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Experience of One and Half Decades of Newborn Screening in India

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Abstract

Background: Newborn screening saves lives and can ensure better survivability, as it detects the disorders at the earliest and helps in preventing serious consequences that may arise in the future.

Objective: To present data on NBS from our tertiary centers along with the success of implementing therapy and follow up.

Methods: We retrospectively reviewed NBS data from January 2005 to May 2020 from three tertiary centers. The incidence of congenital hypothyroidism (CH), congenital adrenal hyperplasia (CAH), galactosemia, glucose 6 phosphate dehydrogenase (G6PD) deficiency, amino acids/urea cycle disorder, fatty acid/organic acid disorder, cystic fibrosis, biotinidase deficiency and phenylketonuria (PKU) among neonates was recorded. We also report on their follow up to explain its implications.

Results: A total of 668,327 neonates were screened for fifty conditions. While hemoglobinopathies (1:70 of 28392 total screens) had the highest presumptive incidence followed by G6PD deficiency (1:280 of 98,052 total screens), phenylketonuria (1:16,408 of 57,675 total screens), followed by galactosemia (1:7188 of 933,318 total screens) and biotinidase deficiency (1:5440 of 63,598 total screens) had the lowest incidence. The incidence of CH and CAH was found to be 1:594 from 102,903 total screens and 1:4567 from 95,155 total screens, respectively. Metabolic conditions though individually rare, collectively accounted for significant numbers.

Conclusion: The current study highlights the incidence of several conditions including hemoglobinopathies, G6PD deficiency, congenital hypothyroidism (CH) and congenital adrenal hyperplasia over one and a half decades in a large pool of neonates. This study also demonstrates the feasibility of early testing of screen positive neonates and establishing a complete diagnosis and initiating therapy in the recommended time.

Keywords: *Dried Blood Spot; Inborn Errors of Metabolism; Newborn Screening; Neonatal Disorder*

Introduction

Newborn screening (NBS) is an indispensable, preventive public health program for the early diagnosis of treatable diseases/disorders in neonates that can influence long-term mortality and morbidity [1]. Of note, NBS programs are well established in developed countries and some developing countries as well, incorporating a wide range of conditions into their NBS programs. Congenital hypothyroidism (CH), phenylketonuria (PKU), congenital adrenal hyperplasia (CAH), medium-chain acyl-CoA dehydrogenase deficiency (MCADD), cystic fibrosis (CF), biotinidase deficiency, maple syrup urine disease (MSUD), and sickle-cell anemia are a few important disorders covered under NBS programs in Europe and United States [2-5]. Most Asian countries have included erythrocytic glucose-6-phosphate dehydrogenase (G6PD) deficiency and CH into their NBS programs. Some countries also screen for PKU, MSUD, histidinemia, homocystinuria, and galactosemia [6].

In India, NBS was first initiated as a pilot project in 1980 in Karnataka [6]. The second pilot project from Hyderabad was completed in the early 2000s and concluded that CH was the most common disorder, followed by CAH and G6PD deficiency [7]. The Rashtriya Bal Swasthya Karyakram (RBSK) has identified prevention of disability as a key aim of the program. Screening of CH and instituting early replacement therapy is probably the most cost-effective way of preventing disability. Newborn screening poses significant economic burden on the government. Approximately 1.2% of the yearly budget allocation is needed for the screening of CH [8]. A public private partnership may be an option which can be explored as has been done in Goa. However, it is essential to build follow up and therapy into the screening program in order that NBS program is sustained and fruitful.

Cloudnine hospitals have been conducting NBS in their tertiary care centers and the gathered data highlight the need for NBS across India. The incidence of CH and CAH was reported at 1:1042 and 1:2800, respectively, from 2007 to 2013 [9,10]. In this study, we present observations and experience related to NBS over a period of 15 years at our tertiary care centers.

