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Use of Umbilical Cord Blood TSH as a Marker for Screening Of Congenital Hypothyroidism in a Tertiary Care Centre in Jharkhand

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Abstract:
INTRODUCTION:
Congenital hypothyroidism is the most common preventable cause of mental retardation. Features of congenital hypothyroidism are nonspecific and difficult to identify in the neonatal period. They become prominent with increasing age. However the window period for neurological intervention has elapsed in most patients by this time. The female to male ratio is 2:1. If congenital hypothyroidism is diagnosed promptly and treated early irreversible mental retardation can be prevented.
AIMS AND OBJECTIVES:*The aim of neonatal screening program is to detect affected neonates and provide replacement to them as early as possible so that severe physical and mental handicap can be prevented by early treatment.To evaluate the effectiveness of cord blood TSH screening to detect cases with hypothyroidism.*
METHODS: *A cross sectional study conducted on babies born in department of obstetrics and gynaecology,RIMS Ranchi. Umbilical cord blood sample was collected in a sterile container drawn from the umbilical cord incised at the time of birth. TSH level was estimated within 24 hours by chemiluminescent microparticle immunoassay (CMIA) method in department of laboratory medicine/biochemistry RIMS,Ranchi.*
RESULT: *Number of confirmed case of congenital hypothyroidism was 1/200 . There were total 7 cord blood samples whose TSH values ≥20mIU/L but a repeat test on 2-4 days of life confirmed CH in one of these samples. Mean TSH value female was 7.27± 0.89mIU/Lwhile mean TSH value for male was 6.89±0.38mIU/L. Mean TSH value for preterm was 10.99±0.62mIU/L. Mean TSH value for term was 6.81±0.60mIU/L. Mean TSH value for post term was 4.38±0.75mIU/L.*
DISCUSSION*: Present study was carried out in the department of Pediatrics and neonatology,RIMS,Ranchi. TSH cut off values for screening of neonates: Initial TSH value≤10 mIU/L-Normal Initial TSH value 10.1-19.9mIU/L- Borderline Initial TSH value ≥20 mIU/L- Abnormal These studies need larger sample size and stronger logistic effort with team approach.7.5% of newborns in our series had values between 10.1-19.9mIU/L.This is the group which needs further evaluation to confirm thyroxine deficiency either acquired or congenital.*
CONCLUSION: *Due to the practice of early discharge in our country cord blood estimation remains a very practical method for screening purpose.Use of cord blood TSH as a screening tool is an attractive method because of its simplicity and accessibility.The Indian Academy of Pediatrics recommends the use of cord blood samples for screening for congenital hypothyroidism.*
Key Words:*Congenital hypothyroidism, Mental Retardation, Neonatal Screening, Umbilical cord blood TSH*

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I. Introduction:

Congenital hypothyroidism is the most common preventable cause of mental retardation. Features of congenital hypothyroidism are nonspecific and difficult to identify in the neonatal period. They become prominent with increasing age. However the window period for neurological intervention has elapsed in most patients by this time.Most infants with congenital hypothyroidism are asymptomatic at birth, even if there is complete agenesis of thyroid gland. This situation is attributed to transplacental passage of moderate amount of maternal T4, which provides fetal levels that are approximately 33% of normal at birth. Despite this maternal contribution of thyroxine, hypothyroid infants still have a low serum T4 and elevated TSH level and so will be identified by newborn screening programs.Screening is a public health service in which members of a defined population, who do not necessarily perceive that they are at risk of, or are already affected by, a disease or its

