Severe myxedema coma and pericardial effusion in a child with Down syndrome: the importance of adherence to levothyroxine therapy

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ABSTRACT

Background. Myxedema coma is a rare, but life-threatening endocrinological emergency. Myxedema is characterized by altered mental status, and is accompanied by hypotension, bradycardia, hypothermia, bradypnea, hyporeflexia, hyponatremia, and hypoglycemia, all stemming from reduced metabolism due to severe hypothyroidism. Additionally, patients may exhibit signs of low cardiac output, edema in the extremities, peripheral circulatory disturbances, shock, and the development of pericardial and pleural effusions, ultimately leading to confusion and coma. We present a successfully treated case of severe myxedema coma with recurrent pericardial effusion and hypotensive shock. This case is characterized by an unusual clinical presentation and required a distinct treatment strategy highlighting its exceptional rarity.

Case. A 2-year-old boy with Down syndrome presented with recurrent pericardial effusion attributed to medication non-adherence. The critically-ill patient, experiencing a severe cardiogenic shock required mechanical ventilation and inotropic infusions in the pediatric intensive care unit. Elevated thyroid stimulating hormone (TSH), and low free T4 (fT4) and free T3 (fT3) levels prompted consideration of myxedema coma. Upon reviewing the patient’s medical history, it was ascertained that he had an ongoing diagnosis of primary hypothyroidism, and exhibited non-adherence to the prescribed treatment regimen and failed to attend scheduled outpatient clinic appointments for follow-up assessments. The treatment plan, devised by the pediatric endocrinology team, included the peroral administration of L-thyroxine (L-T4) at a dose of 50 micrograms per day. After beginning regular oral L-T4 treatment, a gradual improvement in the patient’s condition was observed. Notably, by the 15th day of oral therapy, the patient had made a full recovery. Contrary to the recommended intravenous treatment for myxedema coma, this patient was successfully treated with oral levothyroxine, due to the unavailability of the parenteral form in Türkiye.

Conclusions. This case report presents an instance of non-adherence to L-T4 therapy, which subsequently progressed to severe myxedema coma. Changes in neurologic status and hemodynamic instability in a patient with a history of hypothyroidism should raise the concern of nonadherence and, though rare, myxedema coma should be in the differential diagnosis.

Key words: Hypothyroidism, recurrent myxedema coma, cardiogenic shock, levothyroxine, child.

Myxedema coma is a rare and life-threatening endocrinological emergency with an incidence of 0.22/1,000,000 persons per year and a mortality rate of 30-50%.1,2 Symptoms and findings such as altered mental status, hypothermia, hypotension, bradycardia, hypoventilation, bradypnea, hyponatremia, hyporeflexia, and hypoglycemia are observed with decreased metabolism.3 These symptoms are followed by low cardiac output and associated edema of the hands and feet, vasoconstriction, peripheral circulatory disturbance, shock, pericardial and pleural
effusion, cerebral anoxia, confusion, and coma. The main treatment strategy, alongside supportive care, involves the administration of thyroid hormone replacement. The risk of hypothyroidism in children with Down syndrome is 28 times higher than other children. Furthermore, children with Down syndrome showed a significant decline in thyroid hormone levels, dropping from 90.8% to 41.7% in a follow-up study.

In this case report, we present a successfully treated case of severe myxedema coma in a 2-year-old child with Down syndrome, featuring recurrent pericardial effusion and hypotensive-cardiogenic shock. This case is particularly intriguing due to its rare clinical presentation, and unique treatment strategies employed.

Case Report

A 2-year-old boy with Down syndrome (regular trisomy 21) was admitted to the pediatric emergency department due to altered mental status and respiratory distress. The patient, who was born at term via normal spontaneous vaginal birth from a healthy mother, was using hydrochlorothiazide and spironolactone as regular medications due to a known atrial septal defect and pulmonary stenosis and was additionally using levothyroxine (L-T4) therapy due to hypothyroidism. Thyroid agenesis had been identified as the cause of the patient’s hypothyroidism through ultrasonography. The parents were not consanguineous, did not have a known hereditary disease, and had a healthy 5-year-old girl. His family stated that the patient was able to sit without support and walk on his own in his daily life and was able to take solid and liquid foods by mouth.

