Central Hypothyroidism in Thalassemic Children

Thesis submitted for partial fulfillment of MSc degree in pediatrics

By

Nanice Nasser Ashour

MBBCh, Faculty of Medicine, Cairo University, 2007

Supervised by

Prof. Mohsen Saleh El Alfy

Professor of Pediatrics

Faculty of Medicine, Ain Shams University

Prof. Heba Hassan Elsedfy

Professor of Pediatrics

Faculty of Medicine, Ain Shams University

Dr.Nermine Helmy Mahmoud

Assistant professor of clinical pathology

Faculty of Medicine, Ain Shams University

Faculty of Medicine

Ein Shams University

2013

Summary

Objective:

To determine the frequency of hypothyroidism in patients suffering from thalassaemia major.

Methods:

This descriptive study included .128 diagnosed thalassaemia major patients aged (3-17) years not known to be thyroid

History of blood transfusion and chelation therapy was collected. Random blood samples were drawn and thyroid profile (serum thyroxine[fT4] and thyroid stimulating hormone concentrations [TSH]) was done by enzyme-linked immunosorbent assay (ELISA). Primary hypothyroidism was defined by a TSH level >4DIU/ml.

Serum ferritin was measured using immunoenzymometric assay

Results:

Subclinical hypothyroidism was seen in .15 (.12%) patients .with normal f T4 levels and elevated TSH levels. No cases with secondary hypothyroidism were diagnosed as all fT4 levels were normal. Mean serum ferritin level was 907.58±685.4 ng/ml. There was no significant difference between serum ferritin level in children and adolescents with normal thyroid function and those with subclinical hypothyroidism .

Conclusion:

Our study showed a low prevalence of hypothyroidism among patients with TMp with no difference between normal and subclinical hypothyroid children and adolescents in ferritin level. Regular follow-up for early detection and .the use of proper chelation therapy could improve the quality of life of these patients

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. Usually, the diagnosis of CH will rely on the concomitant finding of a low tT4 or fT4 level together with a low or normal TSH concentration. In b- thalassemic children with regular blood transfusion iron start to accumulate in parenchymal tissue of various organs with possibility of endocrine dysfunction in patients with thalassemia in earlier periods. Hypothyroidism may be partly related to the accumulation of iron in thyroid glands due to blood transfusion by iron overload leading to gland dysfunction. Iron overload of tissue is the most important complication of beta-thalassemia and is a major subject of management.

Table of Contents

List of Tables

List of Figures

Introduction

Thyroid dysfunction in thalassemia may start early in life though with a low frequency. Therefore, thyroid function should be followed periodically, particularly when other iron overload-associated complications occur. Early recognition and hence prevention of these complications might help improve the quality of life of these patients. This is particularly true for thyroid dysfunction, because hypothyroidism could be associated with growth problems so commonly seen in these patients.

Aim of the work

The aim of this study is to assess the level of serum TSH, fT4 and the ferritin level in β-thalassemia children with lifelong blood transfusion and the possibility of occurrence of hypothyroidism due to iron overload deposition.

Literature Review

Thyroid Physiology

The fetal thyroid does not become functional until the 12th week of gestation. The fetus is therefore dependent 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 later in development is also associated with impaired neuro development***(Morreale et al., 1988; Pacaud et al., 1995; Francis and Riley, 1987; Rovetand Hepworth, 2001; Zoeller and Rovet,2004).***

Thyroid-stimulating hormone (TSH), secreted by the anterior pituitary gland, controls the synthesis and secretion of the thyroid hormones, thyroxine (T4) and triiodothyronine (T3). Regulation of TSH levels is controlled by two mechanisms. The first is classic negative feedback to serum thyroid hormone concentration. Large inverse changes in TSH levels are precipitated by small changes in free thyroid hormone concentrations. Secondly, TSH concentration is regulated by the hypothalamic hormonethyrotropin-releasing hormone (TRH). The systems are interrelated in that the negative feedback of thyroid hormone probably affects TRH release from the hypothalamus in addition to TSH release from the pituitary. TRH secretion is also affected by input from higher cortical centers ***(Farwell and Ebner, 2001).*** This system of thyroid hormone production is referred to as the hypothalamic-pituitary-thyroid axis ***(Dillman, 2000).***

