Hong Kong Journal of Paediatrics

香港兒科醫學雜誌 (New Series)
An Official Publication of
Hong Kong College of Paediatricians &
Hong Kong Paediatric Society
c/o Hong Kong College of Paediatricians, Room 801, Hong Kong Academy of Medicine Jockey Club Building, 99 Wong Chuk Hang Road, Aberdeen, Hong Kong.

Publisher
Hong Kong Journal of Paediatrics is published by Medcom Limited, Room 504-5, Cheung Tat Centre, 18 Cheung Lee Street, Chai Wan, Hong Kong.
Tel: (852) 2578 3833, Fax: (852) 2578 3929,
Email: mcl@medcom.com.hk

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

Website: www.hkjpaed.org

ISSN 1013-9923

Editorial

Universal Newborn Screening in Hong Kong: Time for Change?

The article on neonatal seizure by Siu et al[1] highlighted two problems, recent advances in metabolic causes of neonatal epilepsy and whether such disorders could be detected by an expanded neonatal screening programme. Treatable metabolic causes of early epilepsy are uncommon but they should be considered once conditions like infection, electrolyte disturbances, hypoxia, hypoglycaemia and structural brain malformations have been excluded. Many inborn errors of fatty acid oxidation, amino acid and organic acid metabolism can present as encephalopathy with seizures in the neonatal period. The management algorithm and therapeutic drug trials shown in this article follow on from our recent understanding of treatable neonatal epilepsy. Pyridoxine – dependent epilepsy is the result of mutations in the ALDH 7A1 gene leading to central nervous system α-aminoadipic semialdehyde dehydrogenase deficiency.[2] The disorder responds promptly to 100 mg of intravenous pyridoxine and these children require life-long pyridoxine treatment. Treatable neonatal epileptic encephalopathy can also occur as a result of mutations of PNPO gene encoding pyridox(am)ine 5'-phosphate oxidase.[3] A therapeutic trial of two doses of pyridoxal phosphate (10 mg/kg per dose) 2 hours apart can be initiated as the test for documentation of PNPO mutations is not available in most centres. Two doses of folinic acid (5 mg) 6 hours apart can be tried if seizures do not respond to pyridoxal phosphate. The etiology of folinic acid-responsive seizure remains elusive and this form of neonatal seizure is characterised by characteristic unidentified markers and elevated neurotransmitters (homovanillic acid, 3-methoxytyrosine and vanillactic acid) in the cerebrospinal fluid when analysed by high performance liquid chromatography.[4] Other treatable neonatal metabolic seizures that paediatricians should be aware of include serine deficiency disorders,[5] cerebral creatine deficiency syndromes,[6] and glucose transporter GLUT 1 deficiency.[7] The condition described by Siu et al, D-bifunctional protein deficiency is an inherited defect of peroxisome biogenesis and a characteristic acylcarnitine profile in patients affected by such disorders could be detected using tandem mass spectrometry (TMS).[8] The next question that arises is whether expanded newborn screening using tandem mass spectrometry should be introduced in Hong Kong to detect rare metabolic disorders.

In a recent coroner inquest into the death of a 14 year old boy due to an inborn error of metabolism (IEM), the report included a rider that the authorities should look into the feasibility of establishing universal newborn screening for IEM in Hong Kong. This is a timely recommendation as Hong Kong, Asia's World City, is really lagging behind in this aspect of preventive health care, even in the Asia Pacific region.[9] Since the pilot screening programme for congenital hypothyroidism in 1982[10] and the initiation of universal newborn screening for congenital hypothyroidism and glucose-6-phosphate dehydrogenase deficiency by the Clinical Genetic Service of the Department of Health in 1984, there has been dramatic technological advances in the field of newborn screening. The introduction of analysis of acylcarnitines and amino acids by electrospray ionisation tandem mass spectrometry (TMS) has made possible the detection of a large number of metabolic disorders in a single analytical run. "A new grassroot movement is raising a ruckus about genetic screening" was highlighted in an article in Science, reaffirming that advocacy groups are championing for expanded neonatal screening of genetic diseases.[11] In line with Barack Obama, the President-Elect of the United States, who spoke so eloquently of change, is it time for the Department of Health to review whether there should be "changes" to the existing neonatal screening programme in Hong Kong? It is likely that public pressure and technology will drive a change in the newborn screening programme in Hong Kong in the future. Expanded newborn screening programmes covering many metabolic diseases have been introduced in Europe, United States and Australia.[11-13]

