INTRODUCTION

Hypothyroidism results from inadequate circulating levels of thyroid hormone (TH), or rarely, is due to peripheral resistance to hormonal action. Primary hypothyroidism is the most common type of hypothyroidism. The most common cause of primary hypothyroidism is autoimmune disease. Secondary and tertiary hypothyroidism are due to pituitary and hypothalamic dysfunction, respectively. Secondary hypothyroidism results from inadequate release of thyroid stimulating hormone (TSH). This may be due to tumor, infarction trauma, radiation or surgical treatment of pituitary gland ***(Heymann, 1992).***

The skin of patients with hypothyroidism is a reflection of the resultant hypometabolic state and subsequent reduced core body temperature and reflex cutaneous vasoconstriction ***(Leohardt and Heymann, 2002).*** The skin is cold, dry and pale, especially on the extensor surfaces ***(Heymann et al., 2001).***

Head and body hair is typically dry, coarse, and brittle; it tends to fall out, resulting in a diffuse, partial alopecia. Loss of hair from the lateral third of eyebrow (madarosis) is a common finding. The rate of hair growth is slowed. The nails of hypothyroid patients appear dry, brittle and dull in appearance with slow growth and longitudinal and transverse striations ***(Heymann, 1992).***

Other cutaneous findings can be seen in the face. Facial changes such as periorbital edema, a broadened nose, swollen lips, macroglossia, and a flat facial expression are pathognomonic of hypothyroidism ***(Daven et al., 2008).*** The dermatologic manifestations of hypothyroidism may vary depending on the extent and duration of thyroid disease ***(Burman and Mc Kinley-Grant, 2006).***

Many dermatological diseases are associated with hypothyroidism. Among these diseases are chronic urticaria (CU), vitiligo and alopecia areata (AA) which are associated with autoimmune hypothyroidism ***(Heymann, 1999).*** Chronic mucocutaneous candidiasis and acanthosis nigricans (AN) have been also reported in association with hypothyroidism but AN is not directly related to thyroid dysfunction but rather to the resulting effect of hypothyroidism including obesity and subsequent insulin resistance ***(Kuroki et al., 1999).***

The skin presents important external markers associated with thyroid disease that can signal dermatologists to investigate and diagnose thyroid disorder ***(Daven et al., 2008).***

AIM OF THE STUDY

The aim of this study is to assess cutaneous manifestations among patients with primary hypothyroidism.

HYPOTHYROIDISM

Hypothyroidism is one of the most common disorders encountered in an endocrine office practice. Hypothyroidism results from reduced TH actions at the peripheral tissues. This reduction in TH action is, in the vast majority of cases, secondary to reduced TH synthesis and secretion by the thyroid gland. Occasionally, peripheral resistance to TH is the culprit. The availability of sensitive biochemical tests and effective therapies has simplified the diagnosis and management of this endocrine condition ***(Madhuri et al., 2007).***

Epidemiology

Hypothyroidism is more common in women than in men (in the UK, female: male ratio of 6:1) ***(Vanderpump et al., 1995).*** In areas with high iodine intake, the incidence of hypothyroidism can be higher than in areas with normal or low iodine intake. In Denmark, where there is moderate iodine insufficiency, the overall incidence of hypothyroidism is 1.4/10,000 per year, increasing to 8/10,000 per year in people over 70 years ***(Laurberg et al., 1999).*** The incidence of subclinical hypothyroidism increases with age. Up to 10% of women over the age of 60 years have subclinical hypothyroidism (evaluated from data from the Netherlands and USA) ***(Canaris et al., 2000).***

According to the National Health and Nutrition Examination Survey (NHANES) III study, 4.6% of the population

in the United States suffers from hypothyroidism (0.3% overt and 4.3% subclinical) ***(Sandra et al., 2008).***

Pathophysiology

The normal thyroid produces all of the circulating thyroxine (T4) and about 20% of the circulating triiodothyronine (T3) ***(Surks et al., 1973).*** Because 80% of serum T3 is derived from the deiodination of T4 in tissues such as the liver and kidney, and as the TH receptor preferentially recognizes T3, T4 is considered a prohormone ***(Braverman et al., 1970).***

Most of the biologic activity of TH is due to the cellular effects of T3, which has a greater affinity for the TH receptor and is approximately 4-10 times more potent than T4 ***(Sawin et al., 1977).***

