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HYPERTHYROIDISM IN ELDERLY PATIENTS AND HYPERTHYROID MYOPATHY: CASE REPORT AND LITERATURE REVIEW

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Abstract: Hyperthyroidism is the excessive production of thyroid hormone causing palpitation, hypertension, weight loss, heat intolerance, tremor, anxiety, etc. Hyperthyroidism in elderly patients does not display typical features, making diagnosis difficult. Hyperthyroid myopathy in elders is often mistaken for normal aging. It involves mostly proximal muscles for unclear reasons. This case reports hyperthyroidism in an elderly patient. A 70-year-old female was presented with chest discomfort intermittently for over 10 years and exacerbated for 10 days. This discomfort was described as chest tightness and palpitation. She also experienced shortness of breath. On physical examination, an enlarged thyroid was palpated. Thyroid ultrasound revealed diffuse thyroid nodules. Thyroid function tests showed increased free and total triiodothyronine, free thyroxine, thyrotropin receptor antibodies, as well as a decreased thyroid-stimulating hormone. Her clinical findings and lab tests were consistent with Graves' disease, a condition of hyperthyroidism. Her condition was well managed with an antithyroid drug and beta-blocker. Hyperthyroidism in elderly patients may present only with cardiovascular disorders such as atrial fibrillation. In this case, the patient only displayed chest tightness and palpitation. Diagnosing hyperthyroidism in elders requires vigilance and we should not dismiss any diagnostic hint. Through literature review, a potential link between hyperthyroid myopathy and mitochondrial pathology is observed, which can be further investigated using mitochondrial histochemistry and beta-blockade experiment. This study hopes to promote awareness of thyroid diseases in the elderly population and address the issue of myopathy in elders due to thyroid diseases.

Keywords: hyperthyroidism, senile hyperthyroidism, Graves' disease, hyperthyroid myopathy, mitochondrial myopathy, elderly patients

Introduction

Hyperthyroidism is a condition of thyroid hormone overproduction by the thyroid gland. Too much thyroid hormone sensitizes the tissues to catecholamines causing palpitation, hypertension, weight loss, heat intolerance, tremor, anxiety, etc. (O'Neill et al., 2007; Paravati et al., 2021).

Elderly patients are at high risk for thyroid disease and other metabolic diseases. Older patients with hyperthyroidism may only have a few symptoms and typical clinical manifestations are often absent, making diagnosis difficult (Liu et al., 2021). Symptoms in the elderly may be mistakenly attributed to normal aging or coexisting illnesses. Older patients may nonspecifically present with cardiac or

systemic disorders such as atrial fibrillation or general weakness (Rehman et al., 2005). Thyroid gland shrinks with age also making it challenging for physical diagnosis through palpation (Rehman et al., 2005; Riek et al., 2020). Therefore, missed or misdiagnosis is common in elderly patients due to the subtleness or absence of symptoms.

The diagnosis and treatment of hyperthyroidism in elders are nonetheless important because of the higher prevalence of subclinical hyperthyroidism among older populations (Vidili et al., 2020). Among hyperthyroidism patients, 10% to 15% of them are 60 years or older (Kennedy et al., 1996). With many of them remaining subclinical, it is difficult to diagnose and treat. Older patients with thyroid diseases have a higher risk of coexisting cardiovascular and central nervous system diseases (American Thyroid Association [ATA], n.d.; Vidili et al., 2020).

Hyperthyroid myopathy is a non-hereditary autoimmune muscle disease caused by excessive thyroid hormones (Muscular Dystrophy Association [MDA], n.d.). It causes muscle weakness, particularly in the proximal muscles. Masked by normal aging, this concomitant of hyperthyroidism is also easily missed in elderly patients.

This case report presents an elderly patient with hyperthyroidism who did not display other classical hyperthyroidism symptoms aside from chest discomfort. Hyperthyroid myopathy is also examined through literature review to understand its pathophysiology.

