Keynote Lecture

Improving Child Health – Newborn Screening for All?

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Abstract

Over the last 40 years newborn screening has been an undoubted success and many thousands of children have been saved from mental retardation and other problems because of early diagnosis of their disorders. Now many diseases can be diagnosed early by newborn screening and many more are on the horizon. It must be a long-term goal to extend newborn screening tests to all children but, in areas of the world where healthcare delivery is insufficient, solving other health problems has to take precedence over introducing newborn screening. If it is decided to introduce newborn screening in a region where currently there is none screening for congenital hypothyroidism alone should be started before anything else at all is attempted so that proper systems can be put in place. There is an exciting future for newborn screening ahead. If new programmes are approached with proper caution maximal benefit will be achieved from newborn screening, which is one of the few clearly effective preventive strategies in healthcare.

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Congenital hypothyroidism occurs worldwide, and is relatively frequent, so it is no surprise that newborn screening for this disorder is the most widespread testing in use. "*No type of human transformation is more distressing to look at than an aggravated case of cretinism*". Thus wrote Sir William Osler in 1897.[1] It is interesting to note that the knowledge of goitre and its successful treatment by seaweed was known in China by 1600 BC.[2] In Europe, very much later, the Swiss Physician Paracelsus (1483-1541) related cretinism to endemic goitre.[2] The effective treatment of hypothyroidism was (re) discovered in 1891 by George Murray,[3] who used sheep thyroid extract – and patients were also given thyroid sandwiches to eat. And Sir William Osler was able to declare, "*That we can restore to life the hopeless victims of myxoedema is a triumph of experimental medicine... The results as a rule are most astounding, unparalleled by anything in the whole range of curative medicine*".[1] But treatment didn't completely address the problem of congenital hypothyroidism, as some intellectual deficit is permanent if treatment is not offered early. This of course is only one of the many disorders that need to be identified in the newborn period for treatment to be effective.

A Potted History of Newborn Screening

Dr Robert Guthrie's seminal paper on the feasibility of mass screening for phenylketonuria (PKU), using a bacterial inhibition assay and dried blood spot samples, was published in 1963[4] and this can reasonably be regarded as the birth of newborn screening. While some other bacterial inhibition assays were used for the diagnosis of other rarer disorders such as Maple Syrup Urine Disease and homocystinuria the next significant step forward was the description in 1973 and an assay for thyroxine, using dried blood spots.[5] This work on congenital hypothyroidism earned Dr Jean Dussault the Order of Canada in 1989. Other disorders which were able to be screened for in the late 1970s and 1980s included cystic fibrosis, congenital adrenal hyperplasia, biotinidase deficiency, and sickle cell disease. Not all of these were widely adopted. Many screening programmes were confined to screening for PKU and hypothyroidism.

Two advances then had a considerable impact. The use of dried blood spots in DNA analysis was first reported in 1987,[6] and initially mutation analysis was applied as a second tier test for haemoglobinopathies and later for cystic fibrosis screening. The full impact of DNA

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possibilities in newborn screening is yet to be felt. Unquestionably, the most significant advance has been the application of tandem mass spectrometry to newborn screening, with the ability to test for 30 or 40 disorders in a single test, using a single 3 mm blood spot.[7] This single advance has completely changed the face of newborn screening.

The Undoubted Successes of Newborn Screening

Because of PKU screening, thousands have been saved from severe mental retardation. Where screening is undertaken many doctors have never seen an untreated patient, and are shocked at their first encounter with a patient born before screening started – often mute, wheelchair bound, aggressive, and miserable. Now, children and young adults with PKU generally have normal development. Dietary treatments have improved, but are still somewhat onerous, and young women with PKU must adhere to diet very strictly before conception to avoid foetal damage, but there is no doubt about the overwhelming success of screening. Hypothyroidism screening too has been a clear success. Over the years, some 200 million newborns have been screened worldwide, almost all getting treatment by 2 to 3 weeks of age, and largely achieving normal growth and development. Early detection of sickle-cell anaemia has resulted in a saving of lives, as shown by a Cochrane review.[8] The rationale of screening for cystic fibrosis was under attack for some time. Two randomised controlled trials and many observational studies have now shown great benefits in nutrition and growth, reduced mortality, pulmonary benefits, and even a benefit in cognitive function.[9] The new expanded newborn screening by tandem mass spectrometry is also now being evaluated, with clear benefits so far demonstrated for only two or three conditions.[10-12] This may be largely due to the rarity of detectable disorders, and the consequent problem with showing benefit at an early stage. More outcome studies are certainly needed. But this type of screening for a large number of rare disorders has caught the imagination of the newborn screening community. Almost everyone seems keen to introduce the technology.

