PATHCHAT

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The case for Newborn Screening in South Africa: A personal perspective

Newborn screening (NBS) is a public health measure that is recognised worldwide. It is aimed at the early screening, diagnosis and management of selected, inherited diseases. Such diseases are selected based on the current ability to detect and treat them, and the demonstration of the positive economic impact of such interventions.

Newborn screening is probably the pinnacle of preventative medicine: early diagnosis and treatment ensures optimal living and allows an individual to contribute to society as opposed to becoming a long-term societal responsibility.

The history of Newborn Screening

Newborn screening started in the 1960s with the advent of the bacterial inhibition assay developed by Dr Robert Guthrie for the early detection of phenylketonuria (PKU). Classical PKU is an autosomal recessively inherited deficiency of the enzyme phenylalanine hydroxylase, which catalyses the conversion of phenylalanine to tyrosine. Patients present with progressive, irreversible neurological impairment and reduced pigmentation. The clinical presentation is the end result of a complex interplay between the accumulation of phenylalanine and phenylalanine derivatives, and a deficiency in tyrosine, which – due to the lack of phenylalanine hydroxylase – now becomes an essential amino acid. PKU was first described in 1935 by Asbjorn Fölling, and by 1950 it was known that the associated neurotoxicity could be prevented through the early restriction of phenylalanine-containing foods. The ferric chloride test available at the time was not sensitive enough to detect the disease before irreversible neurological deterioration had set in. Dr Guthrie, who had been doing cancer research, was motivated to pursue research aimed at the prevention of mental disabilities after his second son was born mentally handicapped and his niece was diagnosed with PKU at the age of 15 months. In the late 1950s, he developed a bacterial inhibition assay that was of sufficient sensitivity to detect early increases in phenylalanine in dried blood spots on filter paper. With this newly developed assay, 400 000 children were screened between 1960 and 1962, and 39 newborn babies were detected with PKU, with no missed cases.

Due to Dr Guthrie's success, the National Association for Retarded Children lobbied the United States government, and by 1967, 35 states had passed laws that mandated screening. Today, developed countries and much of the developing world – with the notable exception of Africa – have implemented national screening programmes that screen the majority of all newborn babies.

Newborn screening took a giant leap forward when tandem mass spectrometry technology was implemented in the clinical laboratory. The instrument allows for the simultaneous determination of amino acids, carnitine conjugates and other compounds. The multiplex nature of the instrument made it cost-effective and practically feasible to rapidly expand the testing panel of screening programmes. Most newborn screening laboratories today use a combination of tandem mass spectrometry and other analytical modalities to test for multiple inherited diseases through metabolic, endocrine, immune and haematological analytical profiling.

The incidence of inherited metabolic diseases in South Africa

There appears to be a perception among many South African clinicians that inherited metabolic diseases are exceedingly rare in our country.

Hitzeroth and co-workers found one case of PKU and one case of tyrosinemia among 60 000 screened cases, and concluded that metabolic diseases in South Africa were too rare to justify screening(1). However, they did not state which diseases had been included in the screening panel. On the other hand, Van der Watt et al predicted an incidence of 1 in 5 000 newborns for type I glutaric acidemia, one of the highest incidences in the world, in a selected South African black population through estimation of the carrier frequency of a commonly occurring mutation(2).

Prof LJ Mienie, who has been Head of the Metabolic Laboratory on the Potchefstroom Campus of the North-West University for the past 30 years, has received more than 50 000 requests for the metabolic workup of patients. His experience has demonstrated that the most frequently occurring metabolic diseases that are also included in the newborn screening panel are isovaleric acidemia, propionic acidemia, galactosemia, vitamin B-responsive methylmalonic acidemia, maple syrup urine disease and glutaric acidemia type I.

A number of other conditions, most notably peroxisomal biogenesis disorders, are also common, but do not currently form part of the screening panel.

Furthermore, based on the experience obtained from the screening programme, it appears as if biotinidase deficiency may also be quite common.

The *March of Dimes Global Report on Birth Defects* has established that genetic and congenital disorders are found across all nations with little regard for ethnic background and socioeconomic status(8).