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 ***(Jackson,1982; Martino etal.,1987;Gkonos etal.,1989; Jeffcoate et al.,1976; Bruhn et al., 1994; Bilek, 2004; Bodó et al., 2010).*** In the myocardium, over expression has been associated with left ventricular hypertrophy in the animal model***(Schuman et al, 2011).***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 hypothyroid state, transcription is activated in the PVH only, which can be switched off within 5 hours of instituting exogenous thyroid hormone ***(Sugrue etal., 2010).***

The pre-pro-TRH fragment stimulates TSH β gene expression on chromosome 1in the pituitary gland, which enhances TRH-induced release of TSH and prolactin (PRL) from the pituitary***(Jackson, 1982; Nillni and Sevarino, 1999; Pekary, 1998).***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 ***(Zanger etal., 1999; Hashimotoet al., 2000).***

TSH is synthesized and secreted by the thyrotrophs of the anterior pituitary***(Shupnik etal., 1989; Grossmann etal., 1997; Naylor etal., 1983).*** The βsubunit is unique and determines the biologic specificity. The α subunit is identical to the α 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***(Amir etal., 1987; Menezes etal., 1986).***

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 ***(Petersen etal., 1978; Beck-Peccoz etal., 1985; Dacou-Voutetakis etal., 1990).***

At the molecular level, T4 is actually a prohormone and T3 is the biologically active chemical. All T4 is synthesized within the thyroid gland, whereas only 15% to 20% of T3 is synthesized directly. T4 is converted toT3 in peripheral organs, including the kidneys and liver ***(Dillman, 2000; Ross, 2001).*** Thyroglobulin is a thyroid-hormone– containing protein stored in the colloid within thyroid follicles. T4synthesis occurs within these follicles. Dietary iodide is trapped, oxidized, and combined with tyrosine residues. Coupling of these iodotyrosines produces T4 ***(Dillman, 2000; Gilkison, 1997).*** The major metabolic pathway of T4 is monodeiodination. The outer ring is removed, producing T3. Inactive RT3 is formed when the inner ring is removed. In healthy patients, about 41% of T4 is metabolized to T3 and 38% converts to RT3. Other pathways account for the remainder ***(Farwell and Ebner, 2001).***

The daily requirement for thyroid hormone is less than 1% of the amount stored within the gland, allowing maintenance of normal function when a person is deprived of iodine. The excess capacity, however, creates a vulnerability to thyrotoxicosis when the thyroid gland becomes inflamed and excess thyroid hormone is released ***(Gilkison, 1997).***

Over 99.5% of T4 and T3 are protein bound in the serum. Thyronine-binding globulin (TBG) binds approximately 80% of circulating hormone. Transthyretin and albumin are minor serum binders ***(Farwell and Ebner, 2001).*** Bound hormone is metabolically inactive; thus, only the tiny percentages of free thyroid hormone are metabolically active and clinically relevant. Measurements of thyroid hormone can be misleading if only total thyroid hormone levels are obtained. Free T3 (FT3) and free T4 (FT4) serum levels provide more valuable clinical information. Variables that affect TBG levels such as disease, nutritional status, and medications will affect free thyroid hormone levels; however, the hypothalamic-pituitary-thyroid axis gradually reestablishes homeostasis ***(Bouknight, 2003).***

TSH secretion rhythmically varies between day and night. More than half is secreted in pulsatile fashion between 10:00 p.m. and 4:00 a.m. Sleep deprivation increases pulses, whereas sleep diminishes the pulses. The TSH molecules secreted at night demonstrate less hormonal activity than do daytime molecules. Therefore there is no nocturnal surge in thyroid hormone levels in response to the increased secretion of TSH ***(Ross, 2001).***

