ABSTRACT

Central hypothyroidism (CH) is an uncommon cause of hypothyroidism due to failure on the part of hypothalamic-pituitary-thyroid regulatory mechanism. Patients with CH frequently present with multiple other pituitary hormone deficiencies. In addition to classic CH induced by hypothalamic-pituitary tumors or Sheehan syndrome, novel causes include traumatic brain injury or subarachnoid hemorrhage, bexarotene (a retinoid X receptor agonist) therapy, neonates being born to mothers with insufficiently controlled Graves disease and lymphocytic hypophysitis. Growth Hormone therapy, which may be used in children and adults, is now also recognized as a possible cause of unmasking CH in susceptible individuals. In addition, mutations in genes have been associated with CH. The difficulty in making a clear diagnosis of CH makes one frequently tend to overlook this condition. Appropriate doses of levothyroxine for T4 replacement therapy need to be higher than presently used empirical doses in patients with CH. It should be adjusted according to age and other hormone deficiencies to achieve free T4 concentrations in the upper end of the normal range. Apart from central hypothyroidism other hormonal deficiencies should be looked for and suitable replacement therapy be initiated.

DEFINITION

Central hypothyroidism (CH) is defined as hypothyroidism due to insufficient stimulation of the thyroid gland by Thyroid Stimulating Hormones (TSH), the secretion or activity of which is impaired at the hypothalamic or pituitary level. Consequently despite low thyroid hormones TSH is low or sometimes paradoxically normal.

PREVALENCE

The precise prevalence of CH is unknown but is thought to be much lower than that of primary hypothyroidism. Considering that the most frequent course of CH is due to sellar or suprasellar pathology and that of prevalence of pituitary tumours in the general population is greater than 10% the true prevalence of CH might be higher than reported. Martino et al found that 15% of the 300 patient with pituitary adenomas examined in one year had CH. Vern Tijn et al reported the evidence of congenital CH to be one in 16,404 neonates with 13.5% of them having permanent hypothyroidism. Similarly traumatic brain injury, subarachnoid hemorrhage, Sheehan’s syndrome and lymphocytic hypophysitis may all cause CH along with deficiency of multiple pituitary trophic hormones up to several decades.

PATHOPHYSIOLOGY

As has already been brought out the primary pathology/pathophysiology in CH is at the hypothalamo-pituitary level (HPT axis). The normal function of the HPT axis involves thyrotrophin releasing hormones (TRH) secreted mainly from the paraventricular nucleus of hypothalamus in the thyrotrphs of the anterior pituitary which produces the thyrotrophic secreting hormones (TSH). The TRH binds to the TRH receptors in the anterior pituitary and apart from the thyrotrphic effect also regulates the conjugation of TSHα and β chains and glycosylation of TSH molecule to control its biochemical activity (Fig-1 and Fig-2). The mature TSH secreted from the pituitary gland reaches the thyroid gland where it stimulates the thyroid hormone production.
and release. The main hormone secreted by the thyroid is T₄ which reaches the peripheral organs and is converted to T₃ by deiodinisation. T₃ enters the cell nuclei and binds to thyroid hormones receptors α and β isoforms on targeted genes thereby regulating gene transcription. At the hypothalamic and pituitary level the thyroid hormones inhibits production and secretion of TRH and TSH – the negative feed back, thus establishing H-P-T axis. CH will result if any factor in this axis is disturbed.

Till recently it used to be the practice to designate CH in to ‘secondary’ when the problem is at the level of pituitary and ‘tertiary’ if the hypothalamus is disturbed. Due to the close anatomical functional and complex mechanism of TRH-TSH secretion and the diagnostic difficulties of determining the primary insult at either of these locations these terms are now being abandoned.

CAUSES OF CENTRAL HYPOTHYROIDISM

Depending upon the frequency with which one would encounter different underlying causes of CH they are classified as ‘Classic’ if they are common and ‘Non-classic’ when they are uncommon. Table 1 lists these separately. The relative incidence, the underlying mechanisms and the clinical and hormonal profile of these conditions will now be outlined.

CLASSIC (COMMON) CAUSES:

Pituitary Adenoma

This is the most frequent cause of CH accounting for more than 50% of cases in most of the studies. In a Spanish study where 45 cases of CH occur annually per 1,00,000 of general population as many as 61% were due to pituitary adenomas. Various patho-physiological mechanisms are implicated in the causation of CH in pituitary tumors. Mechanical compression of portal vessels and pituitary stalk caused by expanding adenoma seems to be the predominant mechanism leading to multiple hormonal deficiencies including TSH. Apart from the impairment of blood supply – which may lead to ischemic necrosis of the pituitary cells, delivery of the hypothalamic releasing hormone, in this case TRH, may also be impaired. In most cases CH occurs concurrently with other pituitary hormone deficiencies – a state of panhypopituitarism but isolated TSH deficiency has also been reported. In general LH/FSH deficiency occurs first and is noted in 85% of patients followed by GH (45%), ACTH (62%) and TSH (60%). ADH and TRL are preserved till the last. In fact in most cases due to pressure on the stalk and interruption of prolactin inhibitory hormone there is often elevation of prolactin, leading to mistaken diagnosis of prolactinoma.

