Original Article

Newborn screening for congenital hypothyroidism, congenital adrenal hyperplasia and glucose-6-phosphate dehydrogenase deficiency in Bihar: A pressing priority in today's time

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Abstract

Background and Objective: Newborn screening (NBS) aims towards early detection of congenital disorders or prevention of intellectual and physical defects and life-threatening illness. Three disorders namely congenital hypothyroidism (CH), congenital adrenal hyperplasia (CAH) and glucose-6-phosphate dehydrogenase deficiency (G-6-PDD) were selected for a preliminary study for NBS. The study aimed to establish NBS in the Indian scenario that could lay a framework for future such initiatives. **Methods:** A screening programme was conducted at a tertiary care hospital for 1 year. All the neonates born at All India Institute of Medical Sciences (AIIMS), Patna, were screened for their blood levels of glucose-6-phosphate dehydrogenase (G-6-PD), 17-hydroxyprogesterone (17-OHP) and thyroid-stimulating hormone (TSH). Heel-prick blood samples were collected within 48–72 h of birth, and the level of these parameters was accessed by enzyme immunoassay (EIA). **Results:** A total of 492 neonates were born from January 2020 to December 2020, of which 369 newborns were screened for CAH, CH and G-6-PDD. Of 369 neonates, one case (male) had an increased level of TSH, six cases (all males) had an increased level of 17-OHP and no case was found with G-6-PDD. **Interpretation and Conclusions:** Preliminary data on the prevalence of various genetic disorders revealed that CAH is the most prevalent disorder followed by CH in the population of Bihar. More efforts need to be undertaken to create awareness and to make screening a successful programme in India. A cost-effective nationwide screening programme is highly recommended for the detection of such cases at the earliest to avoid their future complication.

Keywords: Congenital adrenal hyperplasia, congenital hypothyroidism, glucose-6-phosphate dehydrogenase deficiency, newborn screening

Introduction

Newborn screening (NBS) is the most modern public health screening programme, focused on the preventable causes of disability and death in newborn babies through early diagnosis, treatment and counselling.[1] Disorders included in NBS programmes are often not detectable at birth and may not

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show signs and symptoms for weeks, months or even years. This programme has been discovered by Prof. Robert Guthrie in 1960 in the USA, and the first metabolic disorder tested was phenylketonuria.[2] At present day, NBS has become an integral part of neonatal evaluation in many countries worldwide. A successful NBS programme needs skilled effort, understanding and teamwork by many individuals, from sample collection to the newborn's primary care and parent counselling. The conditions for which the NBS programme has been suggested in the Indian scenario include congenital hypothyroidism (CH), congenital adrenal hyperplasia (CAH), G-6-phosphate dehydrogenase deficiency (G-6-PDD), total galactose, maple syrup urine disease, biotinidase deficiency, cystic fibrosis and phenylketonuria.[3,4]

CH is one of the most common preventable causes of mental retardation in children,[5] and it happens in approximately 1:2,000 to 1:4,000 newborn.[6] NBS shows the biochemical evidence of CH before the physical signs appear. Early detection of CH allows the initiation of treatment within the first 2 weeks after birth,[7] thus preventing mental retardation and neurodevelopmental complications.[8] CH occurs when the thyroid gland fails to develop (dysgenesis) or does not function properly (dyshormonogenesis). CH is defined as the dysfunction of the hypothalamic–pituitary–thyroid (HPT) axis present at birth, resulting in insufficient thyroid hormone (TH) production and mild-to-severe TH deficiency.[9]

Thyroid-stimulating hormone (TSH) is produced by the anterior lobe of the pituitary gland, which is a glycoprotein. It is carried to the thyroid gland where it stimulates the synthesis and secretion of the THs—triiodothyronine (T3) and thyroxine (T4). An increase in TSH level above the normal range indicates CH in the newborn.

