Review Article Open Access

Thyroid disorders in elderly people: challenges, pearls and updates

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Abstract

Hypothyroidism is common in elderly people and a part of hyperthyroid people are elderly. Thyroid disorders are associated with many of geriatric giants like dementia, osteoporosis and frailty, so screening is recommended especially in elderly females. Diagnosis may be challenging, and requiring physicians' attention. This review gives highlights on epidemiology, age related changes, presentation, challenges with diagnosis and treatment, complications, relation to Alzheimer's disease myths and reality, what is new in thyroid and role of resveratrol

Keywords: Hypothyroidism- Hyperthyroidism- Elderly

Background

Thyroid diseases are common in elderly population. They are also more challenging because of the occurrence of age related changes in the thyroid gland leading to subtle symptoms, increase in subclinical hypothyroidism and hyperthyroidism, in addition to atypical presentation. Thyroid disorders are associated with significant morbidity and careful clinical evaluation and interpretation of laboratory tests is warranted to ensure adequate and correct management [1, 2]

Epidemiology of thyroid diseases

Primary hypothyroidism which is the most common hormone deficiency, increases in incidence with age and occurs more frequently in elderly women than in men [3]. It occurs in about 10% of women and 2% of men after the age of 60 years [4]. In contrast, hyperthyroidism is more common in the younger population. Although the prevalence in the elderly is about 2% in women and much less in men; which is lower than hypothyroidism, from another perspective, 10 to 15% of patients diagnosed with hyperthyroidism are older than 60 years [5, 6].

Changes of thyroid functions with aging

With increasing age, the thyroid gland undergoes fibrosis and atrophy which are progressive, leading to reduction in thyroid size and weight, making palpation of the gland a difficult issue and can be misleading in clinical examination [7]. Prevalence of thyroid autoantibodies increases with age, especially women over the age of 60 years, and this can be partly responsible for some of the anatomic changes in the thyroid gland [8].

Iodine uptake by the gland decreases with age. As a result, T4 secretion decreases in the elderly. This reduction is compensated by decreased T4 clearance due to decreased 5'deiodinase activity with increasing age leading to maintenance of normal T4 level. A number of previous studies in healthy elderly people found a decline in free T3 levels with age, associated with an increase in reverse T3 [9,10]. Studies found that thyroid stimulating hormone (TSH) concentration has a physiological shift and increases with age, this change may be a normal adaptive response associated with aging or may be abnormal function of the thyroid gland [11]. Other studies have demonstrated normal thyroid function until the age of 80 years, with increase in serum TSH and a decrease in serum free T3 concentrations only in centenarians [12].

Subclinical hypothyroidism

Subclinical hypothyroidism is characterized by increased serum TSH with normal serum free T4 and free T3 levels. It can be subdivided on the basis of serum TSH concentrations into mild form (serum TSH 4.5–9.0 mIU/l) and severe forms (TSH ≥10.0 mIU/l) [13]. Prevalence increases in elderly people and is considered the most common thyroid disorder in elderly people. It is seen in up to 7–10% of women over the age of 60 years [14], so it is recommended to screen for thyroid problems in elderly people with TSH level, especially elderly women. It was found to be associated with increased levels of anti-thyroid peroxidase (TPO) antibody. However when considering the increase in TSH level with age , the prevalence of subclinical hypothyroidism can, therefore, be overestimated unless age-specific reference ranges are available [11,15].

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Clinical outcome

Increased risk of heart failure was found in patients with subclinical hypothyroidism aged >65 years. Some studies recorded an increased incidence of heart failure only if serum TSH levels is above >10 mIU/l [16, 17]. Results of epidemiological studies regarding cardiovascular disease were inconsistent. Numerous large cohort studies found that total mortality was not increased, although the risk of coronary heart disease (CHD) events and mortality because of CHD increased in the severe form; with TSH levels 10 mIU/l or higher [18].