Materials and Methods

Newborn screening is universally offered to neonates born in tertiary hospital in Bangalore since 2005. This retrospective study was conducted at these three tertiary centers in Bangalore. The NBS data were collected retrospectively from January 2005 to May 2020 for analysis. As this was a retrospective data analysis, the tests had been done per hospital policy. So ethics permission was not required as per the Medical Director. The screening included the following diseases/disorders: CH, CAH, galactosemia, G6PD deficiency, amino acids/urea cycle disorders, fatty acid/organic acid disorders, CF, biotinidase deficiency, phenylketonuria, and hemoglobinopathies.

Data for the years 2005 - 2020 and 2014 - 2020 have been evaluated separately due to variations in the diseases screened over the years.

Blood samples were collected at 36 to 48 hours and as needed for other investigations after birth as per the hospital protocols. Verbal consent for screening procedures was obtained after parental counseling on the need and benefits of NBS. Blood samples were collected using either the Heel prick technique or by vene-puncture depending upon other investigations advised by the pediatrician, and the dried blood spot method was employed for screening.

Quantitative determination of thyroid-stimulating hormone (TSH) was carried out on dried filter paper blood by DELFIA neonatal hTSH time-resolved fluorenseimmuno assay (TRFIA) kits of Perkin Elmer. Of note, TSH serum levels up to 12 μU/mL of whole blood were considered 'disease negative' and levels above 12 μU/mL were considered as 'screen positive'. Those who tested screen positive were sub-

jected to confirmatory testing with FT4 (Free thyroxine) and TSH - those who had confirmatory tests positive were subjected to scanning of thyroid gland by nuclear medicine. A technetium scan of the thyroid gland was done to measure uptake. Perchlorate discharge was done in those who were noted to have thyroid gland but still had elevated TSH. Thyroxine replacement at 10 - 15 mcg/kg was started orally for all neonates who were confirmed to have CH within 2 weeks of birth.

Quantitative determination of CAH was carried out on dried filter paper blood by DELFIA Neonatal 17 alpha-OH-progesterone kits of Perkin Elmer. 17-hydroxy -progesterone serum levels up to 30 nmol/L of whole blood were considered disease negative, and above 30 nmol/L were considered screen positive. Screen positives were confirmed by corticotropin stimulation test. Molecular diagnosis was also done in some confirmed cases. Screen positive were subjected to complete adrenal hormone assay as well as for pituitary insufficiency. The neonates were started on glucocorticoid and mineralocorticoid supplementation under the supervision of a pediatric endocrinologist.

Galactosemia was screened using a neonatal total galactose kit. Serum galactose levels less than 8 mg/dL were considered normal, while levels above 8 mg/dL were considered screen positive.

Quantitative determination of G6PD deficiency was carried out using the neonatal G6PD kit on spectrophotometer analysis. Values less than 2 U/g Hb were considered normal and above 2 U/g Hb as screen positive. The screen positive was confirmed by a quantitative estimation of G6PD level by spectrophotometry.

Cystic fibrosis screening was done using immunoreactive trypsinogen (IRT). Serum levels ≤ 29 mmol/L were considered normal and levels ≥ 60 mmol/L as screen positive. Screen positive neonates were subjected to sweat chloride estimation.

For screening of biotinidase deficiency, > 30% of mean normal serum biotinidase activity was considered normal and < 10% mean normal serum biotinidase activity was considered biotinidase deficiency. Screen positive neonates underwent a quantitative assessment of biotinidase. Following confirmation, neonates were started on biotin supplement of 5 mg per day.

Phenylketonuria was screened using a neonatal phenylalanine NP kit. Serum phenylalanine levels less than 127 µIU/L were taken as normal and above 127 µIU/L were considered screen positive. Definite confirmation was made by plasma GCMS with neonates with levels > 600 Micromol/L being treated with diet restriction.

Hemoglobin assays were employed to determine the hemoglobinopathy. All screen positive neonates were subject to a full capillary electrophoresis between 6 - 9 months of age to confirm the diagnosis. Those with anemia were later started on folic acid supplements.

For all screen-positive cases, the treating pediatrician was informed to initiate follow-up and carry out confirmatory tests. Most of these neonates had confirmatory testing and those who required treatment were initiated on therapy at the earliest.

