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Pediatrics

CONGENITAL HYPOTHYROIDISM SCREENING IN A SERVICES HOSPITAL IN CENTRAL INDIA

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ABSTRACT Newborn screening is a cost-effective preventive health measure . Congenital hypothyroidism is one of the commonest preventable cause of mental retardation in India and worldwide. Early diagnosis of congenital hypothyroidism and targeted management strategies may prevent this epidemic. Various guidelines recommend measurement of Thyroid stimulating hormone(TSH),Thyroxin (T4) or both TSH and T4, for screening of this epidemic of Congenital hypothyroidism within 2--4 days of life, and in Preterms and low birth weight babies additionally after 2 weeks. There should be a follow up screening if lab test is positive along with non invasive scintigraphy and/or USG. L-Thyroxin is the first line treatment with standard dosages of 10-15 µg/kg/day based on severity ,with regular follow up to 03 years of age thereafter. The government and the policymakers should bring out mandatory newborn screening programmes for early detection and treatment of Congenital hypothyroidism. In India Congenital hypothyroidism is compounded by a lack of efficient newborn screening programmes, non availability of infrastructure and the rising cost of health care.

Objective: To study the incidence of congenital hypothyroidism in a services hospital in central India.

Design: Prospective observational study.

Setting: Military hospital Jabalpur.

Participants: All babies born in Military hospital Jabalpur during the study period Jul 2012 to Jun 2015.

Methods: Cord blood samples were collected immediately after birth and assayed by chemiluminiscenct immunoassay method. Age related cut-offs were applied for recall for TSH.

Main outcome measure: Recall rate for hypothyroidism, diagnosis of congenital hypothyroidism

Results: Screening for congenital hypothyroidism was carried out for 1030 newborns. Hundred percent of those recalled for confirmatory sampling responded. Using fixed TSH cut off of 20 µIU/L, yielded high recall rate of 20 %. Three babies were found to have congenital hypothyroidism. The mothers of these babies were all undiagnosed cases of hypothyroidism. The incidence of Congenital Hypothyroidism in this study was 1:340.

Conclusions: There is very high incidence of congenital hypothyroidism as reported in this study 1:340. and is higher than most of the studies in India. Effective treatment is available and if started timely will prevent a lot of morbidity. There is urgent need to incorporate newborn screening for congenital hypothyroidism at all levels, government and public. Newborn screening can be successfully carried out in India.

KEYWORDS : Congenital Hypothyroidism (CH) Levothyroxin, Newborn Screening, Thyroid-stimulating Hormone (TSH)

Introduction

Pediatricians, Pediatric Neurologists and Physicians should always exercise their clinical judgment and experience whenever faced with normal newborn thyroid test results (AAP). When there is a strong suspicion of hypothyroidism, regardless of newborn screening results serum free thyroxin and thyroid stimulating hormone estimation should be done (AAP).Unrecognized congenital hypothyroidism can lead to mental retardation The main purpose of newborn screening is to recognize congenital hypothyroidism as early as possible, so that timely intervention may prevent consequences like cognitive development. Ideally newborns should be screened before discharge from the hospital because of the high incidence of congenital hypothyroidism. Screening of CH is universal in almost all developed countries. This has brought down the incidence of MR due to simple therapeutic measures and excellent response that follows early detection and treatment. In developing countries like India we do not have a newborn screening policy leading to very high and lifelong morbidity due to this disorder.(1). Availability of an epidemiological data regarding disease burden is the basic requirement for a successful screening programme and it is lacking in our country. India has a very high incidence of congenital hypothyroidism. The incidence of CH varies from 1:3000 to 1: 4000 globally. (2).In India the reported incidence is 1:2640.(3).The statewide incidence of congenital hypothyroidism in India is Hyderabad - 1:1988, Kochi - 2.1:1000,Chennai -1.6:1700 , Andhra Pradesh-1:1700, and U.P.-1:1221.(4,5,6,7).

The cause of high incidence could be as result of advancement in screening methods and increased preterm birth rates. A recent study by ICMR in between 2007 to 2012 reported an overall incidence of 1 in 1130 newborns.(8)

Congenital hypothyroidism could be permanent, transient and syndromic.(23) In permanent congenital hypothyroidism there is sustained deficiency of thyroid hormone and requires lifelong treatment. In the temporary or transient variety, hormone deficiency is present at birth but recovers to normal thyroid levels. In syndromic hypothyroidism this is associated with impairment of other organ systems.(9).

