PERSPECTIVE

National Newborn Screening Program – Still a Hype or a Hope Now?

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The year 2013 marks 50 years of both newborn screening and the Indian Academy of Pediatrics. India has seen a lot of change in terms of motivation, evolution and implementation of newborn screening as pilot projects for few disorders. Facilities for implementing screening using tandem mass spectrometry or what is termed as 'expanded newborn screening' have also become available. We attempt to discuss the evolution of newborn screening and the way to carry it forward in the country. The current strengths, the major obstacles and gritty challenges are enlisted. No moment could be so opportune than this year to discuss the rainbow of hope with all its colors with respect to newborn screening in our country.

Keywords: *Newborn, India, Screening, National Program.*

Newborn screening was initiated in 1963 and the year 2013 marks the celebration of its 50 years. It is indeed a co-incidence that the Indian Academy of Pediatrics also celebrates its golden jubilee in 2013. We take this fortunate moment to discuss newborn screening and its evolution in India. The Health Ministry's desire to introduce newborn screening [1], and the recommendations of the multicentre task force study of the Indian Council of Medical Research (ICMR) for inborn metabolic disorders (to be released soon)[2], have begun to catalyse the initiation of a National Newborn Screening Program. Time is now ripe to discuss universal newborn screening and expanded screening with their current feasibility in India. This communiqué discusses screening for inborn metabolic disorders.

Since our last perspective published in in 2010 [3], there has been a surge of publications [4-6] from different parts of the country narrating their experience with newborn screening for a selected group of disorders. It is vital to understand the terms "core" and "expanded" panel of disorders. The term core indicates the basic minimum set of disorders for which screening should be advocated at a national level. Since all countries chose the set of disorders to be initiated in their domain based on epidemiologic prevalence and resources, the panel across the world is not uniform This distinction not only outlines the group to be tested but also the differences in technology for the set of disorders included in each category. The term expanded newborn screening emerged after the introduction of tandem mass spectrometry (MS/MS) into the newborn screening program [7]. It utilizes the same modality of sample collection on filter paper (dried blood spot technology) as for the core set of disorders. When introduced it was used as- 'one drop-phenylketonuria (PKU) and later for congenital hypothyroidism (CH). The simultaneous screening of multiple analytes from the same drop of blood by a technology known as MS/MS paved the way for "expanded newborn screening".

The core or traditional newborn screening is intended to test infants for medical conditions that might cause significant morbidity and mortality like CH. With the availability of multi-analyte testing in the expanded program, identification of disorders of ambiguous medical significance like short chain acyl CoA dehydrogenase deficiency and histidinemia along with identification of mild variants of diseases which may decompensate in adulthood like Citrullinemia Type 1 started appearing. So overall, there was a distinct change in focus in countries adopting expanded screening. Each country had to use available data, resources and significant brainstorming to decide on any new disorder that needed inclusion in the expanded panel. There was lack of broad consensus even in developed nations at the level of National Policy making on what to include in the core panel of disorders. Pollit [8] compared the disease panels recommended across the United States of America (USA) and four European countries using MS/MS. The two extremes were represented by the United Kingdom (UK) where only phenylketonuria and medium chain acyl co-A dehydrogenase (MCAD) deficiency were recommended for newborn screening with MS/MS and in the USA where up to 40 disorders were tested. There was

a common core panel which was screened for in most of these nations and included CH and other disorders depending upon respective national regulations. We now propose to discuss the set of conditions that should be included in the core panel for the nation using the template laid down by Wilson and Jeugner (***Table* I**).

Core Panel

What are the disorders with significant public health relevance? The first criterion for inclusion of a disorder for screening is that the disease should be of a magnitude to qualify to be called a significant public health problem.

Congenital hypothyroidism. Data from various parts of India for CH suggests varying incidences; from North India (Chandigarh) 1 in 3400[4], Southern India (Kochi) 1 in 500 [9], and Eastern part of the country 1in 600 (10). The data clearly suggests the significant burden of CH in India. The data for congenital hypothyroidism appears to be discrepant from various parts of the country. One of the reasons to explain the discrepancy could be the region from which the data originated. TSH is a marker of iodine deficiency and in belts where this continues to be an important health issue, a high TSH may not be due to problems inherent to neonatal thyroid pituitary axis but as a result of iodine deficiency. Use of thyroid stimulating hormone (TSH) levels to screen for CH could over diagnose possible CH, especially in preterm babies due to combination of low iodine stores achieved in utero and the immaturity of the hypothalamic- pituitary axis [11]. Both these conditions reflect transient CH. Delay in diagnosis in CH is evident from recent data from an endocrine clinic in Delhi [12] wherein nearly one third of children presenting beyond 5 years had CH. The mean age of presentation of symptoms in the CH group was 35.2± 25.9 months (range: 12-132 months] and the average interval between onset of symptoms and diagnosis was nearly 51 months.