Results

A total of 668,327 neonates were screened for various disorders using NBS between 2005 and 2020. Congenital hypothyroidism, amino acids/urea cycle disorder, fatty acids/organic acid disorder, galactosemia, and CF were the disorders initially screened at our centers in 2005, while G6PDand CAH screening were included in 2006 and 2009, respectively (Table 1). Biotinidase deficiency has also been included in our NBS program from 2014 (Table 2). A summary of the gathered data is presented in table 3.

Name of analyte	TSH	17-OHP	TGAL	G6PD	AA	AC
Name of disorder	CH	CAH	GAL	G6PD	AA/UCD	FA/OAD
Total babies screened	102,903	96,155	93,318	98,052	83,531	74,765
Total screen positives	276	280	26	650	317	307
Screen positives incidence 1 in	372.83	343.4	3589.15	150.84	263.5	243.53
% of screen positives	0.26	0.29	0.027	0.66	0.38	0.41
Final presumptive positives	149.89	18.03	11.17	300.225	56.17	112.76
Final presumptive incidence 1 in	594.45	4567.66	7118.88	280.62	1242.31	541.1
% of final presumptive positives	0.17	0.02	0.01	0.35	0.08	0.18

Table 1: *Disorder wise details of NBS from screening to incidence rate (2005 - 2020).*

AA: Amino Acid; AC: Acylcarnitine; CH: Congenital Hyperthyroidism; CAH: Congenital Adrenal Hyperplasia; FA: Fatty Acid; Gal: Galactose; G6PD: Glucose-6-Phosphate Dehydrogenase; NBS: Newborn Screening; OAD: Organic Acid Disorder; TSH: Thyroid-Stimulating Hormone; TGal: Total Galactose; UCD: Urea Cycle Disorder.

Name of analyte	IRT	BIOT	Phe	HB
Name of disorder	CF	BIOT	PKU	HBP
Total infants screened	63,598	64,680	57,675	28392
Total screen positives	199	46	17	575
Screen positives incidence 1 in	319.58	1406.08	3392.64	49.38
% of screen positives	0.31	0.07	0.03	2.02
Final presumptive positives	28.64	11.89	3.515	404
Final presumptive incidence 1 in	2220.6	5439.86	16,408.25	70.23
% of final presumptive positives	0.05	0.02	0.01	0.91

Table 2: *Disorder wise details of NBS from screening to incidence rate (2014 - 2020).*

BIOT: Biotinidase; CF: Cystic Fibrosis; HB: Hemoglobin; HBP: Hemoglobinopathy; IRT: Immunoreactive Trypsinogen; PA: Phenylalanine; NBS: Newborn Screening; PKU: Phenylketonuria.

Total samples vs. all disorders	668,327
Final Presumptive Positives	802.09
Final Presumptive Incidence 1 in	824.91
% of Final Presumptive Positives	0.121

Table 3: *Summary of overall data until 2020.*

Congenital hypothyroidism: Of 102,903 neonates screened, total screen positives were 276, and the incidence was 1:373. The final presumptive incidence was 1:594 (0.17%). The false-positive rate was less than 1%. All the neonates were investigated with estimation of FT4 and TSH, and Technetium scan of the neck if the confirmatory test showed CH. In our series most (60%) of the congenital hypothyroidism was due to iodine uptake defect, and 40% were due to agenesis or dysgenesis. Any newborn who had TSH levels of more than

100 were noted to be due to agenesis of thyroid gland and newborns with levels of 40 to 100 turned out to be iodine uptake defect on perchlorate test and most newborns with TSH less than 40 turned out to be false positive. All of the neonates who were confirmed as having CH were started on thyroxine replacement therapy by 15 days of age as per WHO recommendations. All these neonates are on follow up with a pediatric endocrinologist and on regular hormone replacement therapy program.

Congenital adrenal hyperplasia: Of 96,155 neonates screened, the total screen positives were 280, and the incidence was 1:343. The final presumptive incidence was 1:4567 (0.02%). The false-positive rate was 2%, more so in premature newborns. These neonates were subjected to further detailed testing and are on follow up with a pediatric endocrinologist.