Blood collection after 72 hours and within 7 days of life on a filter paper is the standard method of screening of newborn for hypothyroidism and other metabolic disorders. Alternatively congenital hypothyroidism can also be screened by measuring TSH in cord blood where the recall rates may be high.(10)

The main aim in treatment of congenital hypothyroidism is to measure frequent total thyroxin or free thyroxin in the upper half of the reference range during the first 3 years of life and normalize the TSH concentration to ensure optimal thyroid hormone dosage. Thyroid hormone regimes used today are more aggressive in targetting early correction of TSH leading to better intellectual and neurological prognosis. (1).The Thyroid hormone concentrations are low in the fetus during the first half of pregnancy and the fetus is entirely dependent on maternal Thyroid hormone, its supply to the fetus is controlled by the placenta and the thyroid status of the mother. The fetal hypothalamic- pituitary -thyroid axis begins to function by midgestation and is mature in the term infant at delivery. Despite the critical importance of thyroid hormone on multiple organs ,especially the brain, most infants with congenital hypothyroidism appear normal at birth. The hypothyroid fetus is protected from in part by placental transfer of maternal thyroid hormone. This is best demonstrated by the fact that cord blood thyroxin (T4) concentration at birth in infants,

unable to synthesize T4, is one third to one half that of normal infants.(9). There is increased intracerebral conversion of T4 to T3, resulting in increased local availabity of T3 despite the low serum concentrations. (11,12)Normal and near normal cognitive outcome is possible in even the most severely affected infants with congenital hypothyroidism. This is true as long as post natal treatment is early and adequate and maternal thyroid function is normal. When both maternal and fetal hypothyroidism are present due to severe iodine deficiency, potent thyrotropin receptor (TSH-R) blocking antibodies (TRB Abs) or TSH-blocking immunoglobulin, or maternal PITI deficiency, there is a significant impairment in neurointellectual development, despite therapy, soon after birth. (6,13,14) Maternal hypothyroid alone during early gestation can lead to mild but significant cognitive impairment of the offspring. (6,15,16) Identification and treatment of maternal hypothyroidism is the subject of recent reviews.(16-17)

Maldevelopment (aplasia, hypoplasia) and maldescent of thyroid gland (ectopic) is commonly grouped together as thyroid dysgenesis & are the usual causes of primary congenital hypothyroidism. Some of the genes proposed as operative in dysgenesis have been recently identified as TITF1,TITF2,PAX8 and TSHR.(18)

Table 1.Causes of congenital hypothyroidism.(10)

Permanent Hypothyroidism	Transient hypothyroidism
a. Thyroid dysgenesis b.Thyroid hormone biosynthetic defects c.Iodine deficiency d.Hypothalmic - pituitary hypothyroidism	a.TSH binding inhibitory immunoglobulins b.Exposure to goitrogens (iodides or antithyroid drugs c.Transient hypothyroxennemia of prematurity

Maternal iodine deficiency affects neuropsychological development and functional abnormalities of the fetus. It also indirectly impairs fetal brain development by causing hypothyroidism in both mother and fetus. Maternal iodine deficiency also impairs fetal thyroid function causing increased TSH level in the neonate .Screening is not a confirmatory diagnosis it requires further investigation.

Determination of the incidence of neonatal hypothyroidism by measuring the cord blood thyroxin levels at birth is the most useful and reliable method to assess the risk of brain damage in infants and children growing up in iodine deficient environment. Elevated serum TSH in the neonate indicates insufficient supply of thyroid hormones to the developing brain and therefore constitutes the only indicator that allows the prediction of possible impairment of mental development at a population level. After birth the term baby experiences a surge of TSH as a physiological response to cold environment. The TSH concentration rises to 60 -80 µIU/L within 30 to 60 minutes after delivery and falls quickly in the first 24 hours to about 20 µIU/L, followed by a slower decrease to below 10 µIU/L after the first postnatal week. The rise in TSH initiates increase of T4 and free T4 to peak levels of 17 µg/L, and 3.5 ng /dl respectively at 24 to 36 hours after birth with a slow decline to adult values over 4-5 weeks. Preterm infants demonstrate a similar but blunted response due to Hypothalamo Pituitary Thyroid axis immaturity.Ideally universal screening at 3-6 days of age should be done for detecting CH. Alternatively cord blood can also be used if screening is being done for CH and not other inborn errors of metabolism .