complications, are asked a question or offered a test to identify those individuals who are more likely to be helped than harmed by further tests or treatment to reduce the risk of disease or its complications.The purpose of neonatal screening is to detect disorders immediately after birth. Earlier the detection of disorders, better the intervention and least the effect of disease, which otherwise could have created serious handicap in the children.Early and accurate diagnosis and intervention will lead to an improved prognosis in almost all of the patients. At this stage, treatment may be needed to be less radical. Scarce health services resources will be saved by treating disease before they progress, and those with true-negative test results can be reassured.Congenitalhypothyroidism(CH) is one of the most common preventable causes of mental retardation. Neonatal hypothyroidism causes irreversible brain damage, retarded physical growth and various organ dysfunctions. Early diagnosis and adequate treatment of neonatal hypothyroidism from first week of life results in normal growth and development of the affected child, even if he is suffering from thyroid deficiency. The most common cause of congenital hypothyroidism is thyroid dysgenesis (85%) which includes aplasia, hypoplasia or an ectopic gland ($2/3^{rd}$). Iodine is essential for thyroid hormone synthesis and is present in soil, water and air. Neonatal thyroid screening using serum thyrotropin (TSH) as the primary screening test detects not only permanent sporadic congenital hypothyroidism, whose incidence is about 1 per 4000 births, but also compensated or transient primary hypothyroidism, whose incidence can be as high as 1 in 10 neonates and whose main cause is iodine deficiency. Down syndrome have a 35 fold increased risk for primary congenital hypothyroidism.Newborn screening also has revealed the prevalence of the various causes of congenital hypothyroidism, including a series of transient disorders found predominantly in preterm infants. The incidence of CH has been found to be 4-5 times more common than phenylketonuria, for which screening programs were originally developed. The main objective of screening, the eradication of mental retardation after CH, has been achieved by these screening programs. In addition to the profound clinical benefit, it has been estimated that the cost of screening for congenital hypothyroidism is much lower than the cost of diagnosing CH at an olderage.Significant information regarding the prevalence of CH has been accumulated in the last few years from India and many of them point towards higher incidence of CH in India. The probable reason for the increased prevalence could be due to improved testing strategies, increasing number of preterm births or the actual incidence of a condition that was not studied in a large scale in the second most populous country in the world.In India IDD is a public health problem. The elimination of IDD is a health and developmental goal. In Jharkhand, IDD is a public health problem too. Data about congenital Hypothyroidism in children is not available in Jharkhand. Present study tries to screen by random sample survey, presence of congenital hypothyroidism in Jharkhand. If incidence of congenital hypothyroidism is low then elimination of acquired deficiency may lead to control of hypothyroidism. **SEX RATIO**-Female to male ratio is 2:1 for permanent CH. Female to male ratio is approximately 1.0 for inherited cases of CH. It follows that the preponderance of female cases is mostly associated with dysgenesis of the thyroid gland. Female to male ratio in the group of infants with transient CH it was approximately 1.**SCREENING METHODS**-Ideally universal newborn screening at 3-4 days of age should be done for detecting CH (coupled with screening of other inborn errors of metabolism, wherever it is undertaken). If screening is being done only for CH, cord blood may also be used. Universal newborn screening is currently being done in many parts of the world. Three approaches are being used for screening :

1) Primary TSH, back up T4
2) Primary T4, back up TSH
3) Concomitant T4 and TSH

The advantages and disadvantages of these approaches are as follows:

1) Primary TSH, back up T4: TSH is measured first and T4 is measured only if TSH is ≥20 mU/L. This approach is most widely used and cost-effective, but likely to miss central hypothyroidism, thyroid binding globulin(TBG) deficiency and hypothyroxinemia with delayed elevation of TSH.
2) Primary T4, back up TSH: T4 is checked first and if low, TSH is also checked. This is likely to miss milder/subclinical cases of CH in which T4 is initially normal with elevated TSH.
3) Concomitant T4 and TSH: Most sensitive approach but incurs a higher cost.

Klein *et al.* showed that serum measurements of thyroid hormones (T4-TSH) in cord blood could detect hypothyroidism in the neonatal period.Screening of neonates for congenital hypothyroidism was commenced at the Malankara Orthodox Syrian Church Medical College, Kochi in October 2006. 2964 term babies were screened over a 12 month period between 1^{st} October 2006 and 30^{th} September 2007. 2872 of these were inborn and were considered for calculating the hospital based incidence of CH. Serum T4 and TSH assay confirmed neonatal hypothyroidism in 6 of them. All of them were inborn infants. The study revealed congenital hypothyroidism incidence of 2.1 per 1000(6/2872) amongst inborn term infants, much higher than the incidence of 1 in 4000 reported in western literature and 1 in 1700 from other regions of India. The better pick up rate and

