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Myxedema coma in children and adolescents: A rare endocrine emergency - Personal experience and review of literature

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Abstract. Decompensated hypothyroidism, formerly known as myxedema coma, represents the most extreme clinical expression of severe primary or secondary hypothyroidism in which patients exhibit multiple organ abnormalities and progressive mental deterioration. The exact incidence of myxedema coma in adults is not known, but some authors have estimated that is approximately 0.22 per 100.0000 per year in the western world. Myxedema coma is more common in females and during winter months. The diagnosis of myxedema coma is primarily clinical with supportive evidence of the abnormal thyroid function tests. Clinical features vary depending on a several factors including the age of onset and the severity of the disease. In the majority of patients (95%), the cause of underlying hypothyroidism is autoimmunity, i.e., Hashimoto thyroiditis or congenital abnormalities. Rarely it occurs in secondary (central) hypothyroidism, due to thyrotropin deficiency related to pituitary disease, or pituitary-thyroid damage due to iron overload. Treatment consists of thyroid hormone replacement, correction of electrolyte disturbances, passive rewarming, treatment of infections, respiratory and hemodynamic support, and administration of stress-dose glucocorticoids. Prognosis seems to be better in children and adolescents compared to adults. The present review reports personal experience and the literature data on 13 patients. (www.actabiomedica.it)

Keywords: Myxedema coma, hypothyroidism, iron overload, aplastic anemia, Hashimoto thyroiditis, treatment, prognosis

Introduction

Decompensated hypothyroidism, formerly known as myxedema coma, is an endocrine emergency leading to altered mental status or mental slowing, associated with hypothermia, and other signs and symptoms associated with hypothermia and poor functioning of multiple organs due to severe primary or secondary hypothyroidism (1,2).

Primary hypothyroidism results from the inability of the thyroid gland to produce adequate amounts of thyroid hormone. Typically, patients with myxedema coma have primary hypothyroidism diagnosed by low serum levels of free-thyroxine (FT_4) and triiodothyronine (T_3) and a high thyroid stimulating hormone (TSH) level. However, primary hypothyroidism should be differentiated from secondary or tertiary hypothyroidism (low-normal or decreased TSH and

low FT_4 levels). Secondary hypothyroidism is a result of pituitary dysfunction; tertiary hypothyroidism is caused by a hypothalamic abnormality (2-4).

Thyroid hormones are key regulators of metabolism and development and are known to have pleiotropic effects in many organs. Thyroid hormones regulate normal growth and development (particularly in bone and the central nervous system), lipids (adipose tissue) and protein breakdown in muscle, increase absorption of carbohydrates from the intestine and increase dissociation of O2 from hemoglobin by activating red cell 2,3-diphosphoglycerate (DPG) (4-6).

Thyroid hormones regulate virtually all anatomic and physiologic components of the cardiovascular system. The major effects of thyroid hormones on the heart are mediated by triiodothyronine. T3 increases the force and rate of systolic contraction and diastolic relaxation (7), decreases vascular resistance, including coronary vascular tone, and increases coronary arteriolar angiogenesis (7). Thyroid hormones also act on the liver, white adipose tissue, skeletal muscle, pancreas and carbohydrate metabolism, influencing plasma glucose levels and insulin sensitivity (8).

The suspected diagnosis is primarily clinical and is confirmed by thyroid function tests. Clinical findings are similar to hypothyroidism but of greater severity. Myxedema refers to the nonpitting puffy appearance of the skin and soft tissues related to hypothyroidism and the term coma is largely a misnomer, as patients commonly present with an altered mental status or mental slowing.

Mechanisms underlying the development of hypothermia include increased heat loss, decreased heat production, and impaired thermoregulation; however, some patients may present with a normal temperature. Bradycardia, flattened T waves, low voltage, bundle branch blocks, and complete heart blocks are common EKG findings (9). Low voltage on EKG maybe a sign of pericardial effusion due to the accumulation of fluid rich in mucopolysaccharides and merits investigation (10). Pericardial effusion tends to accumulate slowly and is unlikely to produce clinically significant cardiovascular effects (11).