1.A primary TSH/backup T4 method and
2.A primary T4/backup TSH method (Fig 1).
3.Combined primary TSH plus T4 approach.

In the first approach TSH is measured first.T4 is measured only if TSH is 20 µIU/L .This approach misses central hypothyroidism, thyroid binding globulin deficiency and hypothyroxennemia with delayed elevation of TSH. In the second approach T4 is checked first and if low TSH is also checked. This is likely to miss milder or subclinical cases of CH in which T4 is initially normal with elevated TSH. Concomitant measurement of T4 and TSH is the most sensitive approach but is costlier. Most of the screening programs use either percentile based cut -offs(e.g.T4 below 10th centile or TSH above 90th centile or absolute cut-offs such T4 < 6.5 µg/dL and TSH > 20µIU/L .Abnormal values on screening should always be confirmed by a venous sample (using age specific cut-offs given in Table).Most centers initiate treatment after drawing the samples if TSH > 30µIU/L or T4 is low and the decision to continue or withhold treatment is taken after obtaining the blood report. For intermediate screening values of TSH, with normal T4, the treatment is initiated only after confirmation of diagnosis based on the blood report. Among infants with proven Congenital Hypothyroidism, TSH is > 50 µIU/L in 90% and T4 is < 6.5 µg/dL in greater than 75% of cases.

Table 2-Reference ranges for T4, fT4 and TSH in term infants according to age.(10,19,20,21)

Age	T4(µg/dL) mean range	FT4(pg/ml) mean(SD)/range	TSH(µU/L
Cord blood	*10.8(6.6-15)*	*13.8(3.5)*	*10.0(1-20)*
1-3 days	*16.5(11-21)*	*	*5.6(1-10)*
4-7 days	*	*22.3(3.9)*	
1-2 weeks	*12.7 (8.2-17.2)*	*	*2.3(0.5-6.5)*
2-6 weeks	*6.5-16.3***	*9.0-22.0*	*1.7-9.1*
6 weeks to 12 months	*11.1 (5.9-1.3*	*13.0-24.0***	*2.3(0.5-6.5)*

**No data available, **data for mean/median not available*

Table 3.Reference ranges for serum free T4 (fT4) and TSH in preterm infants.(10,19,20,21)

Age in weeks	*Free T4(ng/dl)*	*TSH(µU/L)*
25-27	*06-2.2*	*0.2-30.3*
28-30	*0.6-3.4*	*0.2-20.6*
31-33	*1.0-3.8*	*0.7-20.9*
34-36	*1.2-4.4*	*1.2-21.6*

Material and Methods

This was a prospective analysis of umbilical cord blood Thyroid stimulating hormone(TSH) values in all the babies and newborns delivered at a services hospital in central India (Military hospital, Jabalpur Madhya Pradesh)over a period of three years 2012 to 2015. All babies born at this hospital during this period were included excluding the Preterms, babies whose mothers were diagnosed case of congenital hypothyroidism on eltroxin and babies with demise & wherever there was improper sampling. Armed forces comprise of people from all parts of country and all ethnic groups and the study may present a reference for the country as a whole. In most of the screening programs blood samples are collected at 5-6 days age, but with large number of babies being discharged early, cord blood samples is a good alternative. (27,30). The Indian Academy of Pediatrics recommends the use of cord blood samples for screening for CH (31). Very few reports of cord blood values of TSH or T4 exist in Indian literature (32,33).There were a total of1230 babies born during this period of Jul 2012 to Jul 2015.Out of this 24 babies were excluded from analysis due to perinatal deaths, babies whose mothers were diagnosed case of hypothyroidism on eltroxin, or in cases of improper cord blood sampling. Another 176 babies were excluded as they were preterm. The total number of samples included was 1030 of term babies, 540 males and 490 females.TSH, T4 and T3 was assayed by chemiluminiscenct immunoassay method . A mixed cord blood sample was obtained soon after birth in sterile container drawn from the umbilical cord while severing it at the time of birth, and was sent immediately for assay of TSH. All cord blood TSH values more than 20 µU/L were followed up to 14 days with a repeat T3,T4 and TSH estimation. Congenital Hypothyroidism was diagnosed if TSH was > 20 µU/L with low T4 at two weeks. Radionuclide scanning was not done instead USG scanning was done.