At the time of admission, his weight was 10 kg (3.75p; -1.78 SDS) and length was 78-cm- (1.07p; -2.3 SDS) he had bradypnea (respiratory rate 10/ min (<-2 SDS)), bradycardia (heart rate 72/ min (<-2 SDS)), hypotension [blood pressure 72/36 mmHg (13p, -1.13 SDS; 34p, -0.41 SDS)], altered mental status [Glasgow coma scale (GCS) score: 13], hearth sounds were barely audible and a cardiac murmur on auscultation, hypothermia (body temperature 35.5°C), capillary refill time was increased (4 seconds), cutis marmoratus, extensive dry skin with hard, non-pitting edema on the dorsum of the hands and feet, tongue edema (Fig. 1). The patient had a typical Down syndrome facial appearance with slanted eyes, a flat nose, small ears, and a large tongue. The patient also had short stature, brachydactyly and Simian creases. There was no hepatosplenomegaly on abdominal palpation. According to his medical history, he had experienced pericardial tamponade and underwent pericardiocentesis on two separate occasions. The family stated that the patient had benefited clinically from

Fig. 1. The apperance of the patient on admission: typical phenotypes of Down syndrome and extensive dryness of the skin with hard, non-pitting edema on the dorsum of the hands and feet, and tongue edema.
previous pericardiocentesis procedures, but the same clinic developed after a period of time. In previous hospitalizations, hormone tests were not performed because the family stated that the patient had regular outpatient check-ups and was taking his medications regularly.

The patient’s arterial blood gas, complete blood count, organ function tests (heart, liver, kidney), and serum electrolyte levels were within normal limits. The chest X-ray revealed an enlarged heart silhouette (Fig. 2), while the electrocardiogram (ECG) indicated a reduction in QRS voltage. Given the patient’s altered mental status and hemodynamic instability, he was promptly transferred to the pediatric intensive care unit (PICU) for close monitoring, further assessment, and treatment.

Intravenous bolus administration of normal saline and an adrenergic inotropic infusion with adrenaline were initiated. However, the patient exhibited persistent refractory hypotension. Adrenaline and noradrenaline infusion rates were meticulously adjusted based on age-appropriate criteria. Endotracheal intubation was performed to reduce respiratory effort. A bedside echocardiography, overseen by the pediatric intensive care team, revealed a normal ejection fraction. Nonetheless, a diffuse pericardial effusion, not indicative of tamponade, was observed (Fig. 3). Adrenaline and noradrenaline doses were incrementally increased to 0.6 µg/kg/min to maintain normotension. Stress-related hyperglycemia was considered the cause of the patient’s high serum glucose level of 243 mg/dL, given the absence of diabetes symptoms and the spontaneous resolution of hyperglycemia. Additionally, the urine ketone test was negative. Therefore, HbA1c and C-peptide levels were not tested. Empirical antibiotics were administered to address potential sepsis, and a hydrocortisone infusion (85 mg/m²/day) was initiated due to suspected catecholamine resistant septic shock. Following hemodynamic stabilization, fluid restriction was implemented, and diuretic therapy was initiated. Given the patient’s history of primary hypothyroidism and treatment non-adherence, thyroid function tests were performed, revealing markedly elevated thyroid stimulating hormone (TSH) level (311.24 mIU/L), along with suppressed free T3 (<1.07 pg/ml) and free T4 (<0.40 ng/dL) levels. In the patient’s previous history, although he was diagnosed with primary hypothyroidism and his parents were giving him 50 µg of L-T4, thyroid function tests were not checked and cardiac causes were considered first because
the family reported that the treatment was being given regularly and that the patient had regular pediatric endocrinology visits. The patient was followed up because he benefited from pericardiocentesis. However, due to the severe clinical picture at the last hospitalization and the recurrence of the pericardial effusion, myxedema coma was considered. Before the diagnosis of myxedema coma, blood, urine, and endotracheal aspirate cultures were obtained for differential diagnosis. Hemodynamic instability prevented imaging, but we performed a detailed neurological examination and hourly GCS calculation of the patient. Due to the possibility of intoxication, the family was interviewed and urine toxicology tests were performed.

