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Can one die because of Hashimoto's disease? – a clinical review of diagnosis, clinical features and treatment of myxedema coma

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ABSTRACT

Introduction and Purpose

Hashimoto’s disease is the most common reason of hypothyroidism. Usually, it is easy to recognize and treat. However, under certain circumstances, it may develop into the most severe manifestation of hypothyroidism known as myxedema and can lead to a threat to the patient's life.

Hypothyroid crisis, or myxedema coma, is an extremely rare but fatal medical emergency. If the condition is not promptly diagnosed and treated, the mortality rate is high as 50%. Even with immediate recognition and appropriate medical intervention, mortality rates of up to 25% have been observed. Myxedema coma must be recognized and treated emergently, usually prior to laboratory confirmation. Treatment consists of correction of electrolyte abnormalities, passive rewarming, treatment of infections, respiratory and hemodynamic support, administration of glucocorticoids, and thyroid hormone replacement.

This article aim is to enhance medical community awareness by examining features of myxedema, prevalence, and associated risk factors, contributing to improved clinical management. Emphasizing tailored treatment strategies for hypothyroidism, coexisting illnesses, and metabolic decompensation, it ultimately seeks to enhance outcomes for patients with severe hypothyroidism.

Material and methods

Conducting a systematic review of medical articles from 1997 to 2024 using PubMed, this study analyzed articles with keywords such myxedema coma, hypothyroidism, Hashimoto’s thyroiditis. Inclusion of pertinent articles ensured a comprehensive exploration of myxedema coma literature during the specified time frame.

Summary

Myxedema coma is a thyroid emergency linked to hypothyroidism. This review sheds light on the etiology of myxedema, clinical manifestations, diagnostic criteria and comprehensive treatment options. In order to reduce mortality in patients, there is a need to increase knowledge of the risk of development, clinical features and management not only for emergency physicians but also for physicians of all specialties..

Keywords: Hashimoto’s disease, myxedema coma, hypothyroidism, hypothyroid crisis

INTRODUCTION

Hashimoto's disease is an autoimmune disorder causing hypothyroidism. It is a term quite well known not only among people professionally dealing with health, but also elsewhere. You can find many articles about this disease in glossy magazines, especially those intended for women. Many well-known people, such famous actors or celebrities in interviews admit to having this disease. There are many manuals for patients on the market about Hashimoto's disease, with advice on for example: how to cope with it, what effects it may have, and what diet to follow. Although many of these pieces of advice have no scientific justification, the commonness of this disease makes such articles and guides very popular.

Despite widespread knowledge among the general public about Hashimoto's disease, there is little awareness of the life-threatening risk of this disease. Unfortunately, sometimes also among doctors and other medical staff [1,2]. Treating a patient in the event of a hypometabolic crisis is difficult and often ineffective. The condition is often caused by an inciting event, which may lead to significant delays in the diagnosis and proper

management of this disease [3]. Therefore, there is a need to draw attention to the possibility of a life-threatening condition resulting from hypothyroidism and recall the rules of optimal conduct in the event of this problem occurring.

STATE OF KNOWLEDGE

1. Hypothyroidism

1.1 Definition

Hypothyroidism is a clinical syndrome resulting from a deficiency of thyroid hormones, which in turn results in a generalized slowing down of metabolic processes. It can result from any of a variety of abnormalities that lead to insufficient secretion of thyroid hormones.

1.2 Classification

Hypothyroidism can be classified on the basis of its time of onset (congenital or acquired). Congenital hypothyroidism (CH) develops secondary to incomplete thyroid development or inadequate thyroid hormone production. State-mandated newborn screening increases the detection rate of CH, allowing for early intervention and proper development of the child [4,5]. Acquired hypothyroidism is not present at birth but came along later in an individual over the course of their lifetime.

The levels of thyroid hormones in the blood is under control of hypothalamus–pituitary–thyroid axis in feedback mechanism. Disturbance can occur at any level of this axis [1,3,6,7].

Hypothyroidism can be divided into a primary form due to failure of thyroid tissue itself, secondary form due to a deficiency of thyroid-stimulating hormone (TSH) secretion by anterior pituitary or tertiary form when the hypothalamus produces insufficient thyrotropin- releasing hormone (TRH) [8, 9]. Very rare cause are mutation leading to peripheral resistance to the action of thyroid hormone [9,10].

Primary hypothyroidism is the most common form. Central hypothyroidism (including both secondary and tertiary) and peripheral hypothyroidism are rare and account for less than 1% of cases [1,8,9,11].

Depending on the severity of symptoms, hypothyroidism can be divided into subclinical, overt and hypometabolic crisis.

