October 2015 to March 2016) of its implementation for all babies born in QEH and QMH of ≥34 weeks of gestation and birth weight >2000 g with DBS taken in postnatal ward (namely Babies of Category A). In Phase II from April 2016 to the end of the Pilot Study in March 2017, three additional diseases were included in the programme (Table 1) and all newborn babies were recruited. Besides babies of Category A, babies born with preterm <34 weeks of gestation; or birth weight <2000 g; or being admitted to Neonatal Intensive Care Unit (NICU) (namely Babies of Category B) were also included in Phase II (Table 2). Other differences between Phase II and Phase I of the Pilot Study were the number of dry blood spot (DBS) required for screening and the timing of DBS taking among babies classified under different categories according to different clinical circumstances (Table 2).

The workflow of the Pilot Study started with parental education. Video and education pamphlet were distributed

Table 1 24 inborn errors of metabolism included in the Pilot Study

Disorders of Organic Acids (7) (Phase I & II)	**有機酸障礙（七項）(第一及第二階段)**
Multiple carboxylase deficiency	多發性羧化酶缺乏症
Glutaric acidaemia type I	戊二酸血症 I 型
Methylmalonic acidaemia	甲基丙二酸血症
Propionic acidaemia	丙酸血症
Isovaleric acidaemia	異戊酸血症
3-hydroxy-3-methylglutaryl-CoA lyase deficiency	白胺酸代謝異常症
Beta-ketothiolase deficiency	貝塔酮硫解酶缺乏症
Disorders of Amino Acids (8) (Phase I & II)	**氨基酸障礙（八項）(第一及第二階段)**
Classical phenylketonuria	苯丙酮尿症
6-pyruvoyl-tetrahydropterin synthase deficiency	六 - 丙酮酰 - 四氫蝶呤合成酶缺乏症
Argininosuccinic acidaemia	精氨酸血症
Maple syrup urine disease	楓糖尿病
Citrullinaemia type I	瓜氨酸血症 I 型
Citrullinaemia type II	瓜氨酸血症 II 型
Tyrosinaemia type I	酪氨酸血症 I 型
Homocystinuria	高胱氨酸尿症
Disorders of Fatty Acid Oxidation (6) (Phase I & II)	**脂肪酸氧化障礙（六項）(第一及第二階段)**
Carnitine uptake deficiency	卡尼丁吸收障礙
Carnitine-acylcarnitine translocase deficiency	卡尼丁穿透障礙
Carnitine palmitoyltransferase II deficiency	卡尼丁結合酵素 II 缺乏症
Medium-chain acyl-CoA dehydrogenase deficiency	中鏈醯輔酶 A 去氫酶缺乏症
Very long-chain acyl-CoA dehydrogenase deficiency	極長鏈醯輔酶 A 去氫酶缺乏症
Glutaric acidaemia type II	戊二酸血症的 II 型
Others (3) (Phase II)	**其他（三項）(第二階段)**
Congenital adrenal hyperplasia	先天性腎上腺增生症
Biotinidase deficiency	生物素缺乏
Classic galactosaemia	半乳糖血症

Table 2 Number of DBS specimen and timing of DBS taking for screening

	Babies of Category A	**Babies of Category B**
Criteria	• ≥34 weeks + 0 day of gestation and birth weight >2000 g with DBS taken in postnatal ward (Phase I & II)	• Preterm <34 weeks + 0 day of gestation; or birth weight <2000 g; or being admitted to NICU (Phase II)
No. of DBS required	• Single	• Serial of three
Time of DBS taking	• Within 24 to 72 hours of life and before discharge	• 1st specimen should be collected on admission regardless of the age and before any treatment except respiratory support • 2nd specimen should be taken at 48 to 72 hours of life • 3rd specimen should be taken at discharge or on day 28 of life whichever comes first