CAH is an autosomal recessive disorder that occurs due to a deficiency of enzymes 21-hydroxylase and 11β hydroxylase, involved in cortisol biosynthesis, the most common being 21-hydroxylase deficiency caused by a mutation in Cytochrome P450 Family 21 Subfamily A Member 2 (CYP21A2) gene that leads to the deficiency of mineralocorticoids, glucocorticoids and excess of sex steroids.[10,11] It is a common treatable disorder that is associated with life-threatening conditions such as adrenal crisis, sexual ambiguity and abnormal growth if undiagnosed. CAH occurs in approximately 1:16,000–1:20,000 births.[12] NBS for CAH is performed by assessing the level of 17 hydroxyprogesterone (17-OHP). 17-OHP is a C-21 steroid hormone produced during the synthesis of glucocorticoids and sex corticoids in the adrenal glands.

G-6-PDD is an X-linked recessive disorder frequently associated with an increased risk of neonatal hyperbilirubinaemia and acute haemolytic crises.[13] Glucose-6-phosphate dehydrogenase(G-6-PD) is a cytoplasmic enzyme in the pentose monophosphate pathway that catalyses the conversion of nicotinamide adenine dinucleotide phosphate (NADP) to nicotinamide adenine dinucleotide phosphate (NADP), reduced form. It protects the red blood cells (RBCs) from oxidative damage. Due to the low activity of G-6-PD, the RBCs become susceptible to haemolysis under certain conditions such as ingestion of fava beans, antimalarial drugs and severe infections such as viral hepatitis, pneumonia and typhoid fever.[14] G-6-PDD is one of the most common human enzyme deficiencies, affecting more than 400 million people worldwide.[15] Common clinical manifestations of G-6-PDD are neonatal jaundice and acute haemolytic anaemia.

Materials and Methods

The study was conducted in the Department of Biochemistry in collaboration with the Department of Neonatology, All India Institute of Medical Sciences (AIIMS), Patna. A total of 492 neonates were delivered in the Department of Obstetrics and Gynecology, AIIMS, Patna, from January 2020 to December 2020, of which 369 newborns were screened for CH, CAH and G-6-PDD. Early discharge, admission to the neonatal intensive care unit (NICU) and refusal to participate in the NBS programme comprised the major reasons for drop out. Approval taken, Ref no: AIIMS/Pat/IEC/PGTh/July19/07, Dated: 09.06.2020.

This was a hospital-based, observational study on a total of 369 newborns fulfilling the inclusion criteria for the study. Permission for the study was taken from the Institution's Ethical Committee. Informed consent was obtained before sample collection from the parents of the newborns. The preferred time of sample collection was 48 hr to 72 hr of birth by the heel-prick method. A heel-prick blood sample was collected on grade 903 filter paper. Testing of samples was performed by enzyme immunoassay (EIA). BioTek Gen5 Software was employed for the estimation of TSH, 17-OHP and G-6-PD enzymes.

All newborns of ≥34 weeks of gestational age and those newborns whose parents agreed to participate in the study and gave informed consent for the same were included in the study. All newborns who were admitted to the NICU due to any reason were excluded from the study.

CH: Quantitative determination of neonatal TSH was performed on dried blood spots (grade 903 filter paper) using Labsystems Diagnostics Neoscreen Human thyrotropin (hTSH) EIA Kit. TSH value <20 mIU/ml was taken as normal, and values above 20 mIU/ml were considered high risk for CH. All newborns with elevated TSH levels were to be called again for a diagnostic serum thyroid function test to evaluate T3, T4 and TSH for confirmation of CH.

CAH: 17-OHP estimation was performed on dried blood spots using Labsystems Diagnostics Neoscreen 17-OHP EIA Kit. 17-OH*P* value up to 55 μU/ml was taken as normal, and values above 55 μU/ml were considered high risk for CAH. The positive cases were to be recalled for confirmatory testing by serum sample.

G-6-PDD: G-6-PD enzyme was measured on dried blood spots using Labsystems Diagnostics Neoscreen G-6-PD EIA Kit. Neonates with G-6-PD enzyme activity values less than 2 U/gm Hb were considered positive for G-6-PDD. The positive cases were to be recalled for confirmatory testing.