the lower costs make TSH assay a better screening tool than T4 assessment.In India today, access to NBS is growing but remains partial and incomplete. Access to the screening procedures is primarily available in private laboratories.The Indian Council of Medical Research has worked since 2005 to initiate pilot projects in five cities, each screening 500,000 newborns free of charge, to establish the prevalence of certain genetic defects in population.In January 2007, the Union Territory (UT) of Chandigarh was declared the first state or UT in India to fund mass genetic screening (NBS and prenatal diagnosis), with a reduced fee for all and free access for the poor. In February the following year, Goa was said to be the first state to introduce mandatory NBS. Finally, in February 2009, the union cabinet was reported to have approved a proposal to establish an institute in kalyani (West Bengal) to launch a large-scale program for NBS.Nair, *et al* in their study from December 2005 to November 2006 reported on re-evaluation of the thyroid axis in 36 toddlers, now aged 3 years, diagnosed to have CH. The study highlights that at least 50% of the patients would have had lifelong therapy unnecessarily had they not been re-evaluated.Kishore KR *et al.* screened all babies born at Cloudnine Hospitals, Bangalore, India during the period from Jan-2007 to Oct-2013 accounting for nearly 19800 samples. The screening used > 12 µU/ml of whole blood as abnormal. Screening identified 32 babies with initial elevated TSH. Of those 32 babies, 8 had normal TSH on repeat testing. Remaining 24 were confirmed to have elevated TSH. 19 of those 24 babies had CH with TSH between 100-350 µU/ml and had congenital absence of thyroid gland. Remaining 5 of the 19 babies had an ectopic thyroid gland but had dyshormonogenesis.In this cohort study screening 19800 babies, 19 babies with CH had absence of thyroid gland giving incidence of 1:1042.Since remaining 5 were picked up by newborn screening only, if these are also considered then the incidence would be 1:825 for CH.For a treatable disorder this is far too high and surely reflects the tip of the iceberg.Stephen *et al*. summarized that majority of infants with hypothyroxinemia of prematurity recover normal thyroid.Leger*et al*. in their observational study showed that only 70% of patients with CH have adequate treatment in early adulthood. This inadequacy of treatment, with non-optimal follow-up or poor compliance with treatment in young adults, is reflected in uncontrolled hypothyroidism or, less frequently subclinical hypothyroidism.Wassner*et al.* concluded that apparent incidence of CH has more than doubled in recent years because of several factors, including more inclusive diagnostic criteria, shifting demographics and increasing survival of preterm infants. Recent studies of defects in thyroid hormone synthesis have focused on the role of mutations in the dual oxidase system and of a novel apical iodide transporter, anoctamin.Kerala health department newborn screening programme was selected the top innovation in the area of child health in the country at the National Summit on Good and Replicable Practices and Innovations in Public Healthcare system in India. The programme was launched by the state in September 2012. Of the 1.4 lakh newborns screened, 70 babies were found to be having congenital hypothyroidism.

AIMS AND OBJECTIVES:

1) To study the incidence of congenital hypothyroidism among term and preterm babies born at Rajendra Institute of Medical Sciences,Ranchi.
2) To evaluate the effectiveness of cord blood TSH screening to detect cases with hypothyroidism.

II. Materials And Methods:

Source of data:

1) Department of Obstetrics and Gynaecology, RIMS, Ranchi
2) Department of Pediatrics and Neonatology, RIMS, Ranchi
3) Laboratory data from Department of Biochemistry, RIMS, Ranchi and department of Laboratory Medicine, RIMS, Ranchi

Study Period:
MAY 2015-MAY 2016
Study design:
This is a cross-sectional study during the study period.
Sample size: 200

Inclusion criteria

1) Babies born at RIMS, RANCHI
2) Babies born to mother with no history of thyroid disease

Exclusion criteria:
Mother on antithyroid medications.

Methodology:
Umbilical cord blood sample was collected in a sterile container drawn from the umbilical cord incised while severing it at the time of birth of the baby.
Mothers age, use of iodine antiseptics on the mother prior to delivery was recorded. The type of medications, anesthesia given to the mother till birth of baby was recorded.
At birth babies weight, sex, time to first cry, apgar score was noted.
Sample was collected and transported to processing laboratory.

