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Research Article

Utility of Knee Radiographs as a Supportive Diagnostic Screening Tool for Early Therapy in Neonates Detected with Congenital Hypothyroidism at a Primary Health Care Centre - A Pilot Study from India

Sudha Rathna Prabhu*

Paediatrician and Clinical Research Scholar, The Tamil Nadu Dr MGR Medical University, Chennai, Tamil Nadu, India

***Corresponding Author:** Sudha Rathna Prabhu, Paediatrician and Clinical Research Scholar, The Tamil Nadu Dr MGR Medical University, Chennai, Tamil Nadu, India.

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Abstract

The most common preventable and treatable endocrine cause of mental retardation in paediatric population is congenital hypothyroidism. Early diagnosis and initiation of therapy within two weeks of age with adequate dosage of thyroxine are essential to prevent neurological impairment. The impact of thyroid gland dysfunctions especially if it occurs early in utero manifest as severe epiphyseal agenesis and dysgenesis of ossification centres. Normally at birth five ossification centres are present. Most consistent centres are situated around knee joints at lower end of femur and upper part of tibia. This physiological phenomenon can be utilized as a supplementary tool to assess and support diagnosis of congenital hypothyroidism to initiate early thyroxine. This pilot study demonstrates that radiograph of knee showing combined mean epiphyseal size of 6 mm or less indicates delayed bone maturation and with newborn screening results screen positive with elevated thyroid stimulating hormone (TSH) confirms cause to be due to congenital hypothyroidism warranting early thyroxine therapy. The practical utility of this supportive tool in a neonate detected to have CH when there is a delay likely to occur in a large population in India where more than two thirds of world live births occur and prevalence of CH being much higher is emphasized in this conceptual research paper. Out of a total of 101 neonates evaluated 21 were confirmed positive for congenital hypothyroidism with TSH values above 10 mIU/L. Newborns with a screening TSH above 10 and with repeat confirmation in serum with TSH above 50 mIU/L had mean epiphyseal diameters of 6 mm and below indicating delayed bone maturation most probably due to thyroid hormones deficiency and need to start early therapy with thyroxine. This practical concept is particularly relevant at primary health care centres level in India where blood samples have to be sent to tertiary centres to do further testing which involves both time and cost constraints. An easily and immediately available plain radiograph of knee showing mean epiphyseal sizes below normal will guide to initiate timely therapy which is the most crucial factor to prevent mental impairment in affected neonates.

Keywords: *Epiphyseal Dysgenesis; Mean Epiphyseal Diameter; Thyroid Stimulating Hormone; Congenital Hypothyroidism; Mental Impairment*

Introduction

The most common preventable and treatable endocrine cause of mental retardation in paediatric population is congenital hypothyroidism (CH). While world incidence of CH is currently at 1 in 3000, in India prevalence is 1 in 1172 [1]. The first all India pilot multi centric project study was launched by Indian Council of Medical Research (ICMR) National Task Force Team, New Delhi in five selected cities all over India. New Delhi, Chennai, Mumbai, Kolkata and Hyderabad were selected representing North, South, West, East and Central geographic regions in India and with a target to screen one lakh neonates born in India [2]. ICMR project results are even more alarming

at Chennai centre which is a reflection of thyroid disorder status in South India within Tamil Nadu where incidence is 1 in 727. New born screening for congenital hypothyroidism is done by estimation of the analyte thyroid stimulating hormone (TSH) in a dried blood spot obtained by heel prick technique. Subsequently specific confirmatory protocols are followed for early diagnosis and initiation of therapy within two weeks of age with adequate dosage of thyroxine in affected neonates which are essential to prevent long term neurological impairment.

Significance

Normal thyroid gland functioning is vital for complete bone maturation. In addition to brain development, thyroid hormone is essential for normal skeletal development. Epiphyseal ossification is delayed in congenital hypothyroidism and is often associated with growth arrest, failure of chondrocyte differentiation and abnormal matrix synthesis. Longitudinal skeletal growth occurs by endochondral ossification, the sequential process of growth plate chondrocyte proliferation, matrix synthesis, cellular hypertrophy, matrix mineralization, vascular invasion, and apoptosis. The process is precisely regulated by systemic hormones and local paracrine factors including T3, fibroblast growth factors (FGFs), and hedgehog (lhh)/PTHrP feedback loop [3,4]. Childhood hypothyroidism causes growth arrest, epiphyseal dysgenesis and delayed skeletal development [5] whereas T4 replacement induces rapid catch-up growth. In contrast, untreated childhood thyrotoxicosis advances skeletal maturation and results in premature fusion of the epiphyses and short stature, with early fusion of the cranial sutures and craniosynostosis occurring in severe cases. The autosomal dominant syndrome of resistance to thyroid hormone which results from dominant-negative mutations of the T3 receptor (TR) β protein, is associated with skeletal abnormalities and short stature [6]. Taken together, these observations indicate the developing skeleton is exquisitely sensitive to thyroid hormones.

