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COMMENTARY

# Treatment of central hypothyroidism*

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Central hypothyroidism (CH) is a rare cause of hypothyroidism.[1,2] Its prevalence in the general population is estimated to be around 1:80 000–1:120 000 individuals. About 1 out of 30–40 newborns with congenital hypothyroidism is affected with CH. CH is the consequence of insufficient stimulation of an otherwise normal thyroid gland and is caused by either pituitary (secondary hypothyroidism) or hypothalamic (tertiary hypothyroidism) defects due to neoplastic lesions, infective and inflammatory diseases, autoimmunity, traumatic brain injury, etc. Secondary hypothyroidism usually implies a reduction in the number of functioning thyrotrophs, as documented by impaired TSH secretion and by the blunted response of TSH to TRH. Tertiary hypothyroidism is characterized by normal or slightly elevated serum concentrations of immunoreactive TSH and qualitative abnormalities of TSH secretion, such as decreased bioactivity of circulating molecules, lack of nocturnal TSH surge, and delayed and/or exaggerated and prolonged TSH response to TRH.[1] The genetic forms of CH can be isolated, if the defect is limited to thyrotroph function (isolated TSH deficiency), or associated with combined pituitary hormone deficiency (CPHD), if the defect involves other pituitary cell lineages.[3] In the case of isolated TSH deficiency, mutations in thyrotroph-specific genes, such as TSHβ or TRH-Receptor (TRH-R), have been demonstrated. In the case of CPHDs, various genes encoding transcription factors required for correct development and/or function of several pituitary cell lineages, such as HESX1, LHX 3, LHX 4, SOX 3 and PROP1, may be involved.

Although most of the aetiopathological mechanisms of CH have been recognized, both the diagnosis and the treatment of CH can still be difficult. In fact, the clinical picture of many patients with CH is mild and the onset can be progressive. The clinical consequences of CH in both children and adults may vary greatly depending on the aetiology, the severity of thyroid impairment, the extent of any associated hormone deficiencies, and the age of the patient at the time of the onset of the disease. In general, acquired CH is less severe than the congenital form because some thyroid hormone secretion is assured by constitutive activity of the TSH receptor.[4] Symptoms and signs of thyroid insufficiency are usually milder than those of primary hypothyroidism and goitre is always absent.[2] In the case of CPHD, most patients have other endocrine manifestations of the disease (growth failure, delayed puberty, adrenal insufficiency, diabetes insipidus) that lead them to seek medical attention before their hypothyroidism becomes severe. Early diagnosis of the congenital form by neonatal screening for hypothyroidism, based on both T4 and TSH measurement, is strongly recommended in order to avoid possible development of cretinism.[5]

Due to the difficulties in recognizing CH on clinical grounds, the diagnosis is usually made on a biochemical basis. The measurement of circulating free thyroxine with direct 'two-step' methods remains the most important approach. Indeed, serum TSH levels are usually low/normal, though in most patients with tertiary (hypothalamic) hypothyroidism high normal or even elevated levels may be found. We have demonstrated that the biological activity of circulating TSH in these cases is low.[6,7] Indirect information on TSH bioactivity may be achieved by finding a lack of response of FT4 and FT3 to endogenous TRH-stimulated TSH.

In recent years, several papers dealing with substitutive LT4 therapy in patients with CH have been published and all have underlined the pitfalls in achieving optimal replacement because the inability to be guided by serum TSH levels.[8–10] The article of Koulouri *et al.*[11] in this issue of Clinical Endocrinology approaches the topic in a new and interesting way. They used their Depatment's clinical information system to identify all patients with hypothalamo-pituitary lesions and divided them into high risk and low risk of CH. They then compared FT4 values in these groups of patients with patients with primary hypothyroidism adequately treated with LT4, i.e. those with normal levels of circulating TSH during replacement therapy. The authors conclude that CH patients are generally undertreated. Moreover, they suggest that levels of FT4 around 16 pmol/l (their laboratory reference range being 9–25 pmol/l) might represent an appropriate target in treated CH patients.

Interestingly, this conclusion is quite similar to the one we reached in the past,[8] i.e. to target FT4 values at the middle of the laboratory range of normal values. In our paper, we took into consideration CH patients' weight, age and sex. Moreover, we measured some parameters of peripheral thyroid hormone action, though they were more useful in detecting overtreatment than undertreatment. Finally, we suggested measuring FT3 in addition

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to FT4 levels. However, most current methods of measuring FT3 are generally inaccurate and are rarely used in the follow up of CH patients.

Results similar to those of Koulouri *et al.*[11] and Ferretti *et al.*[8] have been reported by others.[9,10] Alexopoulou *et al.*[9] underlined the importance of concomitant replacement with other pituitary hormones, in particular rhGH substution. It is well known that rhGH treatment interferes with the activity of the hypothalamo-pituitary-thyroid axis and may either unmask a state of central hypothyroism or render a LT4 substitutive therapy insufficient.[12–14]

In conclusion, LT4 substitutive therapy might be optimal if the following conditions are fulfilled: (i) maintain levels of circulating FT4 in the middle of the laboratory reference values, (ii) reassess the dose of LT4 whenever additional replacement with other pituitary hormones is necessary, (iii) be sure during the follow-up that blood for FT4 measurement is withdrawn before ingestion of daily LT4 tablets, and (iv) in iodine-deficient countries, consider the possible presence of a nodular goitre with autonomous thyroid hormone secretion in order to prevent possible LT4 overtreatment.

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