Severe hypothyroidism affects ventilation, which manifests as a decreased central response to hypoxia and hypercapnia resulting in respiratory acidosis. Renal function is impaired due to decreased glomerular filtration leading to symptomatic hyponatremia as the kidneys lose their ability to excrete free water load because of decreased delivery of water to the distal nephron. Decreased cardiac output and hypovolemia sensed by baroreceptors may lead to a stimulation of antidiuretic hormone (ADH) release, further contributing to hyponatremia and impaired free water excretion (Figure 1). Low blood sodium is likely to play a major role in the pathophysiology of lethargy, disorientation or coma (12).

The exact incidence of myxedema coma in adults is not known, but some authors have estimated that is approximately 0.22 per 100.0000 per year in the western world (13,14). Myxedema coma is more common in females and during winter months (15).

Since >95% of reported cases of myxedema coma are due to primary hypothyroidism, the laboratory findings include an elevated serum TSH and low or undetectable total and free serum T4 concentrations. There is little correlation between the decrease in thyroid hormone and the presentation of myxedema coma (14,15).

Myxedema coma must be differentiated from any illness that can cause altered mental status, such as sepsis, central nervous system (CNS) events and drugs (sedatives). In addition, hypoglycemia, hypothermia

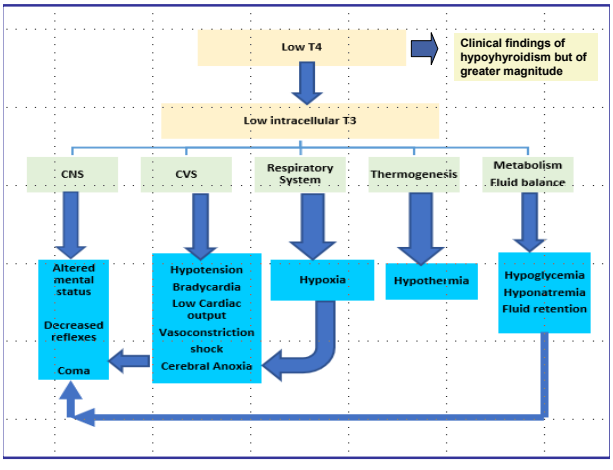

Figure 1. Pathophysiology of myxedema coma.

and protein-calorie malnutrition can present with a similar clinical picture. All these conditions may also precipitate myxedema coma (14-16).

Profound hypothyroidism leading to coma has rarely been reported in children and adolescents. This article reviews personal experience and that of the literature .

Personal experience

1. Case presentation

A 13-year-old adolescent girl presented with coma to the Pediatric Department of Hamad Medical center of Doha (Qatar) (17). The personal history, reported by the mother, included: fatigue, increased sleepiness, deterioration of school performance, apathy, secondary amenorrhea, change in voice, and weight gain for 5 months. There was no history of dyspnea, palpitations or chest pain, drug intake, trauma, or any systemic illness. No family history of endocrine disorders was reported.

The mother also reported that the girl lost consciousness after 30 minutes of feeling dizzy.

Clinical findings included hypothermia (36° C), hypotension (blood pressure: 90/55 mmHg), and bradycardia (50 regular beats/min). Glasgow Coma Scale (GCS) was 8/15, associated with periorbital edema, loss of the lateral eyebrows, dry skin, and a large smooth symmetrical firm goiter.

Thyroid-stimulating hormone (TSH) was 417 mU/L (normal values: 0.4-4.0 mU/L) and free-thyroxine (FT4) 1.7 pmol/L (normal values: 11-19 pmol/L). The anti-thyroid peroxidase (TPO-Ab) antibodies were elevated at 1800 IU/mL (normal values:<35 IU/ml). These laboratory data confirmed the presence of severe primary hypothyroidism due to autoimmune thyroiditis. Thyroid ultrasonography revealed bilaterally enlarged thyroid lobes with a heterogenous echo pattern and multiple pseudo-nodules. Magnetic Resonance Imaging (MRI) of the sella turcica revealed global diffuse enlargement of the pituitary (Figure 2A).