Subclinical hypothyroidism (SCH), also called mild thyroid failure, is diagnosed on the base of laboratory results, when peripheral thyroid hormones triiodothyronine (T3) and thyroxine (T4) levels are within normal reference laboratory range but serum thyroid-stimulating hormone (TSH) level is mildly elevated [1,8,9]. Usually it is asymptomatic, does not cause any symptoms. However, it can sometimes present with mild symptoms of, such as fatigue or unexplained weight gain. The prevalence of subclinical hypothyroidism is about 4 to 8.5 percent of the population, and may rise to about 20 percent in women older than 60 years [12]. Subclinical hypothyroidism may progress to overt hypothyroidism in approximately 2-5% cases annually. They patients with subclinical hypothyroidism do not need any treatment until their hypothyroidism become clinically overt. So they require regular observation. Most guidelines recommend not to treat of subclinical hypothyroid patients unless the TSH levels is higher than 10mIU/L.[8]

Overt hypothyroidism is defined as elevated thyroid stimulating hormone (TSH) with low level of thyroxine (T4) and/or triiodothyronine (T3). The symptoms of hypothyroidism occur as a result of generalized slowing down of metabolic processes. The symptoms are related to the duration and severity of hypothyroidism and the velocity with which hypothyroidism occurs [8].

They include: hypersensitivity to cold, decreased peristalsis leading to constipation or even ileus, weight gain despite worse appetite, puffy face, loss and thinning hair, muscle aches, tenderness and stiffness, fertility problems, low libido. The classic skin is myxedema, which refers to the edema-like skin condition caused by increased glycosaminoglycan deposition. Skin may be scaly and dry, especially on the extensor surfaces, palms, and soles. Menstrual cycles are irregular, heavier than usual. Bradycardia is observed and may lead to hypotonia and heart failure. Tiredness, exertional dyspnea, and exercise intolerance are likely associated with a combination of limited pulmonary and cardiac reserve in addition to decreased muscle strength or

increased muscle fatigue. Hypotonia of the gallbladder and altered bile composition may lead to biliary stone formation. The patients with hypothyroidism may also have hoarse voice, slow speech, movements and thoughts, depression, dementia or memory loss. Some patients can have an accumulation of fluid in the pleural and pericardial cavities [1,2,9,13,14,15].

The most severe status is decompensated hypothyroidism, called myxedema coma or hypometabolic crisis, which leads to slowing of function in multiple organs. It is a medical emergency and requires immediate specialist input because of high mortality rate, historically as high as 80%, but still between 30 and 60% [1,3,9]. Usually it occurs in patients with long-standing primary hypothyroidism, in whom treatment has been interrupted or in whom the diagnosis has not yet been made and adaptive mechanisms fail to maintain homeostasis [16]. Most patients who might present with myxedema coma are women. Because hypothyroidism is most common in the later decades of life, most of these women are elderly, 60 years and older [17,18]. Much more rarely, in perhaps 5% of cases of myxedema coma, the underlying cause is hypothalamic or pituitary disease rather than primary thyroid failure as the cause of hypothyroidism [17].

Because the symptoms of hypothyroidism usually develop slowly, the doctors during taking medical history must always remember about the risk factors of hypothyroidism such as Down and Turner's syndrome, previous Graves` disease, other autoimmune disorders, e.g. vitiligo, adrenal insufficiency, pernicious anemia, rheumatoid arthritis, type 1 diabetes [9]. It is necessary to ask about previous thyroid surgery or radioactive ablation of the thyroid, treatment of advanced head and neck cancer, examination with iodinated contrast. Many drug can cause primary hypothyroidism so the patients should be ask about any drug treatment especially with interferon α for hepatitis, tyrosine kinase inhibitors for several cancers, lithium for bipolar disorder or amiodarone for arrhythmias. It is important because the effects of such therapy tend to show up several years later rather than immediately [1,2,9,13,14,19,20].

The risk of hypothyroidism increases with age, and individuals over the age of 60 are more susceptible. It is worth remembering, however, that symptoms of hypothyroidism are sparse and non-specific in older people [21,22].

In worldwide the most common cause of hypothyroidism is lack of dietary iodine but in the developed world Hashimoto's thyroiditis is the most common cause [9,14].

2. Hashimoto's thyroiditis

Hashimoto's thyroiditis (HT) also known as autoimmune or chronic lymphocytic thyroiditis, was first described in 1912 and the first surgery case was reported in 1942 [15,23]. The pathology of the disease involves the formation of antithyroid antibodies that attack the thyroid cells, causing progressive fibrosis. The most common antibody is anti-thyroid peroxidase (anti-TPO). Some patients form antithyroglobulin (anti-Tg) and TSH receptor-blocking antibodies (TBII) but 10% of patients may be antibody negative [14]. Raised concentrations of thyroid peroxidase antibodies are also detected in about 11% of the general population. In patients with subclinical hypothyroidism, thyroid peroxidase antibody measurements help to predict progression to overt disease [9].