Case Presentation

Chief complaint and history

A 70-year-old woman had intermittent discomfort in the precordial region for over 10 years. Her precordial discomfort included chest tightness and palpitation. Each episode lasted for a few minutes and was alleviated after resting. 10 days before admission, the symptoms of chest tightness, shortness of breath, and palpitation were more severe and prolonged. She had a history of hypertension.

Physical examination

Palpation revealed enlarged thyroid (Grade I°). The thyroid's consistency was fair and there was no pain on palpation.

Laboratory tests

Thyroid function tests were performed. The results showed an increase in free triiodothyronine (FT3), free thyroxine (FT4), total triiodothyronine (TT3), and thyrotropin receptor antibodies (TRAb); and a decrease in thyroid-stimulating hormone (TSH) (Table 1).

Table 1: Thyroid function test results

Description	Value	Reference interval
FT3	6.38 pg/mL ↑	2 - 4.4 pg/mL
FT4	2.00 ng/dL ↑	0.93 - 1.7 ng/dL

TT3	281.3 ng/dL ↑	80 - 200 ng/dL
TT4	12.43 ug/dL ↔	5.1 - 14.1 ug/dL
TSH	0.005 µIU/mL ↓	0.27 - 4.2 µIU/mL
TRAb	3.05 IU/L ↑	< 1.75 IU/L

FT3, free triiodothyronine; FT4, free thyroxine; TT3, total triiodothyronine; TT4, total thyroxine; TSH, thyroid-stimulating hormone; TRAb, thyrotropin receptor antibodies

Imaging test

Thyroid ultrasound revealed diffuse thyroid nodules and bilateral multiple cystic structures on thyroid lobes.

Diagnosis

The patient was diagnosed with Graves' disease (GD). The diagnosis was based on the symptoms of increased metabolism (heart palpitations, sweating, and weakness), enlarged thyroid glands (Grade I°, fair consistency with no palpitation pain), and thyroid function tests (↑ FT3, ↑ FT4, ↓ TSH, ↑ TRAb).

Management

To manage, beta-blocker bisoprolol was given to treat hypertension and methimazole (MMI) was given as antithyroid agent.

Discussion

The prevalence of hyperthyroidism, subclinical hyperthyroidism, and GD in the elderly population approximately ranges from less than 1% to over 3% among different populations (Cappola et al., 2006; de Jongh et al., 2011; Liu et al., 2021; Maugeri et al., 1996; Wang et al., 2021). It is not a matter of insignificance, especially in this rapidly aging society.

Younger patients of hyperthyroidism have classical manifestations showing multiple symptoms, yet the elderly patients may only have a couple of or even an absence of symptoms. Hyperthyroidism in the elderly population is of concern because of an increased risk of coexisting cardiovascular, nervous system, and metabolic diseases (ATA, n.d.; Liu et al., 2021).

In the study by Bhalla et al. (2021) involving patients aged 60 or above, they suggest an association between low TSH (which occurs in hyperthyroidism and GD) and frailty. Subclinical hyperthyroidism is also associated with an increased risk of vertebral fractures among elderly men (Svensson et al., 2021).

COVID-19 is also a risk factor for hyperthyroidism (Kahaly, 2020). Recent clinical observations have suggested the link between SARS-CoV-2 infection and GD relapse. Therefore, active monitoring of thyroid function even in euthyroid patients is recommended to avoid missed diagnosis and delayed treatment (Jiménez-Blanco et al., 2021).

According to the expert consensus by Liu et al. (2021), attention should be given to the elderly patients for they are at high risk for thyroid disease and other metabolic diseases. Although elderly patients are often subclinical, they are highly subjected to cardiovascular complications such as atrial fibrillation. Therefore, comprehensive assessment, including cardiovascular functions, bone health, and cognitive ability, to detect frailty is important (Liu et al., 2021).

For the diagnosis of hyperthyroidism in elderly patients, since physical diagnosis is challenging we rely more on imaging and laboratory tests. In particular for patients with GD, thyroid ultrasound imaging is a sensitive diagnostic tool (Kahaly, 2020). Likewise, TRAb, a specific biomarker for GD, plays an important role in the laboratory diagnosis of GD (D'Aurizio, 2021; Kahaly, 2020). Using the combination of results from the physical examination (enlarged thyroid gland), imaging (thyroid nodules), and laboratory tests (raised TRAb level along with other thyroid hormone levels), our patient was diagnosed with GD.