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Fig. 1: The hypothalamic-pituitary-thyroid axis.

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Central Hypothyroidism: A Diagnosis Overlooked?

Pituitary Tumor Apoplexy

Untreated macro-adenomas run the risk of infarction, outgrowing their blood supply, leading to pituitary apoplexy—a catastrophic event often leading to secondary adrenocortical failure, a life-threatening emergency. CH occurred in 54% of patients in one study needing thyroxin therapy. Also these patients need life-long thyroxin replacement along with other hormones—particularly cortisone. It is reported that patients with prolactinoma and macroadenomas treated with dopamine agonists reduced levels of LH/FSH in 77% and TSH in 41% of patients.

Craniopharyngioma

A common parasellar tumor arising from embryonic squamous remnants of Rathke's pouch, they are often large, aggressive and infiltrating. Gross hypopituitarism and hypothalamic disturbances are common and CH occurs in more than 90% of cases.

Empty Sella Syndrome

Primary empty sella syndrome has been reported in (6-20%) of unselected autopsies. It is more common in obese women with hypertension. Hypopituitarism occurs in 10-57% with mainly GH and FSH/LH deficiency and CH occurring occasionally. Secondary empty sella follows pituitary apoplexy, surgery or radiation therapy and pan-hypopituitarism with CH is common requiring life long hormonal replacement.

Sheehan’s Syndrome

Pan-hypopituitarism as a result of ischemic pituitary necrosis following severe postpartum hemorrhage occurs in 56-84% of cases and CH has been reported in as many as 90% of them. Serum TSH levels are often paradoxically elevated due to reduced biological activity. Also the time from childbirth to onset of hormone deficiency can vary from several days to a few decades.

Radiation Therapy

External radiotherapy to head and neck might affect the hypothalamus, pituitary and/or the thyroid gland. CH has been observed in 20-50% of patients who have been irradiated for nasopharyngeal and paranasal tumors. Primary hypothyroidism due to radiation thyroiditis occurs in another 20% of patients with a clinical extency of 4.8 to 7 years.

NON-CLASSIC CAUSES:

Traumatic Brain Injury and Subarachnoid Hemorrhage

Several studies have shown a surprisingly high prevalence of hypopituitarism including CH brought about by traumatic brain injury (TBI) and subarachnoid hemorrhage (SAH). In long term follow up the prevalence of hypopituitarism was 28% after TBI and 47% after SAH. Since the signs and symptom of hypopituitarism might be subtle and could overlap with neurologic and psychiatric sequelae of TBI and SAH it may remain undiagnosed in many cases. CH is however observed in 1-10% of patients after TBI and 3-9% after SAH.

Lymphocytic hypophysitis

CH is present in 44% of lymphocytic hypophysitis, an auto-immune inflammatory disease of the pituitary gland. Women are slightly more affected than men with the difference being greatest during pregnancy and shortly after delivery.

Infants born to mothers with Grave’s diseases

Transient thyrotoxicosis effects occur in above 1% of babies born to mothers with either active or previously treated Graves disease. By contrast CH is also observed in neonates born to mothers with inadequately controlled thyrotoxicosis during the last trimester of pregnancy. The incidence of this type of CH is noted in at least 1 in 35000 neonates. Transient CH has been shown to become permanent with need for thyroid hormone replacement therapy. Insufficient TSH secretion due to excessive maternal to fetal thyroid hormone transfer could inhibit development of thyroid gland leading to low thyroid hormone levels.

Growth Hormone Therapy

Growth hormone deficiency masks CH and this disorder may become evident only after administration of GH replacement therapy. A notable reduction in serum T4 levels without substantial increase in serum TSH was reported in 36% of euthyroid adults with GH deficiency and T4 replacement therapy was required. The mechanism of hypothyroidism after GH therapy remains unclear. GH therapy has been reported to increase peripheral deiodination of T4 to T3, perhaps producing more of inactive T3. Also, the increased secretion of somatostatin may block TSH secretion. Whether this effect is mediated by insulin like growth factor I (IGF1) or is controlled directly by growth hormone is not known.

Therapy with Retinoid Analogues

Bexarotene is synthetic retinoid analogue which is approved for treatment of cutaneous T cell lymphoma. In clinical trials bexarotene therapy was associated with development of CH in 40% of patients with reduction of serum TSH and T4 levels. In one report 19 out of 27 patients receiving bexarotene had symptoms or signs of hypothyroidism. This drug probably has two effects on thyroid function: suppression of TSH production and increased thyroid hormone metabolic clearance by mechanisms moderated by deiodinisation and non-deiodinisation mechanisms.