However, earlier on in the course of the disease, patients may exhibit signs, symptoms, and laboratory findings of thyrotoxicosis. This is because the destruction of the thyroid gland cells may be intermittent. Patients may have bouts of hyperthyroid symptoms, as the initial destruction of thyroid cells may lead to the increased release of thyroid hormone into the bloodstream. This status is called hashitoxicosis. It usually requires only supportive care and implementation of β-blockers rather than therapy with thyreostatics, and it subsides within 3–24 months [15].

In some patients, enlargement of the thyroid gland can be observed at the beginning of the disease. The goiter is diffuse and symmetric. Later, there is usually a decrease in the size of the goiter and even its atrophy. In some patients, the gland may become nodular or asymmetric [14].

The diagnosis of HT is based on clinical symptoms, positivity to serum antibodies against thyroid antigens (thyroid peroxidase and thyroglobulin) and lymphocytic infiltration on cytological examination [23,24]. In patients with TPOAbs-negative HT the ultrasound examination may help with differential diagnosis. The typical ultrasound features include decreased echogenicity, pseudonodules, heterogeneity, hypervascularity, and presence of small cysts [15,25].

Incidence of HT increases. Currently, its incidence is 0.8 per 1000 per year in men and 3,5 per 1000 per year in women. The risk of developing HT in adult women is approximately 4 times than that of adult men [1]. More than 10% of women display positive antibody and around 2% show clinical manifestations; men present one-tenth of this prevalence [14,15]. Most women are diagnosed between the ages of 30 to 50 years. The white race shows a higher incidence than black. For example, in the United States, 10% of the population had thyroid antibodies, a prevalence of 14% in whites and about 5% in blacks [26]. Disease prevalence increases with age [9,14,24].

Hashimoto thyroiditis may be a component of the autoimmune polyglandular syndrome type 2 (APS-2) along with autoimmune adrenal deficiency and type 1 diabetes mellitus. Such patients may also develop primary hypogonadism, myasthenia gravis, celiac disease, pernicious anemia, alopecia, vitiligo and serositis [14,27].

An uncommon and severe form of hypothyroidism is consumptive hypothyroidism syndrome (CHS). It occurs due to high levels of type 3 deiodinase (D3) expression by neoplastic tissues. Type 3 deiodinase (D3) turns T4 and T3 into its inactive products reverse T3 (rT3) and diiodothyronine (T2). This form of hypothyroidism may develop in children and adults, usually linked to hepatic vascular tumors. The condition is associated with high lethality. Optimal treatment consists of an aggressive high-dose replacement of thyroid hormones along with early effective tumor-directed treatment approaches [28,29].

For the patients with temporary iatrogenic hypothyroidism caused by thyrostatic overdose dose reduction or discontinuation of treatment may be sufficient. In the case of persistent hypothyroidism, thyroxine supplementation treatment should be implemented.

3. Myxedema coma

3.1 Definition

Myxedema coma, also called hypometabolic crisis, is a rare life-threatening clinical condition in patients with longstanding severe untreated hypothyroidism, in whom adaptive mechanisms fail to maintain homeostasis, the body's compensatory responses to hypothyroidism are overwhelmed by a precipitating factor. They exhibit multiple organ abnormalities and progressive mental deterioration [18,30].

3.2 Precipitating event

The hypothyroid crisis almost always occurs in elderly patients, mainly women with climate-induced hypothermia and can also be precipitated by multiple factors: use of sedatives, anesthetics, and antidepressants, phenytoin, diuretics or other intercurrent illness such as burns, stroke, congestive heart failure, myocardial

infarction, gastrointestinal bleeding, pneumonia or SARS-CoV-2 infection [13,17,26]. Sepsis should also be suspected in every case. Hypoventilation, leading to hypoxia and hypercapnia, plays a major role in pathogenesis of myxedema. Hypoglycemia and hyponatremia also contribute to the development of hypothyroid crisis.

3.3 Clinical feature of myxedema

Patients usually look classically hypothyroid with non-pitting oedema, facial coarsening, macroglossia, ptosis, loss of hair, cool, doughy and dry skin, etc [1,18]. The presence of a scar in the lower neck might suggest postsurgical hypothyroidism and may be an important clue in the diagnosis of a patient who is comatose [18].

All patients with myxedema coma display deterioration of their mental status Mental status is affected though symptoms may vary between confusion, lethargy, stupor, delirium or coma, and may progress over weeks to months [18].

Hypothermia is usual, present in approximately 40-100% of patients. The patient's temperature is usually less than 35.5°C, can reach 23^0C [3,18,31].

Bradycardia is usual, with hypotension and low output cardiac failure possible. Electrocardiogram will confirm bradycardia, and may also exhibit small complexes, evidence of acute ischaemia, or “J” waves in hypothermia [32]. Type 2 respiratory failure with hypoventilation and respiratory acidosis may be present. Slow relaxing reflexes will be present, though they may also be present in other causes of hypothermia. Focal or generalized seizures may occur in up to 25% of patients, possibly related to hyponatremia, hypoglycemia, or hypoxemia because of reduced cerebral blood flow [17].

