Universal Newborn Screening – Is it Going to be a Reality in India?

Neonatologist's Perspective

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Universal newborn screening is quite well established in most of the developed countries. In India, the exact prevalence of various metabolic disorders is not known due to lack of any large scale multicentric study to screen metabolic disorders and absence of any organized system of universal newborn screening. Like other developing countries, India is facing an increasing challenge of non-communicable diseases, of which many are preventable. Endocrinopathies and other genetic/metabolic diseases constitute an important proportion of such problems. The unique clinical dilemma with these disorders is that either they are asymptomatic or have only non-specific signs and symptoms in the early stages, thereby rendering their early diagnosis almost impossible without a screening program. Some of these disorders like congenital hypothyroidism have a debilitating impact on the developing neonatal brain, if not diagnosed early.

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. The Wilson criteria [1] mandates such factors and data for the cost effective and efficient running of a screening program, including diseases like congenital hypothyroidism. However, recent developments in the health infrastructure of India and the availability of data on some of these conditions have addressed these problems to a certain extent. For example, in a hospital based survey, 5.75% of all intellectual disability were attributed to metabolic diseases [2]. A previous pilot newborn screening program conducted in Southern India screened 1,25,000 infants and identified homo-cystinemia, hyperglycinemia, Maple syrup urine disease, phenylketonuria, hypothyroidism and Glucose-6-phosphate dehydrogenase (G6PD) deficiency as the most common metabolic errors [3]. A more recent study documented similar results with particularly high incidence of congenital hypothyroidism (1 in 1700); congenital adrenal hyperplasia, G6PD deficiency and

amino-acidopathies were the other common disorders. This study estimated the prevalence of any metabolic disease as 1 in 1000 [4]. More recent preliminary results from Chandigarh [5] and Andhra Pradesh [6] also indicate a high incidence of metabolic diseases in Indian population.

The sample collection and processing have been simplified by the establishment of filter paper sampling method (dried blood) from a heel prick. This allows a convenient way for collection and transport of the sample. The advances in the tandem mass spectroscopy allow the detection of most of the inborn errors of metabolism relatively easily. One major obstacle in our country is the timing of sampling. The general guidelines of obtaining a heel prick sample between day 3 to 7 is very difficult to follow in India due to massive load of deliveries leading to early discharge from the hospital, and a high proportion of home deliveries. To counteract this problem, countries like Malaysia and Cuba have tried screening with cord blood sample for congenital hypothyroidism, but this strategy is not valid for other metabolic diseases like aminoacidopathies. In a Quebec–New England collaborative study of normal newborns, it was shown that the TSH estimation at 24-48 hours of life is comparable with estimation at a later duration [7]. The study in this issue by Gopalakrishnan, *et al.* [8] used the same strategy. The concern of diagnostic cut-off of TSH level is an important point in our set up. Selecting a lower universal cut-off point may increase the sensitivity but will hugely increase the false positive results and recall rates which will overload the facilities. The usage of age appropriate cut-offs is the most logical method in this setting and this was ably demonstrated in the current study. The problem of loss to follow-up and non-availability of the newborn for recall for a confirmatory sample (in case the screening test is abnormal) still exists. In the current study, the authors could not perform the repeat test in 15% of babies. The MCTS (Mother child tracking system), an initiative launched by the Government of India, once fully implemented may play a pivotal role in rectifying this problem.

In the current study, authors tried the feasibility of screening and recall system for newborn screening for congenital hypothyroidism, galactosemia and biotinidase deficiency, in a rural population of UP, India. They used heel prick sample, collected at 24 hours of life in 13426 newborns, constituting 73% of all deliveries. From those with abnormal screening results, 85% could be recalled for the confirmatory test and they identified 11 babies with congenital hypothyroidism. Compared to Western data, this loss to follow-up is significant but previous experience from India [5] documents even a higher loss to follow-up. As the loss to follow-up will reduce the impact of the program to a great extent, this emphasizes the need for a proper tracking schedule. The Goa screening program has shown that an effective follow-up can be ensured even in a public set up [9].

The authors have shown that the neonatal screening program is feasible even at a rural set up and also demonstrated the high incidence of congenital hypothyroidism. The failure to sample about 27% of newborns and the significant loss to follow-up are the matters of concern. This paper further establishes the need of a nationwide screening strategy and strengthening the follow-up care. The establishment of a screening program in a country like India will require huge investment by the government, but as evidenced by the experience in developed countries, this strategy will be cost effective in the long run. Experience from the public (Goa and Chandigarh) and various private sectors in India should provide the platform to the Government for establishment of an effective neonatal screening program.

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Newborn Screening: The Critical Importance *Biochemist's Perspective*

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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 [1,2] and European countries [3] despite different approaches to timing of screening, follow-up testing and intervention [4]. In India, the concept of NBS is in the nascent stages, and as of now is

more focused on detecting congenital hypothyroidism, congenital adrenal hyperplasia, galactosemia, Glucose-6-phosphate dehydrogenase deficiency, biotinidase deficiency and cystic fibrosis. Screening for inborn errors of metabolism, including aminoacidopathies, organic acidurias and fatty acid oxidation disorders are yet to pick up as the costs involved are daunting [5]. False positive alarms and recall rates of a NBS program depend on methodology used and quality of diagnostic services. For

example, as a good quality practice, sample storage and test performance should be carried out at same temperature throughout the year.

