Congenital Hypothyroidism

Judith A. Gravdal, MD, Anna Meenan, MD, and Anne E. Dyson, MD
Park Ridge and Rockford, Illinois

This paper presents a case report of congenital hypothyroidism that illustrates some of the issues in screening for this disorder. Congenital hypothyroidism has several causes, the most common of which is thyroid dysgenesis. Most affected infants have no historical clues or physical findings to suggest diagnosis. Neonatal screening combining thyroxine and thyrotropin screening have resulted in increased detection, although false-negatives do occur, and the physician must carefully observe all newborns for the findings of congenital hypothyroidism. Early treatment improves the prognosis considerably. This paper reviews the pathophysiology, diagnosis, and treatment of congenital hypothyroidism.

The incidence of primary congenital hypothroidism is about 1 in 4,000 live births,[1,2] making it the most common endocrine disorder of infancy.[3] The irreversible mental retardation associated with untreated congenital hypothyroidism necessitates an urgency in arriving at the diagnosis and initiating treatment. Currently, the initiation of treatment before 3 months of age is the acceptable goal. It is unclear whether there are advantages to even earlier treatment.[4,5]

Early screening and treatment for congenital hypothyroidism can prevent mental retardation (cretinism) if timely follow-up and compliance are achieved. Neonatal screening programs for congenital hypothyroidism were initiated in Quebec in 1972 and Pittsburgh in 1973.[1] Recently, the technology for measuring thyrotropin (thyroid-stimulating hormone, TSH) by radioimmunoassay from capillary blood collected on filter paper has been developed.[6] Since then, TSH screening has been carried out in the Northwest and New England with recommendations that it be incorporated into all screening programs. In this paper, an illustrative case demonstrates the advantage of combined thyroxine (T_4) and TSH testing.

CASE REPORT

The patient, A.M., a male infant, was a product of a 41-week uncomplicated pregnancy. The 32-year-old, gravida 2, para 2, mother had taken no medication except for prenatal vitamins during pregnancy. No history of thyroid disease was elicited. The patient weighed 7 lb 3 oz at birth, and physical examination revealed no objective signs of congenital hypothyroidism.

Neonatal screening by capillary blood collected on filter paper at 48 hours yielded the following results: T_4, 156 nmol/L (12.0 μg/dL), normal >77 nmol/L (>6.0 μg/dL); TSH, 78 mU/L (78 μU/mL), normal <2 mU/L (<2 μU/mL). A repeat serum sample at age 4 weeks revealed a T_4 of 84.5 nmol/L (6.5 μg/dL) and a TSH of 35.1 mU/L (35.1 μU/mL).

The infant underwent technetium 99m pertechnetate scanning at 4 weeks of age, which revealed a focal area of midline increased isotope activity consistent with lingual or sublingual thyroid tissue (Figure 1).

The infant was started on L-thyroxine 25 μg(7 mg/kg) by mouth daily, at 4½ weeks. TSH at age 2 months was 1.3 mU/L (1.3 μU/mL). At age 12 months, he was clinically and chemically euthyroid (on L-thyroxsine 37.5 μg daily). His height was in the third percentile and weight was in the 15th percentile for age. His T_4 was 119.34 nmol/L (9.18 μg/dL) and TSH 11.8 mU/L (11.8 μU/mL).

CLINICAL PICTURE

Early signs and symptoms of congential hypothyroidism are variable and may be subtle. They include feeding problems, failure to thrive, constipation, a hoarse cry, somnolence, and other findings as shown in Table 1. A protuberant abdomen, mottled or rough, dry skin, delayed tooth eruption, and developmental delay, although more impressive, manifest much later. History of post-date birth, macrosomia, neonatal jaundice, distressed or noisy respira-

Submitted, revised, May 1, 1989.

From the Lutheran General Hospital, Park Ridge, the University of Illinois College of Medicine at Chicago, and the University of Illinois College of Medicine at Rockford, Rockford, Illinois. Requests for reprints should be addressed to Dr Judith A. Gravdal, Division of Family Practice, Lutheran General Hospital, 1775 Dempster St, Park Ridge, IL 60068.