Congenital adrenal hyperplasia.(CAH). The next disorder that deserves mention is CAH. Data from Chandigarh suggest a prevalence of 1 in 6813. Previous data also suggest a high incidence of CAH [13]. Recent published data from eastern part of the country by Maiti and Chaterjee [14] suggested that the mean age at diagnosis in the salt wasting group of CAH was 0.5 years compared to 9 years in the simple virilizing group, majority being girls. Similar observations were made in North India. The study had evaluated 62 patients; 50 were simple virilizers and 12 saltwasters [15] and 90% being girls. The skewed male to female ratio in these studies suggests that a substantial proportion of males were being missed due to early demise and non-recognition of the disease. Given the fact that transgenders are encountered at street crossings, bus stops and during social events at Indian homes, it is possible that a fair proportion of them could be simple virilizers (21- α hydroxylase deficient). There thus seems to emerge a need to screen for CAH.

Glucose 6- phosphate dehydrogenase deficiency (G6PD). This is another disease that has been targeted for screening in India. The author's data (unpublished) suggests an incidence of 1 in 192 for G6PD deficiency. Data from Chandigarh suggests an incidence of 1 in 112 and from eastern India [16] an incidence of 1 in 15. This disorder that has been genotypically well mapped from different parts of the country with G6PD Mediterranean (563 C-T) being seen commonly in North India, G6PD Kerala- Kalyan (949 G-A) in Maharashtra, Kerala, Andhra Pradesh, Tamil Nadu and Punjab and G6PD Orissa (131C-G) in tribals of central, eastern and southern India. Nair also highlighted the need for a screening program for G6PD in our country and from the existing prevalence he extrapolated that the burden due to this disorder is likely to be nearly 390,000 births per year [17].

Based on the information provided in the preceding section, we suggest that in India core screening should include CH, CAH and G6PD. Besides, multi-analyte screening is more cost effective than screening for a single disease. Alternatively, if it is likely to impose significant burden on the State's health budget, screening

TABLE I WILSON AND JUEGNER CRITERIA FOR DISEASE SCREENING

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.

may be initiated for congenital hypothyroidism, and subsequently the remaining two conditions can be added in a phased manner.

Is there an accepted treatment policy for these conditions? The second criterion for including a disease in the screening panel is that facilities for confirmatory diagnosis and treatment should be available. Since dried blood spot can be easily collected from any part of the country, couriered to enabled laboratories, diagnosing these disorders would no longer be rate limiting. Both ELISA based assays and assays based on time resolved fluorimetry are reliable, though the ones using ELISA show some cross reactivity. But both do well in the pathologic ranges. MS/MS technology is also available in both the private and public sector, hence it would also be possible to screen for the expanded panel of disorders when needed. Treatment for CH, CAH and G6PD are available. CH requires supplementation with L-thyroxine, CAH would require glucocorticoids with/ without mineralocorticoid therapy along with surgical intervention like clitoral resection. G6PD just requires avoidance of certain drugs and food stuffs which may initiate hemolysis.

Do these disorders have a latent recognizable phase? The next important criterion is that there should be a latent recognizable phase during which symptoms have not become manifest and initiation of therapy can avoid the sequelae. For all the disorders in the core panel such a phase exists. But for defects of urea cycle, organic acidemias and nonketotic hyperglycinemia, there may be no window period and these may present before the results of screening are available early in the first week of life.

Is there a policy on whom to treat? The next outlined criteria is that there should be an agreed upon policy on whom to treat as patients. For the group of disorders where a biochemical abnormality translates into a defined clinical phenotype such as CH and CAH, there would be no debate. However for certain disorders there is no distinguishable phenotype and an example of this is histidinemia, a biochemical entity with non-significant clinical phenotype.

What is the likely cost of screening versus case finding? These are important issues. Clearly for CH there is sufficient evidence that screening and treatment is cost effective compared to cost of case-finding and of permanent mental subnormality with its attendant loss of productivity. Cost benefit analysis for CH in Iran suggests a benefit of 22 times [18]. The same can be said for CAH and G-6-PD. Presently the costs of expanded screening are probably not cost effective for India. It is important to underscore that screening is an on-going activity and not a one-time health screening event, if the nation has to accrue the benefits just described.