‘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 – as in the study in this issue of *Indian Pediatrics* [6] – may circumvent the problem of loss to follow-up. It is important to define criteria for permanent and transient hypothyroidism and exclude cases of transient hypothyroidism [7]. Workshops and pilot studies are required for standardization of diagnostic criteria for congenital hypothyroidism.

Screening and surveillance should go hand in hand. Newborn screening model should comprise screening, follow-up, diagnosis, management, and education. Teaching guide for parents should be made available as public awareness of these disorders is very poor in India.

Success of any newborn screening program depends on coordination of efforts of many stakeholders.

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Post-discharge Growth of Extremely Low Birth Weight Neonates

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Rapid advances in perinatal and neonatal care in the last two decades have led to a dramatic increase in the survival of extremely low birth weight (ELBW; birth weight <1000 g) neonates.

This assurance of survival has now shifted the main focus of concern from short term outcome to the adequacy of growth and development in later life. Extra-uterine growth failure is extremely common in this group of infants; weight at discharge of almost 90% is below 10th percentile of reference value, despite planned nutritional management, including total parenteral nutrition and trophic feedings in the first few days of life [1]. There is paucity of literature regarding the long-term growth

trajectory of ELBW infants. The usual norms for the growth of infants with higher birth weight may not be applicable to this group. Moreover, growth in the small for gestational age (SGA) ELBW infants is characterized by great heterogeneity with remarkable variability [2].

Nutrition of the ELBW infants after hospital discharge is an area of growing interest. Though the goal of nutrition is to maintain the rate of growth and the body composition comparable to that of a normal fetus of the same postmenstrual age [3], both high and low nutrient intakes as well as fast and slow rates of growth have been shown to have some long-term adverse effects. On one hand, studies have shown that inadequate early nutrition at a vulnerable period of brain development may exert an adverse

influence on long-term neurodevelopment by causing a reduction in the number of brain cells leading to deficits in behavior, learning, and memory. Both quantity as well as the quality of enteral nutrition provided during the early days of life may influence ultimate neurodevelopment and intelligence quotients in childhood [4]. On the other hand, concerns have been expressed that aggressive nutritional support causing accelerated growth rates and adiposity in infancy and early childhood may be associated with obesity and metabolic syndrome, including increased risk for cardiovascular disease and diabetes in later life [5,6]. Till date, there are no consensus guidelines regarding the ideal dietary requirement for ELBW infants which will lead to optimum somatic growth without producing any metabolic stress.

In the current issue of *Indian Pediatrics*, Mukhopadhyay, *et al.* [7] described longitudinal growth and post-discharge mortality and morbidities in a cohort of 149 ELBW neonates at corrected age of 2 years from a tertiary care teaching hospital of India. In the study group, 51 (64.5%) infants were SGA indicating high rate of intrauterine growth restriction in Indian neonates, probably secondary to maternal malnutrition or placental insufficiency. A high mortality rate (47%) and high readmission rate (44%) during first year of life were other notable features. Only less than half of survivors could be followed up till the corrected age of 24 months showing difficulties associated with regular follow-up. At corrected age of 2 years, significant growth restriction was observed in all gestational age groups. However, no difference was observed between the catch-up growth patterns of SGA and their appropriate for gestational age (AGA) counterparts. Inclusion of the details of average daily calorie intake, feeding pattern and nutritional supplementation in the current study group would have been more informative. Inclusion of data on the mean weight and Z score at birth would have made the comparison with the later values easier.

The quality of neonatal care has improved in India but there is a wide variation in outcome across the country. However, there is a paucity of published information regarding this aspect; this article is thus timely. Earlier, Bhargava, *et al.* [8] and Bavdekar, *et al.* [9] reported long term growth of low birth weight infants. Recently, Modi, *et al.* [10] reported significantly lower growth at one year in a cohort of very low birth weight infants. Long term follow-up studies are usually lacking in India. Poor health tracking system and economic constraints of the parents are the major limiting factors for regular follow-up.

ELBW infants are a major group of neonates admitted in any neonatal intensive care unit (NICU) requiring

advanced care, manpower and hospital resources. This study draws our attention not only towards the high mortality and morbidity but also towards poor long term growth in this vulnerable population. There is an urgent need of upgradation of our NICUs with a uniform management protocol all over the country. Along with provision of immediate postnatal nutrition, emphasis should also be given on regular pre- and post-discharge counseling, ensuring adequate intake of macro- and micronutrients, regular monitoring of growth and appropriate timely intervention to ensure better growth and long term outcome. There should be a better patient tracking system to ensure regular follow-up making the pre- and post-discharge nutritional management a continuum. Similar longitudinal studies from different places of India should be encouraged to optimize the neonatal care.

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