Early in the disease process, compensatory mechanisms maintain T3 levels. Decreased production of T4 causes an increase in the secretion of TSH by the pituitary gland. TSH stimulates hypertrophy and hyperplasia of the thyroid gland and thyroid T4-5'-deiodinase activity. This, in turn, causes the thyroid to release moreT3. Because all metabolically active cells require TH, deficiency of the hormone has a wide range of effects. Systemic effects are due to either derangements in metabolic processes or direct effects by myxedematous infiltration (ie, accumulation of glycosaminoglycans in the tissues) ***(Shikha et al., 2010).***

Etiology

A summary of the most common causes of hypothyroidism is given in table (1)

Table (1): Causes of hypothyroidism ***(Madhuri et al., 2007).***

Central hypothyroidism
* Pituitary tumors, metastasis, hemorrhage, necrosis, aneurysms
* Surgery, trauma
* Infiltrative disorders
* Infectious diseases
* Chronic lymphocytic hypophysitis
* Other brain tumors
* Congenital abnormalities, defects in thyrotropin releasing hormone (TRH), TSH, or both
Primary hypothyroidism
* Chronic autoimmune thyroiditis
* Subacute, silent, postpartum thyroiditis
* Iodine deficiency, iodine excess
* Thyroid surgery, I-131 treatment, external irradiation
* Infiltrative disorders
* Drugs
* Agenesis and dysgenesis of the thyroid

Central hypothyroidism

Central hypothyroidism is classically divided into secondary hypothyroidism, where the defect is in the pituitary gland, and tertiary hypothyroidism, where the defect is in the hypothalamus. From a practical Point of view, the end result is the same a reduction in the release of biologically active TSH. A variety of disorders can cause central hypothyroidism. In clinical practice, pituitary adenomas are the most common. Less prevalent conditions

include pituitary apoplexy and infiltrative disorders of the hypothalamus pituitary axis, such as sarcoidosis, tuberculosis, and other granulomatous diseases. Depending on the extent of the damage incurred by the hypothalamus-pituitary axis, central hypothyroidism may be reversible or permanent. Although isolated deficiency of TRH or TSH is possible ***(Doeker et al., 1998).***

The patient who has central hypothyroidism presents with deficiency of other pituitary hormones, and central hypothyroidism is only part of the larger clinical picture of hypopituitarism ***(Madhuri et al., 2007).***

Primary hypothyroidism

Primary hypothyroidism is responsible for the majority of hypothyroid cases ***(Madhuri et al., 2007).***

Hashimoto's Thyroiditis

The most frequent cause of acquired hypothyroidism is autoimmune thyroiditis (Hashimoto thyroiditis) (HT). The body recognizes the thyroid antigens as foreign, and a chronic immune reaction ensues, resulting in lymphocytic infiltration of the gland and progressive destruction of functional thyroid tissue. Up to 95% of affected individuals have circulating antibodies to thyroid tissue. Antimicrosomal or antithyroid peroxidase (anti-TPO) antibodies are found more commonly than antithyro-globulin antibodies (95% vs 60%). These antibodies may not be

present early in the disease process and usually disappear over time ***(Eskes et al., 2010).***

Hashimoto's thyroiditis has two variants, the goiterous and atrophic. Genetic differences have been identified; the atrophic form has been linked to HLA-B8 and HLA DRw3, whereas the hypertrophic form has been linked to HLA-DR5. In addition, the atrophic variant has been identified that is associated with cytotoxic thyroid antibodies that appear to cause thyroid atrophy ***(Daven et al., 2008).***

The appropriate evaluation of a patient with HT includes assessment of free T4, total T3, TSH, and thyroglobulin and thyroid peroxidase antibodies, if the diagnosis is in doubt, it might be reasonable to obtain a fine needle aspiration biopsy and also perform ultrasonographic examination and/or a radionuclide scan. However, the utility of a radionuclide scan has been diminishing with the advent of ultrasonography and fine needle aspiration biopsy ***(Uematsu et al., 1998).***

Other causes

Thyroidectomy and radioactive iodine therapy of patients who have Graves's disease, toxic thyroid nodules, or toxic multinodular goiters are common causes of hypothyroidism ***(Mc Henry and Slusarczyk, 2000).***

Hypothyroidism can occur after external radiation of the head and neck and after whole-body radiation. It usually takes

several years for hypothyroidism to develop in these circumstances ***(Mercado et al., 2001).***

