

CONGENITAL HYPOTHYROIDISM

Thyroid hormone deficiency at birth is one of the most common treatable causes of mental retardation. There are multiple etiologies of this disorder, both heritable and sporadic, varying in severity. There is an inverse relationship between age at diagnosis and neurodevelopmental outcome; the later treatment is started, the lower the IQ will be. Most infants seem to be protected for the first few weeks of life by the fraction of maternal thyroid hormone that crosses to the fetus. Because of the urgency in detection and initiating treatment to prevent mental retardation, screening newborns for this disorder was added to existing programs in the mid-1970s.

Incidence

Congenital hypothyroidism (CH) occurs in 1 in 4000 to 1 in 3000 newborns. Programs reporting a higher incidence may include some transient cases. CH seems to occur more commonly in Hispanic and American Indian/Alaska Native people (1 in 2000 to 1 in 700 newborns) and less commonly in black people (1 in 3200 to 1 in 17000 newborns). Programs report a consistent 2:1 female/male ratio, which is unexplained but speculated to be related to an autoimmune risk factor. Newborn infants with Down syndrome are at increased risk of having CH (approximately 1 in 140 newborns).

Clinical Manifestations

Most affected infants appear normal at birth, without obvious manifestations of CH. This is likely the result of transplacental passage of some maternal thyroid hormone; cord thyroxine (T_4) concentrations are approximately one third of maternal concentrations. In addition, many infants have some functioning thyroid tissue. Gestational age is 42 weeks or greater in approximately one third of these infants. Their birth weight and length fall into the normal range, and their head circumference may be at a slightly higher percentile because of brain myxedema. Approximately 5% of these infants, generally those who are more severely affected, have recognizable features at birth, including large fontanelles and wide suturae, macroglossia, distended abdomen with umbilical hernia, and skin mottling. As maternal thyroid hormone is excreted and disappears in the first few weeks, clinical features gradually become apparent. These infants are slow to feed, constipated, lethargic, and sleep more ("sleep through the night" early), often needing to be awakened to feed. They may have a hoarse cry, may feel cool to touch, may be hypotonic with slow reflexes, and may have prolonged jaundice because of immaturity of hepatic glucuronyl transferase. A goiter is seen in 5% to 10% of these infants, most commonly in those with an inborn error of T_4 synthesis. If hypothyroidism goes undiagnosed beyond 2 to 3 months of age, infants will begin to manifest slow linear growth. If this disorder is untreated, studies show a loss of IQ proportionate to the age at which treatment is started: if treatment is started at 0 to 3 months of age, mean IQ is 89 (range: 64–107); if

treatment is started at 3 to 6 months of age, mean IQ is 71 (range: 35–96); if treatment is started at older than 6 months, mean IQ is 54 (range: 25–80). Other long-term neurologic sequelae include ataxia, gross and fine motor incoordination, hypotonia and spasticity, speech disorders, problems with attention span, and strabismus. Approximately 10% of these infants will have an associated sensorineural deafness, and approximately 10% will have other congenital anomalies, most commonly cardiac defects.⁶⁰ Some newborn screening programs also detect secondary or hypopituitary hypothyroidism in infants. These infants may have associated midline defects, such as the syndrome of septooptic dysplasia or midline cleft lip and palate. Other pituitary hormones, such as growth hormone, may also be missing.

Pathophysiology

The most common cause is some form of thyroid dysgenesis: aplasia, hypoplasia, or an ectopic gland; thyroid ectopy accounts for two thirds of thyroid dysgenesis. The cause of thyroid dysgenesis is unknown; rare cases result from mutations in the genes that control thyroid gland development, including thyroid transcription factor (TTF-2) and paired box-8 protein (PAX-8). Inborn errors of T_4 synthesis, secretion, or utilization account for two thirds of heritable cases. Errors in iodide trapping, organification of iodide to iodine by thyroid peroxidase (most common inborn error), coupling of monoiodothyronine and diiodothyronine, deiodinase, and an abnormal thyroglobulin molecule all have been described. In mothers with autoimmune thyroiditis, transplacental passage of a thyrotropin-receptor–blocking antibody is associated with transient hypothyroidism. Infants born to mothers with Graves' disease treated with antithyroid drugs also may have transient hypothyroidism. Worldwide, iodine deficiency resulting in endemic cretinism is the most common cause of hypothyroidism at birth. Exposure of the neonate to excess iodine, as with topical antiseptics, can also cause hypothyroidism.

Inheritance

Approximately 85% of cases are sporadic, and 15% are hereditary. Each of the inborn errors of T_4 synthesis is autosomal recessive except thyroid hormone receptor defects, which are autosomal dominant. In the cases associated with transplacental passage of a maternal blocking antibody, future siblings are at risk of having the same problem.

