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Causes, Diagnosis, and Management of Hypothyroidism

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ABSTRACT

Background: Among hormone deficiency, hypothyroidism is considered to be the most common disease, and is subdivided into congenital or acquired, based on the onset. The exact site of dysfunction can further classify the disease into primary and secondary. It is crucial to determine the level of severity of the disease as severe cases may end up in a coma. On the other hand, mild cases may be asymptomatic. Diagnosis is mainly based on serum thyroid hormones levels, and the treatment depends on thyroxine administration with an excellent prognosis.

Aim of this review: was to explore the types of hypothyroidism, its diagnosis, and study the best course of management that must be followed.

Methodology: We conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE, January 1985, through February 2017. The following search terms were used: hypothyroidism, myxedema, classification of thyroid diseases, investigation of hypothyroidism, management of hypothyroidism.

Conclusion: Hypothyroidism is a common disease that usually affects females more than males. Populations at higher risk include, old women, pregnant women, dyslipidemic patients, and patients with a history of radiation exposure. Diagnosis is based on measurement of TSH along with the thyroid hormone levels. Management includes administration of thyroxine, and must be done early.

Keywords: hypothyroidism, myxedema, manifestation of hypothyroidism, thyroid diseases, management of hypothyroidism

INTRODUCTION

The hypothalamaic-pituitary-thyroid axis works as a feedback loop that plays as the main system regulating thyroid hormone secretion normally. This loop starts with the hypothalamus that secretes the thyrotropin-releasing hormone (TRH), which in turn, induces secretion of thyrotropin from the anterior pituitary (the thyrotroph cells specifically). Thyrotropin will induce secretion of tri-iodothyronine (T3) and thyroxine (T4) from the follicular cells of the thyroid. When T3 and T4 serum levels become sufficient, this will suppress the release of TRH and thyrotropin from the hypothalamus and the pituitary. Most T3 present in the serum is the result of peripheral deiodination of T4, with only twenty percent secreted from the thyroid [1].

Among hormonal deficiencies, hypothyroidism is considered to be the most common disease, and is subdivided into congenital or acquired, based on the onset. The exact site of dysfunction can further classify the disease into primary and secondary (central). Hypothyroidism is also divided according to severity into subclinical (mild) or severe (clinical) hypothyroidism. It is crucial to determine the level of severity of the disease as severe cases may end up in a coma, whereas mild cases may be asymptomatic. Diagnosis is mainly based on serum thyroid hormones levels, and the treatment depends on thyroxine administration with an excellent prognosis [2].

METHODOLOGY

- **Data Sources and Search terms**

We conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE, January 1988, through February 2017. The following search terms were used: hypothyroidism, myxedema, classification of thyroid diseases, investigation of hypothyroidism, management of hypothyroidism

- **Data Extraction**

Two reviewers have independently reviewed the studies, abstracted data, and disagreements were resolved by consensus. Studies were evaluated for quality and a review protocol was followed throughout.

Etiology

Primary hypothyroidism

When the pathology is in the thyroid gland itself, it is considered primary hypothyroidism. About half primary hypothyroidism cases are due to autoimmune destruction (like chronic autoimmune thyroiditis). The other half is due to other etiologies or exposures. Silent thyroiditis and postpartum thyroiditis are classified as a result of chronic autoimmune thyroiditis [3].

The prevalence and incidence if chronic autoimmune thyroiditis is about five times higher in women than men, and usually affects middle aged women as well as elderly and children. On histology, diffuse infiltrates of lymphocytes are present with the

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presence of circulating antibodies in most patients [4]. In fact, about 95% of chronic autoimmune thyroiditis have high levels of anti-TPO antibodies, and about 60% of patients have antithyroglobulin antibodies especially in atrophic forms. Micronodular goiter is strongly associated with Hashimoto's thyroiditis [5].

The development of chronic autoimmune thyroiditis is linked with several genetic and environmental factors. Genetic factors are relatively few and mainly include the HLA complex, and the CTLA-4. However, it is still unknown how these genes predispose to the development of Hashimoto thyroiditis [6].

Among environmental and exposure factors, infections and iodine intake are the most common factors which contribute to Hashimoto thyroiditis. Present evidence suggests that several infections are strongly associated with the disease. For example, EBV antibodies were found to be present in higher levels in children with the disease. Acute parvovirus B19 infection was also associated with the development of Hashimoto thyroiditis in children. The mechanisms of these associations are not well known, but it is thought that molecular mimicry is the main mechanism by which autoimmunity will cause tissue destruction [7; 8]. In areas where iodine is deficient, levels of antithyroid antibodies were found to have lower prevalence when compared to areas where iodine is well provided. Overt hypothyroidism incidence was found to have a higher incidence in areas where salt iodination is applied. Iodine plays an important role in increasing thyroglobulin antigenicity and reacts with oxygen metabolites to produce iodine free radicals that are thought to predispose to inflammation [9].