3.4 Diagnosis

There is no possibility to recognize hypothyroid crisis as the reason of coma on the base of laboratory findings. Therefore, attempts were made to create a point scale taking into account data from the interview as well as symptoms and signs that would make the diagnosis and differentiation more objective.

The scoring system included a composite of alterations of thermoregulatory, central nervous, cardiovascular, gastrointestinal, and metabolic systems, and presence or absence of a precipitating event [33].

Diagnostic Scoring System for Myxedema Coma

Precipitating Event	**Points**
Absent	0
Present	10
Thermoregulatory dysfunction (Temperature ºC)	
>35	0
32=35	10
<32	20
Central Nervous System Effects	
Absent	0
Somnolent/Lethargy	10
Obtunded	15
Stupor	20
Coma/seizures	30

Gastrointestinal Findings	
Anorexia/abdominal pain/constipation	5
Decreased intestinal motility	15
Paralytic ileus	20
Metabolic Disturbances	
Hyponatremia	10
Hypoglycemia	10
Hypoxemia	10
Hypercarbia	10
Decrease in GFR	10
Cardiovascular Dysfuntion	
Bradycardia/Heart rate	
Absent	0
50-59	10
40-49	20
<40	30
Other EKG changes*	10
Pericardial/pleural effusion	10
Pulmonary edema	15
Cardiomegaly	15
Hypotension	20

Total score above 60 points highly suggestive/diagnostic of myxedema coma, 25-59 points supportive of diagnosis. Total score less than 25 points suggests that myxedema coma as unlikely [33].

3.5 Management of a patient in myxedema coma

3.5.1 Admission to hospital

Due to a significant threat to life, a patient with suspected myxedema coma should always be immediately admitted to the hospital and treated, preferably in an intensive care unit (ICU) to permit continuous close monitoring of their pulmonary and cardiac status. Such patient usually requires intubation and ventilatory support [1].

A vigorous search for preceding events is necessary. Typical signs of infection (such as fever, tachycardia, leucocytosis) may be absent [30].

Some patients slowly develop coma in the hospital setting after being admitted with other event, such as a fracture. In such cases, the underlying diagnosis may not have been suspected. The slower metabolism of drugs and higher attendant risk of adverse events are not appreciated. Thus, carbon dioxide retention leading to coma could be a feature of relative drug overdosage associated with suppression of respiratory drive, such as from sedatives, narcotic analgesics, antidepressants, hypnotics, and anesthetics [17].

3.5.2 Additional examinations

First, access to the vein must be provided. The blood simples should be taken for TSH, free thyroxine (fT4), free liothyronine (fT3), creatinine, urea, sodium, potassium, full blood count (FBC), cortisol, glucose, CK, arterial blood gases [13].

A septic screen should be done: chest radiograph, blood and urine cultures.

A central venous pressure monitoring may be may be necessary to helps to guide fluid status [17].

Because of the possibility of hypoglycaemia capillary blood glucose should be checked 4 hourly [30].

3.5.3 Laboratory examination

To confirm the diagnosis hypothyroidism the concentration of thyroid hormones in the serum should be examined. In primary hypothyroidism free thyroxine usually is very low or undetectable, TSH is extremely high. In rare cases TSH can be low or normal, however, due to the presence of central hypothyroidism.

Other laboratory test often show anaemia and macrocytosis, hyponatraemia, hypoglycaemia. Creatine kinase concentration (CK) may be elevated indicating either hypothyroid myopathy or rhabdomyolysis [14,30].

3.5.4 Warming the patient's body

Because patients with severe hypothyroidism have decreased metabolic rate and thermogenesis, their temperature is low. The cutaneous blood flow is markedly reduced in in order to conserve body heat. In many of the reported cases, hypothermia was the first clinical clue to the diagnosis of myxedema coma [17]. Because of unusual hypothermia - the use of special thermometers that record temperatures below 32.2° C may be necessary to determine the patient's actual temperature and monitor rewarming.

External warming is indicated only if the patient's temperature is less than 30^0C. Otherwise slow re-warming using a space blanket in a warm room, preferably with a continuous cardiac monitor. is sufficient to prevent further heat loss.

Active rewarming of a hypothermic patient should be avoided. Central warming may be attempted, but peripheral warming should not, as this may lead to vascular dilation and shock [30,36].

3.5.5 Mechanical ventilation

Mechanical ventilation may be needed, particularly for obese patients because of blunted hypercapnic and hypoxic ventilatory drives [13,30].

Intubation in these patients may be necessary but often a difficult procedure. The risk of intubation difficulties is independent of the degree of external facial swelling [34]. Patients can often be overweight, coupled with the potential for airway myxedema, making airway management difficult. One should be aware that unanticipated posterior pharyngeal edema in myxedema coma may severely complicate airway management. [34]. Patients may have already developed hypercapnia caused by hypoventilatory effects of their illness, have

reduced lung volumes, pleural and pericardial effusions, which can lead to cardiovascular and respiratory collapse if not managed appropriately [1].

