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Presentation and Management of Central Hypothyroidism

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Abstract **Review Article**

Primary disorders of the thyroid gland are a common presentation in both primary and secondary care and are typically identified through abnormalities in thyroid-stimulating hormone (TSH) and thyroxine levels. Central hypothyroidism (also referred to as secondary or tertiary hypothyroidism) is a relatively rare disorder and usually arises from anatomical or functional disorders of the pituitary and / or the hypothalamus glands. This results in reduced (or inappropriately normal) TSH secretion and consequently decreased thyroid hormone production (Beck-Peccoz *et al.,* 2017). Patients present with symptoms similar to those of primary hypothyroidism including fatigue, weight gain, intolerance of cold, depressive mood changes, dry skin and hair loss (Leung, 2023). This review discusses the presentation, diagnosis and management of central hypothyroidism.

Keywords: Central hypothyroidism, Pituitary adenoma, TSH, Free T4, Levothyroxine, Hypothalamus.

INTRODUCTION

Central hypothyroidism is a rare condition with estimates of incidence between 1 in 16,000 to about 1 in 100,000 (Persani *et al.,* 2018) although others estimate it to be less common with figures between 1 in 80,000 to 1 in 120,000 (Gupta & Lee, 2011). About 1 in 1,000 patients with hypothyroidism will have a central cause, (Marlier *et al.,* 2022) highlighting the importance of clinical recognition.

Central hypothyroidism can be further classified into secondary hypothyroidism, which results from pituitary dysfunction and impaired TSH secretion, and tertiary hypothyroidism resulting from hypothalamic dysfunction and impaired thyrotropin-releasing hormone (TRH) production. Both secondary and tertiary forms ultimately lead to reduced thyroid hormone production.

The most common cause of central hypothyroidism remains pituitary mass lesions, especially pituitary adenomas (Bates *et al.,* 1996). However, other mass lesions implicated include cysts, meningiomas, and tumour metastases.

Central hypothyroidism can be caused by other disorders affecting the function of the hypothalamus or pituitary such as infections, which include tuberculosis, syphilis, fungal infections and toxoplasmosis. Non-infectious causes include sarcoidosis and haemochromatosis (Beck-Peccoz *et al.,* 2017; Modan-Moses *et al.,* 2001). Other causes can include head trauma, cranial surgery or radiation and drugs such as oxcarbazepine (Beck-Peccoz *et al.,* 2017).

In patients who have received pituitary radiation, between 3% to 8% have shown to be hypothyroid (Darzy & Shalet, 2009). In those receiving radiotherapy for head and neck tumours, around 5% have clinical central hypothyroidism (Bhandare *et al.,* 2007).

A detailed history inclusive of these risk factors should be undertaken in the presence of abnormal thyroid function test results.

Although acquired central hypothyroidism remains the most common underlying cause, congenital causes also exist. These can include mutations in the TSHB gene which encodes for the beta subunit of TSH, TRHR variants which encodes the TRH receptor, and X-linked recessive pathogenic variants in the IGSF1 gene (Lauffer *et al.,* 2021).

In congenital forms of central hypothyroidism presenting in infancy or childhood, some occur in isolation, however the majority of cases (60%) are associated with multiple pituitary hormone deficiencies (Lauffer *et al.,* 2021). Therefore, early recognition in this group is particularly important to prevent adverse neurodevelopmental outcomes.

Pathophysiology:

TSH is secreted by the anterior pituitary and stimulates the thyroid gland to produce and release triiodothyronine (T3) and thyroxine (T4). Its secretion is regulated by thyrotropin-releasing hormone (TRH) from the hypothalamus and by circulating thyroid hormones. TRH stimulates the synthesis and release of TSH (Jackson, 1982), whereas T3 and T4 exert negative feedback at both the pituitary and hypothalamic levels, suppressing TSH production.

In this way, in primary hypothyroidism, reduced thyroid hormone levels result in loss of negative feedback, leading to elevated TSH concentrations.

Central hypothyroidism is characterised by impaired TSH production or secretion due to dysfunction of the hypothalamus or pituitary gland.