DBS: dried blood spots; NICU: Neonatal Intensive Care Unit

during both the antenatal and postnatal periods to help parents understand IEM and the Pilot Study. Parents decided whether they would voluntarily to join the Pilot Study or not. Consent was obtained from parents of eligible babies before DBS were collected by heel pricking. The number of DBS collected would depend upon which category the baby belonged to (Category A or B). Collected DBS were dispatched to NSL by pre-arranged courier services. Laboratory results were issued as one of the following three categories viz. normal results, invalid specimens and positive results (with two sub-categories – uncertain result and abnormal result). Normal results would not be notified with no further action necessary. For invalid specimens, resampling was required upon notification of individual birthing units. Babies with positive results would be recalled for clinical assessment with repeat DBS testing +/- further diagnostic and confirmatory testing by the respective paediatric department which would be responsible for the subsequent on-going treatment and monitoring of these babies. In the Pilot Study, residual DBS were stored for six months in the screening laboratory and were discarded afterwards. Positive DBS specimens would be kept for quality assurance purpose.

Results

15,138 out of 15,361 (98.5%) eligible newborn babies were included in the Pilot Study. All DBS were sent together with completed particulars of babies and mothers to the NSL within three working days of specimen collection. 99.5% specimens were collected within the required time according to the babies' category. More than 99.8% of DBS were received by the NSL as valid and optimal for testing.

Among the total of 15,138 babies screened, 53 showed positive results. Nine (four boys and five girls) were subsequently confirmed to have various IEM conditions (Table 3). The collective incidence of IEM of the Pilot Study was calculated to be 1 in 1,682 (9 confirmed cases from 15,138 babies screened (CI: one in 909 to one in 3,333).

Eight of the nine patients were in stable clinical condition when the screening result became available. They were treated with appropriate dietary advice +/- medication as indicated for their specific conditions. Confirmatory genetic testing with counselling were given to the parents. Only the baby who was subsequently confirmed to have Methylmalonic acidaemia presented symptomatically prior to the availability of the screening result. Baby presented early with shortness of breath and poor feeding on Day 3 of life (Sunday) before the availability of the screening result on the following working day (Monday). The baby required intensive care unit support initially but her condition gradually stabilised with medical treatment.

Incidentally, two babies (one male and one female) with abnormal screening results were confirmed not to be affected with IEM. Their screened false positive results were explained by their mothers who were, afterwards, diagnosed to have carnitine uptake deficiency (CUD) and classic phenylketonuria respectively.

Although there was no established mechanism to report false-negative cases (i.e. babies having normal screening results but finally diagnosed to have IEM) in the Pilot

Table 3 Summary of nine babies with confirmed diagnoses

Sex	Ethnicity	Diagnosis	Any symptom when being picked up by screening
F	Chinese	Carnitine uptake deficiency (CUD)	Asymptomatic
F	Nepalese	Phenylketonuria (not classic PKU) (Mild PKU)	Asymptomatic
M	Indian	Medium-chain acyl-CoA dehydrogenase deficiency (MCADD)	Asymptomatic
M	Chinese	Citrullinaemia type II (CIT type II)	Asymptomatic
F	Chinese	Citrullinaemia type II (CIT type II)	Asymptomatic
F	Chinese	Very long-chain acyl-CoA dehydrogenase deficiency (VLCADD)	Asymptomatic
F	Chinese	Methylmalonic acidaemia (MMA)	Symptomatic
M	Chinese	Carnitine uptake deficiency (CUD)	Asymptomatic
M	Chinese	Carnitine uptake deficiency (CUD)	Asymptomatic

Study, we were informed of two babies (one male and one female) with normal screening results who were subsequently confirmed to have Citrullinaemia type II (CIT type II) after their symptomatic presentation with prolonged jaundice at one month of age.

Discussion

The purpose of conducting the Pilot Study was to look into the feasibility of trying out in the public healthcare system a screening programme for newborn babies for IEM. Being the first of its kind to be conducted in a large scale among babies born in the government birthing units, careful design and effort would need to go into the protocol design to ensure seamless collaboration among the various stakeholders who are involved in the screening programme. Upon the smooth implementation of the pilot study, this same protocol was then adopted for subsequent territory-wide extension after some modifications. With the changing needs and advancement of screening technology, the scope of IEM for screening would continue to be monitored and reviewed on a regular basis.

