Review Article

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Neonatal Screening: Current Perspective

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Abstract

Newborn screening (NBS) is a public health program designed and developed to screen infants shortly after birth. The principle of NBS Program is to detect potentially harmful disorders that are not clinically evident at birth. Newborn screening is a success story in USA and European countries despite different approaches to timing ofscreening, follow-up testing and intervention. In India, the concept of NBS is in the nascent stages. Screening and surveillance should go hand in hand. Newborn screening model should comprise screening, follow-up, diagnosis, management, and education. For this review, PubMed & Google Scholar were searched for review articles. Of these, those related to Indian scenario were reviewed & appropriately used to prepare a final review.

Keywords: NBS; Heel Stick; Cord Blood.

Introduction

The general term "newborn screening" is used to describe various tests that can occur during the first few hours or days of anewborn's lifeandwhich,when properly timed and performed, have the potential for preventing severe health problems, includingdeath.

In the USA, newborn screening dates back to the 1960s with the introduction of the filter paper test for diagnosis of phenylketonuria (PKU) by Guthrie. In his seminal paper Guthrie described how he went about laying the foundations of NBS.

He stated *"While I recognize how pivotal the phenylalanine assay was for the development of newborn screening, I have always considered the filter paper blood specimen to be my most important contribution. In the simplicity of its collection, the ease of its transport and the facility with which it can be handled and processed in the laboratory, this specimen has made the multiple newborn screening conducted today possible."* [1]

Newborn screening has evolved from a relatively simple blood or urine screening test, originally used for detecting a single congenital condition, to a more comprehensive and complex screening system that can detect over 50 different conditions. While typically using blood taken from a heel stick, more recent newborn screening expansion has included bedside testing to detect conditions such as hearing loss and cardiac disease [2].

Universal newborn screening is quite well established in most of the developed countries. Though universal screening is a cost-intensive exercise, the benefits far exceed the cost as it helps in reducing the mortality and morbidity of these diseases [3].

In India, the exact prevalence of various metabolic disorders is not known due to lack of any large scale multi-centric study to screen metabolic disorders and absence of any organized system of universal newborn screening. Newborn screening aims at the earliest possible recognition of disorders to prevent the most serious consequences by timely intervention. Screening is not a confirmatory diagnosis and requires further investigations [4].

Newborn screening for common metabolic and genetic disorders should be an integral part of neonatal care as early detection and treatment can help prevent

intellectual and physical defects and life threatening illnesses. The list of conditions for which screening is carried out differs from country to country, based on the prevalence of the condition and available resources. Universal screening for about 40 to 50 metabolic disorders is mandatory in US, Europe and many other countries across the world [3].

A template laid down by Wilson and Jeugner is widely used to decide as to which conditions should be included for screening (Table1).

Table 1: Wilson And Juegner Criteria For Disease Screening (1968) [4]

1	The condition sought should be an important health problem.
2	There should be an accepted treatment for patients with recognized disease.
3	Facilities for diagnosis and treatment should be available.
4	There should be a recognizable latent or early symptomatic stage.
5	There should be a suitable test or examination.
6	The test should be acceptable to the population.
7	The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8	There should be an agreed policy on whom to treat as patients.
9	The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10	Case-finding should be a continuing process and not a "once and for all" project

Wilson and Jungner observed that "in theory, screening is an admirable method of combating disease … [but] in practice, there are snags" [1].

Over the years modifications to these criteria have been suggested, especially when applied to screening of genetic disorders like inborn errors of metabolism. (Table 2).

Table 2: Synthesis of Emerging Screening Criteria [1]

1	The screening program should respond to a recognized need
2	The objectives of screening should be defined at the outset.
3	There should be a defined target population.
4	There should be scientific evidence of screening program effectiveness.
5	The program should integrate education, testing, clinical services and management.
6	There should be quality assurance, with mechanisms to minimize potential risks from screening.
7	The program should ensure informed choice, confidentiality and respect for autonomy.
8	The programme should promote equity and access to screening for the entire target population.
9	Program evaluation should be planned from the outset.
10	The overall benefits of screening should outweigh the harm.

When to Introduce Newborn Screening in a Country?

India is going through a progressive transitional phase of control over infant mortality and morbidity due to infections, and emergence of genetic conditionsIntroducing NBS is akin to introducing genetic services in a country. The WHO has often recommended that genetic services should be introduced in countries with an IMR less than 50. If we apply this criteria, the urban areas in all states should introduce newborn screening and genetic services as the IMR is less than 50 [1].

