CHILDREN WITH PRADER–WILLI SYNDROME FREQUENTLY HAVE CENTRAL HYPOTHYROIDISM

Vaiani E, Herzovich V, Chaler E, Chertkoff L, Rivarola MA, Torrado M, Belgorosky A. **Thyroid axis dysfunction in patients with Prader–Willi syndrome during the first 2 years of life.** Clin Endocrinol 2010;73:546-50.

SUMMARY

BACKGROUND

Prader–Willi syndrome is a rare genetic disease with an incidence of 1 in 10,000 to 1 in 16,000 newborns. The endocrine abnormalities show evidence of hypothalamic pituitary dysfunction, and magnetic resonance imaging occasionally shows pituitary hypoplasia, empty sella syndrome, and a small or absent posterior pituitary gland. Central hypothyroidism has been reported in 20% to 30% of patients. This study is a prospective investigation of thyroid function in all infants diagnosed at the Hospital de Pediatria Garraham in Buenos Aires over a period of 5 years.

METHODS

Eighteen patients (11 boys and 7 girls) up to 2 years of age were included in this prospective study. The diagnosis was documented by molecular biology, and mutations were identified in all cases. At birth, neonatal thyrotropin (TSH) screening was normal. The diagnosis was established as early as 1.9 months to 2 years postnatally. The presumptive diagnosis of thyroid dysfunction was based on serum TSH, triiodothyronine (T_3), thyroxine (T_4) and free T_4 levels. Their normal ranges were established specifically for the hospital laboratory. The values were considered pathological if serum free T_4 was less than the 2.5th percentile of the reference age-matched population and if there was absence of the expected increase in serum TSH. This definition of a possible thyrotropin-releasing hormone TRH/TSH dysfunction was based on international laboratory medicine recommendations. A T_4 below 2 SD was further indicative of hypothyroidism.

RESULTS

Mean length and weight at the time of diagnosis was slightly decreased as compared with the reference population. Four patients were small for gestational age and two were born prematurely. In 61% (11 of 18), free T_4 values were below the 2.5 percentile, and in two additional cases the value was just borderline. With the exception of one case, all patients had normal serum T_3 levels. Interestingly, body length was significantly shorter in the hypothyroid patients than in the small group of patients without thyroid dysfunction.

CONCLUSIONS

In Prader–Willi syndrome, the presence of TRH/TSH dysfunction is more frequent than had been reported earlier and is seen at a very early stage of life. At present, it is not clear whether this dysfunction is transient or permanent. It is suggested that this represents subclinical central hypothyroidism.

COMMENTARY

Prader–Willi syndrome is a genetic disorder. Patients with this disorder have moderate to severe mental retardation, hypotonia, and short stature. They rarely achieve coherent speech. Hyperphagia is a constant feature of the syndrome resulting in severe obesity. Puberty is retarded. Deficiency of luteinizing hormone, inhibin and increased follicle-stimulating hormone, a mixed form of central and peripheral hypogonadism, are part of the syndrome. It is suggested that the phenotype is secondary to hypothalamic dysfunction.

In the article under discussion, the authors consider their findings to be indicative of hypothalamic thyroid dysfunction. They do not use the term central hypothyroidism because despite the low free T_4/TSH ratio, serum T_3 levels were normal. The strength of the study is the large number of cases collected prospectively in one institution and the careful

establishment of an age-dependent reference range for the thyroid tests. Obviously, TRH testing would have been helpful, but the test is no longer available, although it was used in a limited number of cases reported earlier.

Patients with Prader–Willi syndrome benefit from growth hormone treatment in two ways: the treatment improves final height, but more importantly, it reduces severe obesity. The patients do not have an absence of growth hormone but only a partial deficiency. In view of the crucial role of thyroid hormones for early brain development, one can only agree with the authors, who raise the question of whether infants with Prader–Willi syndrome who have an abnormal free T_4/TSH ratio, but normal serum T_3 levels, will benefit from thyroid hormone treatment.

— Albert G. Burger, MD