Regarding cognitive function and psychological problems, some studies have demonstrated that subclinical hypothyroidism in elderly people is not associated with cognitive impairment, or depression. Also it is not related to poor physical function or poor quality of life. In contrast, other studies demonstrated the presence of mild cognitive impairment and even dementia in those elderly people [19, 20].

Treatment

Any decision about treatment should consider comorbid cardiovascular disease, level of TSH and the presence of frailty. It is almost universally accepted to treat patients presented with high TSH levels (≥10 mIU/L) and normal FT4, while there is controversy about when to treat patients presented with TSH between 4.5 and 10 mIU/L [21,22]. According to the American Association of Clinical Endocrinologists (AACE) and the American Thyroid Association (ATA), in patients with TSH between 4.5 and 10, treatment can be given to patients with evidence of heart failure, atherosclerotic cardiovascular disease, symptoms related to hypothyroidism and positive TPO antibody [21]. Elderly people with TSH level above the upper limit of normal should be reassessed 6 to12 months later to confirm the presence of persistent subclinical hypothyroidism and exclude that this is a transient increase in TSH level, which may represent a brief disturbance of the pituitary–thyroidal axis [23]. For elderly patients, a small dose of Levothyroxine should be started, 25 or 50 μg daily and even 12.5 ug per day in cardiac patients to avoid complications. The dose of Levothyroxine should be increased gradually till reaching a full replacement dose [24]. The response to treatment depends on the presence or absence of thyroid antibodies and the level of TSH levels. Thus, there is high rate of reversion of subclinical hypothyroidism to normal euthyroid state in elderly people with lower baseline TSH levels and negative TPO antibody. Moreover, TSH levels ≥ 10mIU/l were independently associated with progression to overt hypothyroidism [25].

Overt Hypothyroidism

Prevalence of hypothyroidism increases with aging. Hashimoto thyroiditis which is due to autoimmune thyroid failure is the most common cause of hypothyroidism in the elderly. Iatrogenic hypothyroidism after surgery or radioiodine ablation is also an important cause. Incidence of hypothyroidism due to drugs like amiodarone and radioiodine contrast agents is high in elderly people [26, 27].

Elderly patients with hypothyroidism mostly present with fatigue, weakness and present also with mental slowness, drowsiness, depression, dry skin and constipation. Classical cold intolerance and weight gain seen in younger patients may be absent in the elderly. Symptoms of hypothyroidism are often missed because they are attributed to normal age related changes, so physicians should have a high index of suspicion. It is important to say that depression and dementia in the case of hypothyroidism are reversible. Hypothyroidism can also present with cerebellar dysfunction, macrocytic anemia, and peripheral neuropathy and is associated with dyslipidemia [28, 29].

Treatment

Guidelines recommend a starting dose of levothyroxine of 50 μg daily in people aged 50–60 years with no evidence of CHD. In patients with known CHD, the usual starting dose should be reduced (typically to 12.5–25.0 μg daily) and clinical monitoring for fear of occurrence of angina symptoms is essential. Serum TSH level should be rechecked 4–8 weeks after either the start or change of levothyroxine dose and every 6–12 months once an adequate replacement dose has been determined. It should be taken on empty stomach and should be separated from other drugs affecting absorption like calcium, iron supplements, bisphosphonates and proton pump inhibitors by at least 4 hours [21].

Subclinical Hyperthyroidism

Subclinical hyperthyroidism is defined biochemically as low TSH levels in the presence of normal free T4 and free T3. It occurs in 1-5% of the elderly population if endogenous, whereas the prevalence increased when considering iatrogenic hyperthyroidism [30].

Clinical outcome

Some studies report increased risk of coronary artery disease and cardiovascular mortality with subclinical hyperthyroidism. Recent studies found that higher free T4 levels even within the normal range greatly affects morbidity. It was associated with frailty in men over the age of 70 years and lower values of hip bone mineral density, increasing ten year fracture risk in postmenopausal women [31, 32].

