Published in final edited form as:
Am J Med Genet A. 2004 February 1; 124A(4): 436–437. doi:10.1002/ajmg.a.20356.

Hypothyroidism in Down Syndrome: Screening Guidelines and Testing Methodology

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To the Editor

Individuals with Down syndrome (DS) are at an increased risk of developing thyroid disease, primarily autoimmune, with a lifetime prevalence ranging from 13% to 63% [Mattheis, 1997]. Fort et al. [1984] also found congenital hypothyroidism to be about 28 times more common among infants with DS than in the general population with an incidence of 1% (0.7% permanent and 0.3% transient congenital hypothyroidism) detected by newborn screening. Beyond the newborn period, the incidence of elevated TSH values in DS increases and has been reported to be as high as 85% of infants under the age of 12 months [Sharav et al., 1988]. This is a treatable cause of mental retardation, thus early detection and treatment are essential in order to maximize cognitive abilities in this already impaired population. Unfortunately, there are few studies systematically examining the frequency of thyroid disease in very young children. Current health supervision guidelines for children with DS suggest reviewing results of the newborn thyroid function screen, then repeating thyroid function tests at the age of 6 months and 12 months, and then annually [Cunniff et al., 2001].

Most state newborn screening programs use a twotiered screening approach [AAP Policy Statement, 1993; Hunter et al., 1998]. In North Carolina an initial filter paper blood spot T4

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measurement is followed by a measurement of TSH in specimens with low (less than or equal to 5 mcg/dl) or the lowest 13% of T4's measured in that assay. This approach will identify infants with primary hypothyroidism but will miss infants who have a normal T4 value but elevated TSH (compensated hypothyroidism). Some programs use simultaneous measurement of both T4 and TSH, a method the state of North Carolina began to implement after August 2002. Unfortunately, regardless of the type of approach used, 0.1-1% of newborns with congenital hypothyroidism will have normal screening hormone concentrations due to errors in sample collection and processing, delayed TSH rise and mild forms of disease. This could be higher in individuals with DS because of pituitary thyroid axis dissociation, amongst other factors.

We report a male patient with nondysjunction trisomy 21 by karyotype born at term to a 30-year-old primigravida woman with an uncomplicated pregnancy and unremarkable family history. Initial exam revealed physical features consistent with DS. Newborn screen, which tests total T4 (back-up TSH in our state), was reported as normal. At a routine 3 month old visit to our DS clinic, the patient was noted to be growing appropriately (weight was 75% and length was 90% on DS growth curve which he was following appropriately) and had no signs or symptoms suggestive of illness. A thyroid profile was obtained as part of his evaluation which yielded a TSH of 306 μIU/ml (normal range 0.34-5.66 μIU/ml) and free T4 of 0.4 ng/dl (normal range 0.52-1.21 ng/dl). Repeat values 1 month later proved consistent with hypothyroidism with a TSH of 289 μIU/ml and free T4 of 0.24 ng/dl. In an effort to verify that this was not a case of undiagnosed congenital hypothyroidism, we requested the total T4 and TSH results from the original newborn screen which were 17 mcg/dl (normal range 11-25 mcg/dl) and 11.2 μIU/ml (normal range <20 μIU/ml), respectively.

The patient was referred to a pediatric endocrinologist and a diagnostic workup revealed a normal appearing thyroid gland on technetium scan and negative anti-microsomal and anti-thyroglobulin antibodies. L-Thyroxine therapy was initiated and values immediately returned to normal ranges.

With the advent of newborn screening, it was realized that biochemical evidence of severe hypothyroidism preceded clinical symptoms. This case illustrates the particular difficulty in clinically diagnosing hypothyroidism in children with DS. The onset of hypothyroidism may be associated with symptoms and clinical findings that are subtle (e.g., macroglossia, developmental delay, feeding difficulties) and attributed to the underlying disorder. The current guidelines for children with DS recommend thyroid function tests at the age of 6 months and 12 months and then annually. This case and the reports of abnormal thyroid function tests in infants that were not identified by newborn screening [Selikowitz, 1993] suggest the need for longitudinal studies to determine if current recommendations should be modified for timely detection of thyroid disease in individuals with DS.

Acknowledgements

Grant sponsor: National Center for Research Resources, General Clinical Research Centers Program, NIH (to P.S.K.); Grant number: 1 K23 RR16060-01.

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