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Review Article

Newborn screening: Need of the hour

Anil B. Jalan[1], Ketki V. Kudalkar[1]

[1]Department of Biochemical Genetics, NIRMAN, Mumbai, Maharashtra, India.

***Corresponding author:**
Anil B. Jalan,
Department of Biochemical Genetics, NIRMAN, Mumbai, Maharashtra, India

jalananil12@gmail.com

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ABSTRACT

Newborn screening (NBS) is the process by which newborns are screened just after birth for disorders that can cause severe illness or death unless detected and treated early. At present, there is no national NBS program in India. Although the exact incidence in India is not known, approximately 4:1000 and 5:1000 are estimated to have hearing defects and congenital heart abnormalities, respectively, whereas the incidence of IEMs is estimated to be approximately 1:1000. This high incidence is due to high prevalence of consanguinity in our country. If undiagnosed and untreated many children develop mental retardation, learning disabilities, autism, dyslexia, behavioral abnormalities, and scholastic backwardness later in life. There is also considerable burden-financial and emotional on the parents to diagnose, treat, and manage these children. The most rational and cost-effective way of preventing such tragedies would be to have a NBS program which will detect most of the preventable or treatable, if not all IEMs and other genetic disorders. Hence, all hospitals in urban areas in India should initiate NBS at least for the common disorders: CH, CAH, and G6PD deficiency.

Keywords: Inborn errors of metabolism, Dried blood spots, Hearing screening, 2nd tier test, Newborn screening

INTRODUCTION

Newborn screening (NBS) is the process by which newborns are screened just after birth for disorders that can cause severe illness or death unless detected and treated early. The delay or lack of diagnosis of an Inborn Error of Metabolism or other conditions which can be detected at birth, for example, hypothyroidism, G6PD deficiency, etc., can lead to severe mental deterioration. NBS tests newborns for certain metabolic and other disorders so that intervention is possible before symptoms or mental and/or physical disabilities develop. It is a norm in the developed countries and is recommended to prevent morbidity and mortality. Depending on the incidence, different countries screen for disorders ranging between 5 and 50+ disorders.

NBS was introduced in early 1960s by the pioneering work of Dr. Robert Guthrie in the USA, with the discovery of bacterial inhibition assay to detect Phenylketonuria from dried blood spots.[1] As the concept of NBS was accepted as an essential preventive public health policy, newer techniques developed and soon began to include other IEMs. Since its commencement NBS has progressed with increase in the number of metabolic/genetic disorders screened, type of samples used (from invasive to non-invasive), and improvements in technology (from bacterial inhibition assays to ELISA and RIA and now to LC/MS/MS techniques). In 1990, it was proposed that MS/MS could be used to test for multiple analytes simultaneously in dried blood spots[2] and about 40 conditions are now screened from a single blood spot by LC/MS/MS in routine NBS programs.[3,4]

In India, NBS was first carried out by Dr. Appaji Rao and Dr. Radha Rama Devi. Subsequently, many small studies were carried out at various centers across India and now many private hospitals and labs have initiated their own NBS programs. Many state level NBS programs have been initiated and of note among these are the Chandigarh Program initiated in 2007 which screened for CH, CH, and G6PD;[5] Kerala State NBS program[6] and Goa state NBS Program carried out by Dr. Rohit Cariappa.[7] However, NBS as a National Health Service program is yet to be initiated in India.

WORLD HEALTH ORGANIZATION (WHO) GUIDELINES

NBS is not simply a test for diagnosing disorders but a coordinated comprehensive system consisting of other aspects such as education, follow-up of abnormal results and confirmatory testing, diagnosis, treatment, management, periodic outcome evaluation, quality assurance, and evaluation of the whole program. The WHO has issued guidelines and criteria for selecting disorders in NBS program. Wilson and Jungner in 1996 have outlined the selection criteria for disorders in NBS program. These criteria are applicable to systematic or population-based screening of any type of disease and not only to inherited disorders.

Box 1: Wilson-Jungner criteria for disease selection in NBS

1. The condition should be an important health problem
2. Natural history of the condition should be well understood
3. It should be detectable at an early age
4. Treatment at an early stage should be beneficial
5. Suitable test should be devised for early detection
6. The test should be acceptable
7. Intervals for repeating the test should be available
8. Adequate health service provision should be made for the extra clinical workload resulting from the screening
9. The risks, both physical and psychological should be less than the benefits.
10. The cost should be balanced against the benefits.