Mechanical ventilation is required typically for 24 to 48 hours, especially in patients whose hypoventilation and coma result from drug-induced respiratory depression. Some patients may require it for several weeks [17].

3.5.6 Pharmacotherapy

3.5.6.1 General rules

It is widely accepted that due to worse absorption (due to ileus) and circulation disorders because of generalized oedema in severe hypothyroidism, all drugs should be administered intravenously by injection or infusion.

Rapid administration of thyroid hormones and adequate supportive measures are essential for a successful outcome.

3.5.6.2 Glucocorticoids

It is generally deemed prudent to treat with hydrocortisone because of the possibility of coexistent adrenal insufficiency but also because of the possibility that thyroid hormone therapy may increase cortisol clearance and precipitate adrenal insufficiency. Patients with myxedema coma can have concomitant primary adrenal insufficiency, while patients with secondary hypothyroidism may have associated secondary adrenal insufficiency.

Stress doses of glucocorticoids are usually used, such as hydrocortisone 100 mg every 8 hours intravenously for 48 hours [17,30]. As a rule the dose should be gradually reduced over several days. Glucocorticoids should be administered until the possibility of adrenal insufficiency is excluded in a sample collected before the administration of hydrocortisone [17]. Such short-term glucocorticoid therapy is safe and can be discontinued even without tapering when the patient has improved and pituitary-adrenal function has been assessed to be adequate. A random serum cortisol result of less than 3 μg/dL strongly suggests adrenal insufficiency. An adrenocorticotropic hormone stimulation test can be administered if clinically warranted [18]. Patients who have cortisol levels of 3-18 μg/dL require further testing with the adrenocorticotropic hormone (ACTH) stimulation test; this test can be done after a few days of glucocorticoid therapy. A level of 18 μg/dL or above is normal. Hydrocortisone administration may be quickly discontinued if the cortisol concentration in the initial examination is 30 μg/dL or higher. Such a cortisol concentration in conditions of hypothyroidism and stress such as hypometabolic crisis undoubtedly excludes the coexistence of adrenal insufficiency.

3.5.6.3 Thyroid hormones

Causal treatment involves supplementing thyroid hormones. The patients will die without it. The most recommendations recommend intravenous administration of levothyroxine (T4) at an initial dose of 300-400μg

in a single infusion or using an infusion pump to saturate T4 binding sites in plasma binding proteins. In the following days the dose of 50-100 μg of T4 intravenously daily should be maintained. Arguments in favour of the intravenous route are risk of aspiration and the uncertainty of absorption with the nasogastric route [1,8,13,17,30,33].

The special precautions should be taking in patients with coronary heart disease due to the high risk of triggering angina, heart failure, or arrhythmia. Elderly patients and those with ischemic heart disease may need smaller doses of thyroid hormone. Then dose of 50 μg should be used.

All patients should have the heart rhythm continuously monitored during the early phases of replacement. High daily doses of thyroid hormone replacement (LT4 ≥500 μg or T3 ≥75 μg daily) are associated with increased mortality, especially in the elderly.

When improvement is seen, it is allowed to switch to oral administration. It is not necessary to start with a low dose of T4 and titrate it up [30].

Some authors propose parallel intravenous administration of liothyronine (T3) due to impaired T4 to T3 conversion and better T3 passage through the blood-brain barrier. Recommended doses of T3, in addition to T4, are initially 20 μg , then 10 μg every 8 hours until the patient regains consciousness. Levothyroxine doses may be lower when used simultaneously with T3 [1,30].

Due to infrequent occurrence of myxoedema coma, intravenous levothyroxine and liothyronine are not always immediately available in hospitals. If suitable intravenous preparations are not available, the same initial dose of thyroid hormones can be given by nasogastric tube with good results [36, 16].

A convenient form of levothyroxine is its liquid form which can be given enterally through the tube. This form allows to achieve a rapid improvement of thyroid function after implementation of enteral liquid T4. Considering the effectiveness and also the number of ready-to-use doses and convenience of administration in the life-threatening situations, there are suggestions that liquid T4 should be available in every hospital pharmacies [35].

Oral combinations containing 20 μg of T3 and 100 μg of T4 in one tablet may be also used. on day 1 administer 3 to 4 tablets once daily via a nasogastric tube; on subsequent days, 1 or 2 tablets via a nasogastric tube.

It is believed that oral treatment is less reliable than the intravenous route due to the possibility of malabsorption. This fact should be taken into account when switching T4 treatment from intravenous to the enteral route, in which absorption is reported to be approximately 70–80% of the administered dose [32]. However, some authors claim that intravenous administration of hormones is not always necessary and present cases of their patients in which enteral therapy was effective [33].