Materials required:
a) A pair of clean gloves
b) A 5 ml syringe
c) Sterile cotton
d) 70% isopropyl alcohol
e) A red topped plastic tube containing a clot activator
All appropriate precautions were taken including changing gloves between infants, taking blood handling precautions and disposing the needle with syringe properly.
Intended use- TSH assay is a chemiluminescent Microparticle Immunoassay (CMIA) for the quantitative determination of human Thyroid Stimulating Hormone (TSH) in human serum and plasma.

III. Results:

TABLE 1: SEX DISTRIBUTION OF NEONATES

SEX	NO. OF NEONATES	PERCENTAGE
MALE	84	42
FEMALE	116	58

TABLE-2: DISTRIBUTION OF NEONATES ACCORDING TO GESTATION

GESTATION	NO OF NEONATES	PERCENTAGE
PRETERM	18	9
TERM	176	88
POSTTERM	6	3

TABLE -3: WEIGHT DISTRIBUTION OF NEONATES

WEIGHT	NO OF NEONATES	PERCENTAGE
<1.5	14	7
1.5-2.5	50	25
>2.5	136	68

TABLE 4: DISTRIBUTION OF RESULT OF TSH VALUE

RESULT (mIU/l)	NO. OF SAMPLES	PERCENTAGE
≤10	178	89
10.1-19.9	15	7.5
≥20	7	3.5

TABLE 5: MODE OF DELIVERY OF NEONATES

MODE OF DELIVERY	NO. OF NEONATES	PERCENTAGE
LSCS	80	40
NVD	120	60

IV. Discussion:

Present study "Use of umbilical cord blood TSH as a marker for screening of congenital hypothyroidism" was carried out in The Department of Pediatrics and Neonatology, Rajendra Institute of Medical Sciences,Ranchi,between May 2015 to MAY 2016 to evaluate the incidence of congenital hypothyroidism among babies born at RIMS,Ranchi. In this study total number of newborns enrolled were 200 out of which15newborns had TSH level in the borderline zone.
Table 1 shows sex distribution of neonates screened. In this study 42% were males and 58% were females. Mean TSH value in males is 6.896±0.382 and in females TSH value is 7.272±0.889. .

Table 2 shows distribution of neonates screened according to their gestation. In this study there were 9% preterms, 88% term and 3% post-term neonates.

The gestational age of newborns was determined according to the history and new Ballard scoring system. Preterm newborns are <37 completed weeks age, term newborns are 37-42 weeks of age and post-term

neonates are >42 weeks of age. The mean TSH value in preterm is 10.997±0.624, in term neonates 6.810±0.600 and in post-term neonates is 4.385±0.753.

Table 3 shows weight of neonates screened. 7% were very low birth weight, 25% were low birth weight and 68% were of normal birth weight.

A high risk of CH among infants with low or high birth weight was observed by EmanuelaMedda*et al.* in population case-control study (1997-2003). They also observed that some neonatal features were significantly associated with the birth of a permanent CH infant: female gender, twinning, additional birth defect and gestational age>40 weeks.

Table 4 shows distribution of result of TSH assay. This shows that 89% of newborns had TSH level <10 mIU/litre. 7.5% of newborns had TSH level between 10.1-19.9 mIU/litre. 3.5% of newborns in our study had TSH level >20mIU/litre.

TSH CUTT-OFF VALUES FOR THE SCREENING OF NEONATES-

Umbilical Cord blood TSH level <10mIU/L whole blood units- Normal

Umbilical Cord blood TSH level, 10-20 mIU/L whole blood units- Borderline

Umbilical Cord blood TSH >20 mIU/L whole blood units- Abnormal

The average prevalence of congenital hypothyroidism world-wide is about 1 in 4000 (range of 1:3600 to 1:5000 newborns).

Screening of neonates for congenital hypothyroidism (CH) was commenced at the Malankara Orthodox Syrian Church Medical College,Kochi between 1st October 2006 and 30th September 2007. The blood is sampled between 72-120 hours of life by heel prick and TSH levels estimated by Sandwich Enzyme Linked Immunoassay using Bio-radQuantase TM kit. TSH levels less than 10 mU/L were considered normal, 10-20 mU/L considered borderline and >20 mU/L as abnormal. 2872 of these were inborn and were considered for calculating the hospital based incidence of CH. TSH values were >10 mU/L in 106 infants. This study showed 3.7 % of neonates with TSH level >10 mIU/L. Serum T4 and TSH assay confirmed neonatal hypothyroidism in 6 of them. The study revealed CH incidence 2.1 per 1000.

