RESEARCH PAPER

Diagnostic Re-evaluation of Children with Congenital Hypothyroidism

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Objectives: To investigate the causes of congenital hypothyroidism in children more than 3 years of age and to document the frequency of transient *vs* permanent hypothyroidism.

Design: Hospital based observational study.

Setting: Pediatric endocrine clinic of a medical college.

Patients: Children over 3 years of age, on treatment for congenital hypothyroidism.

Intervention: Thyroid function test (TFT) and thyroid ultrasound was done. Children with agenesis or hemiagenesis in thyroid ultrasound were identified. In children with normal or equivocal thyroid ultrasound, thyroxine was stopped and followed. Children with abnormal TFT on follow up had thyroid scintigraphy with or without potassium perchlorate discharge, after which, thyroid hormone supplement was restarted. Children who remained euthyroid on follow up were labeled as having transient hypothyroidism.

Main Outcome Measure: Proportion of children with transient hypothyroidism.

Results: Among 36 children studied (20 boys and 16 girls), eighteen (50%) had transient hypothyroidism and fifteen (41.7%) had thyroid agenesis. There was one with hemiagenesis, one with ectopic thyroid and another with dyshormonogenesis (2.8% each). Initial TSH level at the time of diagnosis was higher in permanent hypothyroidism as compared with transient group (83.0 ± 31.6 vs 47.0 ± 33.1 mIU/mL; *P*= 0.002).

Conclusions: Thyroid hormone supplementation could be discontinued in 50% of children diagnosed with congenital hypothyroidism.

Key words: *Children, Congenital hypothyroidism, Etiology, India, Transient hypothyroidism.*

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The incidence of congenital hypothyroidism in India varies from 1:2500 to 1:2800 live births(1). Nearly 75% of all infants with congenital hypothyroidism have thyroid dysgenesis, with hypoplasia or aplasia in 50 to 60%, ectopia in 25 to 35% and dyshormonogenesis due to biosynthetic defects in 10 to 30%. Congenital hypothyroidism could also result from transient abnormality in thyroid gland function, which subsequently recovers. The possible explanations include iodine deficiency, transplacental passage of maternal TSH-binding inhibitory antibodies, and maternal exposure to radioiodine, iodine or antithyroid drugs. In such situations, it may be possible to discontinue thyroxine therapy. Trials of withholding thyroxine therapy are reported in the Western literature, but no such data is available from India. This study was done to look at different causes of congenital hypothyroidism and to determine the prevalence of transient hypothyroidism.

METHODS

This hospital based observational study was conducted from December 2005 to November 2006. Children over the age of 3 years attending the pediatric endocrine clinic at SAT Hospital at Medical College, Thiruvananthapuram and diagnosed with congenital hypothyroidism were included. Congenital hypothyroidism was defined as TSH more than 20 mIU/L at less than 2 weeks of age or TSH more than 10mIU/L after 2 weeks of age(2). Exclusion criteria were unwillingness of parents or

guardian to give informed consent and severe illness (e.g. cardiac failure or chronic CNS disorders) which could possibly be worsened by withdrawal of thyroid hormone. All previous investigations such as ultrasound (US) or radionuclide study, which were done to delineate the cause of congenital hypothyroidism, were reviewed. Children who already had an imaging study and were proven to have a form of permanent congenital hypothyroidism were classified accordingly and excluded from further evaluation.

Blood was drawn for thyroid function tests (TFT) at enrolment. A thyroid ultrasound was done. Children with agenesis or hemiagenesis of thyroid on ultrasound were classified as such and excluded from subsequent steps. In children with normal or equivocal US thyroid and normal TFT, thyroxine was stopped. Parents were advised to monitor for signs and symptoms of hypothyroidism. Four weeks after stopping thyroxine, subjects were recalled for follow up. At that time, clinical assessment for signs of hypothyroidism was done and blood was drawn for thyroid function tests. Children with abnormal TFT underwent Tc-99m thyroid scan or I-131 thyroid scan with or without potassium perchlorate discharge, after which, thyroid hormone supplement was restarted at previous dose and titrated for normal TFT.

Children with normal thyroid function at four weeks were followed with serial TFTs at 8 weeks, 14 weeks and 6 months. If the TFT remained normal, they were classified as transient hypothyroidism. If TFT became abnormal in a subsequent follow up, they were investigated with radionuclide scintigraphy. The protocol was approved by the Human Ethical Committee of Medical College, Thiruvananthapuram.

