Central hypothyroidism

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ABSTRACT

Central hypothyroidism is defined as hypothyroidism due to insufficient stimulation by thyroid stimulating hormone (TSH) of an otherwise normal thyroid gland. It has an estimated prevalence of approximately 1 in 80,000 to 1 in 120,000. It can be secondary hypothyroidism (pituitary) or tertiary hypothyroidism (hypothalamus) in origin. In children, it is usually caused by craniopharyngiomas or previous cranial irradiation for brain tumors or hematological malignancies. In adults, it is usually due to pituitary macroadenomas, pituitary surgeries or post-irradiation. Fatigue and peripheral edema are the most specific clinical features. Diagnosis is established by the presence of normal to low-normal TSH on the background of low-normal thyroid hormones, confirmed by the thyrotropin releasing hormone stimulation test. Therapy includes use of levothyroxine titrated to improvement in symptomology and keeping free T4 in the upper limit of normal reference range.

Key words: Hypothyroidism, central hypothyroidism, secondary hypothyroidism, tertiary hypothyroidism, levothyroxine, hypopituitarism, panhypopituitarism, thyrotropin releasing hormone, thyroid stimulating hormone

INTRODUCTION

Central hypothyroidism is defined as hypothyroidism due to insufficient stimulation by thyroid stimulating hormone (TSH) of an otherwise normal thyroid gland. It can occur at the level of the hypothalamus or the pituitary gland. The prevalence is estimated to be around 1 in 80,000 to 1 in 120,000 individuals, is roughly equal in both sexes and can arise from a number of pathogenetic mechanisms involving the pituitary (secondary hypothyroidism) or hypothalamus (tertiary hypothyroidism). In children, this is usually cause by craniopharyngiomas or previous cranial irradiation for brain tumors or hematological malignancies. In adults, it is more commonly due to pituitary macroadenomas, pituitary surgeries or irradiation.

Central hypothyroidism is characterized by insufficient thyroid gland stimulation by TSH, resulting from hypothalamic and/or pituitary dysfunction. It is rarely isolated, and occurs more commonly in conjunction with other pituitary hormone deficiencies as well as neurological symptoms and signs resulting from the hypothalamic/pituitary lesion.

With the use of serum TSH as an initial screening test for thyroid dysfunction, the diagnosis of central hypothyroidism may be delayed or even missed because most of these patients have normal or low TSH levels. Some may even have slightly high TSH levels. Hence, both free thyroxine and TSH should be examined concurrently.

PHYSIOLOGY OF THYROID SECRETION

The fetal thyroid does not become functional until the 12th week of gestation. The fetus is therefore dependant entirely on thyroid hormones of maternal origin during the first trimester. Maternally acquired thyroid hormone is therefore critical in the early fetal development (brain). The timing and severity of thyroid hormone insufficiency predicts the type and severity of the neurological deficits in the newborn. Diminished perceptual and motor ability,
markedly short attention span, lower mental development indices, defects in specific cognitive abilities such as poorer attention, slower and more variable reaction times to visual stimuli and visual processing, have been described. Thyroid hormone insufficiency in the fetus still later in development is also associated with impaired neurodevelopment.[6-10]

Secretion of thyroid hormone by the thyroid gland is tightly regulated by the hypothalamic–pituitary axis. The hypothalamus secretes thyrotropin releasing hormone (TRH), which in turn regulates the release of TSH from the anterior pituitary. The TSH, in a potent negative-feedback system, regulates the release of thyroid hormone from the thyroid gland.

TRH is synthesized as a large pre-pro-TRH protein, secreted under the influence of TRH gene, located on chromosome 3, in the hypothalamus and in several tissues, such as the brain, the β cells of the pancreas, C-cells of the thyroid gland, myocardium, reproductive organs (prostate and testis), spinal cord, skin (epidermis) and in the anterior pituitary.[11-17] In the myocardium, overexpression has been associated with left ventricular hypertrophy in the animal model.[18] The human pre-pro-TRH molecule is a 29 kDa protein synthesized in the paraventricular nuclei (PVN) of the hypothalamus. In vivo studies have shown that, in the euthyroid state, TRH transcription is induced both in the PVH and in the anterior/lateral hypothalamus; however, in the hypothroid state, transcription is activated in the PVH only, which can be switched off within 5 h of instituting exogenous thyroid hormone.[19] The pre-pro-TRH fragment stimulates TSH β gene expression in the pituitary gland, which enhances TRH-induced release of TSH and prolactin (PRL) from the pituitary.[11,20,21] There are two distinct regions of human TSH β gene that respond positively to TRH. This interaction is further dependent on the presence of other factors such as cAMP response element-binding protein (CREB)-binding protein (CBP) and Pit-1, which act synergistically with TRH to stimulate the TSH β gene promoter.[22,23]