Treatment

Guidelines published by the ATA and The AACE, recommend treatment of subclinical hyperthyroidism in the elderly over the 65 years when the TSH is <0.1

mIU/ml and to consider treatment when the TSH is between 0.1 and 0.5 mIU/ml. They suggest treating elderly patients with persistently (more than 3–6 months) subnormal TSH levels but >0.1 mIU/ml on follow up of thyroid functions, especially when associated with cardiac disease or symptoms attributed to hyperthyroidism and osteoporosis [33].

Overt Hyperthyroidism

Graves' disease is the most common cause of hyperthyroidism across all age groups. However the incidence of toxic multinodular goiter increases with age and is more frequent in areas of deficient iodine intake. Also iodine induced thyrotoxicosis has a higher incidence in the elderly; due to increased intake of iodine containing drugs like amiodarone, mucolytics or lithium and the use of radio-contrast dyes in different investigations [8, 34].

Hyperthyroidism in elderly people represents a diagnostic challenge due to atypical presentations. Atrophy of thyroid gland with increasing age makes the clinical diagnosis difficult with difficulty palpating the gland. The classical signs and symptoms of hyperthyroidism present in the younger age group, like tremors, weight loss, diarrhea and heat intolerance, may be absent in the elderly [35]. The presentation may be mainly with cardiac problems, like atrial fibrillation (even with slow ventricular response), symptoms of heart failure or angina. The term "apathetic thyrotoxicosis" is used to describe the symptoms in patients who present with depression and lethargy. On the contrary, some elderly patients present with "thyrotoxic encephalopathy" with agitation and confusion. Sometimes thyrotoxicosis is mistaken for malignancy because of decreased appetite and weight loss. It can aggravate postmenopausal osteoporosis in elderly women [34, 36]. Although graves ophthalmopathy is less common than young adults, when it occurs is more severe [37].

Diagnosis

Elevated levels of free T4 and low levels of TSH suggest primary hyperthyroidism. If free T4 levels are normal with a low TSH level, the free T3 level should be measured to rule out T3-toxicosis. Isolated low TSH can be seen in patients receiving steroid therapy and in patients with non-thyroidal illness. Unfortunately in radio-imaging, nuclear uptake can be normal in up to 30% of the elderly patients with Graves' disease and 70% of toxic multinodular goiter, so it is not useful to rule out hyperthyroidism. A decreased uptake scan can suggest thyroiditis [38]

Long-term outcome

Atrial fibrillation is an independent predictor of mortality in people suffering from thyroid dysfunction and represents one of the most serious consequences of hyperthyroidism with increasing risk of embolic events and cerebrovascular stroke. Hyperthyroidism is also associated with other cardiovascular complications including ischemic heart disease and congestive cardiac failure, as well as increased all-cause and cardiovascular mortality, and this occurs in all age groups [39, 40].

Overt hyperthyroidism is also associated with increased risk of osteoporosis and ten year fracture risk. Moreover, subclinical hyperthyroidism and long-term exogenous suppressive doses of levothyroxine also reduce bone mineral density. In a cohort study of hundreds women over the age of 65 years, the risks of vertebral and hip fractures were increased in those with baseline serum TSH levels <0.1 mIU/l compared with those with normal TSH levels [41, 42].

Treatment

Owing to the increased incidence of toxic nodular hyperthyroidism in the elderly [43, 44,] administration of radioactive iodine should be the preferred treatment approach.

Surgery can be an alternative approach in some patients. However, it is frequently contraindicated because of the presence of multiple comorbidities [45, 33.]

Anti-thyroid drugs are unlikely to induce permanent cure in toxic nodular hyperthyroidism but can be indicated for the treatment of individuals with limited life expectancy or if there are difficulties adhering to radiation protection regulations and also before the start of radioactive iodine to avoid the occurrence of thyrotoxic crisis. In patients with Graves' disease, antithyroid drugs can be given, and rates of remission are higher in older than with younger people, but there is a risk of agranulocytosis and dose dependent elevation of liver function tests [46, 47].