3.5.6.4 Antibiotic therapy

Because the traditional signs of infection may be masked, prophylactic empiric antibiotics are indicated until infection can be ruled out. Broad spectrum antibiotics should be administrated before the culture results [17,18,30,34]. Historically, fatal cases of myxedema coma often had an unrecognized source of infection [34].

3.5.6.5 Fluids

Due to hyponatremia, fluid intake is limited. Fluid restriction and the use of isotonic sodium chloride will usually restore normal serum sodium. Normal saline should not be administered in patients with suspicious hyponatremic encephalopathy. In cases with severe symptomatic hyponatremia, 100 ml of 3% NaCl should be administered. The new vasopressin antagonist conivaptan might be potentially useful in hyponatremia as high vasopressin levels have been observed in myxedema coma; however, no cases of myxedema coma have been reported in which this drug was administered [30].

In case of hypoglycemia, supplementation of hypertonic glucose solutions is necessary, especially if adrenal insufficiency is present [30].

In case of hypotension, if fluid therapy does not restore efficient circulation, dopamine should be added [17,30, 34].

3.6 Complications

Complications of hypometabolic crisis may include: stroke, heart attack congestive heart failure, gastrointestinal bleeding, bowel hypomotility, ventilatory failure, coagulopathy [13,17].

There is high risk of infections, most often of the respiratory or urinary tract with lack of febrile response to sepsis [13].

3.7 Prognosis

Hypometabolic crisis represents the most extreme form of hypothyroidism, so severe as to readily progress to death unless diagnosed promptly and treated vigorously. Even with reasonably early diagnosis and customary therapy, the mortality rate in myxedema coma is high, approaches 20% to 60% [17,38]

4 Conclusions

The phrase: "prevention is better than cure" is known to most of doctors. This is what Hippocrates "father" of rational medicine, said over 2,400 years ago and nowadays despite great medical progress in diagnosis and therapy, this statement is still important [37]. This has a profound justification regarding the hypometabolic crisis. Diagnosing and treating hypothyroidism is relatively easy and inexpensive. On the other hand, treating a patient with myxedema crisis is complicated, expensive and often unsuccessful. Therefore patients diagnosed with hypothyroidism and their caregivers should be made aware of the need to systematically take medications and not interrupt therapy.

Also family physicians are in an important position to prevent myxedema coma by maintaining a high level of suspicion for hypothyroidism especially among elderly women. An early diagnosis of hypothyroidism may well save a patient's life. [18].

Author contributions

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REFERENCES

1. Dubbs SB, Spangler R. Hypothyroidism: causes, killers, and life-saving treatments. Emerg Med Clin North Am. 2014 May;32(2):303-17. doi: 10.1016/j.emc.2013.12.003. Epub 2014 Mar 6. PMID: 24766934.
2. Chen YJ, Hou SK, How CK, Chern CH, Lo HC, Yen DH, Huang CI, Lee CH. Diagnosis of unrecognized primary overt hypothyroidism in the ED. Am J Emerg Med. 2010 Oct;28(8):866-70. doi: 10.1016/j.ajem.2009.04.024. Epub 2010 Mar 25. PMID: 20887907.
3. Bridwell RE, Willis GC, Gottlieb M, Koyfman A, Long B. Decompensated hypothyroidism: A review for the emergency clinician. Am J Emerg Med. 2021 Jan;39:207-212. doi: 10.1016/j.ajem.2020.09.062. Epub 2020 Sep 30. PMID: 33039222.
4. Brady J, Cannupp A, Myers J, Jnah AJ. Congenital Hypothyroidism. Neonatal Netw. 2021 Nov 1;40(6):377-385. doi: 10.1891/11-T-699. PMID: 34845088.
5. Klosinska M, Kaczynska A, Ben-Skowronek I. Congenital Hypothyroidism in Preterm Newborns - The Challenges of Diagnostics and Treatment: A Review. Front Endocrinol (Lausanne). 2022 Mar 18;13:860862. doi: 10.3389/fendo.2022.860862. PMID: 35370986; PMCID: PMC8972126.
6. Feldt-Rasmussen U, Effraimidis G, Klose M. The hypothalamus-pituitary-thyroid (HPT)-axis and its role in physiology and pathophysiology of other hypothalamus-