At present, newborn screening is carried out in cord blood and a new system for screening using dried blood spots on filter paper will need to be developed if new disorders are to be added to the existing neonatal screening protocol in Hong Kong. This will entail a significant start up cost and establishing a new screening organisation requires investment, education and training of clinical biochemists, technical staff and other health care professionals. So what are the disorders to be covered if universal newborn screening for IEM is to be introduced in Hong Kong? The principles of Wilson and Junger[14] should be taken into consideration. However, the availability of effective treatment may not be a prerequisite for screening because the identification of an inherited incurable IEM by screening can be of benefit to the family by providing crucial genetic information for counseling affected families.[15] Although the clinical effectiveness for screening for phenylketonuria and hypothyroidism is generally accepted, formal evidence of the clinical and cost effectiveness of the expanded newborn metabolic screening is scarce. Good quality controlled studies are lacking because of the rarity of genetic metabolic diseases and the conviction by some clinicians that patients will benefit from early diagnosis and treatment. Some form of economic evaluation prior to the introduction of a new programme is required. Some studies showed that adoption of TMS for expanded newborn screening would be cost effective if added onto an existing screening programme.[16,17] The introduction of TMS technology does not mean that it is cost effective to include a "basket" of disorders for screening and the inclusion of each disease requires independent evaluation.[12,17,18] A study from the United Kingdom supported the introduction of TMS into a neonatal screening programme for phenylketonuria and medium chain acyl-Co-A dehydrogenase deficiency (MCADD) combined.[19] There is a great variation in the metabolic disorders included in the screening programmes introduced in different parts of the world.[9,12,13,20] Healthcare planners should be aware of the many limitations when basing policy decisions on experience from other countries. Ethnic differences in the incidence of IEMs must be taken into consideration and one example is that MCADD is common in Caucasian while it is uncommon in Chinese.[21] Organisational structure, staff and treatment costs may be very different in different countries.[18] The involvement of health economists in the planning process and obtaining reliable data on the prevalence of IEMs locally, in China and other Asian ethnic groups will be important to guide decisions on screening policies in Hong Kong.

The newborn screening programme is not just the screening process alone but includes other distinct components like confirmation of diagnosis, management, short-term and long-term follow up.[22] There should be

regular audit and continuous quality improvement of the programme. A secure funding mechanism to cover the expenses of additional personnel, training of medical, technical and allied health professionals, medications, medical foods, start-up and recurrent instrument and operating costs must be in place. With new technology, there would be new legal concerns for us to address.[23] Paediatricians have the responsibility to promote public health through neonatal screening but indiscriminate screening can do more harm than good. The increase in false-positive results following expanded newborn screening for inherited metabolic diseases will impose a burden on the health care system and may have detrimental effects on the family through a combination of unnecessary investigations and hospitalisations, parental stress and parent-child dysfunction.[24] Policy makers and paediatricians should balance the risks and benefits of expanded screening and act as primary gatekeepers of the interest of the child.

We need change but much work needs to be done before any change to the existing newborn screening programme can be implemented.