Result

A total of 369 neonates were screened for CAH, CH and G-6-PDD from January 2020 to December 2020. Of 369 neonates, 53.4% of newborns were male and 46.6% were female. 88.1% of newborns were Hindus. Most of the newborns, that is 99.7%, had no significant family history. The most common mode of delivery was caesarean section (71.5%) followed by vaginal delivery (28.5%). 5.7% of newborns had jaundice at the time of birth. 20.9% of mothers had a history of hypothyroidism, and 20.9% of mothers had a history of antithyroid drug intake during pregnancy. Of 369, one newborn had an elevated TSH level; that is, the frequency of CH was 0.3%. Of 369, six newborns had elevated 17-OHP levels; that is, the frequency of CAH was 1.6%. No newborn had G-6-PDD [Table 1].

The mean age of the mother was 25.83 years (±4.29), the gestational age was 37.89 weeks (±1.48) and the birth weight of the baby was 2.83 kg (±0.45) [Table 2]. There is no statistically significant difference in the mean mother's age, $P = 0.969$, mean gestational age, $P = 0.943$, and mean birth weight of newborns, $P = 0.903$, with CH vs newborns without CH [Table 3]. There is no statistically significant difference in the mean mother's age, $P = 0.213$, mean gestational age, $P = 0.137$, and mean birth weight of newborns, $P = 0.302$, with CAH vs newborns without CAH [Table 4].

The correlation between TSH and mother's age ($P = 0.208$), gestational age ($P = 0.760$) and birth weight ($P = 0.987$) was not significant. There was a statistically significant correlation between 17-OHP and gestational age ($P = 0.000$) and birth weight ($P = 0.049$), but the correlation between 17-OHP and mother's age was not significant ($P = 0.565$). The correlation between G-6-PD and mother's age, $P = 0.681$, gestational age, $P = 0.779$, and birth weight, $P = 0.655$, was not significant [Table 5].

There was no statistically significant association between gender and CH, $\chi2$ (1) =0.875, $P = 1.000$, religion and CH, $\chi2$ (1) =0.136, $P = 1.000$, mode of delivery and CH, $\chi2$ (1) =0.399, $P = 1.000$, jaundice at the time of birth and CH, $\chi2$ (1) =0.061, $P = 1.000$, maternal history of hypothyroidism and CH, $\chi2$ (1) =3.803, $P = 0.209$, maternal history of antithyroid drug intake during pregnancy and CH, $\chi2$ (1) =3.803, $P = 0.209$, and between significant family history and CH, $\chi2$ (1) =0.003, $P = 1.000$ [Table 6].

There was a statistically significant association between gender and CAH, $\chi2$ (1) =5.325, $P = 0.032$. Males had a higher proportion of presence of CAH as compared to females, but

Table 1: Demographic characteristics of newborn screened for CH, CAH and G-6-PDD (*n*=369)

Variables	Frequency	Percentage (95% CI)
Gender of baby		
Male	197	53.4 (48.8-58.0)
Female	172	46.6 (42.0-51.2)
Religion		
Hindu	325	88.1 (84.4-91.3)
Islam	44	11.9 (8.7-15.6)
Any significant family history		
No	368	99.7 (99.2-100.0)
Thalassaemia	1	0.3 (.0-0.8)
Mode of delivery		
LSCS	264	71.5 (66.7-76.2)
VD	105	28.5 (23.8-33.3)
Jaundice at birth		
No	348	94.3 (91.7-96.5)
Yes	21	5.7 (3.5-8.3)
Antithyroid drug intake during pregnancy by mother		
No	292	79.1 (74.9-83.5)
Yes	77	20.9 (16.5-25.1)
Maternal history of hypothyroidism		
No	292	79.1 (74.9-83.5)
Yes	77	20.9 (16.5-25.1)
Congenital hypothyroidism		
Absent	368	99.7 (99.2-100)
Present	1	0.3 (0.0-0.8)
G-6-PDD		
Absent	369	100 (100-100)
Present	0	0.0 (0.0-0.0)
Congenital adrenal hyperplasia		
Absent	363	98.4 (97.0-99.5)
Present	6	1.6 (0.5-3.0)

