MYXEDEMA AND COMA (SEVERE HYPOTHYROIDISM)

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CLINICAL RECOGNITION

Myxedema coma is a rare life-threatening clinical condition in patients with longstanding severe untreated hypothyroidism, in whom adaptive mechanisms fail to maintain homeostasis. Most patients, however, are not comatose, and the entity rather represents a form of very severe, decompensated hypothyroidism.

PATHOPHYSIOLOGY

Usually a precipitating event disrupts homeostasis which is maintained in hypothyroid patients by a number of neurovascular adaptations. These adaptations include chronic peripheral vasoconstriction, diastolic hypertension, and diminished blood volume, in an attempt to preserve a normal body core temperature. Homeostasis might no longer be maintained in severely hypothyroid patients if blood volume is reduced any further (e.g., by gastrointestinal bleeding or the use of diuretics), if respiration already compromised by a reduced ventilatory drive is further hampered by intercurrent pulmonary infection, of if CNS regulatory mechanisms are impaired by stroke, the use of sedatives, or hyponatremia.

DIAGNOSIS AND DIFFERENTIAL

The three key features of myxedema coma are:

1. *Altered mental status.* Usually somnolence and lethargy have been present for months. Lethargy may develop via stupor into a comatose state. There may have been transient episodes of reduced consciousness before a more complete comatose state develops.

2. *Defective thermoregulation: hypothermia.* The lower the temperature, the worse the prognosis. Please check the ability of the thermometer to accurately measure decreased temperatures (automatic thermometers may not register frank hypothermia). Fever may be absent despite infections. With cold weather the body temperature may drop sharply. Myxedema coma commonly develops during winter months.

3. *Precipitating event.* Look for cold exposure, infection, drugs (diuretics, tranquillizers, sedatives, analgesics), trauma, stroke, heart failure, gastrointestinal bleeding. The typical patient often has a *history* of hypothyroidism, neck surgery or radioactive iodine treatment.

Physical examination may reveal hypothermia, hypoventilation, hypotension, bradycardia, dry coarse skin, macroglossia, and delayed deep-tendon reflexes. Absence of mild diastolic hypertension in severely hypothyroid patients is a warning sign of impending myxedema coma.

Laboratory examination may reveal anemia, hyponatremia, hypoglycemia, hypercholesterolemia, and high serum creatine kinase concentrations. Most

patients have low serum FT4 and high serum TSH. Serum TSH can be low or normal, however, due to the presence of central hypothyroidism or the nonthyroidal illness syndrome.

THERAPY

Myxedema coma is a medical emergency. Early diagnosis, rapid administration of thyroid hormones and adequate supportive measures (Table) are essential for a successful outcome. The prognosis, however, remains poor with a reported mortality between 20% and 50%. In-hospital mortality was 29.5% among 149 patients with myxedema coma identified between 2010-2013 through a national inpatient database in Japan (Ono et al. 2017).

MANAGEMENT OF MYXEDEMA COMA	
1.*Hypothyroidism*	large initial iv dose of 300-500 µg T4, if no response add T3;
1a	Alternative- initial iv dose of 200-300 µg T4 plus 10-25 µg T3
2.H*ypocortisolemia*	iv hydrocortisone 200-400 mg daily
3. *Hypoventilation*	don't delay intubation and mechanical ventilation too long
4. *Hypothermia*	blankets, no active rewarming
5. *Hyponatremia*	mild fluid restriction
6. Hypotension	cautious volume expansion with crystalloid or whole blood
7. *Hypoglycemia*	glucose administration
8. *Precipitating event*	identification and elimination by specific treatment, liberal use of antibiotics

Note 1. Administration of thyroid hormone is essential, but opinions differ about the dose and the preparation (T4 or T3). A high dose carries the risk of precipitating fatal tachycardia or myocardial infarction, but a low dose may be unable to reverse a downhill course. Treatment with T4 may be less effective due to impaired conversion of T4 into T3 (associated with severe illness and inadequate caloric intake), but treatment with T3 may expose tissues to relatively high levels of thyroid hormone. In the absence of RCT's, the available case series suggest higher mortality with initial T4 doses larger than 500 µg and with T3 doses larger than 75 µg daily. Treatment should be started intravenously because gastrointestinal absorption may be impaired. Typically, a large initial intravenous loading dose of 300-500 µg T4 may be given, followed by daily doses of 1.6 µg/kg (initially intravenously, and orally when feasible). If there is no improvement in clinical abnormalities within 24 hours, addition of T3 is recommended. An alternative scheme is an initial intravenous dose of 200-300 µg T4 plus 10-25 µg T3, followed by 2.5-10 µg T3 every 8 hours depending on the patient's age and presence of cardiovascular risk factors. Upon clinical improvement, T3 is discontinued and a daily oral T4 replacement dose is maintained.

Note 2. Pituitary-adrenal function is impaired in severe hypothyroidism. Restoration of a normal metabolic rate with exogenous thyroid hormones may precipitate

adrenal insufficiency. It is therefore prudent to administer glucocorticoids in stress doses (e.g., hydrocortisone 100 mg intravenously every 8 hours).

Note 3. Mechanical ventilation may be needed, particularly when obesity and myxedema coexist.

Note 4. The cutaneous blood flow is markedly reduced in severe hypothyroidism in order to conserve body heat. Warming blankets will defeat this mechanism. Thus, central warming may be attempted, but peripheral warming should not, since it may lead to vasodilatation and shock.

Note 5. 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 (Liamis et al. 2017). 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.

Note 6. Volume expansion is usually required in case of hypotension since patients are maximally vasoconstricted. Dopamine should be added if fluid therapy does not restore efficient circulation.

Note 7. Serum glucose should be monitored. Supplemental glucose may be necessary, especially if adrenal insufficiency is present.

Note 8. A vigorous search for precipitating events is mandatory. Signs of infection (like fever, tachycardia, leukocytosis) may be absent. Prophylactic antibiotics are indicated until infection can be ruled out.

FOLLOW-UP

In case treatment was initiated with intravenous T4 but after 24 hours the patient is still comatose or vital functions have not improved, iv administration of T3 should be considered. T3 should be discontinued and replaced by T4 once circulation and respiration have been stabilized. Intravenous administration of thyroid hormones is replaced by oral administration when the patient is fully awake.

GUIDELINES

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