She received intravenous T3 therapy and regained consciousness in 10 hours; treatment continued with L-thyroxine 100 μg/daily. Her energy returned and her voice improved within 2 weeks. FT4 and TSH were normalized in 4 weeks. Pituitary size normalized after 6 months (Figure 2B).

The authors concluded that their case report raises the awareness of physicians to include severe decompensated hypothyroidism in the differential diagnosis of coma in this age group of patients.

2. Case presentation

A 14 year-old girl was admitted to the Department of Pediatrics of Ferrara (Italy) with weakness, altered mental status and abdominal pain of one-day duration. She had a history of Diamond-Blackfan anemia diagnosed at the age of 3.7 years, and since than she had been receiving regular scheduled blood transfusions and chelation therapy with deferioxamine (40 mg/kg of body weight) (18).

On examination she was pale, hypothermic (temperature 34.5°C) and bradycardic (48 regular beats/min) with fine crackles at the base of the left lung, pretibial edema and delayed relaxation phase of the Achilles tendon. The abdomen was soft with hepatomegaly and no masses. Pupils were equally round and reactive to light and fundoscopic exam was normal. Tympanic membranes and oropharynx were clear. There was no goiter or surgical scar of thyroidectomy.

She was short with no signs of pubertal development (Tanner stage 1 for breast and pubic hair). The blood pressure was 90/60 mmHg. Her extremities were cold to touch, with a capillary refill of more than 4 seconds. The Glasgow Coma Scale (GCS) score in conjunction with designed diagnostic scoring system for myxedema coma followed by the Indiana Univer-

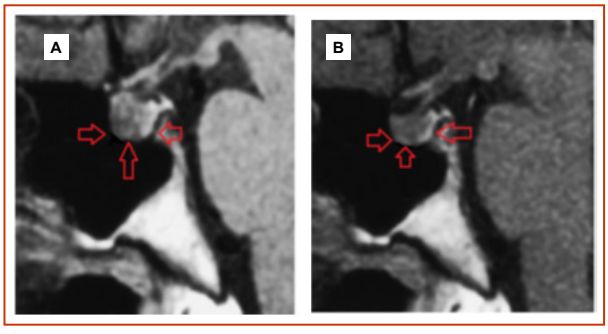

Figure 1. Magnetic Resonance Imaging (MRI) of the sella

sity School of Medicine, Indianapolis was 9 (a score ≥ 7 is considered to be highly suggestive/diagnostic of myxedema coma; Table 1) (19).

Her TSH was elevated at 57.7 mU/L and the FT4 was low at <5.9 pmol/L. She tested negative for thyroglobulin and thyroid peroxidase antibodies. Basal early morning plasma cortisol level was 12.5 μg/dL (normal value: 8-25 μg/dL). One year prior to the current hospital admission her TSH value had been recorded as 6.7 mU/L.

Further testing included a chest radiograph that showed mild cardiomegaly and left lower lobe pneumonia. Urine, throat and blood cultures were negative. Sinus bradycardia, low voltage complexes, prolongation of the QT interval and nonspecific ST-T changes in electrocardiogram were present. An echocardiogram documented normal left ventricular ejection fraction with the presence of mild pericardial effusion.

Arterial blood gas testing revealed hypercapnia ($PaCO_2$ 48 mm Hg) and a pH of 7.35. Serum ferritin level was high (2570 ng/mL; normal values: < 250 ng/mL).

Hypothermia was treated with passive rewarming using ordinary blankets and a warm room. Broad-spectrum antibiotics (ceftriaxone) and hydrocortisone IV were started. Given the lack of imminent life-threatening conditions, the patient was treated with L-thyroxine (initial dose 4 μg/kg of body weight) through a nasogastric tube followed by 100 μg daily orally. Thyroid function was checked every 3 days. Hyponatremia and hypoglycemia were corrected with saline, free water restriction, and intravenous dextrose.