Individual patient factors influence the choice of therapy, particularly in patients with age. In general, administering beta-blockers and providing symptomatic treatment are recommended (Hughes and Eastman, 2021). To manage our patient, thyroid function was first put under control with the antithyroid drug MMI. MMI is the preferred agent for treatment of hyperthyroidism (Kahaly, 2020). Radioactive iodine, which is a more definitive treatment, can be considered for persistent or relapsed GD (Kahaly, 2020). Surgery is avoided due to increased operative risks in older patients (ATA, n.d.; Rehman et al., 2005).

Although the experience in Turkey showed that even after a decade of iodine fortification may not be sufficient to raise iodine levels to adequacy in elderly population, the prevalence of goiter and hyperthyroidism has dropped since the iodization (Atmis et al., 2021). The Thyroid, Iodine, Diabetes Epidemiology study evaluating the thyroid and iodine status in China after two decades of iodine fortification also suggests that iodine deficiency is correlated with GD (Wang et al., 2021). Therefore, to prevent GD relapse and to maintain euthyroid condition, iodine supplementation was also recommended to our patient.

Hyperthyroid myopathy

While investigating our patient's hyperthyroidism, muscle weakness was discovered and determined to be hyperthyroid myopathy. Since thyroid hormone signaling targets the skeletal muscle, thyroid hormone levels are correlated with muscle pathology (Salvatore et al., 2014). Cakir et al. (2003) evaluated the prevalence of multiple musculoskeletal disorders in patients with thyroid diseases and demonstrated their coexistence in many cases. These suggest the need to evaluate musculoskeletal health in thyroid disease patients.

Hyperthyroid myopathy causes weakness and wasting of proximal muscles (shoulder and hip muscles) which contribute to motor disorders (MDA, n.d.). The reason behind this discriminative proximal muscle involvement is not entirely clear.

Why does hyperthyroid myopathy manifest with proximal muscle weakness more than the distal muscle weakness?

To answer this question, we have to take a look at its pathophysiology. Hyperthyroid myopathy is a kind of thyrotoxic myopathy. Thyroid hormones augment beta-adrenergic activity via sensitization and increase mitochondrial respiration via raised Na+-K+ ATPase activity. These result in functional disturbances in muscle fiber leading to hyperthyroid myopathy. (Lin and Huang, 2012).

A study by Pimstone et al. (1968) showed that propranolol (beta-blocker) treatment improved proximal muscle weakness. Pimstone et al. (1968) believed the improvement in muscle power was due to the reduction of ATP demands in muscle cells as amended by propranolol. Olson et al. (1991) also demonstrated that propranolol could improve muscle weakness in GD patients. The speculation was that thyroid hormone and catecholamines together contribute to muscle dysfunction in hyperthyroidism patients which could be corrected by means of beta-blockade.

Current evidence has suggested the culprit of the hyperthyroid myopathy to be thyroid hormones and catecholamines which affect the ATPase activities in the mitochondria. This suggests that mitochondria may play a critical role in hyperthyroid myopathy.

Proximal muscles versus distal muscles

To understand why proximal muscles are involved more, we need to learn about the differences between the two types of muscles. Proximal muscles are axial muscles devoted to postural activities. They are mostly weight-bearing red muscles. In contrast, distal muscles (limb muscles) are appendicular muscles devoted to fine movements. They are mostly white muscles (Nelson et al., 2003).

Red muscles, which depend upon aerobic respiration, consist of more mitochondria. While white muscles depend upon anaerobic respiration and consist of less mitochondria. All muscles in our body are composed of red and white muscle fibers and their proportion is dependent on the anatomical location and function of a certain muscle (Nelson et al., 2003).

Combining the knowledge about hyperthyroid myopathy, mitochondrial pathology, and histological composition of proximal muscles, a hypothesis is formulated: Excess thyroid hormones trigger mitochondrial pathology which affects proximal muscles more than distal muscles due to the discrepancy in mitochondrial distribution in both types of muscles (Figure 1).

