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Myxedema Coma

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Myxedema coma represents the most extreme form of hypothyroidism, so severe as to readily progress to death unless diagnosed promptly and treated vigorously. Two of the 12 patients first reported with hypothyroidism in 1879 likely died as a result of myxedema coma [1]. There are perhaps 300 cases reported in the literature; thus, although it is, fortunately, rare today, it is important to recognize because of the high associated mortality. A number of the case reports have been collated and reviewed over recent years [2–5].

Because hypothyroidism is some eightfold more common in women than in men, 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. It is important to maintain a high index of suspicion, especially if faced with an elderly female patient with signs and symptoms compatible with hypothyroidism who is beginning to manifest mental status changes and some of the typical findings described in this article. Like uncomplicated hypothyroidism, the diagnosis rests on a determination of serum thyroid-stimulating hormone (TSH). Most hospital and commercial laboratories can turn around a TSH result within hours, and once the diagnosis is made, therapy should be initiated immediately. Nevertheless, even with reasonably early diagnosis and customary therapy, the mortality rate approaches 50% to 60%.

Clinical presentation

Precipitating events

A review of the literature indicates that most patients with myxedema coma seem to present in winter and that a low body temperature

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(hypothermia) is usually present. Extremely cold weather actually seems to lower the threshold for vulnerability, with an otherwise stable hypothyroid individual slipping into a coma after cold exposure. The pathogenesis can be more complex, however, with other patients' clinical state evolving into a coma after development of pneumonia, sepsis from any cause, stroke, or cardiovascular compromise (Box 1).

Pneumonia may be a primary initiating event or may occur secondarily after a stroke or aspiration. Other clinical features that are typical of myxedema coma, such as carbon dioxide retention, hyponatremia, hypoglycemia, and hypoxemia, could potentially also contribute to the development of coma in a hypothyroid patient, particularly because they represent potential causes of coma in euthyroid subjects. Patients are likely to present with a slowly developing coma in the hospital setting after being admitted with some other event, such as a fracture. In such cases, the underlying diagnosis may not have been suspected; hence, 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. An association with amiodarone therapy has also been reported [6].

Box 1. Myxedema coma: exacerbating or precipitating factors

Hypothermia
Cerebrovascular accidents
Congestive heart failure
Infections
Drugs
Anesthetics
Sedatives
Tranquilizers
Narcotics
Amiodarone
Lithium carbonate
Gastrointestinal bleeding
Trauma
Metabolic disturbances exacerbating myxedema coma
Hypoglycemia
Hyponatremia
Acidosis
Hypercalcemia
Hypoxemia
Hypercapnia

Whatever the precipitating cause, the course is typically one of lethargy progressing to stupor and then coma, with respiratory failure and hypothermia, all of which may be hastened by the administration of the latter types of drugs that depress respiration and other brain functions. The characteristic features of severe hypothyroidism are present, such as dry skin, sparse hair, a hoarse voice, periorbital edema and nonpitting edema of the hands and feet, macroglossia, and delayed deep tendon reflexes, and moderate to profound hypothermia is common. In addition to hyponatremia and hypoglycemia, a routine laboratory evaluation may indicate anemia, hypercholesterolemia, and high serum lactate dehydrogenase and creatine kinase concentrations [7].

General description

If it is possible to obtain a past medical history of the patient, there could be a prior history of antecedent thyroid disease, radioiodine therapy or thyroidectomy, or thyroid hormone therapy that was inappropriately discontinued. Thus, physical examination may show a surgical scar on the neck and no palpable thyroid tissue, or there could be a goiter. 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. One patient was reported who proved to have myxedema coma attributable to primary thyroid failure and pituitary insufficiency from Sheehan syndrome [7]. For a clinical profile, it is useful to examine the 24 patients (20 women and 4 men, mean age of 73 years) with myxedema coma reported from a hospital survey in Germany (although the authors reclassified 12 patients as having severe hypothyroidism but not coma) [8]. There was underlying primary hypothyroidism in 23 (previously recognized in 9) patients and central hypothyroidism in 1. Presenting findings included hypoxemia in 80%, hypercapnia in 54%, and hypothermia with a temperature less than 94°F in 88%. Six patients (25%) died in spite of treatment with thyroid hormone.