TSH is a 28-kd heterodimer glycoprotein containing approximately 15% carbohydrate, consisting of α and β subunits, tightly, but non-covalently, bound. The α-subunit gene is located on chromosome 6 and the TSH β gene on chromosome 1. Thyroid-stimulating hormone is synthesized and secreted by the thyrotrophs of the anterior pituitary.[24-26] The (beta) subunit is unique and determines the biologic specificity. The (alfa) unit is identical to the (alpha) subunit of luteinizing hormone (LH), follicle stimulating hormone (FSH) and chorionic gonadotropin. TSH glycosylation is essential for it to attain normal bioactivity, a process that requires the interaction of TRH with its receptor on the thyrotroph.[27,28] Once TRH binds to its receptor on the thyrotroph, TSH gets glycosylated into a biologically potent molecule. Glycosylation of the TSH molecule also results in rapid clearance of TSH from the circulation, raising the concept of “qualitative regulation of TSH secretion,” which is mainly achieved through both transcriptional and post-transcriptional mechanisms involved in TSH glycosylation. TRH deficiency results in the production of biologically subpotent isoforms of TSH, which reverse to their active potent form on continuous TRH stimulation.[29-31] The bioactivity of TSH is influenced by specific amino acid sequences like 27CAGYC31 (cysteine-alanine-glycine-tyrosine-cysteine), which are highly conserved in the TSH β fragment, responsible for its efficacy. Mutations in the TSH β gene can result in familial isolated central hypothyroidism. The most frequent mutation is a homozygous single-base deletion in codon 105 (C105D, 114X), leading to unstable heterodimers.[31-39]

Etiology

Genetic defects

1. Pituitary-specific transcription factor defects such as PIT-1, PROP-1 LHX3 or HESX1 can be associated with multiple pituitary hormone deficiencies. PIT-1 defect (combined deficiencies of growth hormone [GH], PRL and TSH)[40] PROP-1 defect (deficiencies of LH, FSH, GH, PRL and TSH)[41]

2. Isolated TRH deficiency[42]

3. Mutations in the TSH-(beta) subunit gene
   - Non-sense mutation in the thyroid-stimulating hormone beta-subunit gene[31]
   - G29R mutation in exon 2[43]
   - Non-sense mutation at codon 49 (Q49X)[35]
   - Frame-shifting 1-base pair deletion in codon 105 (313[DELTA]T: C105V) in exon 3[39,44]
   - Homozygous mutation in the thyrotropin beta-subunit gene follows an autosomal-recessive inheritance[33,34]

4. An inactivating mutation in the TRH receptor gene[45]

5. Biologically inactive TSH isoforms

6. Association with optic nerve hypoplasia in children[46]

Transient central hypothyroidism

1. Sick euthyroid syndrome
2. Over-replacement of T4 in primary hypothyroidism[47,48]

Central hypothyroidism can be temporary in patients with severe non-thyroidal illness (major surgery, trauma, chronic renal failure, depression, anorexia and fasting), in the elderly, up to 1 month after treatment of hyperthyroidism and following withdrawal of T₄ therapy in patients with multinodular goiter.
Tumors
- Primary pituitary adenoma
- Metastatic pituitary lesions (lung [36%], breast [33%], thyroid)\(^{49,50}\)
- Primary extrapituitary (primary intracranial) – craniopharygioma, meningioma, germinoma
- Cystic mass lesions – Rathke’s cysts, arachnoidal cysts, colloid cysts and epidermoid cysts\(^{51}\)

Vascular
Hemorrhage, pituitary-apoplexy, subarachnoid hemorrhage.

Ischemic – post-partum pituitary necrosis (Sheehan syndrome), shock.

Aneurysm.