Within the first year following delivery, up to 10% of women can suffer from postpartum thyroiditis that is associated with elevated levels of antithyroid antibodies. Postpartum thyroiditis typically presents with initial hyperthyroidism that will turn into hypothyroidism, most cases resolve spontaneously without treatment. More severe cases will require thyroxine administration. In about quarter of cases, women can suffer from hypothyroidism for periods as long as four years [10]. A mild recent hyperthyroidism can be the classical presentation of silent thyroiditis that occurs due to the secretion of thyroid hormones into the circulation. About half of the cases will turn into a transient hypothyroid status that will resolve spontaneously in most cases. However, rare cases can develop permanent hypothyroidism [2].

The most common cause of hypothyroidism in developing countries is iodine deficiency, which will cause hypothyroidism along with goiter. Ingestion of iodine in large amounts can lead to a transient hypothyroidism status that is known as the Wolff-Chiacoff effect. The Wolff-Chiacoff effect is a result of synthesis inhibition in the thyroid itself [10].

Radiotherapy and whole body radiation were also found to cause significant injury to the thyroid leading to symptomatic hypothyroidism that presents after a relatively long time following radiation exposure. Pharmacological agents that cause hypothyroidism include amiodarone, interferon-alpha, lithium and the tyrosine kinase inhibitor sunitinib [11]. Secondary (central) hypothyroidism

When the pathology leading to hypothyroidism is present in the pituitary or the hypothalamus, the disease is then called secondary hypothyroidism. In secondary hypothyroidism there is a decline in the synthesis and secretion of TSH that will in turn lead to decreased thyroid hormone levels. In fact, secondary hypothyroidism can be further subdivided into secondary and tertiary, when the cause is in the pituitary or the hypothalamus, respectively. Secondary hypothyroidism can occur as a result of several disorders including pituitary adenomas, radiotherapy, and surgery [2].

Diagnosis

Clinical Examination

The most important determinant of the clinical picture is the severity of the underlying pathology, and the degree it alters biochemical and physiological reactions. Usually, symptoms start as mild manifestations, and patients are usually similar to euthyroid individuals. As time passes, symptoms will increase and patients will start to complain of the disease. A previous study has found that less than one third of hypothyroid patients were symptomatic. Increased weight gain is a classical presenting symptom that may suggest a diagnosis of hypothyroidism. However, some hypothyroid patients may lose body weight. When hypothyroidism is severe, several other manifestations develop including pericarditis, intestinal obstruction or pseudo-obstruction, congestive heart failure, pleural effusion, coagulopathies, depression, ataxia, apathy, psychosis, seizures, and even coma. Dementia and other neurocognitive disorders can also develop in severe cases [12; 13].

Investigations

The first step in diagnosing hypothyroidism is the measurement of T4 and TSH. This will also differentiate primary from secondary hypothyroidism. Elevated TSH levels with reduction in T4 levels usually indicates primary hypothyroidism. The etiology of this primary hypothyroidism is later determined by further investigations like measuring anti-TPO and antithyroglobulin (anti-Tg) antibodies. When TSH levels are elevated with normal T4 levels,

hypothyroidism is considered subclinical. On the other hand, a diagnosis of a secondary hypothyroidism is made when there levels of both TSH and T4 are decreased. TRH levels are further measured to determine the exact site of pathology in secondary hypothyroidism [14].

Treatment

Thyroxine is administrated in all cases of hypothyroidism and is considered the mainstay of therapy. Following administration, thyroxine will peripherally convert into T3. The initial dose of thyroxine is determined based on several factors that include age, weight, comorbidities, and the presence of arrhythmias. The usual dose in adults is 1.8 µg/kg body weight. However, cautious measures should be taken when dealing with elderly, and the complete dose should not be started suddenly. Following administration of therapy, TSH levels should be measured every 6 weeks until it becomes normal. Then, it will be measured once a year for follow up [15; 16]. Extremely severs hypothyroidism will cause myxedema coma, and usually develops following a long untreated case of hypothyroidism. Myxedema coma was associated with a mortality on 70% but medical advances caused a significant decrease in mortality rates, which is still, however, relatively high and can reach 25%. A large dose of 400 g intravenous thyroxine should be initially given. After two days, normal dose is given. Hydrocortisone should also be given on the first day, along with other modalities to treat associated hypoglycemia, hypothermia, hypercalcemia, hypotension, and/or hyponatremia [17].

On the other hand, overestimation of thyroxine dose has been associated with several severe consequences like atrial fibrillation, coronary artery disease, and osteoporosis (in women older than 65 years) [18].

CONCLUSION

Hypothyroidism is a common disease that usually affects females more than males. Diagnosis is based on measurement of TSH along with the thyroid hormone levels. Populations at higher risk include old women, pregnant women, dyslipidemic patients, and patients with a history of radiation exposure.

Intake of drugs like amiodarone and lithium is also associated with relatively high incidence of hypothyroidism. Long term therapy of thyroxine is usually the mainstay of treatment and should be initiated as soon as possible.

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