A pediatric endocrinology consultation was sought, and a decision was made to continue the patient’s oral L-T4 treatment at the same dosage (50 µg/day), with close monitoring of thyroid function tests. Upon conducting an in-depth review of the patient’s medical history, it was ascertained that non-adherence to the prescribed treatment for hypothyroidism and irregularities in attending routine medical evaluations had been observed. Beginning on the 3rd day of PICU hospitalization, inotropic support was gradually tapered. The noradrenaline infusion ceased on day 11, followed by the discontinuation of the adrenaline infusion on day 12. On the 13th day, the patient underwent extubation and was transitioned to noninvasive respiratory support. After achieving hemodynamic stability, the hydrocortisone infusion was gradually tapered and ultimately discontinued on the 15th day. Subsequent thyroid function tests on the 3rd, 6th, and 10th days following the diagnosis of myxedema coma indicated a decreasing trend in TSH levels and an increasing trend in free T4 levels, as detailed in Table I. On the 15th day, the patient achieved hemodynamic stability, exhibited normal neurological, cardiac, and respiratory functions, showed regression of skin findings and edema, and was able to resume total oral feeding. The patient experienced a complete recovery from a severe and life-threatening myxedema coma, with no residual sequelae or complications.

**Discussion**

We present a successfully treated patient with Down syndrome who had severe myxedema coma accompanied by recurrent pericardial effusion and hypotensive shock. This case is characterized by an unusual clinical presentation and a different treatment strategy, highlighting its exceptional rarity. This case report underscores the importance of adherence to LT-4 therapy in children with hypothyroidism. The life-threatening presentation emphasizes the significance of timely diagnosis and treatment of severe hypothyroidism.

The thyroid hormones act as fundamental regulators of metabolism, exerting pleiotropic effects on numerous organs. They play vital roles in orchestrating normal physiological growth, governing protein and lipid metabolism, enhancing the absorption of carbohydrates from the intestine, and activating red blood cell 2,3-diphosphoglycerate, which aids in the dissociation of oxygen from hemoglobin. In the cardiovascular system, particularly through the actions of T3, thyroid hormones increase ejection fractions, reduce vascular resistance, and promote coronary angiogenesis. Beyond their cardiovascular effects, thyroid hormones also regulate the metabolism of various internal organs such as the liver, pancreas,

| Table I. Laboratory changes of thyroid function tests day by day under L-T4 treatment. |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                | 1st day         | 3th day         | 6th day         | 10th day        | Normal          |
| TSH (mIU/L)                    | 311.24          | 65.01           | 31.01           | 2.91            | 0.35-4.94       |
| free T4 (ng/dL)                | <0.40           | 0.46            | 0.90            | 1.32            | 0.7-1.48        |
| free T3 (pg/ml)                | <1.07           | -               | -               | -               | 1.71-3.71       |

T3: free T3, T4: free T4, L-T4: L-thyroxine, TSH: thyroid stimulating hormone.
and muscles. Furthermore, they contribute to the carbohydrate metabolism by maintaining plasma insulin and glucose levels.\textsuperscript{7,8}

Decomposition due to severe hypothyroidism, also known as myxedema coma, is an endocrinologic emergency that can lead to altered mental status and, in severe cases, coma. All clinical signs and symptoms associated with myxedema coma are a consequence of a metabolic slow-down.\textsuperscript{9,10} In line with the typical presentation, our patient, like most individuals with myxedema coma, exhibited primary hypothyroidism. This was substantiated by low serum levels of fT4 and fT3, accompanied by elevated levels of TSH.\textsuperscript{4,11,12}