Effective parental education was crucial for success of any newborn screening programme. This might be reflected by the high uptake rate 98.5% (15,138 out of 15,361 eligible babies participated) of the pilot study. Great appreciation and credit went to the frontline Health care professionals to achieve an overall 99.5% of specimen collection within the required time. More than 99.8% of the specimens were received in the NSL as valid and optimal for screening test. The handling of babies of Category B who needed serial DBS testing created some confusion and stress to the frontline HCPs initially. This was successfully tackled by streamlining the specimen collection arrangement.

With the nine IEM cases confirmed in the Pilot Study, the collective incidence of IEM conditions detected during the pilot study period was one in 1,682 (9/15,138). This incidence was higher than the previously estimated local collective incidence of one in 4,122 to one in 7,580.[8] This collective incidence is higher than those reported worldwide, such as 1 in 5,800 in Mainland China,[9] 1 in 5,882 in Taiwan,[10] 1 in 2,000 in Korea,[11] 1 in 9,330 in Japan,[12] 1 in 3,600 in India,[13] 1 in 6,000 in Australia which excluded hyperphenylalaninemias,[14] 1 in 2,400 in German,[15] 1 in 4,000 in America.[16] Understandably, incidence figures vary dependent on different factors, such as the panels of IEM disorders that were screened for, the proportion of various ethnic group in the community.[17] Also our pilot study only lasted for a relatively short period of eighteen months. Thus more polonged data collection and furhter in-depth study of local epidemiology of IEM cases should be undertaken to reflect the true local incidence figures.

The baby with MMA presented clinically before the screening result became available. It is well known that MMA patients can present acutely even before the screening result becomes available. The issue of specimen transportation and laboratory working hours needs further deliberation to balance between efficient utilisation of facilities and rapid result turnaround time. As the demand increases, the number of laboratory working days should be reviewed and adjusted with additional resources. Also, the schedule of courier service from different hospitals to the NSL should be well planned and monitored.

Two mothers were incidentally found to have IEM conditions - Carnitine uptake deficiency (CUD) and Classic phenylketonuria (PKU). The mother in the first case (CUD) was stable and her baby was asymptomatic since birth. The baby affected by maternal PKU suffered microcephaly, congenital heart defects and developmental delay. The diagnosis of maternal PKU was made only after reviewing the IEM screening result of the newborn. Therefore, the implementation of universal newborn screening may also help to detect undiagnosed IEM in mother in future.

There were two false-negative cases of Citrullinaemia type II (CIT type II) during the pilot study period. Both babies presented with prolonged jaundice. It is well known that Citrullinaemia type II (CIT type II/Citrin deficiency) can be easily missed if newborn screening is performed early during the first week of life. It is important for frontline staff to educate parents on the possibility of false negative results during the education and consent process before blood taking. Paediatricians also need to be alerted to the relative higher false negative rate of certain screened IEM, in particular Citrullinaemia type II in our locality. Paediatricians should proceed to investigate for this possibility in babies presenting with prolonged neonatal jaundice even with a normal newborn screening result. Setting up a notification mechanism for false-negative cases would need to be considered for the future territory-wide implementation of the IEM NBS programme to capture the genuine incidence figures.

Conclusion

The Pilot Study has operated smoothly, especially in

terms of parental education, specimen collection, preparation and dispatch. There were effective communication and cooperation among different parties involved in baby recall, arrangement of further investigations and clinical management. The health education effectively helped parents to make informed decision before joining the Pilot Study and led to the overall encouraging parental consent rate. With the concerted effort from different disciplines, nine IEM cases were identified and treated. Effectiveness in reducing morbidity and mortality due to IEM was well demonstrated in this pilot study. With a collective incidence of 1 in 1,682, IEM should not be considered as rare in Hong Kong.

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Declaration of Interest

The authors declare that there is no conflict of interest.

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Appendix

Member list of The Task Force on the Pilot Study of Newborn Screening for Inborn Errors of Metabolism:

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