There is therefore little evidence to suggest that South Africa is spared from metabolic diseases.

Economic considerations of a Newborn Screening programme

One of the common constraints to the implementation of a newborn screening programme is the perception that such a programme will be a huge expense, which could divert funds from competing health priorities. However, there is ample evidence to prove that the economic benefit of screening offsets the costs, and that it is actually more economical to screen and initiate early treatment than to diagnose late and deal with the associated morbidity and mortality(3, 4, 5, 6, 7).

A more realistic economic barrier is that the cost of screening is immediately incurred, while the benefits are only realised over an extended period. In view of this, most developing countries have opted for an incremental approach to implementation through pilot programmes. Furthermore, a country needs to reach a certain level of economic prosperity to make the implementation of a screening programme feasible. Table 1 compares the economic prosperity (expressed as the GDP per capita) and the percentage of annual newborns screened for selected developing nations.

Considerations for the practising clinician

A number of obstacles face the clinician who would like to offer newborn screening to patients:

- Currently there is no policy in South Africa regarding newborn screening , therefore most [a] medical insurance companies do not reimburse what, in essence, should be a prescribed minimum benefit. This lack of reimbursement creates all sorts of questions about the validity of the service in the minds of patients, who then address these questions to the clinician who has to cope with the additional counselling workload.
- Dealing with false positive screens and the associated anxiety of parents is an intricate part of newborn screening. The United States Centers for Disease Control and Prevention (CDC) advises that the false positive rate should be around 3%, based on extensive experience and the desire for a cost-effective programme. A programme that has a rate lower than this has in all likeliness set its cut-off values too high. This will lead to an unacceptable number of missed cases. On the other hand, the laboratory that is too concerned with the possibility of missing a case will set its cut-offs too

a CAMAF reimburses all newborn screens in full from the MSA if funds are available.

Table 1: A comparison of the economic prosperity and annual percentage of newborn babies screened in selected developing nations

Country	2011 GDP per capita (in thousands of USD)	Newborn screening coverage (year of estimation)
Egypt	6.5	75% (2007)
China	8.3	25% (2006)
Thailand	9.4	97% (2006)
Brazil	11.8	80% (2005)
South Africa	11.0	< 1% (2012)

low, which translates into an unacceptable number of false positives with the associated unnecessary costs of working up a patient further. The estimated combined incidence of the diseases that are typically screened for is 1:1 000 to 1: 3 000. If the South African incidence is 1: 2 000, and the programme has a false positive rate of 5% [b], then a clinician caring for 300 newborns a year may have to deal with 15 false positive cases a year, and will only detect a case every six to seven years. Alternatively stated, 100 false positives will be reported for every true case detected.

- The cost of confirmatory tests can also be problematic. The cost of a newborn screen is around R700 and all follow-up screens are done at no additional cost to the patient. When confirmatory and/or additional testing is required however, costs can run into many thousands of Rands and although it can be reimbursed by medical aids, it comes from the savings account of guarantor. We cap the cost of confirmatory testing at the cost of one organic acid analysis for those confirmatory tests offered by us. When the sample needs to be referred to another laboratory for confirmatory testing the associated cost can be dramatic, and it is often difficult to justify this to the parents of a newborn that appears, and often is, healthy. The solution is to achieve the type of economies of scale that will allow for cost-effective follow-up testing of all conditions. This will only be possible once the request for screening increases dramatically.

Despite these obstacles, there are a number of selected areas in South Africa where fairly advanced screening programmes have become well established. A number of patients have been diagnosed and appropriate interventions have been instigated at a very early stage. The success of these programmes is largely due to the efforts of one or two trained nursing employees of a pathology practice that take charge of the programme. They do the pre- and post-test counselling, as well as the follow ups that require a repeat screen. The clinician only gets involved when the laboratory requests additional tests. I advise the following for paediatricians, obstetricians and general practitioners who would like to start to offer newborn screening to their patients:

- Request a CPD presentation on newborn screening in your area. We offer such presentations in conjunction with pathology groups at no cost. Other than the dissemination of useful information, it also provides the opportunity to get interested clinicians together. The chance of the programme succeeding can be a lot better when most of the clinicians in an area support it.
- Approach a pathology practice and request that the service be made available. The practice will then identify one or two members of the nursing staff who can be trained in the process to enable them to take charge of the service offering.
- After training, the programme can be implemented. Failure to offer training before implementation often leads to frustration due to improper counselling and poor collection techniques that require recollection.