Neuropsychiatric manifestations

In patients with myxedema coma, there may be a history of lethargy, slowed mentation, poor memory, cognitive dysfunction, depression, or even psychosis, as can also be seen in patients with uncomplicated hypothyroidism. They do not complain of these symptoms, however, because of their impaired state of consciousness. Focal or generalized seizures may be seen in up to 25% of patients, possibly related to hyponatremia, hypoglycemia, or hypoxemia because of reduced cerebral blood flow [9].

Hypothermia

As noted previously [8], hypothermia is present in virtually all patients and may be quite profound ($<80°$F). In many of the reported cases,

hypothermia was the first clinical clue to the diagnosis of myxedema coma. The ultimate response to therapy and survival has been shown to correlate with the degree of hypothermia, with the worst prognosis in patients with a core body temperature less than 90°F.

Cardiovascular manifestations

Typical cardiovascular findings in myxedema coma as well as in hypothyroid heart disease include nonspecific electrocardiographic abnormalities, cardiomegaly, bradycardia, and reduced cardiac contractility. One recent case report described a patient who presented with prolonged QT and polymorphic ventricular tachycardia (torsades de pointe) [10]. Low stroke volume and cardiac output occur as a result of the reduction in cardiac contractility, but frank congestive heart failure is rare. Cardiac enlargement may be real and attributable to ventricular dilatation or could represent a pericardial effusion. Hypotension may be present because of decreased intravascular volume and cardiovascular collapse, and shock may occur late in the course of the disease. In shock, the hypotension may be refractory to vasopressor therapy unless thyroid hormone is also being given.

Respiratory system

The reduced hypoxic respiratory drive and decreased ventilatory response to hypercapnia known to occur in hypothyroidism [11] are likely responsible for the respiratory depression commonly seen in myxedema coma, but impaired respiratory muscle function and obesity may exacerbate the hypoventilation [12–14]. The respiratory depression leads to alveolar hypoventilation and progressive hypoxemia and, ultimately, to carbon dioxide narcosis and coma. Although there are many contributing causes to the coma in these patients, the principal factor seems to be a depressed respiratory center response to carbon dioxide [15,16]. Mechanically assisted ventilation is required in most patients, irrespective of the cause of the respiratory depression and hypoventilation. Respiration may be impaired in these patients as well by the presence of pleural effusions or ascites, by reduced lung volume, and by macroglossia and edema (myxedema) of the nasopharynx and larynx, which serve to reduce the effective airway opening. Even after initiation of thyroid hormone therapy, assisted ventilation may have to be continued because of delayed recovery [17].

Gastrointestinal manifestations

Patients with myxedema coma may have anorexia, nausea, abdominal pain, and constipation with fecal retention. A distended quiet abdomen may be present, reduced intestinal motility is common, and paralytic ileus and megacolon may occur. A type of neurogenic oropharyngeal dysphagia has been described that is associated with delayed swallowing, aspiration,

and risk of aspiration pneumonia [18]. Gastric atony, if present, may serve to reduce absorption of oral medications.

Infections

Because hypothermia is the rule in myxedema coma, the presence of a ''normal'' temperature should be a clue to underlying infection. Other signs of infection, such as diaphoresis and tachycardia, are also absent. Patients who fail to survive often have been shown to have had unrecognized infection and sepsis. The possibility of an underlying infection should always be considered while maintaining a low threshold for initiation of systemic antibiotic coverage [19]. The presence of pneumonia also worsens or even causes hypoventilation, and there is a heightened risk of pneumonitis attributable to aspiration caused by neurogenic dysphagia, semicoma, or seizures [9,18].

Renal and electrolyte manifestations

Patients may have bladder atony with urinary retention. Hyponatremia in any patient may cause lethargy and confusion, and hyponatremia and a reduced glomerular filtration rate are consistent findings in patients with myxedema coma. The hyponatremia results from an inability to excrete a water load, which is caused by decreased delivery of water to the distal nephron [20] and excess vasopressin secretion [21]. Urinary sodium excretion is normal or increased, and urinary osmolality is high relative to plasma osmolality.