Congenital hypothyroidism (CH) is the most common preventable cause of mental retardation. The world-wide incidence is 1:2500–2800 live births. Thyroid dysgenesis is the most common cause accounting for 75–80% of all cases of CH. In India, the exact incidence of this disorder is not known, but it seems to have a much higher incidence than the rest of the world.[8-11] It not only constitutes the most common cause of preventable mental retardation but also the therapy is easily available and economically feasible to all. First NBS program for CH was started at BJ Wadia Hospital in Mumbai in 1982 using cord blood TSH and subsequently in 1984 using post-natal T4 on DBS.[12]

Ideally universal NBS at 48–72 h of life should be done for detecting CH. If screening is being done only for CH, the cord blood may also be used. Three approaches are used for screening:[13]

1. Primary TSH (backup T4): T4 is measured only if TSH is >20 mU/L
2. Primary T4 (backup TSH): TSH is measured if T4 is <6.5 ug/dL
3. Both T4 and TSH: Both measured simultaneously. More sensitive approach but is expensive.

Primary TSH screen is more sensitive and specific for diagnosis of primary CH. Abnormal value on screening (T4 <6.5 ug/dL and TSH >20 mU/L) should always be confirmed by a repeat sampling and assays done on liquid blood samples.[14] Most centers initiate treatment after drawing the blood samples for confirmatory results and decision to withhold or continue treatment is taken after obtaining venous blood report.

G6PD deficiency is the most common enzyme deficiency affecting estimated 400 million people all over the world. It is also the most common genetic disorder in India. Although the exact incidence is not known, various studies have reported an incidence ranging from 2% to 27.9% in different communities.[8,15] It is an X-linked recessive disorder presenting with hemolytic anemia and prolonged jaundice and causes significant morbidity and mortality in childhood. There are no primary interventions available for this disease and the only way to avoid adverse outcomes is to recognize it early in life and prevent exposure to agents which can trigger hemolysis. NBS helps to identify these individuals at an early age.

NBS for G6PD has been successfully implemented in countries such as the USA, Malaysia, Singapore, Taiwan, Hong Kong, Philippines, the Middle East, and Europe. In India, NBS for G6PD deficiency has long been perceived by public and pediatric health experts. Introduction of screening program will substantially decrease the hospital admissions due to acute hemolysis, thereby reducing the number of blood transfusions and dialysis needed.

Cystic fibrosis is the most lethal, autosomal recessive monogenic disorder caused due to an abnormal transport of chloride ions across the apical membrane of the epithelial cells. The sweat glands are relatively impermeable to chloride ions resulting in increased concentration of chloride in the sweat reaching the skin surface. To maintain electro neutrality, the reabsorption of sodium ions by the sweat glands is also reduced, thereby increasing the concentration of sodium in the sweat.[16] The prevalence of this disorder in India is not known, however, there have been a few studies to study the prevalence and the common mutations in the CFTR gene in the Indian population.[17-19] Although there is no intervention available for this disorder, early detection can help in reducing the cost of tedious diagnostic procedures later in life. Screening for this is done by analyzing the levels of IRT in DBS.

Congenital adrenal hyperplasia is a group of rare autosomal recessively inherited disorders of cortisol biosynthesis. The classic defect occurs in two forms as CAH with salt wasting and as simple virilizing CAH without salt wasting. The incidence of CAH varies worldwide according to ethnicity and geography. The exact incidence is not known in India. Reported incidence is 1 in 12,000 but in the Southern part of India, the disorder seems to be more prevalent giving an incidence as high as 1:2750.[8,20] The diagnosis of classic CAH can be made at birth based on ambiguous genitalia in a newborn female or during the neonatal period in both sexes based on salt wasting crisis. Elevated 17 OHP indicates a possibility of CAH. The goal of classic CAH-NBS is early detection of the severe salt wasting form, therefore, prevention of adrenal crisis or death.

Galactosemia, caused by the deficiency of the enzyme Galactose-1-phosphate uridyl transferase, has an incidence of 1:30,000–1:60,000 in western countries.[21] Not much is known about the incidence of this disease in India but it is reported to account for up to 4% of children presenting with neonatal cholestasis syndrome in India.[22] NBS for galactosemia can be done by screening either galactose or galactose-1-phosphate levels in dried blood spots. Confirmatory testing requires enzyme analysis and may be followed by mutation studies. It is very essential to diagnose this disorder early in neonatal period as if untreated it may lead to severe life threatening episodes, affecting liver. If diagnosed early, it can be simply treated by omitting galactose from diet.