HYPOTHYROIDISM

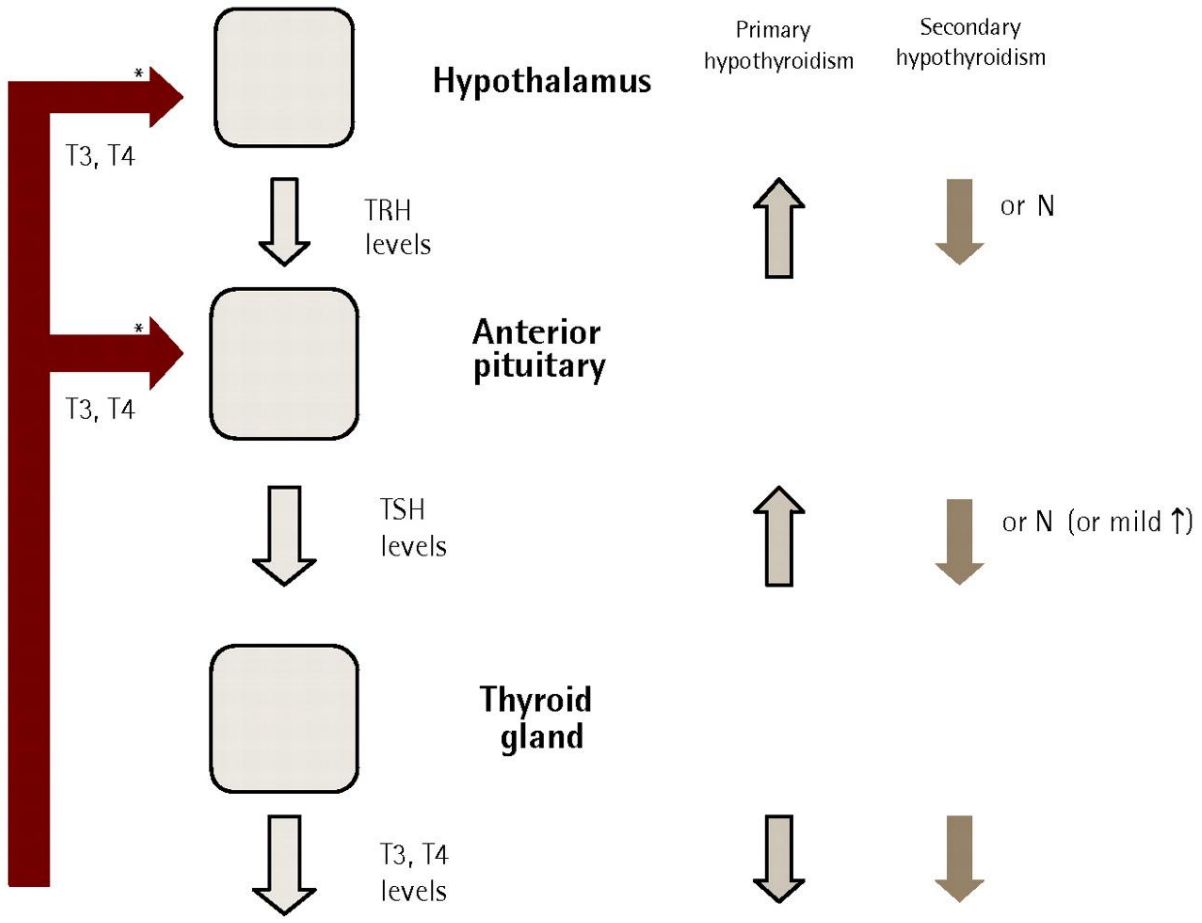
The term *hypothyroidism* encompasses a broad spectrum of disease. Hypothyroidism can be congenital or acquired, primary or secondary, overt or subclinical, and goiterous or nongoiterous. Primary hypothyroidism, caused by thyroid gland failure, is responsible for more than 95% of cases of hypothyroidism. Low TSH or TRH levels from pituitary or hypothalamic failure cause central hypothyroidism, a relatively rare condition.