Empty sella syndrome

Inflammatory
Infectious – bacterial abscess, syphilis, tuberculosis, toxoplasmosis, neurobrucellosis, fungal disease, toxoplasmosis\(^{51-53}\)

Non-infectious – sarcoidosis, granulomatous (idiopathic, secondary), lymphocytic hypophysitis\(^{51}\)

Infiltrative
Hemochoromtosis, histiocytosis, lymphoma\(^{51}\)

Iatrogenic
Post-external radiation therapy – The GH axis is the most vulnerable to radiation damage. TSH deficiency starts to occur with radiation doses exceeding 30 Gy, with a long-term cumulative frequency of 3–6% when doses of 30–50 Gy are used.\(^{54}\) External radiation therapy caused central hypothyroidism in 65% of the patients treated for brain tumors\(^{55,56}\).

Post-pituitary surgery\(^{56}\)

Trauma (Head injury)\(^{57}\)

Drug related
GH therapy, glucocorticoids, somatostain therapy, RXR-selective ligand, bexarotene, salicylates, drugs interfering with the neuro-dopaminergic system and dopamine\(^{58-60}\).

Addictions – glue sniffing,\(^{61}\) morphine.

Clinical features
Thyroid hormone deficiency slows the body metabolism. In patients with complete athyreosis, body energy metabolism falls between 35 and 45% below normal. Body weight increases on average by 10% due to an increase of body fat and retention of water and salt. Serum leptin has been recognized as one of the factors modulating energy metabolism\(^{62}\). Biosynthesis of fatty acids and lipolysis are reduced. Hypothyroidism results in an increase in serum cholesterol, which is largely accounted for by an increase of low-density lipoprotein (LDL)-cholesterol. LDL-cholesterol is cleared less-efficiently from the circulation due to a decreased T3-dependent gene expression of the hepatic LDL-receptor\(^{63}\). Insulin resistance might be

| Table 1: Etiology of central hypothyroidism |
|------------------------------------------|
| **Genetic**                             |
| 1. Pituitary-specific transcription factor defects (PIT-1, PROP-1 LHX3 or HESX1) |
| 2. Isolated TRH deficiency               |
| 3. TSH-(beta) subunit gene mutations (non-sense mutation, 29R mutation in exon 2, non-sense mutation at codon 49 [Q49X], frame-shifting, 1-base pair deletion) |
| 4. Inactivating mutation in the TRH receptor gene |
| 5. Biologically inactive TSH isofoms     |
| **Transitory central hypothyroidism**   |
| Sick euthyroid syndrome, overreplacement of T4 in primary hypothyroidism |
| 1. Primary pituitary adenoma, cystic mass lesions (Rathke’s cysts, arachnoidal cysts, colloid cysts and epidermoid cysts) |
| 2. Metastatic pituitary lesions (lung [36%], breast [33%], thyroid) |
| 3. Primary extrapituitary (primary intracranial) – craniopharygioma, meningioma, germinoma |
| **Vascular**                            |
| 1. Hemorrhage, pituitary-apoplexy, subarachnoid hemorrhage |
| 2. Ischemic – post-partum pituitary necrosis (Sheehan syndrome), shock |
| 3. Aneurysm                             |
| **Empty sella syndrome**                |
| **Inflammatory**                        |
| 1. Infectious – bacterial abscess, syphilis, tuberculosis, toxoplasmosis, neurobrucellosis |
| 2. Non-infectious – sarcoidosis, granulomatous (idiopathic, secondary), lymphocytic hypophysitis, fungal disease, toxoplasmosis |
| **Infiltrative**                        |
| Hemochoromtosis, histiocytosis, lymphoma |
| **Iatrogenic**                          |
| 1. Post-external radiation therapy      |
| 2. Post-pituitary surgery               |
| **Trauma (head injury)**                |
| GH therapy, glucocorticoids, somatostain therapy, RXR-selective ligand, bexarotene, salicylates, drugs interfering with the neuro-dopaminergic system, dopamine, glue sniffing, morphine |
Gupta and Lee: Central hypothyroidism

present in some patients in the fasting state, but is more frequent in the post-prandial state.