Diagnosis

The probable diagnosis of myxedema coma should readily come to mind, given a patient with a history of or physical findings compatible with hypothyroidism in the presence of stupor, confusion, or coma, especially in the setting of hypothermia. Given a reasonable index of suspicion, therapy with thyroid hormone should be begun immediately, while awaiting the results of measurements of serum thyrotropin (TSH) and thyroxine (T4). In elderly patients, however, especially those with underlying cardiac disease, thyroid hormone therapy should be undertaken more cautiously because of the risks. Given the presence of the previously mentioned abnormalities that are characteristic of myxedema coma, such as hypothermia, hypoventilation, and hyponatremia in a lethargic, somnolent, or comatose patient, however, the diagnosis must be entertained, appropriate blood tests drawn and sent to the laboratory, and therapy initiated. Indeed, in many patients, the clinical features may be sufficiently clear to make measurements of serum TSH and T4 necessary only for confirmation of the diagnosis.

Today, in most hospitals, both hormones can be measured in several hours on a routine basis or, if necessary, should be so requested on an emergency basis. Although markedly elevated serum TSH would be expected, patients with severe nonthyroidal systemic illness may demonstrate a phenomenon parallel to the ''euthyroid sick'' syndrome [22], which can be called the ''hypothyroid sick'' syndrome. In such circumstances, pituitary TSH secretion is reduced and the blood levels may not be as high as one might otherwise expect [22,23]. As mentioned previously, approximately 5% of cases of myxedema coma are diagnosed on the basis of central hypothyroidism and could have normal or low serum TSH concentrations. Irrespective of whether the disease is primary or secondary thyroid failure, all patients with myxedema coma have low serum total and free T4 and triiodothyronine (T3) concentrations. In patients with the hypothyroid sick syndrome, serum T3 levels may be unusually low (<25 ng/mL).

Treatment

Therapy with thyroid hormone alone without addressing all the other metabolic derangements described previously would likely be inadequate for recovery. Because of the potentially high mortality without vigorous multifaceted therapy, all patients should be admitted to an intensive care unit to permit continuous close monitoring of their pulmonary and cardiac status. A central venous pressure line should be used to monitor volume repletion therapy, and a pulmonary artery catheter should be inserted in patients with cardiac disease.

Ventilatory support

Thorough attention to an evaluation of respiratory function should include assessment of pulmonary function (blood gas measurements) and physical examination and imaging to rule out pneumonia or airway obstruction attributable to macroglossia or myxedema of the larynx. Insertion of an endotracheal tube or performance of a tracheostomy may be required to achieve adequate oxygenation. Given that an open upper airway is ensured, mechanical ventilatory support is required to relieve or prevent hypoxemia and hypercapnia and antibiotic therapy should be considered. Mechanical ventilatory support is required typically for 24 to 48 hours, especially in patients whose hypoventilation and coma result from drug-induced respiratory depression, and some patients may require it for several weeks [17]. Frequent monitoring of arterial blood gases is warranted during the period of ventilatory support, and extubation should not be considered until the patient is fully conscious. On those rare occasions when a patient with myxedema coma might require emergency surgery, management should follow these same general principles [24].

Hypothermia

External warming of patients with hypothermia with an electric blanket is advisable but should be done cautiously because of the risk of hypotension caused by vasodilatation with a fall in peripheral vascular resistance. Therapy with thyroid hormone is absolutely essential for ultimate restoration of normal body temperature, but the amelioration of hypothermia by thyroid hormone may take several days.

Hypotension

Because external warming may worsen hypotension, it should be preceded and accompanied by careful intravenous volume repletion, initially with 5% to 10% glucose in half-normal saline or as isotonic sodium chloride if hyponatremia is present. Some patients require vasopressors to maintain their blood pressure until thyroid hormone action begins. Because of its nonspecific presumed effects on vascular stabilization, hydrocortisone (100 mg administered intravenously every 8 hours) is usually administered and is definitely warranted if pituitary disease or concomitant primary adrenal insufficiency is suspected.

Hyponatremia

A dilemma that may arise in these patients relates to the need to administer fluids for hypotension and the indication for fluid restriction for hyponatremia. A cautious approach would be to administer some saline (and glucose) intravenously to replace daily losses in the comatose patient but to limit the volume in those with only mild to moderate hyponatremia (serum sodium concentrations of 120–130 mEq/L) such that all water lost is not replaced. Conversely, if the serum sodium concentration is less than 120 mEq/L, it may be appropriate to administer a small amount of hypertonic saline (3% sodium chloride, 50–100 mL), followed by an intravenous bolus dose of furosemide (40–120 mg) to promote water diuresis [25]. Hyponatremia undoubtedly contributes to the mental status changes in patients with myxedema coma, especially in patients with serum sodium concentrations less than 120 mEq/L.