Galactosemia: A total of 93,318 neonates were screened, of whom 26 were screen positives. The rate of incidence was 1:3589. The final presumptive incidence was 1:7119 (0.01%). The false-positive rate was less than 0.1%.

G6PD deficiency: The total number of positives was 650 from 98,052 screenings. The incidence of screen positives was 1:151. The final presumptive incidence was 1:280 (3.5%). Eighteen infants had false-positives due to heat inactivation of G6PD protein. All the true positives have been provided with detailed counselling about avoidance of certain drugs.

Amino acids/urea cycle disorder: Of 83,531 neonates screened, total screen positives were 316, and the incidence was 1:263. The final presumptive incidence was 1:1242 (0.08%). The screen positives included 12 cases of citrullinemia, 20 cases of transient tyrosinemia of newborn, two cases of very-long-chain fatty acid defects, 2 cases of HHH (Hyperornitheinemia-Hyperammonemia-Homocitrullinuria) syndrome; one newborn with of 3MCC disorder (3-methyl crotonyl CoA Carboxylase deficiency), and one with propionic acidemia. Two per cent of cases were false-positive for methylmalonic acidemia (MMA) secondary to maternal vitamin B_{12} deficiency and that resolved after maternal treatment with vitamin B_{12}, while two cases each of ornithine translocase deficiency (OTC), methioninemia, and MCAD deficiency were also false-positive.

Fatty acid/organic acid disorder: In 74,765 neonatal screenings, 307 were screen positives. The rate of incidence was 1:243. The final presumptive incidence was 1:541 (0.18%). The false-positive rate was 1%. There were 6 cases of severe carnitine deficiency and one newborn with Acyl CoA translocase deficiency.

Cystic fibrosis: The total number of positives were 100 from 63,598 screenings. The incidence of screen positives was 1:319. The final presumptive incidence was 1:2220 (0.05%). The false positive rate was less than 1%. The confirmatory testing for cystic fibrosis was fraught with difficulty as sweat chloride was done in another institution and there was a significant loss to follow up.

Biotinidase deficiency: Of 64,689 neonates screened, the total screen positives were 10 and the incidence was 1:1406. The final presumptive incidence was 1:5440 (0.1%). Initial 6 months when we had a different lab, we had a false positive rate of 10% and then after we changed the lab none of the infants had false-positives. These neonates have been started on Biotin supplements and are on regular follow up.

Phenylketonuria: The total number of positives was 17 from 57,675 screenings. The incidence of screen positives was 1:3393. The final presumptive incidence was 1:16,408 (0.01%). Only 2 samples were false-positives.

Hemoglobinopathies: Of 28,392 neonates screened, the total screen positives were 156, and the incidence was 1:49.38. The final presumptive incidence was 1:70.23 (1.42%). All neonates who tested positive underwent confirmatory electrophoresis and we noted an incidence of beta thalassemia in 0.07%, alpha thalassemia in 0.42%, Hb D in 0.38%, Hb E in 0.6% and Hb S in 0.43%.

Mortality: Despite turnaround time of less than 48 hours or 2 days, some of the neonates with serious metabolic errors could not be saved. The diagnosis in the neonates who could not survive is— 4 cases of citrullinemia, propionic acidemia and 1 undefined organic acidemia who deteriorated and died within 48 hours of birth.

Discussion

This retrospective study reports the incidence of various disorders noted during the NBS of a very large cohort from 2005 to 2020 highlighting that NBS that is doable in a private health set up. Of all the conditions screened at our centers, hemoglobinopathies had the highest incidence. However, the total screenings are very low compared to other conditions. Based on the findings, G6PD deficiency was the most common disorder among all other conditions screened. The least common disorder was phenylketonuria, followed by galactosemia and biotinidase deficiency.