Biotinidase deficiency is a rare but easily treatable disorder caused by mutations in the *BTD* gene. Biotin which is a co-factor for several carboxylases involved in branched chain amino acid metabolism and fatty acid metabolism is recycled by the enzyme biotinidase. The deficiency may cause seizures, immune system impairment, hearing loss, mental retardation, coma, and even death. Other symptoms include apnea, tachypnea, hyperventilation, skin rashes, and alopecia. Later developmental delays, speech problems, ataxia, and hearing problems may occur. Onset of this disease is around 3–6 months of age and hence if it is detected early by NBS, treatment can be started prior to onset of symptoms. Patients with late or no treatment can manifest with permanent neurologic sequelae and hearing loss. Screening for disorder is done as a part of NBS programs in many countries and is a simple colorimetric determination. All positive tests are confirmed by a quantitative assay in serum and also may be confirmed by mutation analysis.

Fatty acid oxidation defects are now being included in NBS programs worldwide. This is a group of disorders with an estimated combined incidence of 1:9,000. Benefits have been proven the most in cases of MCAD deficiency and VLCAD deficiency by NBS for FAODs. Most FAODs are identified by Tandem Mass Spectrometry (TMS or MS/MS). Furthermore, they are treated by simple avoidance of fasting in most cases, whereas metabolic decompensation can be fatal in unsuspected patients. Due to these reasons, FAODs have been included in most NBS program since the mid-1990s.[23] In 2006, the ACMG determined 5 core conditions to be included in a standardized NBS menu. These five conditions were MCAD, VLCAD, LCHAD, CTD, and CPTII.[24] The true incidence in India is not known, however, ICMR multi-centric study has suggested a high incidence of MCAD.[25]

Aminoacidopathies and organic acidemias

Tandem mass spectrometry is also being used for screening of disorders of amino acid metabolism and organic acid metabolism. More than 20 markers for diseases are analyzed in a single assay. Disorders screened by this include PKU, MSUD, tyrosinemia, homocystinuria, argininemia, methylmalonic academia, propionic academia, and isovaleric academia. Most of these disorders present with acute life threatening episodes and may leave the affected child with permanent neurological sequelae. The exact incidence of this group of disorders is not known in the Indian population; however, the ICMR study has suggested that MMA, GAI, NKH, UCDs, MSUD, and PA are the most common disorders in India.[25]

Universal hearing NBS

Congenital hearing impairment occurs in approximately 1–5 per 1000 live births and has an incidence that is twice of all other disorders amenable to NBS. In India, the incidence has been estimated to be between 1 and 8 per 1000 babies screened. Early identification and intervention provides better prognosis.[26] Without NBS the infants may develop language delay, poor social and academic performance, and behavioral issues.[27,28] Screening done by two stage screening tests: Otoacoustic emission and Automated Auditory Brainstem Response Audiometry (BERA) can pick up most of the cases with hearing loss or difficulties.

Congenital heart diseases

Congenital heart diseases account for 5–10% of all infant deaths and about 25% of CHDs are life threatening. Prenatal sonography can identify structural heart defects but sensitivity of CHD detection is only about 50% by this method as it is dependent on expertise, gestational age, fetal position, and type of the defect and may miss some patients. Sensitivity of physical examination is also approximately 50%. Addition of pule oximetry to these 2 modes can improve the chances of detecting CHDs in newborns. Screening by pulse oximetry may be beneficial as it is painless, readily available in all hospitals, and requires less training hence can be handled by anyone. This test measures the percentage of O2 saturated hemoglobin and pulse rate. Overall sensitivity

of pulse oximetry in detection of HDs was 76.5% with a specificity of 99.9%.[29]

Expanded NBS

With the introduction of MS/MS, an accurate and cost-effective diagnosis of numerous disorders on a single sample and through a single analytical process was possible. MS/MS allows for additional disorders to be added without a need for additional sample or analysis time. This allows rapid and high throughput analysis of samples at a very low cost. Today almost all developed countries have expanded NBS (eNBS) that screen from approximately 20-40 inherited metabolic disorders by MS/MS.[30] Expansion of NBS beyond PKU has revolutionized the diagnosis and treatment of metabolic disorders, greatly extending the concept of preventive medicine[31] and this success has resulted in the adoption of eNBS by many NBS programs worldwide.[31,32]

In 2001, an expert panel commissioned by the ACMG evaluated 84 candidate disorders and published in 2006 a universal and uniform list of disorders for NBS. The report defined a uniform panel of 29 core conditions and 25 secondary disorders. Forty of these 54 disorders are diagnosed by MS/MS. The rest of the disorders such as CH, CAH, biotinidase deficiency, and galactosemia are diagnosed by other methods. Recently, ADA-SCID, peroxisomal disorders, DMD, and some lysosomal storage disorders have also been added to this core panel for NBS.[33-35]

LABORATORY WORKFLOW AND MANAGEMENT IN A NBS LAB

A typical NBS laboratory receives approximately 100 to 1000 dried blood spots for analysis per day. The general turnaround time for analysis and reporting is usually 2–4 working days as in some diseases treatment must be started rapidly to prevent irreversible damage. For positive results, confirmatory tests are needed. The NBS laboratory also should implement quality management system. This must be in place to ensure the system's integrity in all phases – pre-analysis, analysis, and post- analysis. NBS laboratories are also a part of several activities such as education, public awareness, training, diagnosis, systematic follow-up, parental counseling, data management, and publications.