In patients who have hypothyroidism at birth, a goiter is not present and thyroid radioiodine uptake is low. Most infants with low FT₄ and low TSH (<20–25 µU/mL) levels are premature, manifesting transient hypothyroxinemia of prematurity. Children may present with short stature, failure to thrive or delayed skeletal maturation, which may also denote underlying concomitant GH deficiency. TSH deficiency is suspected, measurements of GH and cortisol may indicate panhypopituitarism. The presence of hypoglycemia in a term neonate should suggest GH and/or adrenocorticotrophic deficiency. Further evaluation should include a TRH test and imaging of the brain to identify hypothalamic–pituitary anomalies. In addition, DNA tests permit rapid identification of point mutations in the TSH-(beta) gene, as discussed.

Central hypothyroidism in adults is most frequently due to pituitary macroadenomas and iatrogenic causes (pituitary surgery or irradiation). Clinical features may vary, depending on the cause, extent of thyroid hormone deficiency, number of associated pituitary hormone deficiencies and age of disease onset. Acquired central hypothyroidism tends to be less-severe than the congenital form. Patients with central hypothyroidism have clinical features that are generally similar to patients with primary hypothyroidism, but they tend to be milder. In a study reviewing the medical records of patients with central hypothyroidism, it was found that the most common symptoms were fatigue and headaches in patients with adult-onset central hypothyroidism and growth retardation in those who were diagnosed as children. In another study, the most frequent symptoms and signs observed were asthenia and edema, occurring in more than 50% of the patients, followed by drowsiness, adynamia and skin dryness. Patients may complain of cold intolerance, constipation, generalized lethargy and weight gain. The skin may not be as dry and coarse, and features like periorbital edema and voice hoarseness are not as prominent. Bradycardia, hypothermia, slow speech and delayed relaxation of deep tendon reflexes may be present. The occurrence of TSH deficiency occurs usually after loss of GH and gonadotropin secretion in patients with secondary hypothyroidism. Features of other pituitary hormone insufficiencies such as amenorrhea, infertility, hypoglycemia, anorexia, weight loss and diabetes insipidus may be seen.

Thyroid hormones exert important influences on the skeleton, and thyroid-deficient children tend to have retarded skeletal development and delayed bone age. Congenital and childhood-onset hypothyroidism severely delay skeletal development, causing growth arrest and impaired bone maturation. T4 replacement induces a period of rapid “catch up” growth, but attainment of predicted adult height may not be achieved. The resultant height deficit in such cases is related to the duration of untreated hypothyroidism. In the adult skeleton, thyroid hormone is required for bone maintenance. In hypothyroidism, there is reduced bone turnover, affecting both bone resorption and formation, and the prolonged formation phase leads to an increased mineralization phase. The effects of adult hypothyroidism on bone turnover markers are inconclusive due to the small patient numbers studied, but histomorphometry data indicate that thyroid hormone deficiency prolongs the bone remodeling cycle and reduces bone turnover. Large population studies have demonstrated that hypothyroidism is associated with a two- to three-fold increased fracture risk.

Overt hypothyroidism has been linked to various types of cognitive dysfunction. In terms of mood, most studies indicate that hypothyroid patients have increased rates of anxiety and depression that may improve with L-T4 treatment. In a study comparing patients with overt hypothyroidism to controls, it was found that hypothyroid patients had specific deficits in verbal memory, and scored worse on depression rating scales.

Diagnosis
An inappropriately low serum TSH concentration in the presence of subnormal serum T₃ and T₄ concentrations is characteristic of central hypothyroidism. The diagnosis of congenital central hypothyroidism is frequently missed by current routine neonatal thyroid screening programmes as the TSH is usually in the low-normal to normal range. In about 11% cases, however, the TSH can be between 4.2 and 10, which is largely because of bioinactive but immunoactive TSH isoforms secreted by the pituitary.

On the background of an appropriate clinical setting, i.e. symptomatic patient with absent goiter, diagnosis is established by biochemical testing:

1. Serum T₃, T₄, TSH
2. Use of serial T₄ measurement
3. Dynamic testing using the TRH-stimulation test. Serum TSH is measured serially post-TRH at 20 and 60 mts. Some authors advocate the use of the 180-­mt value too. (Normal response is 20 mts TSH value higher than 60 mts TSH. A flat response is seen in pituitary disease and delayed response, with the 60-mt value higher than the 20-mt value, as seen in hypothalamic disease. This distinction is however not always clear.)
Other biochemical markers have been studied in the evaluation of central hypothyroidism. These include cholesterol, sex hormone-binding protein, angiotensin-converting enzyme, carboxyl-terminal telopeptide of type I collagen, bone glucose-lowering agent protein and serum soluble IL-2 receptors. However, they lack specificity. Anti-thyroid antibodies are invariably negative.