Table 2: Descriptive statistics of the age of the mother, gestational age and birth weight of the baby (*n*=369)

Category	Minimum	Maximum	Mean	Std. deviation
Mother's age (year)	18	39	25.83	4.29
Gestational age (week)	34	43	37.89	1.48
Birth weight of baby (kg)	1.48	3.88	2.83	0.45

Table 3: Distribution of mother's age, gestational age and birth weight across categories of newborn with CH vs newborns without CH (*n*=369)

Congenital hypothyroidism	Mean	Std. deviation	Mean difference	*t* (dt)	*P*
Mother's age					
Present	26.00	0.00	-0.166	-0.39 (367)	0.969
Absent	25.83	4.298			
Gestational age					
Present	38.00	0.00	-0.106	-0.71 (367)	0.943
Absent	37.89	1.485			
Birth weight					
Present	2.89	0.00	-0.055	-0.12 (367)	0.903
Absent	2.83	1.485			

there was no statistically significant association between religion and CAH, $\chi 2$ (1) =0.131, P = 0.536, mode of delivery and CAH, $\chi 2$ (1) =0.416, P = 0.679, jaundice at the time of birth and CAH, $\chi 2$ (1) =1.369, P = 0.298, and between significant family history and CAH, $\chi 2$ (1) =0.017, P = 1.000 [Table 7].

Discussion

Due to limited information on the prevalence of genetic disorders in the Indian population, particularly in North India, the three most common inborn errors of metabolism (IEMs) namely CH, CAH and G-6-PDD were selected for this study. A total of 369 neonates were screened for G-6-PD, 17-OHP and TSH levels. Of 369 neonates, one case (male) had an increased level of TSH, six cases (all males) were observed with an increased level of 17-OHP and no cases were observed with G-6-PD deficiency. In this study, the heel-prick method was used for sample collection and the samples were collected between 48 and 72 h of birth.

The metabolism in a newborn is initiated only after the cord is cut, and hence, the cord blood will not reflect the metabolic status of the neonate in a true sense. Thus, cord blood is only useful for screening CH and G-6-PDD, but is not suitable for CAH and Phenylketonuria (PKU) or other metabolic disorders after birth.[6,16] The heel-prick method, besides being minimally invasive and easily accessible, gives the advantage of testing many other disorders simultaneously through the same blood spot. The ideal sample collection time for IEM testing is between 24 hours and 1 week. Because of the thyrotropin surge after birth, the American Academy of Pediatrics (AAP) and the American Congress of Obstetricians and Gynecologists (ACOG) recommend that CH testing be done between 2 and 4 days of age when the TSH surge has subsided; however, early discharge policies around the world make this nearly impossible.[17] The 17-OHP level is normally high at birth due to neonatal stress.[18] In the case of CH and CAH, specimens obtained within the first 24 hours had a significant false-positive rate (FPR), so in this study sample was collected between 48 and 72 hrs of birth.

In our study, the male-to-female ratio of newborn was 1.15:1. The mean age of the mother was 25.83 years, the gestational age was 37.89 weeks and the birth weight of the baby was 2.83 kg. A similar result has been reported by Adeniran *et al.*[19]

In our study, only 77 (20.9%) mothers of the newborn had a history of hypothyroidism and took antithyroid drug during pregnancy. There was no statistically significant association between maternal history of hypothyroidism and maternal history of antithyroid drug intake during pregnancy to CH. In contrast, Manglik *et al.*[20] found a statistically significant association of CH with maternal hypothyroidism and maternal history of antithyroid drug intake during pregnancy. They also found that mothers suffering from hypothyroidism and who did not take the antithyroid drug during pregnancy have more chances to give birth to newborns having CH. Similarly, a study conducted by Anjum *et al.*[21] on 550 newborns found that CH had a statistically significant association with maternal