According to earlier studies in India, the state-wise incidence of CH was 1:1700 [7], 2.1:1000 [11] and 1:1221 [12] cases in Andhra Pradesh, Kochi and Uttar Pradesh, respectively. Recently, the Indian Council of Medical Research (ICMR) has published the results of the multicenter program in five metropolitan centers regarding the incidence of CH. The center-wise incidence as per ICMR was 1:727 in Chennai, 1:1141 in Delhi, 1:1383 in Hyderabad, 1: 1254 in Kolkata, and 1: 1528 in Mumbai. The total number of screening was in the range of 20,000 to 23,000 [13]. The NBS Chandigarh program has reported an incidence of 1:1400 [14]. A recent retrospective study in Bangalore has reported an incidence of 1:2735 from 41,000 screenings [15]. The final presumptive CH incidence of 1:594 is very high compared to other centers across India.

The incidence of CH is expectedly high in the current study, but the relatively higher incidence compared to other studies might be attributed to a significantly high number of screenings. The total number of screens is significantly high, and almost five times more than the ICMR study [13]. Congenital hypothyroidism is the commonest preventable cause of mental handicap with the aid of screening and subsequent treatment. All neonates detected during screening and confirmed as CH positive were started on definitive therapy within 15 days of age as per WHO recommendations. Though the data is abundant on the incidence of disease, only a few studies have reported the actual cause of CH in India. In our study, dyshormonogenesis rather than agenesis was the significant cause of hypothyroidism.

The final presumptive incidence of CAH in our study was 1:4567. Similar to our findings, Kommalur., *et al*. reported an incidence of 1:4102 from a tertiary center in Bangalore [15]. The ICMR task force findings of CAH in five centers were 1:2036 in Chennai, 1: 7608 in Delhi, 0 cases in Hyderabad, 1: 6688 in Kolkata and 1:9983 in Mumbai [13]. The findings from the NBS Chandigarh program revealed an incidence of 1:6334 [14]. The false-positive ratio was 2%. Most of the false positive rates were before 2009. Since 2009, we were using nomograms to refer and to interpret the laboratory findings. In low birthweight newborns, birth weight or gestational age was considered to improve the efficiency of screening in our study [10].

Various studies have reported zero or low incidence of galactosemia. Studies in Andhra Pradesh and Uttar Pradesh have reported zero true positive cases [7,12]. However, the sample size in these studies is very low. A single-center study in Bangalore has reported one incidence among 41,027 screenings [15]. In our study, the final presumptive incidence was 1:7119 from 93,318 screenings.

Glucose-6-phosphate dehydrogenase deficiency was one of the most common disorders reported at our center with the final presumptive incidence of 1:280 (0.35%). Similarly, a recent cross-sectional study in Mumbai has reported the highest prevalence (1.3%) of G6PD deficiency [16]. Kommalur., *et al*. [15] have reported an incidence of 1:414 in Bangalore and Verma., *et al*. [17] reported 1:125 (0.8%) prevalence in New Delhi. Similar to our study, the NBS Chandigarh program also reported a high incidence of G6PD deficiency (1:80) [14].

The final positives of AA/UCD and FA/OAD conditions were 0.08% and 0.18%, respectively, at our center. In contrast, Sharma., *et al*. reported a high prevalence of amino acid and fatty acid disorders from 70,590 cases [16]. Among, AA disorders, MSUD had the highest prevalence (1.2%), and among fatty acid disorders, carnitine uptake defects (CUD) had 0.3% prevalence [16]. We also found a very high incidence of Pseudo-Methyl malonic acidemia and Citrullinemia. Our study and experience suggest that newborns who belong to a high-risk group (previous sibling death, IUD or neonatal death) should be screened at 24 hours and preferably results should be obtained within 48 hours if we want to save the newborns with Citrullinemia, as the neonatal onset of citrullinemia has fulminant course and many of them could be declared sepsis without being diagnosed.

Data on CF are limited among the Indian population. Recently Sharma., *et al.* reported an incidence of 1:993 of CF [16]. Another study in Hyderabad has reported an incidence of 1:1700 [7]. The final presumptive incidence at our center is in line with comparative studies.

With the final presumptive incidence of 1:5440, biotinidase deficiency was one of the least common disorders reported at our center. Sharma., *et al.* have reported 41/70,593 positive screens (1.9% prevalence) [16]. A study in Uttar Pradesh has reported zero positive cases of biotinidase deficiency [12].