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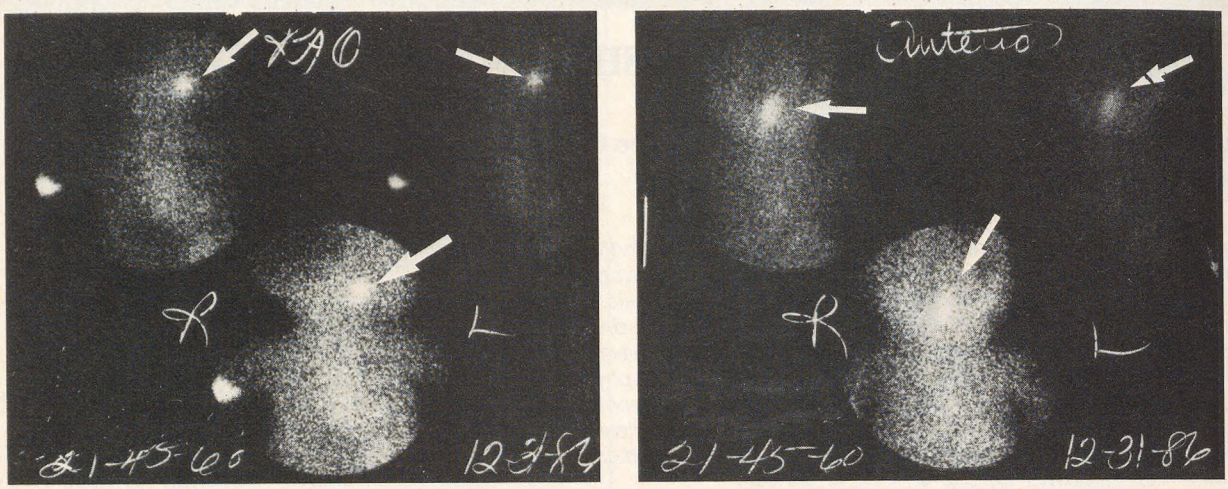

Figure 1. Technetium 99m pertechnetate scan done at 4 weeks of age showing lingual or sublingual location of thyroid tissue (arrows)

tion, and a large tongue have also been associated with congenital hypothyroidism.[7] In one study of 41 hypothyroid infants, female infants were affected twice as often as male infants.[8]

Although Letarte et al[8] have developed a neonatal hypothyroid index, which includes 14 signs and symptoms associated with congenital hypothyroidism, screening tests will continue to be the essential diagnostic tools. Only 3% of hypothyroid infants identified by the five oldest screening programs in North America were clinically suspected to be hypothyroid at the time of screening.[1]

PRENATAL THYROID DEVELOPMENT AND ASSOCIATED ABNORMALITIES

The hypothalamic-pituitary-thyroid system develops during three periods. Abnormalities can occur at each of the three developmental stages (Table 2).

Embryogenesis occurs during the first trimester. By the 12th week, both the thyroid gland and the pituitary gland are histologically differentiated, and T_4 and TSH are measurable in fetal tissue. At this stage in development, thyroid tissue concentrates iodine and synthesizes T_4. Abnormalities of embryogenesis include thyroid dysgenesis (agenesis, hypoplasis, ectopy, dyshormonogenesis, and defective TSH responsiveness), pituitary aplasia or hypoplasia, and TSH deficiency. Thyroid dysgenesis is the major cause of permanent congenital hypothyroidism, accounting for 80% to 90% of cases. Most of these infants are asymptomatic. Up to 60% have some thyroid tissue. A large subgroup of infants with normal T_4 and elevated TSH has been described and may represent 10% to 20% of infants with thyroid dysgenesis.[9] Ten to fifteen percent of infants with primary congenital hypothyroidism have dyshormonogenesis.

Hypothalamic development is a much slower process. Thyrotropin-releasing hormone is first detected between 10 and 12 weeks, but maturation continues through week 35. An increase in the TSH level occurs at 18 to 22 weeks and is followed by an increase in T_4. Hypothalamic dysplasia and thyrotropin-releasing hormone deficiency are the most common abnormality of hypothalamic development.

Later maturation, including responsiveness of target tissues and feedback systems, is still being studied. Full maturity is usually achieved by 4 weeks after delivery. Negative feedback, however, has been demonstrated at term in the human fetus. At birth, TSH is released, an event thought to be triggered by the change in ambient temperature. TSH peaks at 30 minutes and then declines, rapidly over the first 24 hours and more slowly over the next several days. Serum T_4 peaks at 24 hours. Preterm infants demonstrate a similar, though less pronounced, change in TSH and T_4 values. Serum triiodothyronine (T_3) levels follow a parallel pattern. Maturational abnormalities include transient hypothyroxinemia, transient hypothyroidism, transient hyperthyrotropinemia, iodine deficiency or excess, antithyroid compounds, hypotriiodothyroninemia, thyroxine-binding globulin abnormalities, and target-tissue unresponsiveness.

TABLE 1. CLINICAL FINDINGS ASSOCIATED WITH CONGENITAL HYPOTHYROIDISM

Finding	Percent Affected*
Umbilical hernia	14–78
Rough, dry skin	20–73
Large tongue	20–56
Constipation (<1 stool per day)	40–68
Hypotonia	33–66
Inactivity	14–61
Mottled skin	25–63
Feeding problems	25–42
Respiratory problems	0–20

**Percentage of affected infants with finding as described in various studies[2,7]*

TABLE 2. DEVELOPMENTAL ABNORMALITIES CAUSING CONGENITAL HYPOTHYROIDISM (prevalence 1:3,500 to 1:4,000)