References

1. Siu LY, Kwong L, Wong SN, Kwong NS. Neonatal seizure: a rare aetiology easily missed by routine metabolic screening. HK J Paediatr (new series) 2009;14:37-41.
2. Mills PB, Struys E, Jacobs C, et al. Mutations in antiquilin in individuals with pyridoxine independent seizures. Nat Med 2006; 12:307-9.
3. Mills PB, Surtees RA, Champion MP, et al. Neonatal epileptic encephalopathy caused by mutations in PNPO gene encoding pyridox(am)ine 5'-phosphate oxidase. Hum Mol Genet 2005;14: 1077-86.
4. Nicolai J, van Kranen-Mastenbroek VHJM, Wevers RA, Hurkx WA, Vles JS. Folinic-acid responsive seizures initially responsive to pyridoxine. Pediatr Neurol 2006;34:164-7.
5. de Koning TJ. Treatment with amino acids in serine deficiency disorders. J Inherit Metab Dis 2006;29:347-51.
6. Stockler S, Schutz PW, Salomons GS. Cerebral creatine deficiency syndromes: clinical aspects, treatment and pathology. In:Creatine and creatine kinase in health and disease. Salamons GS, Wyss M (Eds). Springer 2007;149-66.
7. Wang D, Pascual JM, Yang H, Engelstad K, Jhung S, Sun RP, Vivo DC. Glut 1 deficiency syndrome: clinical genetic and therapeutic aspects. Ann Neurol 2005;57:111-8.
8. Risso C, Boenzi S, Wanders RJA, Duran M, Caruso U, Dionisvici C. Characteristic acylcarnitine profile in inherited defects of peroxisome biogenesis: a novel tool for screening diagnosis using tandem mass spectrometry. Pediatr Res 2003;53:1013-8.
9. Padilla CD, Therrell BL. Newborn screening in Asia Pacific region. J Inherited Metab Dis 2007;30:490-506.
10. Low LCK, Lin HJ, Cheung PT, et al. Screening for congenital hypothyroidism in Hong Kong. Aust Paediatr J 1986;22:53-6.
11. Marshall E. Fast technology drives new world newborn screening. Science 2001;294:2272-4.
12. Bodamer QA, Hoffmann GF, Linder M. Expanded newborn screening in Europe 2007. J Inherit Metab Dis 2007;30:439-44.
13. Wilcken B, Wiley V, Hammond J, Carpenter K. Screening newborns for inborn errors of metabolism by tandem mass spectrometry. N Engl J Med 2003;348:2304-12.
14. Wilson JMG, Junger G. Principles and practice of screening for disease. Public health papers no.34. Geneva: World Health Organsation 1968.
15. Alexander D, van Dyke PC. A vision of the future of newborn screening. Pediatrics 2006;117:S350-4.
16. Insinga RP, Laessig RH, Hoffman GL. Newborn screening with tandem mass spectrometry: examining its cost-effectiveness in the Wisconsin Newborn Screening Panel. J Pediatr 2002;141: 524-31.
17. Cipriano LE, Rupar CA, Zaric GS. The cost-effectiveness of expanding newborn screening for up to 21 inherited metabolic disorders using tandem mass spectrometry: result of a decision-analytic model. Value Health 2007;10:83-97.
18. Pollitt RJ. Introducing new screens: why are we all doing different things? J Inherit Metab Dis 2007;30:423-9.
19. Pandor A, Eastham J, Beverley C, Chilcott J, Paisley S. Clinical effectiveness and cost-effectiveness of neonatal screening for inborn errors of metabolism using tandem mass spectrometry: a systematic review. Health Technol Assess 2004; 8:iii,1-121.
20. Waisbren SE. Expanded newborn screening: information and resources for family physicians. Am Fam Physician 2008;77: 987-94.
21. Han LS, Ye J, Qiu WJ, Gao XL, Wang Y, Gu XF. Selective screening for inborn errors of metabolism on clinical patients using tandem mass spectrometry in China: a four-year report. J Inherit Metab Dis 2007;30:507-14.
22. Howell RR, Engelson G. Structure for clinical follow-up: newborn screening. J Inherited Metab Dis 2007;30:600-5.
23. Abbing HD. Neonatal screening, new technologies, old and new legal concerns. Eur J Health Law 2004;11:129-37.
24. Waisbren SE, Abbers S, Amato S, et al. Effect of expanded newborn screening for biochemical genetic disorders on child outcomes and parental stress. JAMA 2003; 290:2564-72.

Louis Low
Chief Editor