Table 4: Distribution of mother's age, gestational age and birth weight across categories of newborn with CAH vs newborns without CAH (*n*=369)

Congenital adrenal hyperplasia	Mean	Std. deviation	Mean difference	*t* (dt)	*P*
Mother's age					
Present	28.00	3.28	-2.20	-1.24 (367)	0.213
Absent	25.80	4.30			
Gestational age					
Present	37.00	1.41	0.909	1.49 (367)	0.137
Absent	37.91	1.48			
Birth weight					
Present	2.64	0.49	0.193	1.03 (367)	0.302
Absent	2.83	0.45			

Table 5: Correlation between TSH, 17-OHP and G-6-PD with mother age, gestational age and birth weight of baby (*n*=369)

	Correlation coefficient	*P*
TSH vs mother's age	0.066	0.208
TSH vs gestational age	-0.016	0.760
TSH vs birth weight	-0.001	0.987
17-OHP vs mother's age	0.030	0.565
17-OHP vs gestational age	-0.181	0.000
17-OHP vs birth weight	-0.103	0.049
G-6-PD vs mother's age	-0.021	0.681
G-6-PD vs gestational age	0.015	0.779
G-6-PD vs birth weight	0.023	0.655

Table 6: Association of CH with different variables (*n*=369)

Variables	Congenital hypothyroidism	Chi-square	df	*P*
	Present			
Gender of baby				
Female	0 (0.0%)	0.875	1	1.000
Male	1 (0.5%)			
Religion				
Hindu	1 (0.3%)	0.136	1	1.000
Islam	0 (0.0%)			
Mode of delivery				
LSCS	1 (0.4%)	0.399	1	1.000
VD	0 (0.0%)			
Jaundice at birth				
Absent	1 (0.3%)	0.061	1	1.000
Present	0 (0.0%)			
History of antithyroid drug intake during pregnancy				
No	0 (0.0%)	3.803	1	0.209
Yes	1 (1.3%)			
Any significant family history				
No	1 (0.3%)	0.003	1	1.000
Thalassaemia	0 (0.0%)			

Table 7: Association of CAH with different variables (*n*=369)

Variables	Congenital adrenal hyperplasia	Chi-square	df	*P*
	Present			
Gender of baby				
Female	0 (0.0%)	5.325	1	0.032
Male	6 (3.0%)			
Religion				
Hindu	5 (1.5%)	0.131	1	0.536
Islam	1 (2.3%)			
Mode of delivery				
LSCS	5 (1.9%)	0.416	1	0.679
VD	1 (1.0%)			
Jaundice at birth				
Absent	5 (1.4%)	1.369	1	0.298
Present	1 (4.8%)			
Any significant family history				
No	6 (1.6%)	0.017	1	1.000
Thalassaemia	0 (0.0%)			

hypothyroidism and maternal history of antithyroid drug intake during pregnancy.

In our study, of 369 newborns, one (0.3%) newborns had elevated TSH levels. Hence, the frequency of CH was 0.3%. Similar result has been reported by Manglik *et al*.[20] and Verma *et al*.[22] where the frequency of CH was 0.16% and 0.05%, respectively.

In our study, we found that males had a higher proportion of presence of CH as compared to females, but there was no statistically significant association between gender and CH. Anjum *et al*.[21] also found that males had a higher proportion of presence of CH, but the association between gender and CH was not significant. A recent study in New York also showed that male newborns were more likely to develop CH than female newborns.[23] Similarly, Verma *et al*.[22] found that male newborns were more likely to develop CH than female newborns.

In our study, of 369 newborns, 6 (1.6%) newborns had elevated 17-OHP levels. All positive cases were recalled for confirmatory testing by serum sample, of which five were true positives, while one was a false positive. Hence, the frequency of CAH was 1.4% (5/369). Verma *et al*.[22] conducted a study in India from January 2008 to December 2017 on 13,376 neonates and found that the frequency of CAH was 0.04% (5/13,376).