The patient's body temperature progressively increased to 36 °C over a period of 36 hours.

Over the next 4 days the biochemical parameters returned to normal and after 17 days of hospitalization she was discharged in stable condition on L-thyroxine (75 μg daily) and intensive iron chelation therapy. After 35 days, the FT4 and TSH levels were in the normal range. Thyroid ultrasound showed a reduced volume of thyroid gland and inhomogeneity of the parenchyma.

In conclusion, this was the first case report of myxedema coma, precipitated by infection (pneumonia), in an adolescent with pure red cells anemia (Diamond-Blackfan) and a moderate iron overload (18).

Table 1. Diagnostic criteria for myxedema coma (Six criteria and points assigned; From: Chiong and Mariash et al.: Development of an objective tool for the diagnosis of myxoedema coma. Endocrinology Review. Indianapolis: Indiana University School of Medicine; 2011. pp. 24-6) GCS – Glasgow coma scale, TSH – Thyroid-stimulating hormone, HR – Heart rate.

GCS	0-10 = 4 points 11-13 = 3 points 14 = 2 points, 5 = 0 points
TSH	> 30 = 2 points 15-30 = 1 point
T4 below normal	1 point
Hypothermia (temperature < 96 F)	1 point
Bradycardic (HR < 60)	1 point
Precipitating illness present	1 point
Scoring	Myxedema coma ≥ 7 likely = 5-7 unlikely < 5

3. Patients with transfusion-dependent β- thalassemia and myxedema coma

Recently, we reviewed all cases of severe hypothyroidism due to iron overload registered over the last 46 years by VDS in Ferrara. Two unpublished reports of patients with transfusion-dependent β- thalassemia (TDT) and myxedema coma precipitated by cardiac failure in both patients, and hypoglycemia in one patient with insulin-dependent diabetes, were collected. Both were on treatment with subcutaneous iron chelation therapy with desferioxamine (Table 2) and L-thyroxine for subclinical hypothyroidism. Despite intensive care measures, both patients died.

To the best of our knowledge this is the first report of myxedema coma in patients with TDT. The underlying etiology was a primary thyroid failure, secondary to iron overload, triggered by cardiac failure. We believe that the clinical diagnosis, in some cases, can be difficult, particularly if the TDT patient presents with other complications such as cardiac failure, sepsis, metabolic and electrolyte disorders. An endocrinology consult is warranted once the diagnosis of decompensated hypothyroidism is suspected. If the patient is experiencing multiorgan failure, an interdisciplinary team should be on board, including cardiologists, intensivists and endocrinologists.

Table 2. Clinical, laboratory findings and management of myxedema coma in two patients with transfusion-dependent β thalassemia.

Clinical and laboratory variables	Patient 1	Patient 2
Age	16.3 years	15.4 years
Sex	Male	Female
Clinical findings		
1. Height: percentile	< 3rd centile	3rd - 5 th centile
1. Weight: percentile	< 3rd centile	3rd centile
1. Tanner stage	Prepubertal	Prepubertal
1. Blood pressure (mmHg)	85/55	80/40
1. Chiong diagnostic score for myxedema coma	7	6
Etiology of myxedema	Severe hemosiderosis	Moderate hemosiderosis Diabetes
Hormonal assay		
1. Initial FT4 (normal: 10-22 pmol/L)	< 5	8.6
1. Initial TSH (normal: 0.5-4.0 mU/L)	120	35.4
1. Thyroglobulin antibodies (normal values : < 4 IU/mL)	Negative	Negative
1. Thyroid peroxidase antibodies (normal values: <9 IU/mL)	Negative	Negative
1. Basal cortisol level (normal values:8-25 μg/dL)	9.1 μg/dL	8.3 μg/dL
Complications	Atrial fibrillation Cardiac failure Mild pericardial effusion Hyponatremia	Cardiac failure Hyponatremia Severe persistent hypoglycemia
Laboratory findings		
Serum creatinine (normal values: 0.3 - 1.1 mg/dL)	1.6	1.3
Alanine transaminase (ALT; normal values: ≤ 40 U/L)	72	69
Serum ferritin (normal values: < 250 ng/mL)	5680 ng/mL	2910
Treatment		
1. Intravenous iron chelation therapy (desferrioxamine)	+	+
2. Intravenous glucose		
3. Cessation of insulin treatment	-	+
4. L-thyroxine through a nasogastric tube	-	+
5. Hydrocortisone	+	+
6. Slow correction of moderate hyponatremia	+	+
7. Supportive cardiac and intensive care measures	+	+
	+	+
Outcome	Deceased	Deceased