Severe hypothyroidism can lead to the development of pericardial effusion, although this accumulation typically occurs gradually. Consequently, it is unexpected for this condition to produce clinically significant acute cardiovascular effects. Although rare, there are patients who are monitored in the PICU for myxedema coma. A 10-year-old male patient with the phenotype of Down syndrome and 1q deletion also presented with a low GCS and hemodynamic instability that was severe enough to require intubation. Similar to our patient, he was successfully treated with oral L-T4 but at high doses (400 µg/day) and intravenous hydrocortisone (3 mg/kg/day) for 14 days.\textsuperscript{2} In our pediatric patient, who has Down syndrome, an extraordinary and exceptionally rare occurrence was observed. This involved severe myxedema coma with recurrent pericardial effusion, leading to a life-threatening hypotensive shock. It is noteworthy that such a combination of factors and clinical presentation has been reported very rarely in the literature. Complications arising from hypothyroidism may include pericardial effusions, which have been reported in 3-37% of hypothyroidism patients. Typically, pericardial effusions are associated with severe and long-standing hypothyroidism. However, on rare occasions, they can manifest as an initial clinical presentation of severe hypothyroidism or even mild thyroid dysfunction. Pericardial fluid shares a composition similar to plasma, and its drainage is facilitated by the thoracic and lymphatic ducts. Various theories exist regarding the development of pericardial effusion in hypothyroidism, with the most well-known theory attributing it to increased albumin permeability in pericardial capillaries. This increased permeability is a result of both the direct effects of hypothyroidism and the subsequent increase in histamine release. Consequently, the elevated intrapericardial oncotic pressure leads to an accumulation of pericardial fluid. Furthermore, pulmonary hypertension resulting from hypothyroidism can disrupt lymphatic drainage and elevate right-sided pressures.\textsuperscript{13} In the context of myxedema coma, similar cardiac manifestations have been observed. For instance, a 5-year-old autoimmune thyroiditis patient presented with right ventricular conduction delay and mild pericardial effusion. Similarly, another 6-year-old patient diagnosed with autoimmune thyroiditis displayed prolonged QT interval, mild pericardial effusion, and anuria.\textsuperscript{14,15} In 2019, a more severe clinical presentation was noted in a 2-year-old patient with congenital primary hypothyroidism, who also had acute viral bronchiolitis. Echocardiography revealed pericardial effusion and biventricular hypertrophy in the untreated hypothyroid patient, who presented with altered mental status, hypothermia, and bradycardia. The treatment and follow-up approach for this patient mirrored our previous case. With regular L-T4 treatment, the patient’s thyroid function returned to normal, pericardial effusion decreased within a month, and heart dimensions improved within two months. Additionally, this patient displayed additional findings of rhabdomyolysis and liver failure, which responded positively to treatment.\textsuperscript{16} Another patient with clinical and treatment similarities to the previously mentioned cases was a four-year-old male child experiencing recurrent abdominal pain. Ultrasonography revealed a significant pericardial effusion, which was later confirmed by echocardiography to be approximately 23 mm in size with a volume of
around 600 mL. Despite minimal impairment of heart kinetics, thyroid function testing revealed extremely high thyrotropin levels and low serum-free thyroxine levels, leading to a diagnosis of myxedema coma with pericardial effusion. Treatment involved LT4 replacement therapy administered gradually. Remarkably, after just one month, complete regression of the effusion and normalization of thyroid function indexes were observed.¹⁷

The differential diagnosis of myxedema coma is essential for proper management. There are many clinical conditions that may mimic the myxedema coma, such as sepsis, drug intoxications, central nervous system disorders, or drug-related adverse effects.¹⁸,¹⁹ In our patient, the related disorders had been excluded by physical examination, laboratory, and radiological tests. It is important to note that hypothyroidism leading to coma in children is a very rare condition. Given the limited number of cases in the medical literature, it is challenging to establish a precise mortality rate for this specific population. However, in adults, myxedema coma is associated with a reported mortality rate ranging from 20% to 50%. Even when early diagnosis and prompt treatment are initiated, a poor prognosis has been linked to factors such as advanced age, bradycardia, and prolonged or resistant hypothermia.²⁰ Euthyroid sick syndrome (non-thyroidal illness) was also considered because of the extremely low fT3. However, euthyroid sick syndrome was ruled out due to the extremely high TSH levels in our patient, rather than the normal/low TSH level typically seen in euthyroid syndrome.²¹

Following the diagnosis of myxedema coma, therapeutic interventions include correction of electrolyte imbalances, implementation of passive warming measures, administration of antimicrobial agents for infection control, initiation of respiratory and hemodynamic support, provision of stress-dose glucocorticoids, and initiation of thyroid hormone replacement therapy. Vigilant monitoring and management within an intensive care unit are essential, given the concurrent presence of multiple issues, such as hypotension, hyponatremia, hypoglycemia, and hypothermia. Furthermore, it is noteworthy that when thyroid hormone replacement therapy is employed in conjunction with these supportive measures, a gradual resolution of all symptoms is typically observed.⁴

Myxedema coma can occur when compensatory mechanisms for hypothyroidism are overwhelmed by a precipitating cause, leading to life-threatening consequences. The diagnosis of myxedema coma hinges on a thorough assessment of differential diagnoses, clinical suspicion, patient history, and thyroid function tests. In children with known or suspected hypothyroidism—particularly those predisposed to hypothyroidism, such as individuals with Down syndrome—myxedema coma should be considered in cases of altered mental status.² An illustrative case involves a 17-year-old girl with growth and developmental delay who was followed in the PICU due to confusion, bradycardia, hypothermia, and severe hypotension, requiring vasopressors and hydrocortisone. She had myxedema coma due to severe hypothyroidism and promptly treated with intravenous levothyroxine.²² Similarly to our patient, a 10-year-old child with Down syndrome, was admitted to the PICU with severe myxedema coma accompanied by shock. Mechanical ventilation was initiated for respiratory support, and vasopressors and hydrocortisone were administered to maintain normal blood pressure. Oral thyroid hormone replacement therapy was initiated at a dose of 400 µg/day, with subsequent doses adjusted based on thyroid hormone levels. Unfortunately, despite treatment efforts, the patient succumbed to severe cardiac arrhythmia on the 14th day.² Cases of myxedema coma reported in the literature are usually at the time of the initial diagnosis of hypothyroidism. In our case, the fact that the patient was previously diagnosed is important because it is a clear indicator of treatment noncompliance.

The basis therapeutic approach for myxedema coma patients revolves around optimizing the absorption and distribution of thyroid hormone
replacements, with a focus on achieving safe and efficacious outcomes. It has been reported that treatment with L-T4 may be less effective in cases where the conversion of L-T4 into T3 is impaired. In accordance with the guidelines reported by the American Thyroid Association, IV administration of L-T4 is considered the preferred treatment for managing myxedema coma. It’s important to note that intravenous L-T4 is not readily available in many countries, making oral administration a more common approach. In children with myxedema coma, there is a scarcity of available data and established protocols regarding the oral administration of L-T4. Despite this, it remains a viable option. In this case report, oral L-T4 was administered due to the unavailability of the intravenous form of L-T4 in our country. Additionally, it was also discovered that the patient had not been consistently taking the previously prescribed oral L-T4. To assess the effectiveness of the treatment, regular monitoring of thyroid function, including TSH and fT4 levels, was carried out in collaboration with the pediatric endocrinology team. Clinical symptoms and overall well-being were also closely observed and taken into consideration during the treatment course.²³

According to the guidelines, intravenous L-T4 is used in myxedema coma but this form is not available in our country. If oral administration is preferred, a high dose is recommended, but we discovered that our patient did not take the medication regularly or showed noncompliance by spitting it out when he did take it. For this reason, even before the diagnosis was made, he was followed with close clinical monitoring in the PICU when the normal daily dose was started.

A myxedema coma diagnostic scoring system has been developed for adults. The clinical findings, including thermoregulatory dysfunction, central nervous system involvement, gastrointestinal findings, precipitating factors, cardiovascular dysfunction findings, and metabolic disorders, form the basis of the scoring system.²⁴ Although challenging to apply to children due to age-related changes in vital signs, a separate scoring system for children is necessary.

In summary, our case report highlights a pediatric patient with Down syndrome and a prior diagnosis of hypothyroidism. This patient presented with a severe clinical condition characterized by recurrent pericardial effusion and was effectively treated. Myxedema coma, although rare, carries a high risk of mortality. Consequently, it should be considered as a potential diagnosis in cases of shock and multiorgan involvement, ensuring its inclusion in the differential diagnosis.

Altered neurologic status and hemodynamic instability in a patient with a history of hypothyroidism should raise the concern of nonadherence and, although rare, myxedema coma should be in the differential diagnosis. In addition, regular medication use and outpatient clinic follow-ups should be questioned at every encounter with patients diagnosed with hypothyroidism for any reason, and thyroid function tests should be examined when L-T4 treatment noncompliance is suspected.

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Ethical approval

We obtained informed consent from the patient’s parents for this report.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: HFA and AA; data collection: HFA, AA, ŞD, SFÇ; analysis and interpretation of results: HFA and AA; draft manuscript preparation: HFA and AA. All authors reviewed the results and approved the final version of the manuscript.
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