The IMR in rural areas in all states, except Assam, Madhya Pradesh, Rajasthan and UP is less than 50. The combined IMR in the following states is 25 or less:

Goa (10), Kerala (12), Daman & Diu and Puducherry (18), Chandigarh (20), Lakshadweep (21), Sikkim and Andaman and Nicobar Islands (24), Delhi and Maharashtra (25). Clearly these states deserve to have newborn screening [1].

The major hindrances for establishing an effective screening program in India are the costs involved, the non availability of demographic data about the diseases in question, massive annual birth cohort and the limitations of treatment modalities for some of the diseases. A recent study documented particularly high incidence of congenital hypothyroidism (1 in 1700); congenital adrenal hyperplasia, G6PD deficiency and amino-acidopathies. This study estimated the prevalence of any metabolic disease as 1 in 1000 [6].

Considering the prevalence of these conditions and huge financial implications for universalscreening for a developing country like India, a practical approach will be to categorise the conditions as follows [2]:

Category A (all newborns): Screening for congenital hypothyroidism and hearing should be a must in Indian scenario. Screening for CAH and G6PD deficiency may be added in a phased manner. G6PD screening should be done in Northern states of the country. Screening for Sickle cell disease and other hemoglobinopathies should be undertaken in pockets of high incidence.

Category B (High risk screening): Screening for the following disorders should be conducted in the high risk population (consanguinity, previous children with unexplained intellectual disability, seizure disorder, previous unexplained sibling deaths, critically ill neonates, newborns/children with symptoms/ signs / investigations suggestive of inborn errors of metabolism). These conditions include phenylketonuria, homocystinuria, alkaptonuria, galactosemia, sickle cell anemia and other hemoglobinopathies, cystic fibrosis, biotinidase deficiency, maple syrup urine disease, medium-chain acyl-CoA dehydrogenase deficiency, tyrosinemia and fatty acid oxidation defects.

Category C: Screening (in resource-rich setting/ expanded screening) for 30-40 inherited metabolicdisorders may be offered to 'well-to-do' families, especially in urban settings where facilities for sendingsample to laboratory where TMS (Tandem mass spectroscopy) are available.

Specimen Collection in Newborn Screening

Since dried blood spot remains stable for years, the mode of collection should be capillary bloodfrom the heel, impregnation of drops of blood into filter paper, drying of these blood spots and transport of the specimens to a central screening laboratory. Low humidity and low temperature conditionsare required for transportation and storage of dried blood spots. These observations should be taken into account while introducing NBS in India [2].

Can Cord Blood Samples be Used?

This is a question often asked in India, because of the ease with which cord blood sample can be collected. Studies on cord blood T4, TSH are reliable and comparable to analysis of blood obtained by heelprick on day 3, although TSH cut offs are variable. However, there is a high false positive rate . Secondly, the sample cannot be used to screen for metabolic disorders, as for their manifestation some feeding is required. IEM's cannot be detected biochemically until at-least 12 h after the baby has taken feeds [2].

Optimal Timing and Method of Sampling

The American Academy of Pediatrics has advocated the ideal time of sampling after 72 hours and within 7 days of life. However, this policy would be very difficult to adopt due to high birth rate, limited spacein most hospitals and definite resistance, which we can anticipate from our Obstetric colleagues. A recent document suggests that the analytes canideally be measured at 24-48 hours of life whenenteral feeding has been established, renal function is improving and hepatic metabolism is in the process of becoming mature. Thus it may be ideal for our set up, to take the sample after first 24 hours of life [4].

'*Screening window*', defined as the period between the development of the abnormal test result of NBS and development of symptoms in the infant, may vary from disorder to disorder. It will be most ideal to collect sample on fourth day of life. Samples can be collected from home by trained nurse/phlebotomist. There are many riders associated with interpretation of blood samples collected in the first few days of life; often a repeat testing may be warranted. This not only increases the costs but can also lead to false alarm and cause panic in parents and families. However, defining age-appropriate cut-offs may circumvent the problem of loss to follow-up [7].