Box 2: NBS lab work flow

An NBS laboratory's activities are divided into three phases – pre-analytical, analytical, and post-analytical phases and many activities are involved between the arrivals of the samples for analysis till the reporting of results. Following points are based on the procedures followed at our laboratory, NIRMAN for Newborn Screening of 2 hospitals from South India.

Pre-analytical activities

To ensure accurate results in a NBS laboratory, it is very crucial to collect data such as time of sampling, delay between sampling and analysis, baby's condition (pre-maturity, gestational age, birth weight, para-enteral nutrition, transfusions, etc.) all of which can affect the NBS results. It is also important to check the quality of dried blood spots received so that the error is minimized. In addition to the method of sample collection, methods of storage and transportation also can lead to increase in errors in the results. Hence, it is very important that the NBS laboratory instructs and trains the primary physicians/hospital staff regarding the procedures of sample collection, storage, and transportation.

Sample collection

Few drops from a heel prick are taken on a filter card paper and air dried for few hours before sending them to the NBS laboratory. This filter paper card should be attached or should accompany a card which carries all the information of the baby including full name/unique number/bar code, date and time of birth, date and time of sample collection, birth weight, gestational age, mode of feeding (BF/TF), para-enteral nutrition if any, transfusions given if any, any other important information which may affect the results. Samples must be collected by heel puncture on the planar surface of the foot. Blood must completely fill the circles drawn on the filter paper and applied evenly. It must be air dried for 4 h at room temperature, before it is dispatched to the NBS laboratory.[36]

Time of sample collection

This is very important as it may affect some of the results and may result in some pre-analytical errors as some analytes vary with the infant's age. It is usual practice to collect samples for NBS between 24 and 72 h of age. Prematurity, birth weight, type of feeding, parenteral nutrition, neonatal jaundice, and some drugs may affect the levels of some metabolites.[37]

Transport

Samples should be sent to the NBS laboratory within 24 h of sample collection. Delays or harsh conditions during transport may result in degradation of some metabolites and result in false-negative results.

Once the samples arrive at the NBS laboratory, verification of sample card information, and validation of the dried blood specimen for quality and adequacy is performed. If insufficient or disqualified samples are detected then immediately they are recalled from the source hospitals/clinics.

Analytical phase

This phase is the most important phase. Given the large amount of samples to analyze in a timely and reproducible way, automation of some pre-analytical and analytical steps has been implemented at some NBS laboratories. Use of micro-volume pipetting station, automatic punchers, and bar code readers are used widely. Assays for the desired metabolites are performed and results generated. Accuracy of each assay is very important and hence each assay must involve use of quality control samples (low as well as high levels). For example, we participate in Centre for Disease Control and Prevention's (CDC) Newborn screening Quality Assurance Program (NSQAP) every year to maintain the quality of our analytical methods.

Post-analytical phase

After the analysis of the NBS samples is completed the laboratory needs to produce a report and determine if any of the samples needs confirmatory tests. As the disorders screened are rare, most of the results generated in a NBS program are normal. It is upon the policy of the NBS laboratory to decide the mode for notifying the results to the primary hospital. Most NBS laboratories (like our laboratory) issue reports for each sample analyzed. Some labs inform the primary hospitals only in case of positive results. Interpretation of results is to be done carefully and by a trained person with a sound knowledge of the metabolic disorders included in the NBS program. We have people trained at various universities in Europe in Metabolic disorders and have in-house confirmatory testing facility and management protocols.

NBS laboratories should participate in external control programs and exchange samples with reference laboratories. There are several quality assessment programs for NBS such as CDC NSQAP; College of American Pathologists; European Research Network for Evaluation and improvement of Screening, Diagnosis, Treatment of Inherited Disorders of Metabolism; and Reference institute for Bioanalysis.