In areas of the world where iodine deficiency is unusual, most cases of primary hypothyroidism are associatedwith Hashimoto's thyroiditis. Also known as chronic autoimmune thyroiditis, this disease is characterized by lymphocytic infiltration of the thyroid gland and the presence of antibodies directed against the TSH receptor, thyroperoxidase (TPO), and thyroglobulin. The TSH-receptor antibodies target a different area of the receptor than those found in patients with Grave's disease; these antibodies block the action of TSH rather than stimulate the gland ***(Konishi et al., 1985).*** Seven of 10 patients with Hashimoto's thyroiditis are women, and the incidenceincreases with age. The disease assumes goiterous andatrophic forms; patients with goiter are usually asymptomaticbut sometimes have thyroid tenderness not responsiveto steroids ***(Zimmerman etal., 1986).***

Primary hypothyroidism is usually diagnosed based on an elevated TSH level. In this situation, the failure of the thyroid gland to secrete sufficient thyroid hormone results in decreased levels of T3 and T4. In turn, there is less negative feedback inhibition at the hypothalamus and pituitary, causing TSH levels to increase (Figure 1). Increased TSH levels are therefore indicative of the diagnosis, and normalization is seen during adequate treatment.

In contrast, owing to hypothalamic or pituitary failure, TSH levels might not increase in response to low T3 and T4 levels or central hypothyroidism ***(Lania et al., 2008).***TSH levels can, in fact, be in the low, normal, or elevated range ***(Alexopoulou et al., 2004).***This is because TSH pulse frequency and amplitude might be maintained, and additionally, its biologic activity might be reduced with its immunoactivity still retained ***(Bhandare et al., 2007).*** Furthermore, other hormone deficiencies can affect its measure ***(Yamada and Mori, 2008).***

Therefore, for the diagnosis of central hypothyroidism, one needs findings of low free T3 and T4 levels together with low or "inappropriately" normal TSH concentration in the context of hypothalamicpituitary disease ***(Alexopoulou et al., 2004).***



*Red arrows represent negative feedback inhibition.
N—normal, T3—triiodothyronine, T4—thyroxine, TRH—thyrotropin-releasing hormone, TSH—thyroid-stimulating hormone.

Figure 1 Hypothalamic-pituitary-thyroid axis activity in hypothyroidism (Clemens et al., 2011)

Less common causes of hypothyroidism are listed inTable 1. The initial thyrotoxicosis seen in thyroiditis is often followed by a period of transient hypothyroidism.Iodine deficiency is the most common cause of hypothyroidism and goiter worldwide; it is rare in the United States due to the iodination of table salt. Paradoxically,iodine excess can also cause hypothyroidism as it inhibits the organification of iodine and the synthesisof T3 and T4 (the Wolff-Chaikoff effect) ***(Wolff and Chaikoff, 1948).***

Table 1 Differential diagnosis of hypothyroidism (*Dillman, 2000)*

	Mechanism	**TSH**	**fT4**	**fT3**
Primary hypothyroidism				
Hashimoto disease	Autoimmune disease	High	Low	Low
Surgical thyroidectomy	Iatrogenic	High	Low	Low
External radiation	Iatrogenic	High	Low	Low
Amyloidosis	Infiltrative	High	Low	Low
Lymphoma	Infiltrative	High	Low	Low
Scleroderma	Infiltrative	High	Low	Low
Iron deficiency or excess	Nutritional	High	Low	Low
Drug induced	Iatrogenic	High	Low	Low
Secondary hypothyroidism				
Sheehan's syndrome	Pituitary infarction	Low	Low	Low
Pituitary neoplasm	Infiltrative/malignant	Low	Low	Low
Pituitary radiation/surgery	Iatrogenic	Low	Low	Low
Tertiary hypothyroidism				
Sarcoidosis	Hypothalamic infiltration	Low	Low	Low
Hypothalamic neoplasm	Malignancy	Low	Low	Low

