SUMMARY

**Case Report:** The authors report the 20-year follow-up study of a male subject diagnosed at 15 months of age as a sporadic case of pituitary resistance to thyroid hormone on the combination of clinical hyperthyroidism, elevated serum thyroid hormone (TH) levels and inappropriate TSH. On D-thyroxine (D-T4) therapy from 30 months of age to 12.5 years, hyperactivity and hyperthyroid signs and symptoms as well as growth abnormalities improved, serum L-thyroxine (L-T4) enantiomer normalized, and basal and stimulated TSH decreased significantly without complete suppression. After 8 years off D-T4, at 20 years of age, clinical status was normal despite persisting high TH levels and inappropriate TSH. Evolution of serum markers of TH action and echocardiography measurements followed up from 15 months to 20 years of age either in basal condition or on triiodothyronine (T3), as well as the sequential determination of bone mineral density suggest differences in the tissue responses to T3: normal in bone with a high remodelling rate, heterogeneity for various hepatic markers, and decreased at heart level. No mutations were found in the coding sequence of TRβ1, TRβ2, TRα1, RXRγ, SMRT, NCoR1, and NCoA1. In this patient the putative long-term effects of the persisting high bone resorption are unknown.

COMMENT

This is a fascinating case history. A male child was diagnosed with severe hyperthyroidism in 1984, with the first symptoms appearing around 6 months of age (no family history). Among the amazing early clinical findings were the increased growth velocity (33 cm from birth) and advanced bone age (34 months). At 15 months of age, the diagnosis of RTH (resistance to thyroid hormone) was finally made (free T3 17 pmol/L; non-suppressed TSH 4 µU/ml). To reduce serum TSH and control major tissue thyrotoxicosis, the patient received D-thyroxine (0.30-0.36 mg/kg/d) between the ages of 30 months and 12.5 years, when the treatment was definitively discontinued (various other treatments had also been tried during this long period of follow-up: carbimazole, Triac, T3). On D-T4 treatment, clinical manifestations of thyrotoxicosis improved markedly, serum TSH decreased and remained between 2-4 µU/ml, serum TG and L-T4 enantiomer normalized. Main associated clinical features were ADHD symptoms with learning disabilities throughout school age, a low BMI (between 3rd & 25th percentile), and reduced bone mineral density (with Z-scores at −1 to −1.5). With ageing, however, the metabolic signs of thyrotoxicosis ‘faded away’ and the clinical picture at age 20 yr is that of generalized RTH (while predominantly pituitary RTH in younger age).

Despite extensive laboratory search, no molecular defect was identified. The
pituitary resistance suggests that TRβ does not function properly, but no mutation was found in thyroid hormone receptor gene. Cofactors were analysed (such as RXRγ), with again no mutation found. Thus, the patient belongs to the subgroup of resistance syndromes without identifiable molecular defect. One of the remarkable findings was the progressive disappearance of thyrotoxic-type symptoms (except for increased bone resorption) and, in the absence of a molecular marker of the defect, it is difficult to speculate on the mechanisms that might explain these time-related phenotypic changes.

In the Editorial accompanying the article, Dr Roy Weiss (University of Chicago), a leading expert in this field, insisted on some aspects of RTH. Today, TRβ gene defects have been identified in 344 families comprising 124 distinct mutations, usually with an autosomal dominant mode of inheritance. With the same TRβ mutation, the phenotypes differ, strongly suggesting that factors other than the gene mutation must be responsible for some of the variation in clinical pictures. Starting in 1996, cases were described where no TRβ gene mutations could be identified. These cases are referred to as ‘non-TR RTH’, and our present concept is that cofactors involved in TR-mediated action of thyroid hormone (coregulators) are likely candidates to explain the etiology of ‘non-TR RTH’. Today, 27 families with ‘non-TR RTH’ have been studied in Chicago, representing 15% of all families with RTH. It is quite intriguing that in the end, nothing much allows to distinguish the evolution of patients with RTH due to a TRβ gene mutation from the ‘non-TR RTH’ patients. Finally, as in the patient described in present article, the degree of resistance appears to decrease with age. In summary, ‘non-TR RTH’ is part of the spectrum of syndromes with RTH. More studies are needed of new cases to unravel the specific molecular pathophysiology explaining this fascinating syndrome. (Daniel Glinoer, M.D.; Ph.D.)

See Figure below (serum TSH and free T3 levels up to 20 years of age, on and off several treatments)