Desaie, *et al* in 1987 screened 12407 newborns for CH using cord blood TSH measurements. Incidence extrapolated was 1:2481.

A study was conducted by Arun Kumar Manglik*et al.* to find normative values for thyroid stimulating hormone (TSH) in 1200 cord blood samples of term babies whose mothers were not on any thyroid medications. TSH was estimated within 24 hours by enzyme immunoassay. A full thyroid profile, viz, T3,T4,TSH, fT3 and fT4 was done at 7-10 days of age in all babies with cord TSH >20 mIU/L. The mean, median and standard deviation for the TSH values for the cohort were 6.13 mIU/L, 5.8 mIU/L and 4.523 respectively. 22 babies with TSH values >20 mIU/L were given repeat tests. Hypothyroidism was confirmed in two of these babies.

They concluded that a cut off value of TSH>20mIU/L is adequate for neonatal thyroid screening in Indian settings. Their results showed that only 7.5% (90 cases) samples showed a cord blood TSH value of >10 mIU/L. This is comparable to figures from Ethiopia. Table 5 shows the mode of delivery. 40% of the newborns in our study were born by LSCS whereas 60% of the newborns were born by NVD.

Mean TSH value in our study is 7.114, median is 5.23 and mode is 5.39 . Standard error of mean for the study is 0.539.

Table 5 shows the distribution of TSH according to mode of delivery. Mean TSH value following NVD=6.630±0.344 µIU/L and mean TSH value following LSCS=7.836±1.246 µIU/L.

In our study there were total 7 cord blood samples whose TSH values ≥ 20 mIU/L but a repeat test on 2-4 days of life confirmed CH in only one of these samples.

This is probably due to small sample size (200 newborns). Collection of neonatal blood sample demands strong logistic effort with a team approach. This study highlighted the need of such studies to be undertaken in areas like Jharkhand with a large tribal population and known iodine deficiency.

In our study 7.5% of newborns had TSH values between 10.1-19.9 mIU/L. This is the group which needs further evaluation to confirm thyroxine deficiency either acquired or congenital. We propose to follow up these cases since we have their addresses and phone no.

The average prevalence of congenital hypothyroidism world-wide is about 1 in 4000 (range of 1:3600 to 1:5000 newborns) but in a controlled study in India from Hyderabad revealed congenital hypothyroidism incidence of 2.1 per 1000. The prevalence of newborns with borderline TSH assay was 75 per thousand newborns in our series. If we had some more samples we might have come across more confirmed cases of congenital hypothyroidism.

V. Conclusion

The study was undertaken to screen newborns for congenital hypothyroidism by CMIA method. 200 newborns were enrolled in the study.

It was observed that –

1) No. of confirmed cases of Congenital Hypothyroidism was 1/200.
2) The prevalence of newborns with borderline TSH assay was 75 per thousand newborns.
3) Mean TSH value is 7.11±0.54.
4) Mean TSH level in male newborns is 6.89±0.38,in female newborns is 7.27±0.89. .
5) Mean TSH level in preterm newborns is 10.99±0.62 , in term newborns is 6.81±0.60 and in postterm is 4.38±0.75.
6) Mean TSH value following NVD=6.630±0.344 µIU/L and mean TSH value following LSCS=7.836±1.246 µIU/L. .
7) These studies need larger sample size, stronger logistic, trained staff and a good laboratory.

The incidence of congenital hypothyroidism appears increasing over the last 20 years. Whether the increase is real or is it the result of lowering of screening cut offs, changes in the racial/ethnic population, an increase in preterm births, or something else causing an increase in CH cases is not clear. It is also unclear whether the additional infants now being detected, including those with mild hypothyroidism and those with delayed TSH rise will have permanent or transient hypothyroidism.

Public health agencies should seriously consider implementing screening programme for congenital hypothyroidism in India.The best way to detect infants with CH is by screening large populations of newborns. If diagnosis is made and treatment started within a few weeks of birth, neurodevelopmental outcome generally is normal.

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