The impact of thyroid gland dysfunctions especially if it occurs early in utero manifest as severe epiphyseal agenesis and dysgenesis of femoral and tibial ossification centres occurring in and around the knee joints. Normally at birth, five ossification centres are present. Most consistent centres are situated around knee joints. This physiological phenomenon can be utilized to assess and support diagnosis of hypothyroidism to initiate early, timely thyroxine therapy. As a part of government system in India, radiographers who are routinely employed in each primary health care centre can be trained to perform bedside radiographs of both knee joints in neonates who are detected screen positive for congenital hypothyroidism. Therapy can be initiated at least five to seven days earlier when compared to therapy after performing serum confirmatory tests with both thyroid stimulating hormone and thyroxine respectively. Biochemical confirmation of congenital hypothyroidism with serum TSH and Free T4 after recall of patients can take up to 10 to 12 days in a primary health care centre in our country. Hence when there is a delay likely to occur an easily and immediately available plain radiograph of knee showing mean epiphyseal sizes will help to initiate timely therapy the most crucial factor to prevent mental impairment.

Aim of the Study

The main purpose is to evaluate utility of knee radiographs with mean epiphyseal measurements as supportive diagnostic tool in a neonate detected screen positive for congenital hypothyroidism by new born screening to initiate early therapy with thyroxine and improve outcomes.

Materials and Methods

Study Population

Study group was selected from within all neonates who had screen positive results for thyroid stimulating hormone levels above 10 mIU/L.

Inclusion criteria: Inclusion criteria were neonates with initial screening TSH above 10 mIU/ml, term neonates at 37 weeks and above with birth weight 2500 grams and above. Only singleton pregnancies were included.

Exclusion criteria: Exclusion criteria were neonates with gross congenital anomalies, preterm babies 36 weeks and less, intrauterine growth retardation babies with birth weight less than 2500 grams, twins and triplets were excluded.

Study Number were 101 neonates and study period was from 2010 to 2012.

Study Places: Co-ordinating centres was Fetal Care Research Foundation, Chennai. Institute of Obstetrics and Gynecology and Institute of Child Health and Hospital For Children, Egmore, Chennai Tamil Nadu India were sample collection centres for ICMR project at Chennai centre. Can Ray Radiological Research Institute, Chennai. India was radiology centre.

Study design: Retrospective observational study.

Statistical analysis: Statistical analysis was by descriptive statistics.

Methods

After ethical committee approval and a detailed informed and written consent from patients' families all screen positives neonates after having confirmed positivity with increased TSH and decreased free T4 thyroxine in serum were evaluated with radiographs of knee joints. The radiographs were taken in an approved radiology centre by qualified radiographers and radiologists interpretations were obtained. Special precautions were taken to protect neonates with gonadal shields against radiation hazards even though the risk is zero due to exposure from this methodology (one knee radiograph = 0.5 rads). Technical errors and magnification of images were kept to the minimum with tube table distance at 100cms. The appearances of distal femoral and proximal tibial epiphyses were noted. The greatest and smallest diameter of each epiphysis was measured and mean was calculated as described by Von Harnack [8]. All 101 neonates had knee radiographs taken and mean femoral and tibial diameters were measured with a steel small scale in millimeters directly on the x-ray films by a trained Paediatrician and the same scale was used throughout the research study. The mean diameter of both femoral (MFD) and tibial mean tibial diameter (MTD) epiphyses were added together and the combined mean epiphyseal diameter (MED) was calculated and recorded in mm. MED values were next compared with screening TSH values. Subsequently the same was compared with repeat TSH and free T4 levels in serum and all results were tabulated and analysed.

Results and Discussion

Results research study results are tabulated as follows in table 1.

S .N	Sex M males F females	DBS TSH mIU/L	Serum TSH m IU/L	FreeT4 ng/dL	MED in mm	
					MFD	MTD
1.	F	192	150	0.34	0	0
2.	F	22.8	56.52	1.37	2	0
3.	F	49.7	150	0.65	2.5	0
4.	M	66.4	150	0.65	0	0
5.	M	108	150	0.23	2.0	0
6.	F	16	30	1.74	3.5	0
7.	F	243	150	0.28	3.5	0
8.	M	91.7	150	0.41	2	0
9.	F	227	150	0.15	0	0
10.	F	218	150	0.20	0	0
11.	F	16.7	150	0.38	2.5	0
12.	F	146	150	0.41	2	0
13.	F	189	150	0.04	2.5	0
14.	M	11.2	32	1.53	3.0	2.0
15.	F	199	150	0.33	2.75	0
16.	M	14.6	34	1.34	3.0	0
17.	F	40.6	150	0.6	2.0	0
18.	M	243	240	1.13	2	2
19.	M	11	17	1.1	2.0	2.0
20.	F	106	77.5	0.10	0	2.5
21.	F	34.4	98	1.59	2.0	2.0