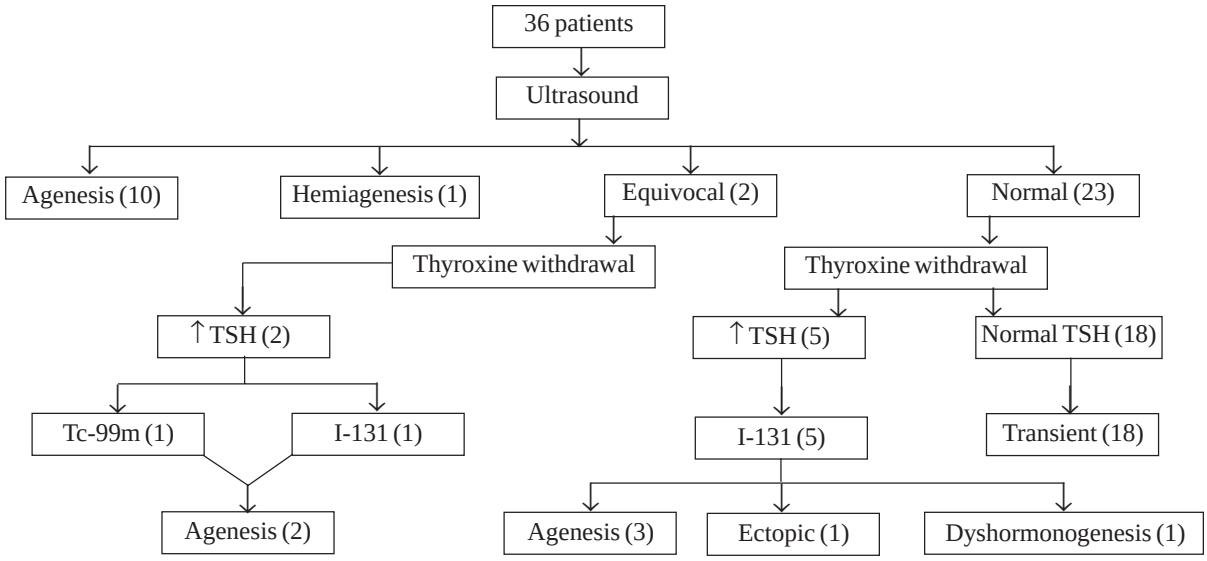
Measurements for serum TSH and total T_4 were obtained at initial visit and at 4 wk; TSH at 8 wk and 14 wk, at the Regional Cancer Center, Thiruvananthapuram, using chemiluminescence immunoassay (reference range: TSH 0.25-6.3 mIU/L and T_4 5.6-15 µg/dL). Thyroid volume was calculated by ultrasonography using the ellipsoidal formula. Data from Gonzalez, *et al*.(3) were used to obtain cut-offs for the lower limit of thyroid size. Normal thyroid volume was taken as 2.2 ± 1.3 mL for children aged 3-6 years, 3.0 ± 1.7 mL for 6-12 years and 5.7 ± 3.1 mL for adolescents. Agenesis was diagnosed if no thyroid tissue was visualized in the neck. If only one lobe of thyroid was visualized normally, while the other lobe was not seen, hemiagenesis was diagnosed. When the thyroid volume appeared smaller than the lower limit of normal or if the radiologist could not say a definite opinion, it was taken as equivocal. Radionuclide tests were done at Regional Cancer Centre, Thiruvananthapuram, if TSH increased on thyroxine withdrawal. I-131 was the radionuclide agent used. Tc-99m study was done for one patient as the probe for I-131 uptake study was not available at that time. Perchlorate discharge test was done for one patient who had normal ultrasound and I-131 scan, but became hypothyroid on thyroxine withdrawal.

Statistical analysis: Statistical analysis was done using the SPSS for Windows statistical package (version 10.0.1). Descriptive analysis and break up of the sample in different etiologic categories was done. Hemiagenesis, ectopic and dyshormonogenesis groups were clubbed together with agenesis and labeled as permanent hypothyroidism. Differences between the permanent and transient hypothyroidism groups were analyzed using *t* test.