The Newborn Screening programme at the North-West University

The Newborn Screening Laboratory was a natural outflow of the Metabolic Laboratory, which has offered a metabolic diagnostic service to the South African health sector for more than 30 years. It was established in 1999, and its initial activities were mainly research based. For the last five years, it has offered a diagnostic service to the private sector. It is equipped with state-of-the-art tandem mass spectrometry technology. The laboratory follows the test panel and guidelines of the American College for Medical Genetics (ACMG) and is a member of the Region 4 Genetics Collaborative, a worldwide initiative aimed at the dissemination of information and the standardisation of methods.

The laboratory is also a participant in the CDC's newborn screening quality assurance programme. In accordance with the ACMG, the laboratory distinguishes between primary and secondary conditions. Primary conditions are the main focus of the programme. These are diseases that can be screened for with a high diagnostic accuracy; that are treatable, or at least partially treatable; and of which the natural history is well understood. Secondary conditions are those that can also be identified due to the multiplex nature of the technology, but do not meet the criteria to be selected as a primary screening target. It is important to note that normal screen implies that there is a high degree of certainty that none of the diseases that are tested for are present. It does not mean that a metabolic disease has been excluded.

The current list of conditions that are screened for, along with typical presentations in the neonatal period, is presented in Table 2. Additional information can be obtained from our websites: www.newbornscreening.co.za and www.pliem.co.za. I would like to make use of this opportunity to thank Ampath's pathologists, among other people, for the key role that they have played in establishing this service in South Africa.

b Large newborn screening programmes do additional tests on the same blood spot when an analyte is marginally abnormal. This limits the number of false positive reports. This is known as second-tier testing. The strategy needs substantial sample volumes to make it affordable. Programmes that do not use this strategy will have a higher false positive rate

Table 2: Comparison of the suggested core screening panel of the American College of Medical Genetics and the current screening panel of the North-West University (NWU)

American College of Medical Genetics core panel	NWU screening programme	Clinical presentation
Amino acid disorders		
Classic phenylketonuria	Yes	Severe intellectual disability, reduced pigmentation, hypertonia and posturing
Maple syrup urine disease	Yes	Acute neurological deterioration, metabolic acidosis, maple syrup odour
Tyrosinemia type I	In development	Liver disease
Argininosuccinic aciduria	Yes	Acute neurological deterioration, hyperammonemia
Citrullinemia type I	Yes	Acute neurological deterioration, hyperammonemia
Homocystinuria	No	Initially normal, developmental delay, thromboembolic complications, osteoporosis, lens dislocation
Endocrine disorders		
Congenital adrenal hyperplasia	Yes	Dehydration, various degree of sexual ambiguity
Congenital hypothyroidism	Yes	Initially normal, failure to thrive, severe intellectual disability, enlarged fontanelles, macroglossia, constipation, dry and thin skin
Disorders of fatty acid oxidation		
Medium-chain acyl-CoA dehydrogenase deficiency	Yes	Sudden unexplained death, hypoketotic hypoglycaemia, liver disease
Trifunctional protein deficiency	Yes	Hypoketotic hypoglycaemia, cardiomyopathy
Very long-chain acyl-CoA dehydrogenase deficiency	Yes	Hypoketotic hypoglycaemia, cardiomyopathy
Carnitine uptake defect	In development	Cardiomyopathy
Long-chain L-3-Hydroxy dehydrogenase deficiency	In development	Hypoketotic hypoglycaemia, cardiomyopathy
Haemoglobinopathies		
Beta-thalassemia	No	Initially normal, failure to thrive, pallor, painful dactylitis, recurrent infections
Sickle cell anemia	No	Initially normal, severe anemia
Organic acidemias		
3-Hydroxy-3-methylglutaric aciduria	Yes	Neurological deterioration, hypoketotic hypoglycemia, metabolic acidosis
3-Methylcrotonyl-CoA carboxylase deficiency	Yes	Acute neurological deterioration, metabolic acidosis, hypoglycemia
Cobalmine responsive methylmalonic acidemia (Cbl A, B)	Yes	Acute neurological deterioration, metabolic acidosis
Glutaric acidemia type I	Yes	Acute brain injury with subsequent neurological impairment
Holocarboxylase synthase deficiency	Yes	Acute neurological deterioration, metabolic acidosis, convulsions, skin rash and alopecia
Isovaleric acidemia	Yes	Acute neurological deterioration, metabolic acidosis, sweaty feet odour
Methylmalonic acidemia (mut)	Yes	Acute neurological deterioration, metabolic acidosis
Propionic acidemia	Yes	Acute neurological deterioration, metabolic acidosis
β-Ketothiolase deficiency	Yes	Initially normal, developmental delay, episodic keto-acidosis
Other disorders		
Biotinidase deficiency	Yes	Hypotonia, developmental delay, skin rash and alopecia, convulsions
Classic galactosemia	Yes	Liver disease
Cystic fibrosis	Yes	Initially normal, chronic lung disease, failure to thrive
Critical congenital heart disease	No	Heart failure, cyanosis
Hearing loss	No#	Initially normal, delayed language development
Severe combined immuno-deficiencies	No$	Initially normal, recurrent serious infections