Table 1: *TSH screening values and repeat confirmatory values with free T4 and bone maturity correlation.*

Table 1 shows thyroid stimulating hormone (TSH) values in both dried blood spot (DBS) performed by dissociate enhanced labelled fluoro immune assay (DELFIA) screening method and by chemiluminescence in serum as confirmatory method for TSH and free T4. Study included a total of 101 neonates in which 101 were screen positive for CH with TSH above 10 mIU/L. Repeat serum tests in 21 neonates were reported as confirmed positives and remaining were screen negative with TSH below 10 mIU/L and served as controls.

It was observed that in neonates who had TSH screening values above 10 mIU/L, mean epiphyseal diameters were below 6 mm. Corresponding neonates who had serum tests with TSH below 10 had MED above 6 mm indicating better bone maturity. In contrast an inverse correlation was observed in our study in that when screening values of TSH by dried blood spot newborn screening were above 10 mIU/L and in those neonates with repeat serum confirmatory TSH above 50 mIU/L, measurements of MED were below 6 mm indicating delayed bone maturation

Discussion

Retarded bone age in 40 - 73% of neonates with congenital hypothyroidism has been described in previous papers [5]. A few have attempted to correlate biochemical tests with skeletal maturity where maturity was assessed in relation to gestation age, using the method of Senecal., *et al.* [8] or to birth weight using the method of Caffey [6]. Illig [6] reported a significant difference between biochemical values and the extremes in the spectrum of size of the ossification centres. Higher TSH and lower T4 and T3 levels were found in infants with absent epiphyses. In a similar study from The New England Congenital Hypothyroidism Collaborative [7] significant correlations were reported between hormonal concentrations and retarded bone age when they grouped infants into 2 classes those with a bone age equivalent to 40 weeks gestation, and those with a bone age less than gestation age. No previous studies however have correlated the biochemical results with the measured epiphyseal size using the method and reference values of Von Harnack [8].

Indian studies on mean epiphyseal diameter sizes in normal term and euthyroid is lacking. Our study is first attempt to measure and correlate epiphyseal diameter in neonates detected to have congenital hypothyroidism. A pioneer study by Illig., *et al.* [5] have published their study with mean epiphyseal diameter of 7 mm as cut off point for bone maturation assessment. As ethnicity plays a major role in deciding human body anthropometric measures and bone configurations, variations in measurements are expected and require larger samples studies from several countries. Another important factor is the nutritional status of the fetus in utero which is again influenced by genetic and environmental factors. It has been reported in several research studies that bone maturity is usually resistant to nutritional deficiency states of both mother and fetus. In our study to minimize bias, we have included only those neonates with birth weight above 2500g and with gestational age 37 weeks to 42 weeks only.

On reevaluation and follow up of same group post therapy, infants had evidence of improved bone maturity. A significant family history of hypothyroidism was documented in 10 neonates with delayed ossification. Interestingly in our study, 5 infants with absent epiphyses had a TSH above 100 and free T4 was well below normal at 0.40 ng/dl in 9 neonates. This study shows clear correlation between screening TSH values above 15 and confirmatory serum TSH values above 50 and correspondingly those neonates had MED of 6 mm or less indicative of thyroxine deficiency and delayed maturation.

The delay in skeletal maturation at birth probably depends upon the severity of the prenatal thyroid deficiency and hence the amount of functioning thyroid tissue. Although radioisotope scans have not been performed in many of our infants it is likely that lower T4 and T3 levels suggest more severe dysplasia or aplasia of the thyroid gland. As repeat serum test particularly in primary care centres need more days to collect and transport to qualified labs with more chances of delay. Therefore as a supplementary tool radiographers can be trained at each centre to take radiographs which is easier, painless, cheaper and will serve purpose of screening with timely intervention.

Despite the prenatal maturational influence of congenital hypothyroidism in many infants, recent studies indicate that most show no long term detrimental effect on mental development when early adequate treatment is instituted [9,10]. This study is first of its kind and has a limitation of small sample size and requires more studies with larger samples to assess its utility as a reliable supplementary tool.

Conclusion

The utility of knee radiographs in a neonate screen positive for congenital hypothyroidism as a supportive diagnostic tool is feasible to initiate timely therapy a crucial factor to prevent mental impairment.

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4. Fetal Care Research Foundation, Chennai, India.
5. Can Ray Radiological Research Institute, Chennai, India.

Conflict of Interest

None.

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