This hypothesis can be dissected into two parts:

1. Proximal muscles are red muscle dominant which contain more mitochondria; distal muscles are white muscles dominant which contain less mitochondria. Since there is a discrepancy in mitochondrial distribution in muscles based on anatomical location and function, proximal muscles are affected more by mitochondrial pathology;

2. Hyperthyroid myopathy causes proximal muscle weakness through mitochondrial pathology.

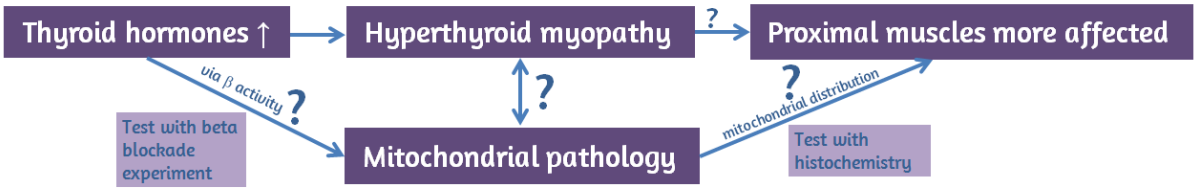

Figure 1: Proposed hypothesis of the pathophysiology of hyperthyroid myopathy and its testing

To test out the hypothesis, the following is proposed (Figure 1):

1. *Histochemical staining to confirm physiological and pathological mitochondrial distribution in muscles*: To test out if proximal muscles are indeed red muscle dominant with a higher mitochondrial content, enzyme histochemistry can be done using myofibrillar ATPase reaction. Structurally abnormal mitochondria are stained red with Gomori Trichrome stains creating ragged-red fibers. These ragged-red fibers are seen in mitochondrial myopathy and can serve as pathological diagnosis (Takizawa, n.d.);

2. *Beta-blockade experiment to verify the interactions between thyroid hormones and ATPases*: Since mitochondria, or more precisely ATPases, are most likely targeted, and thyroid hormones and catecholamines interact with ATPases, beta-blockade experiment can be done to confirm if thyroid hormones and catecholamines are involved in the myopathy through mitochondria. The improvement in muscle weakness from beta-blockade treatment on mitochondrial myopathy shows that thyroid hormones are the mediators and thus shows the connection between hyperthyroidism and mitochondrial pathology.

Combining positive tests should be able to prove the hypothesis that proximal muscles (which have more red muscles and mitochondria) are targeted more in hyperthyroid myopathy via mitochondrial pathology. Therefore, explaining why proximal muscles are involved more than distal muscles in hyperthyroid myopathy.

In summary, thyroid hormone induces increased Na+-K+ ATPase activity and mitochondrial respiration (Lin and Huang, 2012). Excessive thyroid hormone sensitizes cells to beta-adrenergic activities (O'Neill et al., 2007). The combined effect of them results in myopathy (Olson et al., 1991). If the myopathy is mitochondrial, which involves muscle cells with a higher mitochondrial distribution, then proximal muscles should be involved more, hence differentially display weakness.

Implications

This paper hopes to raise awareness of thyroid diseases in the elderly population. Moreover, the investigation of hyperthyroid myopathy would benefit the elderly community because proximal muscles are weight-bearing muscles responsible for falls which are common in elders. By revealing the pathogenesis we could hopefully help address this crucial geriatric issue.

Conclusion

Hyperthyroidism in elders may not manifest typical symptoms of thyrotoxicosis and diagnosing

hyperthyroidism requires vigilance. For similar reasons, hyperthyroid myopathy is likely to incorrectly attribute to normal aging. This case report presents a typical elderly patient with hyperthyroidism which deviates in characteristics from younger adult patients. This elderly patient demonstrated only cardiac discomfort similar to most other reported elderly cases. Elderly patients also have more subtle manifestations of symptoms such as myopathy which unevenly affects more on the proximal muscles and this review suggests a possible hypothesis which involves mitochondrial pathology.

Declaration of Interest Statement

The author declares no conflict of interest.

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