Universal Neonatal Hearing Screening

Permanent hearing loss is one of the commonest congenital disorders with the incidence being much more than the conditions newborns are routinely screened for. Most neonatal hearing loss is sensorineural and a known genetic cause can be found in only 50%. In the absence of a screening program, hearing loss is typically identified with language delay around 24 months of age in contrast to three months or younger in the screened population with intervention by six months. Screening has reduced the age, at which infants receive hearing aids, from 13-16 months to 5-7 months in developed countries [8].

Screening can be performed by otoacoustic emissions (OAE) or automated auditory brainstem response (AABR) testing. OAE is technically easier and faster to perform. It is cheaper but has higher false positive rates of about 15%. It also requires a quite or a soundproof room. In comparison, AABR has less false positives and can also detect patients with auditory neuropathy unlike OAE. It is best to screen after 24 hours as pass rateincrease from 70% to 82% if done after 24 hours. There are limitations with hearing screening. UNHSwill not identify progressive and late onset hearing loss as well as less severe hearing loss (<40dB). The falsepositive

rate is around 2% that is similar to thyroid screening. This can cause anxiety in parents, which should be addressed appropriately [8].

In developing countries like India with the high attrition rate in follow-up, the cost effectiveness of UNHS as well as its comparison with targeted screening needs to be evaluated.

Screening for Critical Congenital Heart Disease

Antenatal ultrasonography and postnatal clinical examination are the current standard methods of screening for congenital heart disease (CHD). However, life-threatening defects often are not detected.

Pulse oximetry screening has been introduced in the West for identifying newborns with critical heart disease. Pulse oximetry is a safe and feasible test that adds value to existing screening. It identifies cases of critical congenital heart defects that go undetected with antenatal ultrasonography, with an additional advantage of early detection of other diseases. It is reasonable to do it in all babies. However, it needs availability of pulse oximeter. Ideally, it must be done in healthy term babies before the baby is discharged. In a metaanalysis, the overall sensitivity of pulse oximetry for detection of critical CHD was 76.5%. The specificity was 99.9%, with a false-positive rate of 0.14% [1].

However, NBS is much more than merely a testing activity . It has six components & all need to be addressed for it to be successful. These include [1] -

i. *Education of the parents / the public* regarding the purpose and benefits of NBS, so that they accept newborn screening and permit their babies to be tested; and the professionals who will be engaged in NBS.

ii. *Screening of the babies*, which involves collection of the sample, its submission to the central laboratory, testing of the sample, and storage of the filter paper specimen;

iii. *Diagnosis* consists of assessment of the results by persons with appropriate training, and preparation of the report;

iv. *Conveying the report* to the parents or the doctor, immediately by telephone if abnormal, or by mail if normal. In cases of + ve results, it is required to provide counselling to the family; *Follow up*, if the results are + ve, comprising recall of the patient, repeating the test, and confirming the diagnosis by biochemical or DNA analysis;

v. *Management* comprises treatment, periodic examination, and monitoring of long term outcome; and

vi. *Monitoring and Evaluation* of the program through quality assurance, outcome and cost effectiveness.

Limitations of Newborn Screening

It is important to emphasize that newborn screening is for a limited number of congenital conditions. Moreover, the results of screening are not to be considered diagnostic; confirmatory testing is required. In the presence of signs or symptoms, diagnostic tests are necessary, even for a condition that has been screened. Organization of follow up and treatment of a positive case are essential. Evaluation, audit and quality control should be an integral part of any screening program [1].

Screening in the high risk population is akin to diagnostic testing and this application cannot be questioned. All diagnostic techniques such as routine biochemical tests, tandem mass spectrometry, GC-MS or Liquid chromatography–mass spectrometry (LC-MS) in the urine, and High-performance liquid chromatography (HPLC) for amino acid analysis should be available for study of sick newborns to exclude or diagnose IEM [1].

Conclusion

Neonatal screening is the most important preventive public health programme of the 21st century. It is implemented in majority of the developed countries. Most of the developing countries are following suit. In India "it is still in its neonatal stage and yet to evolve into childhood" [9]. Currently there is no government funded neonatal screening programme for the masses. It may seem to be an extra financial burden on the country's resources, but when we consider the large population of one billion and a high birth rate, the burden of metabolic disorders with preventable long term morbidity could be very high. Four percent of the population in India are mentally retarded and 5-15% of sick newborns are thought to have a metabolic problem. Thus mass screening will be useful to prevent disability and death by early intervention, follow-up and counselling.

Contributors

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