Revision of literature

a. Information sources and search strategy

Literature was identified by searching the following online databases: PubMed, Google Scholar, and Embase. The search was concluded on 25th of August 2021. The search query in different combinations: "myxedema coma AND decompensated hypothyroidism AND children AND adolescents AND iron overload AND prognosis AND treatment".was used to identify relevant publications.

In our review we preferentially included the relevant peer-reviewed scientific publications written in English.

b. Results

We found nine children and adolescents (aged 10 months-12 years) with a confirmed diagnosis of myxedema coma. Male to female ratio in 8 patients was 1:2,6. Co-morbidities were present in 100% of 7 patients with available data. Pneumonia, influenza and acute viral bronchitis were the precipitating factors in 3 out of 7 patients (42.8%) (Table 3). Three patients out

of 7 were treated with intravenous L-thyroxine (L-T4). The remaining patients received oral L-T4. Full data on the L-T4 dosage are shown in table 3; the data on treatment in 2 patients were not available. Cortisone therapy was used in 5 of 7 patients. Survival rate was 100%.

Treatment

Treatment consists of correction of electrolyte abnormalities, passive rewarming, treatment of infections, respiratory and hemodynamic support, administration of stress-dose glucocorticoids, and thyroid

Table 3. Myxedema coma reported in the literature in 9 children and adolescents

Authors/Year/ Reference	Age (yrs.)	Sex	Signs at diagnosis of myxedema coma	Associated comorbidities	Complications	Thyroid function at diagnosis (TSH and FT4)	L-T4 dosage (µg/kg/day) and other treatments
Schutt-Aine JC. 1980 (20)	8	M	Altered mental status, hypothermia	Epilepsy and panhypopituitarism	Hyponatremia	TSH: 3 mU/L Low FT4	IV (6.4)
Zhu Y, et al., 2017 (21)	6	F	Altered mental status, hypotension and desaturation	Pneumonia and autoimmune thyroiditis.	Prolonged QT interval, mild pericardial effusion; anuria.	TSH: >150 mU/L Low FT4	PO (4) Dexamethasone and antibiotics.
Thompson MD, et al., 2017 (22)	7	M	Altered mental status, hypothermia, bradycardia and hypercapnia	1q deletion and septo-optic dysplasia. Low basal cortisol and poor response to low-dose cosyntropin test.	First-degree atrioventricular block.	TSH: 0.50 mU/L Low FT4	IV (10) Hydrocortisone.
Root J, et al., 2017 (23)	5	F	Altered mental status and hypoxemia	Influenza	NA	NA	NA
Heksch RA, et al., 2018 (24)	0.10	F	Altered mental status, hypothermia, bradycardia, hypotension and hypoglycaemia	Autoimmune polyglandular syndrome type 3C.	Prolonged QT interval	TSH: 422 mU/L Low FT4	IV (10) Dexamethasone and antibiotics. Intubation.
Janson A, et al., 2019 (25)	12	F	Conscious but confused and in cardio-respiratory shock. Bradycardia and hypotension	Down syndrome. Hashimoto's thyroiditis	Elevated aspartate aminotransferase and increased s. creatinine.	TSH: 346 mU/L Low FT4	Nasogastric tube (0.29-2.9) Prednisolone. Antibiotics, Intubation.
Wankanit S, et al., 2019 (26)	2	F	Altered mental status, hypothermia and bradycardia	Acute viral bronchitis and congenital primary hypothyroidism	Pericardial effusion, biventricular hypertrophy and rhabdomyolysis: acute kidney injury	TSH: 224 mU/L Low FT4	PO (6,3) Antibiotics.
Divecha CA, et al., 2020 (27)	10	M	Conscious but confused and in cardio-respiratory shock	Down syndrome	Tachyarrhythmia and pulmonary hemorrhage after 2 weeks of admission	TSH: >150 mU/L Low FT4	Nasogastric tube (0,3-2,5) Injectable steroids.
Hallett TC, et al., (2021) (28)	Teenager	NA	NA	Congenital hypothyroidism	NA	NA	NA