Amiodarone and lithium are among a number of drugs that can cause hypothyroidism. Both drugs are widely used in clinical practice. Thyroid function tests should be obtained before initiating therapy with these agents and periodically thereafter. Other drugs include ethionamide, interferon alfa and interleukin-2. Thyroid function usually normalizes after discontinuation of these drugs ***(Madhuri et al., 2007).***

Very rarely, disorders such as metastatic disease to the thyroid gland or infiltrative disorders such as hemo-chromatosis or sarcoidosis can cause primary hypothyroid-dism ***(Fatourechi et al., 2003).***

Generalized resistance to TH is a rare, autosomal recessive disorder caused by mutations in T3 receptor gene ***(Brucker-Davis et al., 1995).*** The TSH level is usually normal. T4 and T3 levels are elevated. Patients who have this disorder are usually euthyroid and do not require TH replacement. Transient hypothyroidism usually occurs in the setting of thyroiditis ***(Pearce et al., 2003).***

There are several causes of possible transient hypothyroidism to include subacute thyroiditis, silent thyroiditis, and postpartum thyroiditis. Subacute thyroiditis is associated with neck discomfort that may radiate to the chest or jaw. It typically starts with a hyperthyroid phase with associated neck discomfort and then evolves into a

hypothyroid phase that is transient before returning to a euthyroid state ***(Fatourechi et al., 2003).***

The precipitating cause is likely a virus that injures the thyroid gland, resulting in release of stored TH and then gradual restoration of normal thyroid gland synthesis. Only very rarely is there permanent thyroid dysfunction. Silent thyroiditis is similar, but there is no associated thyroid or neck discomfort ***(Slatosky et al., 2000).***

Thyroid dysfunction typically occurs within the first 6 to 9 months after delivery, and hyperthyroidism or hypothyroidism may predominate. There may be evolution through different phases, and, in contrast to subacute thyroiditis, thyroid dysfunction may be permanent in some instances ***(Kenneth and Mc Kinley-Grant, 2006).***

It is well-known that iodine deficiency eventually leads to hypothyroidism due to the requirement of T4 and T3 to iodine ***(Mansourian et al., 2007).*** But there are some rare conditions in which the excess of iodine within the thyroid gland may cause the inhibition of T4 and T3 ***(Mansourian, 2010).***

Subclinical hypothyroidism

Subclinical hypothyroidism is defined as an elevated serum thyrotropin level in the presence of normal thyroid hormone concentrations. Subclinical hypothyroidism is frequently asymptomatic and is relatively common, being found in up to 10% of the adult population ***(Salman et al., 2012).***

Chronic autoimmune thyroiditis is the leading cause. Other common causes of subclinical hypothyroidism include thyroid ablation with radioactive iodine; partial thyroidectomy; antithyroid drugs; external beam radiation; drugs such as amiodarone, lithium, or radiographic contrast agents, and inadequate T4 therapy for overt hypothyroidism ***(Wartofsky et al., 2006).***

Natural history

Mild thyroid failure represents an early stage of thyroid disease, and it has been shown that there is progression to overt hypothyroidism in approximately 4% to 18% of patients who have subclinical hypothyroidism every year ***(Parle et al., 1991).***

The likelyhood of progression to overt hypothyroidism increases in the presence of antithyroid antibodies, positive history of radioiodine ablation therapy, history of external radiation therapy for nonthyroid malignancies, and chronic lithium treatment ***(Madhuri et al., 2007).***

Symptoms

Patients who have subclinical hypothyroidism may be asymptomatic or may present with vague, nonspecific symptoms like fatigue, generalized weakness, depression, and memory, cognitive, and sleep disturbances. As in other thyroid disorders, there is a female preponderance. Women who have subclinical hypothyroidism may present with menstrual irregularities such as menorrhagia or fertility problems ***(Madhuri et al., 2007).***

Clinical Manifestations of hypothyroidism

The manifestations of hypothyroidism result from a reduction in metabolic activity and a deposition of glycosamino-glycans. Clinical findings that may be seen in hypothyroidism are listed in Table (2)