Rationale for and Benefits of Newborn Screening

Most newborn screening programs report no difference in global IQ score compared with sibling or classmate controls, whereas some report a reduction in IQ ranging from 6 to 15 points. Even if there are no differences in global IQ, some show differences in subtest components, such as language or visual-spatial skills. These results are more likely in severely affected infants,⁶¹ those started on

too low an initial dose of levothyroxine sodium, or those who are not optimally managed or poorly compliant in the first 2 years of life. However, these differences in IQ nearly disappeared if higher starting doses of levothyroxine, averaging 11.6 µg/kg per day, were used.⁶² Recent data suggest that a starting dose of 10 to 15 µg/kg per day normalized serum thyrotropin by 1 month and resulted in a higher IQ as compared with infants started on a lower treatment dose.⁶³

Screening

Most screening programs in the United States measure T₄ initially, with a thyrotropin determination on infants whose T₄ level is less than the 10th percentile for that specific assay. Some US newborn screening programs and more in Canada now are screening with an initial thyrotropin measurement. Because there is a thyrotropin surge after birth that decreases over the next 5 days, infants with screening specimens obtained at less than 48 hours of age may have false-positive thyrotropin increases. Each screening program must establish its own T₄ and thyrotropin cutoff levels. Primary T₄ screening programs may identify infants with delayed thyrotropin increase (usually preterm infants) and secondary hypothyroidism. Primary thyrotropin screening programs identify infants with subclinical hypothyroidism (high thyrotropin, normal T₄). The false-positive rate is generally higher for primary T₄ programs compared with primary thyrotropin programs (0.30% vs 0.05%, respectively). Preterm infants have reduced T₄ concentrations and, thus, make up a disproportionate percentage of infants with false-positive results. Neither screening is affected by diet or transfusion, except total exchange transfusion.

Follow-up and Diagnostic Testing

Infants with abnormal screening results must have confirmatory serum T₄ testing and some measure of thyroid-binding proteins (eg, triiodothyronine [T₃] resin uptake), or a free T₄ level, and thyrotropin determination. Once a diagnosis of hypothyroidism is confirmed, studies may be undertaken to determine the underlying etiology. Most useful are imaging studies, either thyroid ultrasound or thyroid uptake and scan, using either technetium 99m pertechnetate or iodine 123. In general, information gained from these studies does not alter management, so they are considered optional; they should never delay onset of treatment. If there is evidence of maternal autoimmune thyroid disease, measurement of thyrotropin-binding inhibitor immunoglobulin in the mother and infant can identify those with likely transient hypothyroidism. If iodine exposure or deficiency is suspected, measurement of urinary iodine can confirm this etiology.

Brief Overview of Disease Management

Levothyroxine is the treatment of choice; only tablets should be used, because liquid preparations are not stable. The recommended starting dose is 10 to 15 µg/kg per day^{62,63}; it is important that the initial dose correct hypothyroxinemia as rapidly as possible.^{64–66} Treatment can be started after confirmatory studies are obtained, pending results. Treatment goals are to keep the serum T₄ or free T₄ in the upper half of the reference range (10–16 µg/dL [130–204 nmol/L] or 1.2–2.3 ng/dL [18–30 pmol/L], respectively) and the thyrotropin in the reference range (<6 mU/L). Laboratory evaluation should be conducted (1) at 2 and 4 weeks after initiation of T₄ treatment, (2) every 1 to 2 months during the first year of life, (3) every 3 to 4 months between 1 and 3 years of age, and (4) 2 to 4 weeks after any change in dosage.⁶⁷ Prolonged overtreatment can lead to disorders of temperament and craniosynostosis and should be avoided. Close monitoring is essential in the first 2 to 3 years of life, a time at which the brain still has a critical dependence on thyroid hormone. If permanent hypothyroidism has not been established by 3 years of age, levothyroxine treatment can be discontinued for 1 month and endogenous thyroid function can be reevaluated.

Current Controversies

Preterm infants with hypothyroidism can have a delayed thyrotropin increase,⁶⁸ most likely because of immaturity of the hypothalamic-pituitary-thyroid (HPT) axis. Such infants may be missed by either the primary T₄ or thyrotropin screening approach. Some programs, therefore, have undertaken or are considering a routine second screening between 2 and 6 weeks of age in preterm infants. Programs that undertake a routine second screening report an additional 10% of cases. In addition, some studies suggest that infants less than 28 weeks' gestational age who lose the maternal contribution of thyroid hormone may benefit from treatment until the HPT axis matures.⁶⁹ Additional studies are needed before this can be considered standard of care. Last, some infants seem to have altered feedback of the HPT axis, manifested as persistently high serum thyrotropin concentrations despite apparent adequate treatment.

Special Issues/Concerns

Managing CH presents challenges with stakes that are far greater than management of acquired hypothyroidism. Laboratory evaluation occurs much more frequently, and target T₄ or free T₄ ranges are different for infants. Infants with an altered HPT axis and persistently high thyrotropin concentrations are difficult treatment challenges. With a goal of ensuring optimal treatment and, therefore, optimal neurodevelopmental outcome, these cases should be managed by pediatricians in consultation with pediatric endocrinologists.

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