Testing for hearing loss is not part of the programme as offered by the NWU, but can usually be requested separately from a practising audiologist.

$ Testing for severe combined immunodeficiencies is not currently part of the NWU screening programme, but can be requested separately from Ampath.

References

1. Hitzeroth H, Niehaus C, Brill D. 1995. Phenylketonuria in South Africa. *South African Medical Journal* 85(1):33–6. [Online]. Available from: http://archive.samj.org.za/1995 VOL 85 Jan-Dec/Articles/01 January/1.9 PHENYLKETONURIA IN SOUTH AFRICA.A REPORT ON THE STATUS QUO. H.W.Hitzeroth, C.E.Niehaus, D.C.B.pdf. Accessed on 23 April 2013.
2. Van der Watt G, Owen EP, Berman P, Meldau S, Watermeyer N, Olpin SE. 2010. Glutaric aciduria type 1 in South Africa-high incidence of glutaryl-CoA dehydrogenase deficiency in black South Africans. *Molecular genetics and Metabolism* 101(2-3):178–82. Elsevier Inc. [Online]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20732827. Accessed on 4 February 2013.
3. Geelhoed EA, Lewis B, Hounsome D, Leary PO. 2005. *Economic evaluation of neonatal screening for phenylketonuria and congenital hypothyroidism* (April):575–9.
4. Lord J, Thomason MJ, Littlejohns P, Chalmers RA, Bain MD, Addison GM. 1999. *Secondary analysis of economic data: A review of cost-benefit studies of neonatal screening for phenylketonuria* 179–86.
5. Carroll AE, Downs SM. 2006. Comprehensive cost-utility analysis of newborn. *Pediatrics*.
6. Venditti L, Venditti C, Berry G. 2003. Newborn screening by tandem mass spectrometry for medium-chain Acyl-CoA dehydrogenase deficiency: A cost-effectiveness analysis. *Pediatrics.* [Online]. Available from: http://pediatrics.aappublications.org/content/112/5/1005.short. Accessed on 22 January 2013.
7. Schoen E, Baker J, Colby C, To T. 2002. Cost-benefit analysis of universal tandem mass spectrometry for newborn screening. *Pediatrics.* [Online]. Available from: http://pediatrics.aappublications.org/content/110/4/781.short. Accessed on 22 January 2013.
8. Christianson A, Howson C, Modell B. 2006. *March of Dimes Global Report on Birth Defects*. [Online]. Available from http://www.marchofdimes.com/downloads/Birth_Defects_Report-PF.pdf. Accessed on 22 January 2013.