Genetic Mutations

Several genetic mutations causing CH have been reported and these include mutations of TSHB, TRHR, POU1F1, PROP1, HESX1, LHX3 and LHX4 genes. The commonest among these is TSHB mutation causing familial isolated TSH deficiency, the inheritance being autosomal recessive. In severe cases of CH typical signs and symptoms of cretinism without goiter occur. Radioiodine uptake in the thyroid is poor and increases after administration of TSH. In the TRH receptor mutation first reported in 1997, the patient should no TSH or prolactin response to TRH administration and CH was mild with normal TSH level and the
only manifestation was short stature. Mutations causing multiple pituitary hormonal deficiencies have been described in HESX1, SOX3, LHX3 and LHX4 genes. Both hormonal deficiencies and the clinical presentations differ in different mutations.

Several animal models have been studied to gain insight into CH caused by genetic mutations. In TRH knock-out mice, typical tertiary hypothyroidism with low serum thyroid hormones and elevated serum TSH levels were observed. As in humans TRH testing revealed exaggerated response of serum TSH. However serum T₄ response to increased TSH was significantly impaired indicating reduced biological activity of serum TSH.

**DIAGNOSIS OF CENTRAL HYPOTHYROIDISM**

Usual screening for hypothyroidism including clinical and measurement of TSH might not detect CH. The most effective way to diagnose CH is by measuring serum levels of free T₄ (FT₄) and TSH. Subnormal levels of FT₄ and inappropriately low level of serum TSH usually indicates CH (Fig-3) although some patients with CH have slightly high TSH levels. Several mechanisms have been suggested to explain the differences and paradoxical values of TSH: hypoadrenalism raising TSH, decreased secretion of somatostatin from hypothalamus leading to increased secretion of TSH and reduced biological and receptor binding activity of TSH.

Administration of TRH to normal individuals produces a consistent rise in serum TSH levels with peak values at 15-30 minutes with notable decrease starting at 60 minutes. In the TRH stimulation test TSH is measured before and at 15, 30, 60 & 180 minutes after intravenous administration of TRH (10 mcg per kg of body weight). Normal responses is defined as TSH greater than 40-50 mIU/L; absent or blunted if less then this and excessive delayed responses as TSH > 20.0 - 25.0 mIU/L or a peak response after 60 minutes. Many CH patients show either blunted or delayed patterns.

Diagnostic value of TRH stimulation test has recently been reevaluated. As a result it is now proposed to test the biological activity of circulating TSH by measuring the increment of serum free T₄ in response to increased TSH. In normal individuals FT₄ response to TRH stimulated TSH have been observed to increase by 29-37% (mean 32%) at 120 minutes after stimulation while FT₄ levels increased by 14%. In CH this response is blunted. Distinguishing between hypothalamic CH and pituitary CH by TRH test can be difficult. Also normal TRH tests do not exclude abnormalities in hypothalamo-pituitary – thyroid axis.

**MANAGEMENT OF CENTRAL HYPOTHYROIDISM**

Although TRH and TSH administration are theoretically ideal for treatment of CH they have been abandoned due to high cost, limited availability and instability of TRH after oral administration. Almost all patients are treated with levothyroxine with an average daily dose of 1.6 mcg / Kg body weight generally restores a euthyroid state in primary hypothyroidism but the optimum dose or dose range for CH is unclear. FT₄ levels need to be kept at the upper end of normal range rather than within the middle and lower values. Also levothyroxine therapy needs to be tailored to the age of the individual. Children require high doses up to 4.0 mcg/ Kg daily whereas in elderly individuals a dose of 1.0 mcg/ Kg would be sufficient. In patients with GH deficiency conversion of T₄ to active T₃ may be deficient and increasing the dose and monitoring FT₃ rather than FT₄ will be necessary. In postmenopausal women on estrogen and people on bexarotene therapy need much higher doses of levothyroxine. Combination therapy using levothyroxine and liothyronine showed no benefit.
over singly therapy.

In many cases of CH measurement of TSH levels cannot be used to monitor therapy since negative feed back regulation of TSH by exogenous T4 can remain intact. When basal level of serum TSH is low levels after treatment. Serum levels of FT4 and FT3 along with plasma cholesterol, CPK, sex hormone binding globulin and ACE are other peripheral markers which may be used.

Some cases of CH might be reversible and monitoring of pituitary function would eliminate the need for life long substitution therapy. For example - surgical excision of pituitary adenoma leads to improvement of anterior pituitary function and CH in as many as 35% of patients in whom T4 supplements were discontinued. Similarly CH in neonates born to hyperthyroid mothers is often transient and requires only short term supplementation.

CONCLUSION

While primary hypothyroidism is fairly common, central hypothyroidism being much less common is often overlooked. However its prevalence is probably higher than reported and one needs to have increased awareness of this condition. It should be suspected when low TSH levels are associated with subnormal FT4 levels and further investigations to pinpoint the underlying cause needs to be carried out. Apart from central hypothyroidism other hormonal deficiencies will have to be looked for and suitable replacement therapy for the deficient hormones needs to be initiated.

REFERENCES: