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Myxedema Coma, What You Need to Know: Review

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ABSTRACT

Myxedema coma, represents the extreme degree of severity of hypothyroidism, whose mortality can reach very high percentages, therefore, it is a true medical emergency. In general, its development is associated with the presence of a triggering factor in a controlled hypothyroid patient and manifests with multisystem alteration. Currently, tools have been developed for clinical diagnosis that use the profile and clinical models, and have good sensitivity-specificity. They allow an early diagnosis which favored the early start of treatment and therefore improves the prognosis. The patient with myxedema coma needs an integral approach, with intensive treatment and close monitoring of hemodynamic parameters. However, the basis of treatment remains hormone replacement, which should be initiated with a combination of levothyroxine and triiodothyronine.

Introduction

This entity was described for the first time at the beginning of 1900, as the result of severe and long-term untreated hypothyroidism (HT). The term myxedema coma (MC), refers to a state that represents the extreme degree of severity HT, whose mortality can be very high, therefore, it is a true medical emergency, which deserves to be diagnosed and managed quickly and intensively. Fortunately, today it is not a frequent entity. An approximate incidence of 0.22 cases per million inhabitants/year is estimated.[2] Currently, clinical tools have been developed for its diagnosis[3,4,] with good sensitivity and specificity, which consider clinical parameters like those considered in a classical way for diagnosis such as mental disorders, hypothermia, a precipitating factor and low levels of T4[5].

The pathophysiological substrate of MC lies in the intracellular decrease of T3 secondary to HT, which causes hypothermia and cardiac depression. Compensating mechanisms such as chronic peripheral vasoconstriction, moderate diastolic hypertension, and decreased blood volume are triggered. At this point, the presence of a trigger would end up breaking this fragile equilibrium [1].

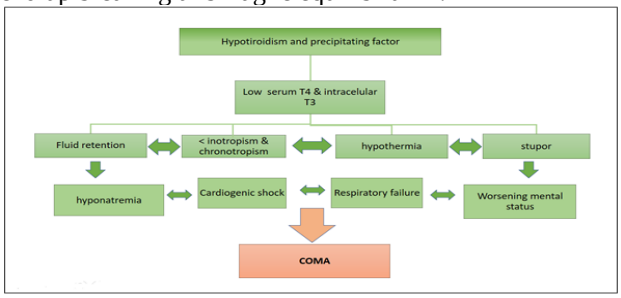

Figure 1. Adapted for Mathew V, et al. Myxedema coma: a new look into an old crisis. J Thyroid Res. 2011.

Etiology

Up to 95% of MC cases occur in patients with primary HT. [6] In most of the cases reported, MC occurs in patients with HT after abandonment of treatment, as well as in those under regular treatment in whom some physiological stress situation would trigger the event. Less frequently, cases of MC have been described in patients who are debutants with HT, in which the multiple clinical manifestations can represent a true diagnostic challenge.

Figure 2. MC TRIGGERING FACTORS

HT debut
Suspension of treatment
Cold exposure
Decompensated Congestive Cardiac failure, Acute myocardial infarction
Burns or trauma
Stroke
Sepsis or infections
Metabolic disturbances (Acidosis, Hypoglycemia, Hyponatremia, Hypercapnia)
Medications
Gastrointestinal bleeding
Anesthetic procedures
Surgical procedures
Labor
Ingestion of raw bok choy

There are multiple possible triggers of MC mostly correspond to situations of physiological stress. They have been described from cold exposure, stroke, heart failure, acute myocardial infarction, infectious processes and sepsis,

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trauma or fractures and electrolyte imbalances5,6. Decompensations of diabetes mellitus such as diabetic ketoacidosis or hyperglycemic hyperosmolar state are less frequent. The use of different drugs (fig 2), especially amiodarone7 , and those used in anesthetic procedures and surgical events8, are another trigger factors. There are some reports of labor as a trigger9. In a trivial way, the consumption of raw bok choy, a food rich in glucosinolates, whose metabolism generates products with inhibitory activity on the uptake of iodine by the Thyroid gland10 has also been described.