Glucocorticoid therapy

As mentioned previously, steroid therapy is indicated in those patients with myxedema coma attributable to pituitary or hypothalamic disease because they may have corticotropin deficiency as well as TSH deficiency. Primary adrenal insufficiency could be present in patients with primary hypothyroidism caused by Hashimoto disease on an autoimmune basis (Schmidt syndrome). There may be other clinical and laboratory clues to the coexistence of adrenal insufficiency in patients with myxedema coma,

such as hypotension, hypoglycemia, hyponatremia, hyperkalemia, hypercalcemia, lymphocytosis, and azotemia. In most patients with myxedema coma, the serum cortisol concentrations are within the reference range.

It is generally deemed prudent to treat with hydrocortisone because of the possibility of coexistent primary or secondary adrenal insufficiency but also because of the possibility that thyroid hormone therapy may increase cortisol clearance and precipitate adrenal insufficiency. Hydrocortisone usually is given intravenously (50–100 mg every 6 to 8 hours for several days), after which it is tapered and discontinued on the basis of clinical response and plans for further diagnostic evaluation. Such short-term glucocorticoid therapy is safe and can be discontinued when the patient has improved and pituitary-adrenal function has been assessed to be adequate.

Myxedema coma and surgery

A brief consideration of operative intervention in the myxedematous patient may be of interest to some readers. Although elective surgery would be out of the question in a patient with myxedema coma, the situation might present on occasion because the diagnosis was made during the postoperative recovery period, as might often be the case in emergency surgery. Myxedema coma has also been described during obstetric labor [26]. The general perioperative management of patients with hypothyroidism has been reviewed [27], and some of the issues have been described in case reports [28]. Perhaps the most important postoperative issue is the maintenance of an open airway [29,30], and this must be closely monitored in the recovery room.

Thyroid hormone therapy

Patients with myxedema coma need thyroid hormone and die without it. Nevertheless, although the need to treat these patients with thyroid hormone is so patently obvious, the regimen by which to conduct this treatment remains somewhat controversial. The question is how to restore the low serum and tissue thyroid hormone concentrations to normal safely, and the controversy, simply put, relates to whether to administer T4 or T3. On the basis of provision of the organism's need for T3, based on the physiologic monodeiodination of T4 and its conversion to T3, we universally aver that therapy of "garden variety" hypothyroidism is best done with T4 alone. An important potential drawback to total reliance on the generation of T3 from T4 is that the rate of extrathyroidal conversion of T4 to T3 is reduced in the sick hypothyroid patient [22]. Perhaps in favor of T3 therapy is the fact that its onset of action is considerably more rapid than that of T4, which could increase chances for survival [25]. An earlier beneficial effect on neuropsychiatric symptoms may be inferred from studies in baboons showing that T3 crosses the blood-brain barrier more readily than does T4 [31].

Whether one is administering T4 or T3, additional concerns relate to the dosage, frequency, and route of administration. We need to choose an approach to thyroid hormone therapy that balances concern for the high mortality of untreated myxedema coma against the risks of high-dose thyroid hormone therapy, which may include atrial tachyarrhythmias or myocardial infarction. Given the high mortality, we believe that there is a benefit to achieving effective tissue levels of the thyroid hormones as quickly as possible. No one really knows what constitutes the optimal therapeutic approach, however, and recommendations tend to be empiric at best. One argument for using T4 is that serum levels are easier to measure than are those for serum T3, but this is really not the case any longer in modern laboratories. Serum T4 measurements may be easier to interpret, however, because the values do not vary as much between doses as would serum T3 values. T4 therapy may also provide a steadier and smoother, albeit slower, onset of action with a lower risk of adverse effects. Conversely, the onset of action of T3 is quicker, and its serum (and probably tissue) concentrations fluctuate more between doses. In either case, monitoring serum TSH values can provide the information necessary to adjust dosage to achieve the desired impact of treatment at the tissue level. In the comatose patient, it is necessary to give the thyroid hormone by nasogastric (NG) tube or by parenteral injection. Risks of aspiration and uncertain absorption obtain when administered by NG tube, particularly in patients with gastric atony. Parenteral T4 preparations are available in vials containing 100 and 500 μg. A high single intravenous bolus dose (usually 300–600 μg) has been used for decades, based on a report suggesting that replacement of the entire extrathyroidal pool of T4 was desirable to restore near-normal hormonal status as rapidly as possible. An average estimate of total body T4 is 500 μg—hence, that initial dose. Thereafter, the body T4 pool is maintained by administration of 50 to 100 μg daily given intravenously or orally [32]. With the large initial dosage, serum T4 concentrations rapidly rise to supranormal values and then fall to within the normal reference range in 24 hours. In sequence, as T4 is converted to T3, the serum T3 concentrations begin to rise and serum TSH concentrations start falling [33].