Expanded Screening

The introduction of MS/MS technology for analysis has led to the expansion of disorders that could be screened. However, for most of these conditions there is no data on the disease burden in the country. MCAD, a disorder of fatty acid metabolism is included even in the most conservative programs of Europe. This disorder needs tandem mass spectrometry for identification and requires frequent feeding for its treatment. This is also a disorder of energy metabolism which may present as SIDS[19]. There is some data for MCAD; 1case was detected of 25578 newborns screened in Goa between 2008-2011 and a single case by screening 4946 neonates in Andhra Pradesh along with a single case from PICU[5,20, 21,22]. Targeted or high risk screening may identify more cases. We admit that each case diagnosed by the technology is important for the family for subsequent genetic counselling; but here we are discussing the feasibility of universal screening. It may be important for regional laboratories to be set up that could cater to the needs of selected NICU patients in whom these conditions are suspected**.** MS/MS technology is now available in both the private and public sector and hence it would be possible to screen for these conditions in the future. Availability of confirmatory testing and treatment appear to be the major rate limiting factor in implementing expanded screening in India. We reiterate that all screening tests need confirmatory testing as there is always an existent possibility of a false positive result.

Scaling up: Hurdles and Challenges

This communiqué would be incomplete without answering the question 'Are we ready for the leap?' The key factors that are critical for scale up are manpower, budget, logistics, infrastructure, and advocacy.

Manpower: The country has a small pool of trained pediatricians and geneticists who have been exposed to newborn screening in India and understand its limitations and strengths. Many more pediatricians, neonatologists, biochemists and geneticists are needed to make this viable. It is worthwhile to reemphasize that newborn screening is not just a test but a program and this networking is crucial for not only for its initiation but sustainability as well.

Budget: The current budgetary allocation for health is 0.9% of GDP and the state expenditure on the health sector is 5.5% of the budget. The central funding in the state for public health is 15% and 70-80% is out of pocket

expenditure for most of the population residing in the states. If India increases its health budget to 2.5% of GDP, it must make provisions then for allocating funds to a national newborn screening program for the core panel.

Phasing out of the program: The introduction of the program must be initially in major metropolitan cities and states with low IMR. Even in these areas, it could be started initially in medical colleges and district hospitals where it may be possible to integrate it with basic newborn care interventions which are already in place. Simultaneously operational research to evaluate feasibility of initiating a newborn screening program in difficult to access areas, tribal areas and states with poor infrastructure should be implemented. Subsequently, one should aim at targeting all institutional births for the three core panel disorders in the rest of the country.

Logistics: The major logistics include training of health care providers such as ANMs and nurses for taking heel prick samples on filter papers, completing required information and transporting them to the designated laboratories for analysis and their subsequent storage for at least 5years, but if a national cold storage is in place one could extend it till 20 years [23]. The labs engaged in screening have to be enrolled into a quality assurance program. An alliance with ERNDIM (External Quality Assurance Programme for Amino Acids, Quantitative Organic Acids, Purines and Pyrimidines, Special Assays in Serum and Urine, Cystine in White Blood Cells and Lysosomal Enzymes) and Center for Disease Control (CDC) could be an interim till the country establishes a national quality assurance centre.

Advocacy and consent: A national advocacy campaign for mass awareness on the utility of newborn screening is important since it involves taking a blood sample (although only a few drops) from an apparently healthy newborn. Partnering with all stakeholders, pediatricians, obstetricians, professional medical bodies such as the Indian Medical Association, government, and civil society and media would help in achieving this objective. Obtaining written consent could be challenge in our country both because of low literacy levels and inherent suspicion of signing on formal papers. Many countries have adopted a policy of parents 'opting out' and have done away with informed consent process. This is also justifiable as it is no longer a research module and has moved into the program phase. Probably India for the reasons cited above should also adopt a similar process and do away with formal consenting procedures.

Finally, the benefits translated to the population at large. Using the SRS 2012 data which estimates the national population to be 1220 million, and birth rate of 20.6, the estimated number of neonates who would have CH alone would be about 17000 births each year. Translated into preventable mental sub-normality and productivity loss, it would amount to millions of rupees each year.

By the time policy makers take note of this plea, more centres would have come for high risk or targeted analysis. Screening not only needs setting up of logistics and infrastructure, but a policy that facilitates manufacture, or easy import of therapeutic agents at affordable prices for these inherited metabolic disorders. This may be a small voice from a select band of professionals, but it speaks also on behalf of the muted sufferers with preventable metabolic disorders. We realize that introducing newborn screen is likely to be complex in India as quoted by Miller. India is at cross roads, on the one hand still grappling with providing equitable health care for all, but on the other it can provide care comparable to the best elsewhere in the world. We believe that we should move forward and contribute to decreasing the burden of disability and ensure equitable quality of life for all.

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