Clinical manifestations

Hypothermia: caused by the decrease in thermogenesis, resulting from hypometabolism, occurs in most cases[19], and can go beyond 24 °C. It has been considered as a prognostic marker, since body temperature is equal to or less than 32°, it is associated with higher mortality, which is why in some patients an extracorporeal circulation rewarming has been and normal temperature, an infectious process should be suspected.used with good results. [20] Hypothermia is so characteristic, that, in patients with compatible clinical symptoms of MC

Figure 3. DRUG EFFECTS FREQUENTLY ON L-T4 TREATMENT

Interference with absorption
Proton pump inhibitors
H2 receptor antagonists
Calcium
Charcoal
Orlistat
Ciprofloxacin
Increased clearance
Phenytoin
Carbamazepine
Oxacarbazepine
Rifampin
Sertraline
Quetiapine
Peripheral metabolism
Glucocorticoids
Amiodarone
Propylthiouracil
b-Blockers
Iodinated contrast

Adapted for Garber J, et al. Clinical practice guidelines for hypothyroidism in adults. ATA 2012[29].

Neurological alterations: Historically, diagnosis was only considered in comatose patients. Today, the spectrum of neurological manifestations from a state of confusion, lethargy, obtundation, and even present seizures and status epilepticus. The etiology of these alterations is considered multifactorial: hypoglycemia, hyponatremia or hypoxemia due to cerebral low perfusion[16]. Anecdotally, even an entity called myxedematous psychosis has been described, characterized by behavioral alterations, aggressiveness, delusional ideation of damage and control[17,18].

Ventilatory alterations: Caused by a poor response to hypoxia and hypercapnia, weaknesses of the respiratory muscles due to myopathy, obstructive sleep apnea and mechanical obstruction due to macroglossia[6]. They present alveolar hypoventilation, hypoxemia and hypercapnia, including requiring mechanical ventilation for prolonged periods[21].

Cardiovascular alterations: considered the main cause of mortality and a common denominator in the patient with MC, which is why it is the most extended part of the spectrum studied. Bradycardia and hypotension decreased myocardial contractility and cardiac output. There is a narrowing of the pulse, with elevation of the systolic pressure[11]. Cases of congestive heart failure have been reported; however, because there is a decrease in oxygen demands[39], it is rare in the absence of persistent heart disease. Pericardial effusion is frequent and can be of large volume without necessarily representing the hemodynamics given the chronicity of its evolution.

An entity known as "heart myxedema" is described, represented by hemodynamic alterations, cardiomegaly, electrocardiographic alterations (Fig. 4), and enzymatic alterations (increase in CPK, LDH and AST). In general, the "heart of myxedema" has a reversible behavior with the specific treatment[11]. The management of these manifestations focuses on hormonal supplementation, in some cases requiring inotropic and aminergic support.

Figure 4. ELECTROCARDIOGRAPHIC ALTERATIONS IN HT

Sinus Bradycardia
PR interval length
Low amplitude of P wave and QRS
Unspecific ST segment manifestations
Flat or investment T wave

Gastrointestinal alterations: There is a decrease in peristalsis; constipation is very frequent[13], which can even manifest as myxedematous megacolon. Myxedematous ileus may also occur, which is a gaseous distension of the abdomen accompanied by a clinical obstructive abdominal syndrome[14].

Renal alterations: It is the most frequent finding in patients with MC, present in 43% of cases[3]. In general, of multifactorial origin, due to a fall in cardiac output and hypoperfusion, due to a decrease in glomerular filtration or a consequence of acute urinary retention, etc. The presentation of acute kidney injury caused by rhabdomyolysis secondary to hypothyroid myopathy has been described[25,26].

Hyponatremia: Frequent electrolyte alteration, secondary of multiple mechanisms. One of them is the hyperproduction of ADH due to excess TSH with the consequent water retention[15] although today it has been questioned[24]. It may also be due to concomitant adrenal insufficiency, to acute renal injury or to being multifactorial. If it is severe it can contribute to neurological deterioration, and if it is mild, it has no clinical significance.

Hypoglycemia: It is present in 29% of cases[3]. It may be secondary to hypothyroidism itself due to a decrease in gluconeogenesis, a decrease in skeletal muscle glucose and adipose tissue[23]; or, it may be due to fasting and gastric paresis. It has been considered secondary to concomitant adrenal insufficiency or panhypopituitarism. In patients with HT, there is an alteration of plasma cortisol response to insulin-induced hypoglycemia. It has also been postulated that adrenal insufficiency is precipitated by stress or by rapid-onset replacement therapy[22]. Recently, it has been documented that women with chronic autoimmune hypothyroidism, the RR of suffering from Adisson's disease is 130[34].

Myxedema: Described as hard, generalized edema, which does not leave a fovea, and includes the peri-orbital and acral area. There is supraciliary madarosis, known as "Queen Anne's sign".

The skin is cold and dry due to reflected cutaneous vasoconstriction, pale yellowish due to anemia and hypercarotenemia, and rough to the touch[27].

Figure 5. MYXEDEMA COMA SCREENING TOOL

CRITERION	Score
Glasgow CS	
0-10	4
11-13	3
14	2
15	0
TSH	
> 30 Mu/L	2
15-30	1
Low T4 L (<0.6 ng/dL)	1
Hypothermia (<95°F)	1
Bradycardia (<60)	1
Precipitating event	1

Total score	Category	Recommendation
8–10	Most likely	Treat
5–7	Likely	Treat if there are no other causes
<5	Unlikely	Consider other diagnosis

Adapted for Chiong, et al. Development of an objective tool for the diagnosis of myxedema coma. 2015[4].

Diagnosis

It is based on the clinical suspicion of a patient with or without a history of hypothyroidism, compatible clinical findings and the presence of precipitating factors.

Currently tools for diagnosis have been developed, which consider the thyroid profile and clinical parameters[3,4]. The "diagnostic scoring system for myxedema coma" [3], developed in 2014, has been validated with better results; includes only clinical parameters, scoring each one. Take as a cut 60 points to consider the diagnosis of MC, with sensitivity of 100% and specificity of 85% (Fig.6). Higher scores increase specificity. This score has the advantage of being based solely on clinical parameters, therefore, the diagnosis will not be delayed until laboratory results are obtained and with this, early treatment could be initiated. Other screening tool, published in 2015[4], includes, in addition to clinical parameters, measurements of TSH and F T-4, classifies the diagnostic probability and issues a therapeutic recommendation according to the score (Fig 5); however, it has lower sensitivity and specificity (80-80%).

Treatment

The management of the patient with MC is a real medical emergency, since the punctual onset of it implies an improvement in the prognosis, delaying diagnosis will increase mortality, so that having a justified clinical suspicion; it should be started as early as possible without waiting the lab results.

The goals regarding MC management should be aimed at improving neurological, cardiovascular and pulmonary manifestations[31]. Management in intensive care should be provided and remain under monitoring of the cardiorespiratory status, receive the pertinent ventilatory assistance, effective water resuscitation and correction of hypotension and electrolyte alterations. It is recommended to initiate passive rewarming, since active rewarming could generate peripheral vasodilatation, generating cardiovascular collapse[43]. The identified trigger must be investigated and treated[42] .

Regarding hormonal supplementation, the current recommendations are based on reports of case series and expert opinions, since due to the low frequency of MC it is not feasible to design appropriate clinical trials.

Figure 6. DIAGNOSTIC SCORING SYSTEM FOR MYXEDEMA COMA

Thermoregulatory dysfunction		Cardiovascular dysfunction	
>35 °C	0	Bradycardia	
32-35 °C	10	Absent	0
< 32 °C	20	50-59	10
Central nervous system effects		40-49	20
Absent	0	< 40	30
Somnolent/lethargic	10	Other EKG changes α	10
Obtunded	15	Pericardial / pleural effusions	10
Stupor	20	Pulmonary edema	15
Coma/seizures	30	Cardiomegaly	15
Gastrointestinal findings		Hypotension (< 90/60 mm/hg)	20
Anorexia/ abdominal pain/ constipation	5	Metabolic disturbances	
Decreased intestinal motility	15	Hyponatremia (< 135mEq/L)	10
Paralytic ileus	20	Hypoglycemia (< 60 mg/dL)	10
Precipitating event		Hypoxemia (s02 < 88, po2 < 55)	10
Absent	0	Hypercapnia (pc02 < 50).	10
Present	10	Decrease in GFR.	10
TOTAL score			
60 / >		Highly suggestive/diagnostic of MC.	
25-59		Suggestive of risk for MC.	
< 25		Unlikely to indicate MC.	