Legend = IV: intravenous; PO: orally; TSH: thyroid-stimulating hormone; FT4: free thyroxine; NA: not available.

hormone replacement.

Hypothermia should be managed with warming blankets and increasing of room temperature. Care in warming the patient is advised as this can cause peripheral vasodilation that may lead to hypotension and shock. As the patient receives thyroid replacement, the hypothermia slowly resolves.

Hypotension requires careful management due to multiple issues that are present concurrently, such as hyponatremia, hypoglycemia, and hypothermia. A flowchart to aid in diagnosis of underlying causes of hyponatraemia is reported in figure 3.

Severe symptomatic hyponatremia must be corrected promptly because it can lead to cerebral edema, irreversible neurologic damage, respiratory arrest, brainstem herniation, and death (Figure 4).

For moderate hyponatremia, treatment includes the use of hypertonic 3% saline (1 litre = 513 mEq Na+) infused at a rate of 0.5 to 2 mL per kg per hour until symptoms resolve (29). It should be carried out in a monitored setting with close observation of serum sodium levels and urine osmolality. Rapid correction of sodium can result in osmotic demyelination syndrome. The hypertonic infusion should be stopped in the presence of clinical improvement or when the serum Na increases by 6 to 8 mmol/L in 24 hours (29). Thereafter, normal saline at the rate of 0.5 mmol/L/hour could be used. Once serum sodium levels rise to 130 mmol/L, fluid restriction should be sufficient to correct the hyponatremia (29,30).

There is a universal consensus that thyroid hormone replenishment is integral for the treatment of myxedema coma. The main considerations with thyroid hormone replacement in patients with this condition are the absorption and distribution of the administered hormone preparation, the onset of action, and the efficacy and safety of the treatment regimen. Treatment with L-T4 may be less effective due to impaired conversion of L-T4 into T3, but treatment with T3 may expose tissues to relatively high levels of thyroid hormone. As per the American Thyroid Association, initial thyroid hormone replacement for myxedema coma should be intravenous L-T4 (31). Intravenous administration of thyroid hormones is replaced by oral administration when the patient is fully awake. However, in many countries, the availability of intravenous L-T4 is limited. Accumulated evidence now shows that proper use of either thyroxine alone or in combination with triiodothyronine may be effective therapy. No data or protocol is available for the administration of oral L-T4 in myxedema coma in children and adolescents. Careful thyroid hormone administration in low doses is essential to reduce the risk of arrhythmia and heart failure in patients with chronic diseases. Monitoring of FT4 level is an objective way to observe improvement in patients with myxedema coma (32). Follow-up care after discharge is necessary to ensure adherence to thyroid hormone replacement.