Table (2): Clinical findings in Hypothyroidism ***(Bhuvana et al., 2002).***

System	Symptoms	Signs
General	Fatigue/lethargy	Periorbital edema
	Weakness	Pallor
Endocrine	Swelling of thyroid	Goiter
	Menorrhagia	Galactorrhea
Metabolic	Cold intolerance	Hypothermia
	Weight gain	Obesity
Psychiatric	Depression	Depression
Musculoskeletal	Arthralgia; myalgia	
Skin	Decreased perspiration	Brittle nails
	Hair loss	Reduced skin turgor; Alopecia/coarse hair; Carotenemia
Gastrointestinal	Constipation	Megacolon
	Decreased appetite	
Respiratory	Snoring	Hypoventilation; sleep apnea
Cardiovascular Bradycardia	Dyspnea	Hypertension*; Pericardial effusion; Cardiomegaly/CHF
Nervous system	Paresthesia	Bradykinesia
	Numbness	Distal sensory loss
	Unsteadiness	Ataxia
	Reduced mentation	Dementia; Hyporeflexia; Pseudomyotonia; Headache; visual disturbances†

* Diastolic hypertension. † Findings in secondary hypothyroidism. CHF = Congestive heart failure.

It is important to note that symptoms may be nonspecific in the early stages of hypothyroidism and do not necessarily occur in sequence. These symptoms may include myalgia, arthralgia, muscle cramps, dry skin, headaches, and menorrhagia. Brittle nails, thinning of hair, pallor, and symptoms of carpal tunnel

syndrome may also be seen. The characteristic delayed-relaxation phase of deep tendon reflexes may be noted, along with relative macroglossia. As hypothyroidism becomes more marked, hoarseness, peripheral edema, constipation, dyspnea, and weight gain may be seen. Other manifestations include pericardial effusion, ascites, decreased hearing, diastolic hypertension, galactorrhea, and hypothermia, along with neuropathy, ataxia, and sleep apnea. Psychiatric presentations may include depression, cognitive impairment, dementia, personality change, and, rarely, frank psychosis ***(Hickie, 1996).***

Primary pulmonary hypertension is often complicated by coexisting hypothyroidism ***(Bogaard et al., 2012).*** Anemia is a relatively frequent finding in overt hypothyroidism. Anemia that normalizes in response to T4 replacement ***(Hakan et al., 2009).***

Macrocytosis is a well-described feature of untreated hypothyroidism. Myopathy may be a dominant presenting feature in some patients with hypothyroidism ***(Cruz et al., 1996).***

Myxedema coma

Myxedema coma is a term used to describe severe manifestations of hypothyroidism. In the past, the overall mortality rate for myxedema coma was 60% to 70%. Early diagnosis and advances in intensive care and management have reduced the mortality to 20% to 25% ***(Rodriguez et al., 2004).*** Myxedema coma can be precipitated by factors such as hypothermia, acute cardiovascular events such as myocardial

infarction and stroke, infection, drugs that can compromise the central nervous system, trauma, and gastrointestinal bleeding ***(Madhuri et al., 2007).***

If hypothyroidism remain unnoticed or unmanaged for a considerable of time the auto-regulatory mechanism collapse and affected individual cardio vascular, respiratory and central nervous system function all are disrupted. The clinical manifestations of affected patients and subsequent symptom eventually enter the affected individual into the comatosed myxedema ***(Mansourian, 2010).***

The typical clinical manifestations including adverse modification of psychomotor ability, intolerance to cold and actual hypothyroidism to the level of life threatening state, finally other metabolic syndrome including heart and cerebral dysfunction are universally accepted conditions of severe hypothyroidism patients, with possibility of entering into a myxedema coma with eventual death if the patient was left undiagnosed and untreated ***(Fliers and Wiersinga, 2003).***

Metabolic Effects of Hypothyroidism

Thyroid hormone deficiency slows metabolism, resulting in a decrease of resting energy expenditure, oxygen consumption, and utilization of substrates. Reduced thermogenesis is related to the characteristic cold intolerance of hypothyroid patients ***(Wiersinga, 2010).***

Changes in protein metabolism

In general, both the synthesis and the degradation of proteins are reduced, but hypothyroid patients are in positive nitrogen balance. Despite both a decrease in the rate of albumin synthesis and degradation, the total exchangeable albumin pool increases in myxedema. A synthesis of thyroid hormone-responsive proteins is clearly reduced in the hypothyroid state, whereas that of proteins such as TSH or glycosaminoglycans may be increased under the same circumstances ***(Wiersinga, 2010).***

Changes in carbohydrate metabolism

Carbohydrate metabolism is also altered and intestinal absorption of glucose is reduced. In practice the patients experience some type of fasting hypoglycemia which may be due to reduction in gastrointestinal motility ***(Mansourian, 2010).***

Gluconeogenesis is decreased in hypothyroidism due to decreased availability of amino acids and glycerol. The latter is caused by diminished glycerol release from adipocytes. Although