Appropriate neuroimaging such as magnetic resonance imaging of the pituitary gland and, less commonly, computed tomography should be employed to help identify any mass lesion as a possible cause.

The most obvious differences between central and primary hypothyroidism have been outlined as follows [Table 2].

**Management**

Theoretically, TRH and TSH administration seem ideal; however, in view of the high costs and limited applicability, they have been abandoned. Majority of the patients are treated with levothyroxine. The principles of treatment include replacement of thyroid hormone as well as treatment of co-existent pituitary hormone deficiencies, in particular glucocorticoid replacement, as administration of levothyroxine in a glucocorticoid-deficient individual may precipitate an adrenal crisis. The dose of levothyroxine required should be tailored to each individual. Children may require higher doses (around 4 mcg/kg daily) to meet the demands of growth and development. Normal infants and children have higher free-thyroid hormone levels. Therefore, higher levothyroxine doses are recommended in this age group. Treatment should be started promptly in order to avoid adverse neurological sequelae associated with hypothyroidism.

The recommended initial dose of T4 is 10–15 µg/kg per day, or 50 µg daily, for the average term infant weighing 3–4.5 kg. Therapy should be monitored at 4- to 6-week intervals during the first 6 months, at 2- to 3-month intervals between ages 6 and 24 months and at 3- to 6-month intervals thereafter. If the initial diagnosis cannot be established definitively, levothyroxine can be withdrawn for 30 days at age 2–3 years without compromising brain maturation to allow reassessment.

The elderly patients may require lower doses (around 1 mcg/kg daily). Adults in general require around 1.6 mcg/kg of levothyroxine daily, but the optimum dose range is still unclear. The aim of treatment is to achieve euthyroidism, but no consensus has been found regarding evaluation of the adequacy of replacement, as serum TSH cannot be used for diagnosis or monitoring. The dose of T4 replacement should be titrated according to the patient’s symptoms and serum-free T4 value, which should be kept in the upper end of the normal range.

There has been a suggestion of the use of T4 plus T3 combination replacement therapy in hypothyroid patients, as it seems more physiological. However, no added superiority over T4 monotherapy was seen with regards improvement in mood and cognitive performance or metabolic parameters.

An important adverse effect of thyroid replacement is hyperthyroidism from over-replacement. It is thought that more than 20% of the patients on treatment are clinically or subclinically thyrotoxic. Depending on the degree of over-replacement, this can be associated with significantly increased risk of hip and vertebral fractures and atrial fibrillation.

**Monitoring**

The TSH is of no value in the follow-up of patients with central hypothyroidism, unlike primary hypothyroidism, where the TSH is the gold standard assessment. Therefore, monitoring needs to be frequent, initially at 1–2-monthly intervals, requiring:

1. Ft4 to be in the upper half of the reference range
2. Improvement of clinical parameters while on T4 replacement, such as symptoms and heart rate response.

**Conclusion**

Central hypothyroidism is most often caused by diseases of the pituitary or hypothalamus. The diagnosis is suspected by the finding of low FT4 and inappropriately low, normal or slightly increased TSH. A delayed TSH response to TRH (TRH stimulation test) supports the diagnosis. In
neonates, central hypothyroidism goes undetected as most centers only use TSH evaluation. This can result in a delay in diagnosis and severe hypothyroidism, with mental and skeletal abnormalities. Fatigue can be the only presenting feature of central hypothyroidism in the absence of other pituitary hormone abnormalities. Treatment with levothyroxine is very reassuring, with dramatic improvement of other pituitary hormone abnormalities. Treatment with levothyroxine is very reassuring, with dramatic improvement of other pituitary hormone abnormalities. Treatment with levothyroxine is very reassuring, with dramatic improvement of other pituitary hormone abnormalities.

In case of associated hypocortisolism, steroid should be replaced prior to thyroid hormone replacement. Worsening of symptoms post-use of levothyroxine can serve as an indirect clue to the same (hypocortisolism).

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