Should We Have Newborn Screening for All?

This conference has been running in the Asia-Pacific region for many years, which shows how the region, with over half the world's population, and half the world's births, values newborn screening. There is some form of newborn screening in 20 different Asian-Pacific countries: 13 offer some or complete screening for hypothyroidism, and at least 6 have screening programmes with full population coverage. In the recent review of screening in the area, only 4 countries appeared to have no newborn screening at all.[13] So it is reasonable to ask what should be aimed at for a region like the Asia-Pacific region? What for other parts of the world? Certainly it is important to aim for improved child health, but where does newborn screening fit into that overarching aim?

My hospital and University in association with the Hoc Mai Foundation have been collaborating with Dien Bien province to help with the development of healthcare, and my colleague, Professor Elizabeth Elliott, shared with me some of the experiences of the team. In this province of North-West Vietnam, as in many similar developing areas, there is a very high perinatal mortality rate, the main causes being prematurity, asphyxia, unidentified foetal death and birth defects. There is also a high maternal death rate, due mainly to haemorrhage, sepsis, and uterine rupture. In this region, the problems in health care delivery are overwhelming – lack of medications and equipment, infrastructure problems – water, sanitation, electricity - lack of training opportunities, language barriers, and huge problems of access. These are physical: poor transport infrastructure, and also cultural: women often being reluctant to consult male doctors. The common medical problems encountered are no surprise – infection, trauma, and malnutrition. But one of the commoner problems here is hypothyroidism. So is there a place in this very poor region for newborn screening? At present it seems as though other problems must be much more pressing.

I visited Northern Thailand in 1995 to look at their screening programmes. Here, the general health problems were far fewer. A pilot programme for PKU and hypothyroidism screening had been in place since 1992. There was village-based follow-up in this rural area (as in other similar areas) which worked very well, and iodination of salt was also done at a local level to combat iodine deficiency. Thailand now has a national programme with near-complete coverage. The many programmes in the region have recently been excellently reviewed.[13]

The Hard Questions

- Should there be newborn screening in every country now? Clearly there should be sometime in the future.
- How do we balance the opportunity costs? What other healthcare will suffer if money is spent on screening?
- Is it right to promote newborn screening in areas where healthcare is very poor?
- Can we ensure equal access? Or should screening be offered, as a start, to those who can pay?
- If newborn screening is undertaken, can follow-up be achieved?
- Can identified patients be treated? Are there a trained medical and auxiliary staff? Are the appropriate medications available and affordable?

If it is decided to introduce newborn screening in a region where currently there is none, it seems that a programme of screening for congenital hypothyroidism alone should be started before anything else at all is attempted. Certainly tandem mass spectrometry screening should not be adopted too early. Screening for hypothyroidism is known to be effective, and the condition is endemic throughout the world. Treatment is usually easily available and cheap, and is easy to administer. If screening for hypothyroidism is implemented first, systems can be developed for staff training, sample taking and dispatch, keeping records, follow-up of cases, and all the other aspects that make up a newborn screening programme. Proceeding slowly in this way enables the development of a firm basis for expansion later.

There is indeed an exciting future ahead. New treatments are already pointing to new possibilities for screening, some of which may be quite complex. So there is a clear need to get current endeavours right now. There needs to be great care taken with decisions on when to start a new programme, with the knowledge of what must be in place before a consideration is given to starting. Evaluation of benefits and drawbacks to individual programmes is extremely important, and going hand in hand with that is the need to have the courage to stop programmes that, after a good trial, are seen to be ineffective.

Screening can certainly improve child health – we have all seen that, and everyone deserves a good start in life. If new programmes are approached with proper caution maximal benefit will be achieved from newborn screening, which is one of the few clearly effective preventive strategies in healthcare.

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