In our study, there was no statistically significant correlation between TSH with mother's age, gestational age and birth weight. Similar results have been reported by Anjum *et al*.[21] Also, there was no statistically significant correlation between G-6-PD with mother's age, gestational age and birth weight. A similar result has been reported by Bisoi *et al*.[24] and Mohammadzadeh *et al*.[25]

In our study, there was a statistically significant but negative correlation between 17-OHP with gestational age and birth weight and a statistically significant association between gender and CAH. Males had a higher proportion of presence of CAH as compared to females. A similar result has been reported by Pearce *et al*.[26] and Kum *et al*.,[27] and they found that low birth weight and premature newborns have higher levels of 17-OHP concentration and males had higher levels of 17-OHP than females.

In our study, no newborns had G-6-PD deficiency.

Early detection of CH allows the initiation of neonatal thyroid replacement therapy within the first week of life, thus preventing mental retardation, growth retardation and neurodevelopmental complications. If they are treated early, there are only minor differences in intelligence, school performance and neuropsychological development between normal and treated newborns.

Early detection of CAH can prevent life-threatening conditions such as an adrenal crisis, sexual ambiguity and abnormal growth. CAH-positive newborn requires urgent treatment with glucocorticoid and mineralocorticoid replacement therapy. The purpose of therapy is to replace deficient hormones and minimise excessive androgen production. Proper treatment can prevent adrenal crisis and virilisation and allows normal growth, normal pubertal development, sexual function and fertility.

Early detection of G-6-PDD can prevent hyperbilirubinaemia, kernicterus or even haemolytic anaemia in the future life of neonates. If the newborn would have been screened positive for G-6-PDD, their parents should undergo counselling regarding contraindicated drugs (antimalarial drug, sulphonamide, isoniazid, trimethoprim, colchicine, L-dopa, nitrofurantoin and vitamin K), dietary restrictions (fava beans) and avoidance of environmental factors that trigger jaundice and kernicterus. Therefore, the study will help in providing prior suggestions to the consulting physician for taking precautions in prescribing the drugs to deficient newborns suffering from pneumonia, typhoid fever, viral hepatitis and malaria.

The primary care physician must be aware of this inborn error of metabolism, so that they can advise the newborns to undergo screening for these prevalent congenital disorders. NBS will prevent mental retardation in the case of CH, adrenal crisis and sexual ambiguity in the case of CAH and those newborns screened positive for G-6-PDD, and their parents should be counselled for contraindicated drugs and dietary restrictions.

We found a non-significant but positive correlation between TSH with mother's age, 17-OHP with mother's age and G-6-PD with gestational age and birth weight and a non-significant but negative correlation between TSH with gestational age and birth weight and G-6-PD with mother's age. There was also a non-significant difference in the mean mother's age, mean gestational age and

mean birth weight of newborns with CH vs newborns without CH and newborns with CAH vs newborns without CAH. This non-significant correlation may be due to the small sample size, thus demanding further studies on a large scale to establish a significant correlation between them.

Conclusion

Establishing cost-effective screening procedures and efficient systems for quality control, patient recall, initiation of treatment and follow-up remains an urgent goal for the success of the NBS programme. Government support is needed at different levels to make neonatal screening a national screening programme throughout the country for the detection of undermined cases as early as possible and treating them to prevent their complication. The goal of this study is to construct an NBS facility and create a foundation for future such programmes.

CH, CAH and G-6-PDD are associated with significant morbidity, mortality and long-term complications. Early diagnosis and treatment are challenging in the absence of NBS. As a result, we advise neonatal screening for CH, CAH and G-6-PDD to reduce mortality and morbidity associated with these illnesses. Through this study, an attempt was made to establish an NBS facility and develop a framework for future such programmes.

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Conflicts of interest

There are no conflicts of interest.

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