A REVIEW ON ETIOLOGY, DIAGNOSIS AND TREATMENT OF CONGENITAL HYPOTHYROIDISM IN NEONATES

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ABSTRACT

Congenital Hypothyroidism is one of the most common preventable cause of mental retardation in children. Usually this disease is caused by an abnormal development of thyroid gland also called as thyroid dysgenesis and occurs in 85% of the cases while the remaining 15% of cases are caused by dyshormonogenesis. The clinical manifestations of this disease are so subtle that many infants remain undiagnosed at birth. Delayed diagnosis leads to the most severe complication of CH. There are various ways of diagnosing the disease which includes dried capillary blood screening where serum is tested for the levels of TSH and T4. The recommended treatment of the disease is levothyroxine which is given at a dose of 10-15 mcg/kg/day.

INTRODUCTION

Congenital Hypothyroidism is one of the most common congenital endocrine disorder that occurs in childhood. With early diagnosis and treatment, neurodevelopmental outcome is normal. Clinical features of this disease are often subtle and many infants remain undiagnosed at birth. This is due to passage of maternal thyroid hormone across the placenta that provides a protective effect to fetal brain. Thyroid hormones are necessary for normal development and growth of brain and the skeleton. Thyroid hormone (TH) is essential for neurodevelopment and even a short period of deficiency of thyroid hormone can cause irreversible brain damage. The fetal brain development is dependent on maternal thyroid function during the first trimester of pregnancy. Another reason is that some forms of CH have moderately functioning residual thyroid tissue making its diagnosis difficult. After few weeks of birth signs and symptoms of the disease becomes more obvious and further complications may occur that affects the growth of the child. Hence early diagnosis and treatment of the disease is very important. In 1970, the importance of early treatment in minimizing the complications of congenital hypothyroidism was demonstrated in various studies. A sensitive and specific radioimmunoassay was introduced for the measurement of T4 in blood and TSH to screen all newborns for congenital hypothyroidism prior to the development of clinical manifestations. Screening has become the best way to detect infants with CH in many parts of the world. Various screening programs have been introduced throughout different countries and are under development in many other parts of the world.

ETIOLOGY
Mostly it is caused by abnormal development of thyroid gland which occurs in 85% of the cases. It presents in three major forms i.e. thyroid ectopy, athyreosis and thyroid hypoplasia. Thyroid ectopy occurs in two thirds of cases of thyroid dysgenesis and it is more common in females. The proper etiology of thyroid dysgenesis is not clear. The mutations that occur in transcription factor genes which regulates the development of thyroid gland [thyroid transcription factor 2 (TTF-2), NKX2.1 (also termed TTF-1) or PAX-8] would explain these defects. Only 2% of cases with thyroid dysgenesis are found to show genetic mutations. For the remaining cases, CH results from absence of thyroid and thyroid hypoplasia. Some are caused due to hereditary inborn errors in the enzymatic cascade of thyroid hormone synthesis called as dyshormonogenesis, or to defects in peripheral thyroid hormone transport, metabolism, or action. Defects in the synthesis of thyroid hormone are familial and are generally inherited in an autosomal recessive manner. These include mutations in the genes coding for the sodium-iodide symporter, thyroid peroxidase, hydrogen peroxide generation [thyroid oxidase and dual oxidase maturation factors (THOX and DUOXA)], thyroglobulin (Tg) and iodotyrosine deiodinase. Defects in thyroid hormone transport, metabolism, or resistance to thyroid hormone action are some rare causes. Mutations in thyroid peroxidase gene are the most common cause of inherited defects in CH.

**DIAGNOSIS**

Newborn screening tests are done to detect Congenital Hypothyroidism in infants. Of the worldwide birth population, only 25% of babies are invited for screening for CH and the remaining 75% infants, particularly concentrated in developing countries, clinical suspicion of hypothyroid leads to thyroid function evaluation.

Newborn thyroid screening tests are carried out between 2 and 5 days of age. If the specimen is collected before 48 hours of age, it may lead to false positive result. Screening of very sick newborn or after blood transfusion may also lead to false negative result.

In a critically ill infant or preterm neonate, blood sample should be collected by 7 days of age. Blood samples from heel prick are placed on specialized filter paper, dried at room temperature, then sent to a laboratory. In some cases, a routine second specimen between 2 and 6 weeks of age is collected.

Earlier, for the purpose of screening of newborn for CH, most programs initially tested serum T4, followed by TSH testing if the T4 value falls under a cut off limit. With increasing accuracy of TSH assays on small blood volumes, many screening programs now have switched to an initial TSH test approach to detect the disease. Both methods allow detection of the majority of infants with CH. At first T4 test is done which is then followed by TSH approach will detect some cases of secondary or central hypothyroidism and infant with “delayed TSH elevation” whereas first TSH testing will detect mild or subclinical forms of hypothyroidism. Mostly, if the screening T4 value is below the 10th percentile of cut off and/or the TSH is greater than 30mU/liter (15mU/liter whole blood), an infant should be subjected for confirmatory serum testing.

**TEST RESULTS**

Low T4 and elevated TSH values

Normal T4 and elevated TSH values

Low T4 and normal TSH values

**TREATMENT**
Treatment should be started promptly. Sometimes, even in case of early diagnosis, neurologic outcome may be poor and this deficit may be due to later onset of treatment, lower starting thyroid hormone dosing and severity of the hypothyroidism, which is associated with the underlying etiology.

Levothyroxine (l-thyroxine) is the treatment of choice. But, triiodothyronine (T3) is the biologically active and most brain T3 is derived from local monodeiodination of T4 and certain studies have shown normal serum T3 level in infant treated with T4 alone, so T3 treatment is not necessary for normal neurological outcome/brain development. Currently, only tablets forms are approved for use in the United States. However, in Europe, for normalizing thyroid function l-thyroxine suspension is available. Currently, in India, only tablet forms of levothyroxine is available.

Levothyroxine (l-thyroxine) tablet is initially crushed and then mixed with breast milk, formula milk or water and formed suspension is poured into cheek pad or can put on open nipple for infant to feed. Various substances interfere Levothyroxine (l-thyroxine) absorption through gut, such as calcium and iron preparation, soy protein formula, sucralfate, aluminium hydroxide and cholestyramine should not be given together.

The aim of treatment is to normalize T4 within 2 weeks and TSH within one month. A study showed that infants who had taken more than 2 weeks to normalize thyroid function had significantly lower cognitive, attention and achievement scores than the ones who achieved normal thyroid function within 1 or 2 weeks of treatment. Recommended dose is 10-15 μg/kg/day as initial dose. Studies have shown that this dose normalizes serum T4 within 3 days and TSH within 2–4 weeks. It is important to start higher initial dose of the recommended range to achieve these goals in severe CH.

**CONCLUSION**

One of the most common preventable cause of mental retardation is congenital hypothyroidism. Screening large populations of newborns is the best way to detect infants with Congenital Hypothyroidism. It is usually caused due to the abnormal development of thyroid gland. If early diagnosis is done and treatment started within a few weeks of birth, neurodevelopmental outcome generally is normal. Levothyroxine the best treatment option for the disease. Proper screening of thyroid levels of newborns at regular intervals is necessary.

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