Thyroid and Alzheimer's disease (AD), is there a myth?

In the past, several studies was performed showing either no association or an association between hypothyroidism and AD and hypothyroidism is considered a cause of reversible dementia [48, 49]. In contrast, a more recent study showed that subclinical hyper- rather than hypothyroidism was associated with a higher risk for AD. These mixed findings may result from limitations in the methodology of study designs. To date, there are few prospective studies that have examined the association between hyperthyroidism and AD. In the Rotterdam Study, researchers found that sub-clinical hyperthyroidism was associated with a higher risk for dementia and AD after a two-year follow-up period [50].

In patients with overt hyperthyroidism, the toxicity of thyroid hormone excess to brain is thought to have direct effects on the processing of cerebral amyloid-β proteins and/or local synthesis and release of acetylcholine from neurons. Thyroid hormone was

shown to regulate gene expression of amyloid-β protein precursor (APP). In parallel, thyroid releasing hormone (TRH) depletion is associated with enhanced phosphorylation of tau protein. Increased oxidative stress has been detected in patients with hyperthyroidism, and exposure to thyroid hormone was reported to enhance neuronal death [51, 52].

The hippocampus is involved in the basal activity of the thyroid axis through hippocampal-hypothalamic connections. With decreasing TRH gene expression in the hypothalamus, the hippocampus has a negative effect on this axis. In AD there is early neuro-degeneration in the hippocampus, this leads to less feedback on the hypothalamo-pituitary-thyroid axis, and then higher levels of free T4 follow these changes [53]. The finding that higher serum freeT4 levels are associated with smaller hippocampal volumes on MRI scans of non-demented elderly people may support this hypothesis [54].

Thyroid functions and longevity

In 2009, Atzmon et al [55] studied the effect of changes in thyroid functions in centenarians of Ashkenazi Jews free from thyroid diseases; who are characterized by exceptional longevity. Serum TSH level was higher in those people, compared to younger Ashkenazi Jews, as well as to control group who were obtained from The National Health and Nutrition Examination Survey (NHANES) studies.

In another study, the role of genetic predisposition in people with exceptional longevity was assessed. Two single nucleotide polymorphisms (SNPs) in TSH receptor (TSHR) gene were found to be associated with increased TSH level in the Ashkenazi Jewish centenarians and their offsprings [56]. In addition, higher TSH associated with lower T4 levels may indicate that lower activity of the pituitary-thyroid axis is a heritable phenotype that can contribute to exceptional longevity in some families [57].

What is new in thyroid research?

The effect of resveratrol; the component of the red grape on iodide uptake has been studied recently. It can increase the uptake of radioiodine by 3.5-fold and elevate the sodium iodide symporter (NIS) protein level by 3-fold at the same time. It is interesting to know that resveratrol increases NIS in a dose and time-dependent manner in TSH deprived cells [58].

These findings can be of great interest, considering the possibility of regulation of iodide transport by resveratrol and its potential application in the treatment of differentiated thyroid carcinoma refractory to radioactive iodine. However, because the magnitude of iodide uptake is low and does not reflect a curative dose for tumors, more studies are needed before introducing resveratrol into clinical oncology [59].
Moreover, resveratrol is a well-known antioxidant agent and free radical scavenger. This property can be of interest in thyroid diseases accompanied by increased production of radical oxygen species, such as autoimmune thyroiditis and Graves' disease. Whether it can be used combined with methimazole in patients with Graves' disease or not, needs further study [60].

Key messages

Thyroid disorders in elderly population need attention. Changes occur with aging in both the gland and functions. Presentation of both hyper and hypothyroidism is different from younger people with more subtle and atypical symptoms leading to difficulty in diagnosis. Timely management is needed to decrease morbidity and mortality especially in patients with hyperthyroidism.

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