pituitary functions. Mol Cell Endocrinol. 2021 Apr 5;525:111173. doi: 10.1016/j.mce.2021.111173. Epub 2021 Feb 4. PMID: 33549603.
7. Leng O, Razvi S. Hypothyroidism in the older population. Thyroid Res. 2019 Feb 8;12:2. doi: 10.1186/s13044-019-0063-3. PMID: 30774717; PMCID: PMC6367787.
8. Khandelwal D, Tandon N. Overt and subclinical hypothyroidism: who to treat and how. Drugs. 2012 Jan 1;72(1):17-33. doi: 10.2165/11598070-000000000-00000. PMID: 22191793.
9. Chaker L, Bianco AC, Jonklaas J, Peeters RP. Hypothyroidism. Lancet. 2017 Sep 23;390(10101):1550-1562. doi: 10.1016/S0140-6736(17)30703-1. Epub 2017 Mar 20. PMID: 28336049; PMCID: PMC6619426.
10. Concolino P, Costella A, Paragliola RM. Mutational Landscape of Resistance to Thyroid Hormone Beta (RTHβ). Mol Diagn Ther. 2019 Jun;23(3):353-368. doi: 10.1007/s40291-019-00399-w. PMID: 30976996.
11. Persani L. Clinical review: Central hypothyroidism: pathogenic, diagnostic, and therapeutic challenges. J Clin Endocrinol Metab. 2012 Sep;97(9):3068-78. doi: 10.1210/jc.2012-1616. Epub 2012 Jul 31. PMID: 22851492.
12. Nakajima Y, Yamada M. [Subclinical thyroid disease]. Nihon Rinsho. 2012 Nov;70(11):1865-71. Japanese. PMID: 23214054.
13. Roberts CG, Ladenson PW. Hypothyroidism. Lancet. 2004 Mar 6;363(9411):793-803. doi: 10.1016/S0140-6736(04)15696-1. PMID: 15016491.
14. Mincer DL, Jialal I. Hashimoto Thyroiditis. 2023 Jul 29. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. PMID: 29083758.
15. Klubo-Gwiezdzinska J, Wartofsky L. Hashimoto thyroiditis: an evidence-based guide to etiology, diagnosis and treatment. Pol Arch Intern Med. 2022 Mar 30;132(3):16222. doi: 10.20452/pamw.16222. Epub 2022 Mar 3. PMID: 35243857; PMCID: PMC9478900.
16. Ueda K, Kiyota A, Tsuchida M, Okazaki M, Ozaki N. Successful treatment of myxedema coma with a combination of levothyroxine and liothyronine. Endocr J. 2019 May 28;66(5):469-474. doi: 10.1507/endocrj.EJ18-0469. Epub 2019 Mar 8. PMID: 30853666.
17. Wartofsky L. Myxedema coma. Endocrinol Metab Clin North Am. 2006 Dec;35(4):687-98, vii-viii. doi: 10.1016/j.ecl.2006.09.003. PMID: 17127141.
18. Wall CR. Myxedema coma: diagnosis and treatment. Am Fam Physician. 2000 Dec 1;62(11):2485-90. PMID: 11130234.
19. Li Z, Qiu Y, Fei Y, Xing Z, Zhu J, Su A. Prevalence of and risk factors for hypothyroidism after hemithyroidectomy: a systematic review and meta-analysis. Endocrine. 2020 Nov;70(2):243-255. doi: 10.1007/s12020-020-02410-5. Epub 2020 Jul 7. PMID: 32638212.
20. Alaie M, Tramutola A, Mukamal D. A Case Report on Methimazole-Induced Severe Hypothyroidism. Cureus. 2022 Jan 17;14(1):e21339. doi: 10.7759/cureus.21339. PMID: 35186597; PMCID: PMC8849643
21. Yamada S, Horiguchi K, Akuzawa M, Sakamaki K, Yamada E, Ozawa A, Kobayashi I, Shimomura Y, Okamoto Y, Andou T, Andou Y, Yamada M. The Impact of Age- and

Sex-Specific Reference Ranges for Serum Thyrotropin and Free Thyroxine on the Diagnosis of Subclinical Thyroid Dysfunction: A Multicenter Study from Japan. Thyroid. 2023 Apr;33(4):428-439. doi: 10.1089/thy.2022.0567. Epub 2023 Mar 22. Erratum in: Thyroid. 2023 Sep;33(9):1134. PMID: 36772798; PMCID: PMC10620437.