Screening Method

Ideally universal screening at 3-6 days of age should be done for detecting CH. Alternatively cord blood can also be used if screening is being done for CH and not other inborn errors of metabolism .

We have used A primary TSH/backup T4 method

Criteria of selection of sample

a. Inclusion criteria--All term newborns of euthyroid mothers
b. Exclusion criteria -
i. Neonates born to mothers having hypothyroidism/any thyroid disorderon drug therapy.
ii. All Preterm babies
iii. Sick newborns and neonatal deaths.
iv. improper sampling.

Results

There were a total of 1230 babies born during the period of Jul 2012 to Jul 2015.. Out of 1230 babies born, 24 babies were excluded from analysis due to perinatal deaths, babies whose mothers were diagnosed case of hypothyroidism on eltroxin, and in improper cord blood sampling. Another 176 babies were excluded as they were preterm. The total number of samples included were 1030 of term babies . Out of this 540 were males and 490 females . The mean cord blood TSH value was 8.761 µIU/L. Babies whose cord blood TSH was >20 µIU/L and required rescreening at 72 hours was 205. Rescreening at 72 hours revealed 40 babies with a rising trend in TSH. Out of these 40 babies, 03 cases were diagnosed to have congenital hypothyroidism on follow up on day 14. Out of 1030 babies 540 were normal vaginal delivery and 460 were caesarian born babies and 30 were vacuum delivered . TSH level showed values varying from 0.23 to 67.12. mean 8.881, median 6.485, SD 8.917. A total of three babies were diagnosed as congenital hypothyroidism. The mothers of these babies were diagnosed as hypothyroidism simultaneously. The recall rate was at 72 hours was 20 % and the recall rate at 2 weeks was 3.88 %.The treatment in all these babies was started immediately.

Table.4.Umblical cord blood TSH Levels

Cord TSH level (µIU/L)	*No. of samples n =1030*
< 10	*723*
10-20	*235*
20-30	*34*
30-40	*14*
40-50	*14*
50-60	*04*
60-70	*03*
70-80	*01*
90-100	*01*
>100	*01*

Discussion

Results in our study population show higher incidence of congenital hypothyroidism 1:340 than reported anywhere in India (24,25,26) and other countries. (27,28,29) but Indian data have quoted figures as low as 1in 248. (36).Screening for congenital hypothyroidism has been carried out at institutional level from various parts of the country. Use of cord blood TSH as screening tool is feasible as it is simple and accessible. Fuse et al. and Arun Kumar Manglik et al. have shown that mixed cord blood is a good sampling technique for screening of CH.(34,35) The incidence of congenital hypothyroidism varies within the same country based on dietary iodine intake, different laboratory methods of screening, different cut-off values, demographic, geographic, racial and ethnic factors. Cord blood TSH provides a suitable first line diagnosis of CH, more so when a 72 hour screen cannot be ensured. This study was a hospital based prospective study on a limited scale. The higher values may represent a true incidence in our country. An interesting fact brought out in this case was that 03 mothers whose babies had congenital hypothyroidism were themselves suffering from undiagnosed hypothyroidism thus making it mandatory for TSH testing in all antenatal cases.

CONCLUSIONS

Newborn screening can be successfully carried out in India. There is very high incidence of congenital hypothyroidism as reported in this study and many other studies in India. Effective treatment is available and if started timely will prevent a lot of morbidity. There is urgent need to incorporate newborn screening for congenital hypothyroidism at all levels ,government and public. The high recall rate due to early discharge was addressed by age-related cut-offs. The study concluded that sex, mode of delivery, maturity, birth weight have relationship with TSH level in newborn's TSH level in cord blood. As the sample surveyed is very small and hospital based more prospective studies on larger number of newborns are required to confirm the findings and analyze the reasons for the increased incidence. We conclude that we may safely use the widely used cut of cord blood TSH value of >20 µIU/L for the purpose of recall and retesting.

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