Due to the possibility of secondary hypothyroidism and associated hypopituitarism, hydrocortisone

Serum [Na+], mEq/L (*)		
<125	125–129	130–135
Severe hyponatremia	Moderate hyponatremia	Mild hyponatremia

Figure 3. Flowchart to diagnosis of underlying causes of hyponatraemia

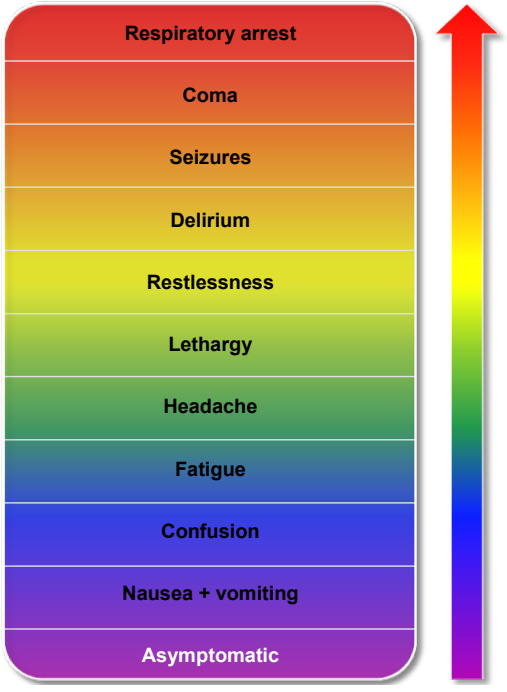

Figure 4. Increasing severity of hyponatremia in relation to Na+ decline (From: Bagshaw SM, Townsend D, McDermid R. Can J Anesth 2009;56:151-67 and Ghali J. Cardiology. 2008; 111:147-57)

should be administered until adrenal insufficiency has been ruled out (33).

Respiratory and airway management is a critical component in the management of the patient. Frequent monitoring of the arterial blood gases should be performed to detect hypercapnia and hypoxemia (2,12,14,16).

Other specific measures include starting broad-spectrum antibiotic treatment early if associated infection is suspected, and treating any other specific triggers discovered (2,12,14,16).

Patients with myxedema coma have an increased risk of bleeding due to an acquired Von Willebrand syndrome type 1 and a decrease in factors V, VII, VIII, IX, and X (34).

Prognosis

The prognosis for patients with myxedema coma is difficult to define because of the small number of cases reported in the literature. The prognosis, however, remains poor with a reported mortality between 20% and 50%. In-hospital mortality was 29.5% among 149 adult patients with myxedema coma identified between 2010-2013 through a national inpatient database in Japan (35). Even with early diagnosis and treatment of myxedema coma, the mortality rate varies between low (20-25%) and high (60%) in different reports in the presence of advanced intensive support care. Factors associated with a poor prognosis include advanced age, bradycardia and persistent hypothermia (36-38).

Conclusion

Myxedema coma is an endocrine emergency resulting from thyroid hormone dysregulation, usually coupled with an acute illness as a precipitant. The presumptive diagnosis of myxedema coma is primarily clinical with supportive evidence from thyroid function tests. Adult patients typically present with altered mental status, confusion, lethargy and myxedema. It may be missed as the precipitating conditions leading to decompensation of hypothyroidism may include sepsis, cardiac failure, metabolic and electrolyte disorders. The most important elements in the treatment of myxedema coma are early recognition, thyroid hormone replacement, hydrocortisone and appropriate supportive care. It is also essential to identify and treat the condition precipitating the coma. Early disease diagnosis and advancements in intensive care support have reduced the mortality rate. The prognosis seems to be better in children and adolescents compared to adults (18.1% vs. 29.5% as per the inpatient database of Japanese patients with myxedema coma) (Table 4).

Table 4. Key points for myxedema coma (decompensated hypothyroidism) in children and adolescents.

- Decompensated hypothyroidism, formerly known as myxedema coma, represents the most extreme clinical expression of severe primary or secondary hypothyroidism.
- The diagnosis is primarily clinical with supportive evidence of abnormal thyroid function tests.
- The clinical diagnosis, in some cases, can be difficult especially in patients with other associated complications.
- Myxedema coma can develop in hypothyroid children with slightly low free T4 level.
- Treatment consists of thyroid hormone replacement, correction of electrolyte abnormalities, passive rewarming, treatment of infections, respiratory and hemodynamic support, and administration of stress-dose glucocorticoids.
- Prognosis seems to be better in children and adolescents compared to adults.

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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