The main aim is to reduce the number of false positive screening reports. False positive rate of < 0.3% and a positive predictive value of > 20 should be the target for any laboratory performing NBS.[38] Recall rate can be reduced by adjusting the cut-offs, second tier tests (e.g., MMA and propionylglycine if C3 elevated, alloisoleucine if leucine elevated) and use of one or more specific markers (e.g., succinylacetone in tyrosinemia type I rather than tyrosine).[39] Second tier testing allows to confirm the results with increased specificity on the same initial blood spot.

Positive results must be informed immediately to the referring hospital so that necessary action can be taken. However, every abnormal result should first be re-checked to ensure that the abnormal result is not due to pre- or analytical error. If it is still abnormal patient, should be recalled for testing. It is important to note that abnormal NBS results do not necessarily mean that the child has the disease, but it indicates the need for additional investigation before a final diagnosis can be reached. Due to inaccuracy of screening tests on DBS, it is important to note that NBS is not diagnostic and any positive result should be accompanied by diagnostic tests, preferably on a new sample for confirmation of the results of NBS, before any intervention is initiated. Newborns screened positive may then be referred to either the primary health care providers or directly to a tertiary specialized health facility. For treatment trained, metabolic pediatricians are necessary. Treatment is initiated only after an appropriate diagnosis is reached and parents are counseled regarding the possible outcome of the disorder. The ACT sheets developed by ACMG are useful for guidance in case of positive NBS results.[40]

IMPORTANCE OF NBS

In a recent study, it was shown that only 2% of cases detected by NBS had clinically severe outcomes compared to 42% of those detected clinically.[41] Clinically, diagnosed patients with several of the disorders have poorer outcomes than those with the same disorders identified by eNBS, including death, organ transplantation, poor developmental outcomes, and intellectual disabilities. Significantly better outcomes are seen in NBS detected patients when compared to clinically diagnosed patients.[41-44] Documented positive outcomes are in terms of lesser intellectual disabilities,[45] better IQs,[41] fewer deaths, and fewer disabilities.[42] Hence, NBS should be adopted as a policy in all countries to reduce the burden of individuals diagnosed with IEMs and other conditions. This will not only help in saving the cost for treatment and hospitalizations needed frequently in these disorders but also reduce the parental stress and anxiety, improving the quality of life for the patient and the family.

INDIAN SCENARIO

At present, there is no national NBS program in India. There is no doubt that NBS can save life, but NBS has not been accepted yet as a governmental policy in India. There is no comprehensible national strategy for implementation of a universal screening program and no guidance on which disorders should be included in the screening panel. Realizing the importance of NBS, ICMR in 2008 launched a pilot multi-center NBS program to screen 100,000 newborns for CH and CAH in 5 metropolitan cities – Chennai, Delhi, Hyderabad, Kolkata, and Mumbai. This study demonstrated the feasibility of NBS in Indian metropolitans.[25] In 2011, the national neonatology forum recommended CH, CAH, and G6PD as the screening panel to implement for NBS in

India.[46] Many small scale or pilot projects were started in India. However, of note among these were the Chandigarh Program, Kerala State NBS program, and Goa NBS Program. Union territory of Chandigarh started NBS for CH, CAH, and G6PD in 2007.[8] In 2008, Goa introduced mandatory expanded NBS for all newborns.[7] In 2009, West Bengal and in 2011 Gujarat governments have approved o launch large scale NBS program. However, these programs remain yet to be implemented. Now many private hospitals and labs offer this facility although at a cost and there is no insurance or government funding for this.

About 27 million babies are born every year in our country. Approximately 4:1000 and 5:1000 are estimated to have hearing defects and congenital heart abnormalities, respectively, whereas the incidence of IEMs in India is estimated to approximately 1:1000. This high incidence is due to high prevalence of consanguinity in our country. IEMs comprise approximately 15% of total admissions in NICUs annually. If undiagnosed and untreated many children develop mental retardation, learning disabilities, autism, dyslexia, behavioral abnormalities, and scholastic backwardness later in life. There is also considerable burden – financial and emotional on the parents to diagnose, treat, and manage these children. The most rational and cost-effective way of preventing such tragedies would be to have a NBS program which will detect most of the preventable or treatable, if not all IEMs and other disorders. Awareness of benefits of NBS is increasing and this could lead to the creation of one national NBS program. Although universal screening is a cost-intensive program, the benefits outweigh the cost as it helps in reducing the mortality and morbidity in these diseases.

CONCLUSION

All hospitals in urban areas in India should initiate NBS at least for the common disorders: CH, CAH, and G6PD deficiency. Expanded newborn screening may follow once these programs are well established and necessary infrastructure is in place. There is also a need to train more physicians in IEMs before expanded NBS is started.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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