In a relatively recent report, Rodriguez and colleagues [34] described their success using a large initial loading dose of T4 as recommended by Nicoloff and LoPresti [5] and Holvey and coworkers [32]. Patients randomly received a loading dose of 500 μg administered intravenously, followed by a daily maintenance dose of 100 μg administered intravenously, or just the maintenance dose. Four of the 11 patients had a fatal outcome, only 1 of whom had received high-dose T4. Mortality correlated with the severity of concomitant illness, with an Acute Physiology, Age, Chronic Health Evaluation (APACHE) score of greater than 20 indicating a potentially poor outcome. Surviving patients tended to be younger and to have better Glasgow Coma Scale scores. T3 is available for intravenous administration in vials containing 10 μg. When given alone, the usual dose is 10 to 20 μg, followed by 10 μg

every 4 hours for the first 24 hours and then 10 μg every 6 hours for 1 or 2 days; by that time, the patient should be alert enough to continue therapy by the oral route. Measurable increases in body temperature and oxygen consumption occur within 2 to 3 hours after intravenous administration of T3 but may take 8 to 14 hours or longer after intravenous administration of T4. These changes after T3 therapy are likely to be accompanied by significant clinical improvement within 24 hours [35] but at a greater risk of adverse cardiovascular side effects. In fact, in one report, high serum T3 concentrations during treatment with T3 alone were associated with a fatal outcome in several patients [36]. This outcome is difficult to assess, because, as mentioned previously, myxedema coma may be associated with high mortality rates in spite of treatment. Thus, in another series of 8 patients, 2 of 3 patients treated with high-dose T3 died of pneumonia, whereas the other 5 who were treated with smaller doses of T4 or T3 survived [37]. When reported cases in the literature were analyzed for associations with mortality, it was seen that advanced age, high-dose T4 therapy, and cardiac complications had the highest association with mortality. The authors concluded that a 500-μg dose of T4 should be safe in younger patients but that lower doses should be considered in elderly patients. Consequently, I have personally adopted what I believe to be a prudent but effective approach to therapy, and that is to administer T4 and T3. T4 is given intravenously at a dose of 4 μg/kg of lean body weight (or approximately 200–250 μg), followed by 100 μg 24 hours later and then 50 μg daily intravenously or orally, as appropriate. Adjustment of the dose is based on subsequent clinical and laboratory results, as in any other hypothyroid patient. With respect to T3, the initial intravenous dose is 10 μg, and the same dose is given every 8 to 12 hours until the patient can take maintenance oral doses of T4.

This approach is not offered as the optimal or preferred manner of treatment with thyroid hormone but rather as one that makes physiologic sense in regard to safety and efficacy. No general guide to treatment can take into account all the factors that might affect sensitivity to thyroid hormone, such as age, intrinsic cardiovascular function, neuropsychiatric status, and comorbid conditions that may affect drug dosages because of alterations in drug distribution and metabolism. Hence, patients should be monitored closely before each dose of thyroid hormone is administered.

With aggressive comprehensive treatment, most patients with myxedema coma should recover. It is better, however, that it be prevented by the early recognition and treatment of hypothyroidism.

Summary

Myxedema coma is the term given to the most severe presentation of profound hypothyroidism and is often fatal in spite of therapy. Decompensation of the hypothyroid patient into a coma may be precipitated by a number of drugs, systemic illnesses (eg, pneumonia), and other causes.

It typically presents in older women in the winter months and is associated with signs of hypothyroidism, hypothermia, hyponatremia, hypercarbia, and hypoxemia. Treatment must be initiated promptly in an intensive care unit setting. Although thyroid hormone therapy is critical to survival, it remains uncertain whether it should be administered as T4, T3, or both. Adjunctive measures, such as ventilation, warming, fluids, antibiotics, pressors, and corticosteroids, may be essential for survival.

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