Phenylketonuria was the least common condition reported at our center (1:16408). Sharma., *et al.* also reported a low prevalence of phenylketonuria, at 0.3% (7/70,590 cases) [16].

Of all the disorders screened at our center, hemoglobinopathies were the most common disorder with an incidence rate of 1:70 (1.42%). In line with the current study, Sharma., *et al*. [16] also reported a high prevalence of hemoglobinopathies (0.5%). Studies from Central India have also reported a high incidence of sickle-cell anemia [18,19]. We have found a high incidence of beta-thalassemia trait and 0.6% of Hb E trait. This may be a reflection of the cosmopolitan nature of our patient population as those testing positives were from the north-eastern states of India.

We also found about 45 cases of transient tyrosinaemia in our study, which on further investigations was found to be transient and not of pathognomonic significance.

Neonatal disorders are a major cause of prenatal and neonatal mortality in India. Over the past thirty years, the rate of under-five year mortality has considerably decreased [20]. However, currently, India is among the top twenty worst countries with regard to neonatal mortality [21]. The rate of neonatal mortality can be reduced by using NBS. Newborn screening saves lives and can ensure better survivability, as it detects the disorders at the earliest and helps in preventing serious consequences that may arise in the future. With routine screening, the neonatal mortality in our centres was very low with 0.7% mortality per 1000 neonates.

Strengths and Limitations

To our knowledge, ours is the only study to report the incidence of so many clinically relevant conditions in a large group of neonates in India. One of the significant observations in the current study is very low mortality of neonates. Proper diagnosis is important rather than being labelled as sepsis for all mortality cases, since their presentation mimics sepsis. Further, our study had the longest duration of 15 years after the study by Verma., *et al*. [17] (9 years; from 2008 to 2017); most other studies are limited to 1 - 3 years. The data are generally consistent with various available studies. Several studies, including the one by the ICMR task force, have established CH, CAH, and G6PD deficiency to be common across India. Though CAH is not common, we noted that fatty acids/organic acid disorders and hemoglobinopathies were the most commonly reported disorders.

Our study has a few limitations. This study is a retrospective analysis and suffers from the risk of bias and lack of generalizability. Gender-based data could not be generated.

Conclusion

This study highlights the incidence of several conditions. With abundant data, we reinforce the need for universal NBS in India and recommend screening in a phased manner to prevent unwarranted morbidity and mortality especially with our National Family Health Survey-5 data showing our infant mortality rate has reduced significantly - further reductions as per experience around the world can happen only with improved neonatal care and newborn screening across the country. The need for screening for congenital hypothyroidism is most pressing as we have demonstrated that it is feasible to diagnose, investigate and institute therapy within 15 days of birth. The next priority is for congenital adrenal hyperplasia- where diagnosis and treatment are also crucial. G6PD deficiency, Biotinidase deficiency and Cystic fibrosis screening could be introduced next. Screening for metabolic errors should probably be introduced last especially in high-risk neonates with previous stillbirths or neonatal deaths or all NICU babies - as confirmatory testing is costly and not available universally.

Key Messages

What is already known?

Neonatal disorders are the major cause of prenatal and neonatal mortality and morbidity in India. Currently, India is among the top twenty worst countries concerning neonatal mortality. The rate of neonatal mortality and morbidity can be reduced using newborn screening.

What this study adds?

The current study highlights the incidence of several disorders over 15 years from a large pool of neonates. Our experience has proven that this is doable in a private health set up. We recommend stepwise implementation of newborn screening with CH and CAH to begin with followed by screening for G6PD deficiency, biotinidase deficiency, galactosemia and PKU. Metabolic disorders screening must be done for all high-risk pregnancies and all neonatal intensive care babies before being extended for all newborns.

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Author's Contribution

Author R. Kishore Kumar has contributed towards conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Authors Akash Nevilebasappa and Hari Das have contributed towards conception or design of the work; or the acquisition, analysis, or interpretation of data for the work and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Authors Arvind Shenoi and Nandini Nagar have contributed towards drafting the work or revising it critically for important intellectual content and final approval of the version to be published.

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Conflicts of Interest

None.

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