RESULTS

Thirty six children were included (***Fig* 1**). None of the patients had any documented proof of permanent congenital hypothyroidism. All the patients were clinically euthyroid on thyroxine replacement at the time of enrollment. The mean (± SD) age of the study sample was 5.4 (± 2.7) years. There were 20 girls. The mean height centile was 27.8 (range 3rd to 90th centile). Hypothyroidism was diagnosed and treatment started at a mean age of 3.8 (± 6.1) months (range newborn to 27 months) (61.1% in the neonatal period, 72.2% by 3 months, 86.1% by 6 months and 91.7% by 1 year of age).

Transient hypothyroidism was seen in 18 patients (50%). The other 50% had some form of permanent congenital hypothyroidism. Among them, 15 patients (41.7%) had thyroid agenesis. There was one patient with hemiagenesis, one with ectopic thyroid and another with dyshormonogenesis (2.8% each). Initial TSH level at the time of diagnosis was



Figures in parentheses indicate number of children; TSH: thyroid stimulating hormone; I-131:Iodine -131.

FIG.1 *Patient flow with summary of results.*

significantly higher in the permanent hypothyroidism group as compared with those with transient hypothyroidism (83.0±31.6 *vs* 47.0±33.1 mIU/mL; *P*=0.002) (***Fig.*2**). There was significant difference in the thyroxine dose between the two groups, when the total T_4 dose was considered. But when weight/kg body weight was considered, although there was a trend towards higher dose requirement in the permanent hypothyroidism group, the difference did not reach statistical significance. There was no difference between the transient and permanent hypothyroidism groups in the height centiles achieved.

DISCUSSION

Among the 36 patients, 18 (50%) had transient hypothyroidism. Previous studies in Indian children did not report any incidence of transient hypothyroidism(4,5). This is probably due to later age at diagnosis of hypothyroidism. In a study done by Eugster, *et al.*(6), 36% had transient hypothyroidism. Studies from other parts of the world have reported transient hypothyroidism in 1-50% of children with congenital hypothyroidism(7-11). TSH level at diagnosis was significantly higher in children with permanent hypothyroidism. It may be of help to the clinician while deciding to stop thyroxine therapy in a child diagnosed with congenital hypothyroidism.

Our study was done in a relatively small sample of children who were already diagnosed with congenital hypothyroidism and were on follow up. Initial diagnostic details of these children were obtained by retrospective chart review. This resulted in incomplete data in some children. We do not have a congenital screening program, but most of our patients were diagnosed early, probably due to higher awareness among parents. We agree that unfortunately in many parts of the country,

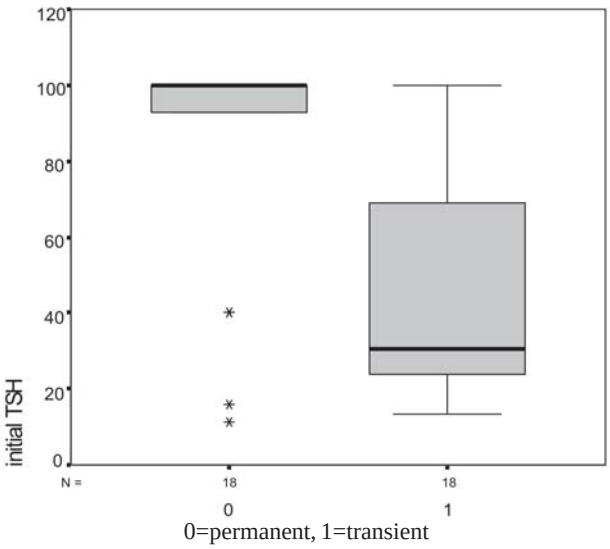


FIG.2 *TSH at diagnosis (Box plot).*

WHAT IS ALREADY KNOWN?

- There is a high prevalence of transient hypothyroidism among children diagnosed with congenital hypothyroidism in the West.

WHAT THIS STUDY ADDS?

- 50% of children in this study had transient type of congenital hypothyroidism. A higher initial TSH level is suggestive of permanent congenital hypothyroidism.

congenital hypothyroidism is diagnosed late. In such a situation, the diagnosis may be unequivocal and permanent. There may not be a need for a trial of thyroxine withdrawal in such children.

We conclude that in children diagnosed with congenital hypothyroidism, a standardized protocol of thyroxine withdrawal as described above, after three years of age, is safe and will identify a large proportion of patients in whom thyroxine could be safely withdrawn.

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