Case Reports

Thyroid Dyshormonogenesis

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Dyshormonogenesis is an uncommon cause of congenital hypothyroidism. The most common abnormality is absent or insufficient thyroid peroxidase enzyme. Perchlorate discharge test can be used to diagnose thyroid peroxidase deficiency. We report three siblings with hypothyroidism due to thyroid dyshormonogenesis. Early institution of therapy in these patients can prevent mental retardation and other features of hypothyroidism.

Key words: *Congenital hypothyroidism, Dyshormonogenesis*

The worldwide incidence of congenital hypothyroidism (CH) is 1:3000 to 1:4000 live births(1). Inherited defects in hormone biosynthesis (dyshormonogenesis) are rare causes of CH and account for 10-15% children with hypothyroidism(2,3). Dyshormonogenesis results from a deficiency or absence of one or more of the enzymes involved in the thyroid hormone synthesis or secretion. The most common enzyme abnormality is absent or insufficient thyroid peroxidase (TPO) activity which results in the failure of oxidation of iodide into iodine. With this type of defect iodine will be trapped but not organified. We report 3 children (siblings) with CH with features of dyshormonogenesis.

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Case 1

A 14-year-old male child was diagnosed as a case of CH at 6 months of life and started on thyroxine replacement therapy. Parents gave history of poor academic performance. his weight was 42 kg (10-25th centile) and height was 151cm (3-10th centile). There was Grade II firm goiter. There were no other clinical abnormalities. A 99m Tc-thyroid scan revealed homogenous tracer uptake in both the lobes of thyroid gland. Thyroid hormone profile revealed FT_3- 4.8 pg/mL (normal 1.3-3.7 pg/mL). TSH was 0.08 uIU/mL (normal 0.3-6.5 uIU/mL). Thyroid hormone profile was carried out when patient had been on regular thyroxine. Ultrasonography scan (USS) of thyroid was normal. Radioactive-iodine uptake (RAIU) & Perchlorate discharge test (carried out after patient had been off thyroxin for 4 weeks) revealed more than 50% drop in values suggesting an organification defect.

Case 2

Younger sister of the first patient, age 12 years, had presented with constipation and poor appetite since birth. She was diagnosed to have CH at 6 months of age. Physical examination revealed an active child weighing 33 kg with a height of 142 cm with a Grade II

goiter. Height between twenty fifth to fifty centile, and weight was between third and tenth centile. A 99m Tc-thyroid scan revealed homogenous tracer uptake in both the lobes. Her thyroid hormone profile revealed T_4-15.2 µg/dL and TSH-1.3 µIU/mL (patient had been on regular thyroxine). USS thyroid revealed no abnormalities. RAIU and Perchlorate discharge test revealed 80% drop in radioiodine uptake confirming an organification defect.

Case 3

A 5-year-old girl youngest sister of the first patient was also diagnosed as a case of CH one month after birth and was started on thyroxine replacement therapy immediately. Developmental milestones were normal in this child. Physical examination revealed an active child weighing 16 kg with a height of 117 cm. Height between ninety and ninety seventh centile, and weight between tenth and twenty fifth centile. No goiter was seen. 99m Tc-thyroid scan revealed homogenous tracer uptake in both the lobes. Her thyroid hormone profile revealed FT_3-4.4 pg/mL and TSH-10.9 uIU/mL. USS thyroid was normal. RAIU and perchlorate discharge test revealed more than 50% drop in radioiodine uptake values confirming an organification defect. Hearing was normal in all 3 siblings.

Discussion

Inherited defects in hormone biosynthesis are rare causes of goitrous hypothyroidism and account for only about 10-15% of cases of CH. In most instances, the defect appears to be transmitted as an autosomal recessive trait. Except for the familial incidence and tendency for affected individuals to develop goiter, the clinical manifestations of CH due to biochemical defect are similar to those in infants with thyroid dysgenesis. In our series, two elder siblings had Grade II goiter since birth, the third child did not manifest any goiter, which may be due to the fact that hormone replacement therapy was started quite early(4).

Senosorineural deafness is a well-known association with congenital hypothyroidism and was first described by Pendred(5). Our patients did not have any evidence of sensorineural or conductive deafness. Individuals with goitrous hypothyroidism are believed to be homozygous for the abnormal gene, whereas euthyroid relatives with slightly enlarged thyroids are presumably heterozygous. In the latter group, appropriate functional testing may disclose a mild abnormality of the same biosynthetic step that is defective in the homozygous individual; however laboratory analysis to characterize the genetic defects in children with thyroid dyshormonogenesis are not yet generally available. In our case, both the parents are euthyroid and most likely to be carriers. The goiter is initially diffusely hyperplastic, often intensely so, suggesting papillary carcinoma, but eventually becomes nodular. In general, the more severe the biosynthetic defect, the earlier the goiter appears, the larger it is, and the greater the likelihood of early development of hypothyroidism or even cretinism.

In patients with iodination defects, only part or none of the iodide taken up is oxidized and organified. In these cases T_4 production is decreased, whereas the synthesis of Tg and transport of iodide are strongly stimulated by TSH. Radioiodine uptake is high, and the block in iodide oxidation and organification results in an increase in intracellular iodide concentration. This can be measured by determining the amount of radioiodine lost from the gland after the administration of potassium perchlorate (Perchlorate discharge test); the percentage released indicates whether a defect is partial or total(6). Total iodide

organification defects are characterized by discharge of more than 50% of the radioiodine in the thyroid gland within two hours after administration of potassium perchlorate. Potassium perchlorate is usually given 2 hours after the administration of radioiodine. Partial defects are characterized by discharge of more than 10% of the accumulated radioiodine(7). In such patients a 99mTc thyroid scan shows increased uptake and can mimic thyrotoxicosis(8). The three patients in our series showed increased uptake of 99mTc on thyroid scan. All the three patients also showed defective organification in the form of radioiodine discharge in the range of 50-80%.

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