Clinical manifestations of hypothyroidism are the consequence of two basic physiologic effects of the lack of thyroid hormone: generalized slowing of metabolic processes and tissue deposition of glycosaminoglycans. Clinical manifestations of hypothyroidism with relative frequencies are listed in Table 2. Because signs and symptoms of hypothyroidism are often nonspecific, develop insidiously, and can be mistaken for normal aging, clinical detection can be difficult. Accordingly, laboratory testing has assumed an increasingly important rolein the detection of hypothyroidism. Myxedema coma is a rare and potentially lethal complication of hypothyroidism. It is usually the result of acute decompensation in a patient with chronic hypothyroidism, often precipitated by stress such as infection, cold exposure, trauma, surgery, or stroke or the use of medications such as amiodorone and lithium ***(Mazonsonetal., 1984; Waldman, 1989).*** The condition is seen almost exclusively in women over 60 years of age and usually occurs during winter months ***(Davis and Davis, 1984).*** Contrary to the name, patients do not necessarily present with coma or edema; clinical findings can include:altered mental status, hypothermia, hypoventilation, hypotension, bradycardia, constipation, periorbitaledema, nonpitting peripheral edema, and delayed relaxationof deep tendon reflexes. Associated abnormal laboratory findings can include

anemia, hyponatremia, hypoglycemia, and elevated total creatinine kinase (CPK)levels. Myxedema coma can result in cardiovascular collapse; prompt recognition and treatment can be lifesaving. Patients presenting with possible myxedema coma should be treated with levothyroxine, 100 µg to 500 µg intravenously. An intravenous glucocorticoid(hydrocortisone) is also recommended until adrenal insufficiency and secondary hypothyroidism have been excluded. Passive rewarming, active respiratory and cardiovascular resuscitation, and admission to a monitored setting are appropriate***(Wall, 2000).***

Table 2: Sensitivity and specificity of the 14 symptoms and signs of hypothyroidism and analysis of their positive and negative predictive values *(Zulewski et al., 1997)*

Symptoms and signs	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Ankle reflex	77	93.5	92.2	80.3
Dry skin	76	63.8	67.7	72.7
Cold intolerance[1]	64	65	64.6	64.4
Coarse skin	60	81.2	76.1	67
Puffiness	60	96.3	94.2	70.7
Pulse rate[1]	58	42.5	50.2	50.3
Sweating	54	86.2	79.6	65.2
Weight increase	54	77.5	70.6	62.8
Paraesthesia	52	82.5	74.8	63.2
Cold skin	50	80	71.4	61.5
Constipation	48	85	76.2	62
Slow movements	36	98.7	96.5	60.7
Hoarseness	34	87.5	73.1	57
Hearing	22	97.5	89.8	52.6

Two signs (cold intolerance and decreased pulse rate) showed positive and negative predictive values below 70% and were, therefore, excluded from the new score.

In patients who have hypothyroidism at birth due to thyroid dysgenesis, a goiter is not present and thyroid radioiodine uptake is low. Most infants with low fT 4 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 ***(Gudmundsdottir and Schlechte, 2002).*** If 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-β gene ***(Gupta and lee, 2011).***

Thyroid hormones exert important influences on the skeleton, and thyroid-deficient children tend to have retarded skeletal development and delayed bone age ***(Bassett and Williams, 2008).*** Congenital and childhood-onset hypothyroidism severely delay skeletal development, causing growth arrest and impaired bone maturation ***(Gogakos et al.,2010).*** 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 ***(Rivkees et al., 1998).*** 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 ***(Eriksen et al., 1986).*** 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 ***(Gogakos et al., 2010).*** Large population studies have demonstrated that hypothyroidism is associated with a two- to three-fold increased fracture risk ***(Vestergaard and Mosekilde, 2002).***

TSH ASSAYS

In patients with an intact hypothalamic-pituitary axis, small changes in thyroid hormone concentration lead to large inverse changes in the TSH level. Therefore, a low serum TSH concentration indicates elevated thyroid hormone activity, whereas a high TSH concentration suggests hypothyroidism. Due to the remarkable sensitivity of the hormonal feedback mechanism, the TSH is a more precise indicator of thyroid status than the actual thyroidhormone level; abnormal TSH values indicate mild thyroid dysfunction (subclinical