Affected Gland	Developmental Abnormality
Thyroid dysgenesis (overall prevalence 1:4,500)	Agenesis Hypoplasia Ectopy Dyshormonogenesis Defective thyrotropin responsiveness
Pituitary (overall prevalence 1:100,000)	Aplasia Hypoplasia Thyrotropin deficiency
Hypothalamus (overall prevalence 1:100,000)	Dysplasia Thyrotropin-releasing hormone deficiency

SCREENING PROGRAMS

The results of several studies indicate that the incorporation of filter paper spot screening by radioimmunoassay for TSH as well as T_4 into an existing neonatal screening protocol is cost effective.[1,2] The combined screening decreases follow-up recall from 30 to 40 down to 4 to 8 infants per case of congenital hypothyroidism.[10]

TSH testing is more sensitive and specific for congenital hypothyroidism except in cases where pituitary abnormalities result in low levels of TSH. Inclusion of TSH screening in some manner, whether it be through secondary screening of patients with T_4 values in the lower 10%, primary TSH screening, or combined T_4 and TSH screening, is strongly recommended.[11] The cost of combined T_4 and TSH screening is currently about $1 per test, with TSH screening accounting for only about $0.15 when added to an existing T_4 screening program. The state of Illinois, where this case occurred, began doing combined T_4 and TSH screening in 1984. The infant's condition described in this case would not have been detected by T_4 screening alone.

Combined screening has a minimal false-positive rate, but false-negative results do occur. Fisher estimates that one case of congenital hypothyroidism is missed for every 37,500 infants screened.[10] False-negatives may be attributed either to low TSH levels or to problems with the screening program. The infants missed by the screening programs are usually detected during the first 3 months because of clinical abnormalities. The physician must be alert to the possibility of congenital hypothyroidism in all infants.

With the cost of detecting each case of hypothyroidism currently at about $4,000, it appears that a considerable cost savings can be realized when the cost of special education and institutional care for infants in whom the diagnosis is delayed is considered. The cost of caring for an untreated patient was estimated to be $330,000 in 1977.[2]

EVALUATION OF ABNORMAL SCREENING RESULTS

If the filter paper screening test results are abnormal, prompt evaluation should be undertaken. The repeat laboratory studies must be performed on serum. A thorough history, encompassing prenatal exposure to drugs (iodides, iodinated radiographic contrast agents, and antithyroid medications), and a family history should be obtained. The newborn's history and physical examination should be carefully conducted with special attention paid to the subtle findings of hypothyroidism. A careful search for other congenital abnormalities should be made, as 20% of infants with congenital hypothyroidism in one series also had various congenital abnormalities not associated with the thyroid gland.[12]

Bone age films of the ossification centers at the knee give some indication as to the duration and severity of the thyroid insufficiency. A biochemical assay may provide this information in the future, as serum α-fetoprotein levels in hypothyroid infants have been found to be increased in inverse proportion to the skeletal maturation index.[8] Duration and severity of the thyroid insufficiency at birth have been shown to correlate closely with ultimate prognosis for intellectual development.[5,6]

Most infants with congenital hypothyroidism have some thyroid tissue. A thyroid scan using 99m pertechnetate or iodine 131 will help locate and quantitate any thyroid tissue the infant may have. This information can have a direct bearing on genetic counseling and prognosis. Thyroid dys-

genesis rarely recurs in the same family, while defects in thyroxine synthesis or release are inherited as autosomal recessive traits.[13]

TREATMENT

Two replacement protocols have been described. The Quebec protocol recommends 5 μg of T_3 three times a day and 25 μg of T_4 daily for the first 2 weeks.[8] After the initial 2 weeks, the T_3 supplement can be stopped, and the infant placed on 50 μg of T_4 daily. The maintenance dose is usually 6 to 9 μg/kg/d, but T_4 and TSH levels must be reassessed at 2 weeks, 6 weeks, and every 6 months thereafter.

Fisher suggests an alternative protocol.[7] A loading dose of 15 to 20 μg/kg/d of T_4 is given for 2 to 4 weeks, followed by 7 to 10 μg/kg/d. Serum T_4 levels should be maintained between 10 to 12 g/dL. The TSH may remain elevated for a prolonged period of time, and simply keeping it under 20 mU/L (20 μU/mL) is acceptable.

It is rarely necessary to exceed a dosage of 75 to 100 μg of T_4 per day during the first 5 years, and excessive doses can lead to premature craniosynostosis.[14] At 36 months, treatment may be stopped and the diagnosis reassessed. Stopping thyroid replacement in patients with lingual or sublingual ectopic thyroid tissue is not recommended because of the possibility of airway obstruction caused by enlargement of the tissue under TSH stimulation.

The patient with dysgenesis or ectopy has a good prognosis if treatment is started early. If no thyroid tissue is identified, the prognosis is more guarded.[3,6] With treatment, patients with congenital hypothyroidism tend to have an accelerated growth curve until approximately 9 months of age.

Screening for congenital hypothyroidism is currently or soon will be mandated by state law in all 50 states. Difficulties are still encountered in doing follow-up testing and in screening infants born outside the hospital. Family physicians who are aware of the value of screening programs can often provide a critical link in this process.

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