Abbreviations: EKG = electrocardiogram; GFR = glomerular filtration rate.
α: QT prolongation, or low voltage complexes, or bundle b blocks, or nonspecific ST-T changes, or heart blocks.

Adapted for G. Popoveniuc, L. Wartofsky, et al. A diagnostic scoring system for myxedema coma. End. Pract.2014.

L-thyroxine, the first synthetic molecule used for the management of hypothyroidism[40], remains the mainstay of treatment. It is suggested to start with initial loading dose of 300-400 mcg, always if possible intravenous (IV). Subsequent supplementation should be continued with 1.6 mcg / kg, or 75% of this dose in case of IV administration[31], this being the ideal route, due to the best clinical and paraclinical results shown in the short term[33]. The enteral route is less preferred due to the alterations in intestinal absorption that these patients have, as well as the need for immediate bioavailability of thyroid hormone.

Taking into account that, in most of cases, MC patients present with peripheral conversion reduction, the adjunctive therapy with L-T4 + L-T3, already recommended in some specific groups of patients with HT [28,29,41] , should also be used in MC. It is also preferred to use it intravenously and administer it at low doses, since it has been documented that doses equal to or greater than 75 mcg / day are associated with higher mortality[32]. An initial dose of 5-20 mcg is recommended, followed by fractionated doses, at a rate of 2.5-10 mcg, 3 times a day, continuing at least until significant clinical improvement is obtained.

Glucocorticoid supplementation is indicated empirically in all cases at a dose of stress, before starting supplementation with levothyroxine, and having previously requested plasma levels of cortisol[31]. It is recommended to initiate hydrocortisone 100 mg intravenously, followed by 50 mg intravenously every 6 hours. It should be continued until concomitant adrenal insufficiency is ruled out.

Figure 7. RECOMENDATIONS OF MC MANAGEMENT

General ICU ADMISSION AND MONITORING VENTILATORY SUPPORT CORRECTION OF HYPOTENSION HYDROELECTROLYTIC RESUSCITATION PASSIVE REHEAT
Hormonal Supplementation. Initial Dose: L-T4 300-400 mcg IV. L-T3 5-20 mcg IV. Continued Dose: L-T4 1.6 mcg/kg (75% if IV) OD. L-T3 2.5-10 mcg q8h.
Corticosteroid. Initial Dose: hydrocortisone 100 mg IV. Continued dose: hydrocortisone 50mg q6h.

Monitoring

The measurement of hormonal levels can be made every 1 to 2 days, with the main objective of documenting the gradual decrease of TSH or increase of the fractions of T4 and T3 depending on the case, without there being consensus of the target figures to be pursued, and rather based on clinical improvement[31]. If this is not the case, it will be justified to increase the dose of hormonal supplementation, while the rapid elevation of T3 will be an indication to decrease the dosage given its association with adverse results.

Prognosis

Today, MC mortality remains high, although it has changed due to better knowledge of the pathology, the development of instruments to facilitate faster recognition and a more intensive therapy. In the 60s, mortality was up to 80% [35]. With the beginning of the use of intravenous L-T4, in the 1990s it decreased significantly, reporting figures of 20-25%[36], identifying cardiovascular failure as the main cause, followed by pneumonia and its complications[32].A retrospective observational study, which included 149 patients, published in 2017, showed that there have been few changes regarding mortality, placing it at around 29%[37], and finding cardiovascular failure as the main cause.

It has been identified that the best predictors of poor prognosis are the deterioration of the level of consciousness, Glasgow scale equal to or less than 5, and a score equal to or greater than 20 for APACHE II[38]. More recently, it was shown that the SOFA score is more effective than other models, so a score of 6 points at the beginning and at 3 days is highly predictive, with mortality greater than 60% from this cut-off point, which increases by increasing the score[44].

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