Investigation and Diagnosis:

Diagnosis can be difficult owing to the lack of specific clinical signs (Grunenwald & Caron, 2015). Symptoms and signs of central hypothyroidism are similar to primary hypothyroidism due to low levels of FT3 and FT4. Key and common features include:

- Weakness
- Fatigue
- Cold intolerance

Other diagnostic factors include:

- Decreased memory
- Constipation
- Muscle cramps
- Weight gain
- Depression
- Dry coarse skin
- Oligomenorrhoea or amenorrhoea
- Bradycardia
- Reduced hair on body and scalp
- Delayed relaxation of deep tendon reflexes (Leung, 2023)

In a patient presenting with these symptoms of suspected hypothyroidism, TSH and free T4 are typically requested as initial lab investigations. In the case of central hypothyroidism, results usually demonstrate a low free T4 with a low or inappropriately normal TSH. In some cases, TSH may be mildly elevated. These findings should prompt further endocrine investigations including serum cortisol, prolactin, FSH, LH and total testosterone levels along with a referral to an endocrinologist. Further investigations would usually include MRI of the hypothalamic-pituitary region to rule out structural abnormalities.

Pitfalls in diagnosis can include reliance on TSH as a sole initial screening test, failure to recognise central hypothyroidism as a possible consequence in patients with known pituitary disease, and misinterpreting mildly abnormal thyroid function tests as subclinical hypothyroidism.

Management and treatment of central hypothyroidism:

The management of central hypothyroidism includes levothyroxine replacement therapy to treat the underlying deficiency, but also assessment of any underlying pituitary pathology (Grunenwald & Caron, 2015).

Treatment with levothyroxine is usually started at 1.6 micrograms/kg/day orally initially, with the dose adjusted every 4-6 weeks according to response. Lower initial starting doses of 12.5 to 25 micrograms/day are recommended in older patients or those with cardiac disease (Leung, 2023).

The aim of treatment is generally to maintain free T4 levels within the upper half of the reference range (Clemens *et al.,* 2011), as this is associated with optimal symptom control while minimising the risk of overtreatment.

In the case of underlying adrenal hormone deficiency, this should be treated (e.g. using hydrocortisone or prednisolone) *before* thyroxine replacement in order to prevent potential acute adrenal crisis (Beck-Peccoz *et al.,* 2017).

Ongoing monitoring includes measurement of T4 levels yearly, or every 4-6 weeks after a dose change (Persani *et al.,* 2018). As discussed, TSH should not be used as a guide for treatment in ongoing management of central hypothyroidism.

In primary hypothyroidism, dose adjustments of levothyroxine are typically made via monitoring of TSH levels. If the TSH is elevated, the dose of levothyroxine is increased, and if TSH is suppressed, the dose is decreased. In central hypothyroidism, FT4 (and often FT3) levels are checked. If these are elevated, the dose of hormone replacement is decreased and if FT4 and FT3 are decreased, the level of hormone replacement is increased.

Clinical vignette:

This brief vignette highlights a brief case of central hypothyroidism.

A 46-year-old man presented to his primary care physician with an 8-month history of fatigue, weight gain and a feeling of reduced exercise tolerance. During the history, he also reported decreased libido and some difficulty with peripheral vision. He had no other significant past medical history.

On examination, he was overweight and had a pulse rate of 55 beats per minute. Visual field assessment revealed bitemporal hemianopia. There was no goitre present.

Initial lab investigations were ordered and showed a low FT4 level of 8 pmol/L (reference range: 10–22 pmol/L) with a low TSH of 0.2 mIU/L (reference range: 0.4–4.0 mIU/L). As he complained of low libido, a testosterone was also ordered as part of the initial investigations and was found to be low. Subsequent further blood tests showed a normal 9 am cortisol.

He was referred to an endocrinologist and underwent magnetic resonance imaging (MRI) of the pituitary which revealed a sellar mass compressing the optic chiasm, consistent with a pituitary adenoma.

He was diagnosed with secondary/central hypothyroidism. He underwent resection of the adenoma and was commenced on levothyroxine with regular endocrine follow-up and monitoring of T4 levels at each visit.

This case emphasises that a low free T4 in the presence of a low or inappropriately normal TSH should prompt evaluation for central causes of hypothyroidism.

Summary:

Central hypothyroidism, although rare, remains a clinically significant endocrine disorder requiring careful evaluation and management. Diagnosis relies on a careful recognition of characteristic biochemical findings, particularly low free T4 with a non-elevated TSH, alongside often nonspecific clinical features. Accurate interpretation of thyroid function tests is essential for diagnosis. Management consists of levothyroxine replacement and identification and management of underlying hypothalamic or pituitary pathology, with ongoing monitoring guided by free T4 levels.

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