22. Arlot S, Debussche X, Lalau JD, Mesmacque A, Tolani M, Quichaud J, Fournier A. Myxoedema coma: response of thyroid hormones with oral and intravenous high-dose L-thyroxine treatment. Intensive Care Med. 1991;17(1):16-8. doi: 10.1007/BF01708403. PMID: 2037720.
23. Caturegli P, De Remigis A, Chuang K, Dembele M, Iwama A, Iwama S. Hashimoto's thyroiditis: celebrating the centennial through the lens of the Johns Hopkins hospital surgical pathology records. Thyroid. 2013 Feb;23(2):142-50. doi: 10.1089/thy.2012.0554. PMID: 23151083; PMCID: PMC3569966.
24. Ralli M, Angeletti D, Fiore M, D'Aguanno V, Lambiase A, Artico M, de Vincentiis M, Greco A. Hashimoto's thyroiditis: An update on pathogenic mechanisms, diagnostic protocols, therapeutic strategies, and potential malignant transformation. Autoimmun Rev. 2020 Oct;19(10):102649. doi: 10.1016/j.autrev.2020.102649. Epub 2020 Aug 15. PMID: 32805423.
25. Wu G, Zou D, Cai H, Liu Y. Ultrasonography in the diagnosis of Hashimoto's thyroiditis. Front Biosci (Landmark Ed). 2016 Jun 1;21(5):1006-12. doi: 10.2741/4437. PMID: 27100487.
26. Hu X, Chen Y, Shen Y, Tian R, Sheng Y, Que H. Global prevalence and epidemiological trends of Hashimoto's thyroiditis in adults: A systematic review and meta-analysis. Front Public Health. 2022 Oct 13;10:1020709. doi: 10.3389/fpubh.2022.1020709. PMID: 36311599; PMCID: PMC9608544.
27. Bakkour A, Zakkor MD, Taha Khairy L, Horo R, Mohammed Sharif Ahmed E, Alhussein H. Autoimmune polyglandular syndrome type 2: A case report. Ann Med Surg (Lond). 2022 May 16;78:103742. doi: 10.1016/j.amsu.2022.103742. PMID: 35600201; PMCID: PMC9121250.
28. Weber Pasa M, Selbach Scheffel R, Borsatto Zanella A, Maia AL, Dora JM. Consumptive Hypothyroidism: Case Report of Hepatic Hemangioendotheliomas Successfully Treated with Vincristine and Systematic Review of the Syndrome. Eur Thyroid J. 2017 Nov;6(6):321-327. doi: 10.1159/000481253. Epub 2017 Oct 13. PMID: 29234626; PMCID: PMC5704697.
29. Huang SA, Tu HM, Harney JW, Venihaki M, Butte AJ, Kozakewich HP, Fishman SJ, Larsen PR. Severe hypothyroidism caused by type 3 iodothyronine deiodinase in infantile hemangiomas. N Engl J Med. 2000 Jul 20;343(3):185-9. doi: 10.1056/NEJM200007203430305. PMID: 10900278.
30. Wiersinga WM. Myxedema and Coma (Severe Hypothyroidism). 2018 Apr 25. In: Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, de Herder WW, Dhatariya K, Dungan K, Hofland J, Kalra S, Kaltsas G, Kapoor N, Koch C, Kopp P, Korbonits M, Kovacs CS, Kuohung W, Laferrère B, Levy M, McGee EA, McLachlan R, New M, Purnell J, Sahay R, Shah AS, Singer F, Sperling MA, Stratakis

CA, Trence DL, Wilson DP, editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000–. PMID: 25905238.
31. Yamamoto H, Hongo T, Nojima T, Obara T, Kosaki Y, Ageta K, Tsukahara K, Yumoto T, Nakao A, Naito H. Successfully treated case of severe hypothermia secondary to myxedema coma. Acute Med Surg. 2023 Mar 14;10(1):e828. doi: 10.1002/ams2.828. PMID: 36936740; PMCID: PMC10014422.
32. Dixit NM, Truong KP, Rabadia SV, Li D, Srivastava PK, Mosaferi T, Calfon Press MA, Donangelo I, Kelesidis T. Sudden Cardiac Arrest in a Patient With Myxedema Coma and COVID-19. J Endocr Soc. 2020 Aug 28;4(10):bvaa130. doi: 10.1210/jendso/bvaa130. PMID: 32984743; PMCID: PMC7499619.
33. Popoveniuc G, Chandra T, Sud A, Sharma M, Blackman MR, Burman KD, Mete M, Desale S, Wartofsky L. A diagnostic scoring system for myxedema coma. Endocr Pract. 2014 Aug;20(8):808-17. doi: 10.4158/EP13460.OR. PMID: 24518183.
34. Lee CH, Wira CR. Severe angioedema in myxedema coma: a difficult airway in a rare endocrine emergency. Am J Emerg Med. 2009 Oct;27(8):1021.e1-2. doi: 10.1016/j.ajem.2008.12.027. PMID: 19857436.
35. Sokołowski G, Motyka M, Gilis-Januszewska A, Stefańska A, Hubalewska-Dydejczyk A. Liquid levothyroxine in the treatment of myxoedema coma. Endokrynol Pol. 2023;74(2):215-216. doi: 10.5603/EP.a2023.0017. Epub 2023 Apr 11. PMID: 37039496.
36. Gadaen RJ, Tummers-de Lind van Wijngaarden RF. Hypothyroid Crisis: Oral or Intravenous Treatment? A Report of Two Cases. Eur J Case Rep Intern Med. 2021 Sep 10;8(9):002752. doi: 10.12890/2021_002752. PMID: 34671573; PMCID: PMC8523370.
37. Brigić A, Hasanović M, Pajević I, Aljukić N, Hamidović J, Jakovljević M. Principles of Hippocratic Medicine from the Perspective of Modern Medicine. Psychiatr Danub. 2021 Spring-Summer;33(Suppl 4):1210-1217. PMID: 35354189.
38. Elshimy G, Chippa V, Correa R. Myxedema. 2023 Aug 14. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. PMID: 31424777.