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Coexistence of Hyperthyroidism and Type 1 Diabetes in a Child with Down Syndrome: A Rare Autoimmune Endocrine Disorder

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ABSTRACT

Down syndrome (DS) is a common chromosomal disorder associated with intellectual disability and various medical issues, including autoimmune endocrinopathies. The prevalence of Type 1 diabetes mellitus (T1DM) in DS is higher than in the general population, with thyroid disorders commonly observed. Hyperthyroidism, although rare, can occur in children with DS, and its coexistence with T1DM is an uncommon but important clinical phenomenon. A 10-year-old girl with DS presented with progressive anterior diffuse struma, weight loss, increased thirst, and frequent urination. Laboratory tests confirmed T1DM with elevated glucose and HbA1c levels, and hyperthyroidism with elevated thyroglobulin and anti-TPO antibodies. The presence of glutamic acid decarboxylase 65 antibodies further supported the diagnosis. The patient was started on insulin therapy and thiamazole for hyperthyroid management, with stable clinical progress during hospitalization. The association between autoimmune disorders, including T1DM and thyroid dysfunction, is well-documented in DS. Children with DS have a heightened risk of developing multiple autoimmune conditions, making early screening for thyroid dysfunction crucial at the time of T1DM diagnosis. This case emphasizes the need for vigilant monitoring of endocrine function in DS patients, particularly for concurrent autoimmune diseases. Early detection and management of autoimmune endocrinopathies are essential in children with DS, especially when T1DM and hyperthyroidism coexist. Regular thyroid monitoring, including TSH and TPO antibodies, can prevent complications and promote optimal health outcomes. Early intervention is key to supporting the overall development of affected children.

Keywords: *Autoimmune Polyendocrinopathy, Pediatric Endocrine Screening, Insulin and Antithyroid Therapy, Glutamic Acid Decarboxylase Antibodies.*

1. INTRODUCTION

Down syndrome (DS) is the most common chromosomal disorder in children, causing moderate-to-severe intellectual disability. Individuals with DS frequently experience multi-organ medical issues, including heart defects, endocrine disorders, hearing and vision impairments, hypotonia, and increased cancer risk. Endocrinopathies are particularly prevalent among these individuals. Although the exact pathophysiology remains unclear, endocrine dysfunction in DS is believed to be multifactorial, involving both autoimmune and cellular mechanisms [1].

The association between DS and autoimmune endocrinopathies is well established, with risk increasing with age. Children with DS are four to six times more likely to develop type 1 diabetes mellitus (T1DM) in their first decade of life compared to the general population. The prevalence of T1DM in DS ranges from 1.4% to 10.6%, and thyroid disorders occur in 30–40% of cases. Although hyperthyroidism is rare and usually appears after age eight, clinical features are similar to those in the general population [2].

A rare case involved a 10-year-old girl with DS who developed both type 1 diabetes mellitus and autoimmune thyroiditis (Hashimoto's disease). Reports of DS patients presenting with more than one autoimmune endocrine disorder are limited. In one study, only 1.1% of patients exhibited both T1DM and hypothyroidism, while 27.2% had a single autoimmune condition [3]. This case represents a state-of-the-art example highlighting the need for vigilant monitoring of endocrine function in children with DS.

2. CASE DESCRIPTION

A 10-year-old girl with Down syndrome presented to the Endocrinology outpatient clinic at Dr. Soetomo General Hospital, with the main complaint of anterior diffuse struma that had progressed over the past three months. She reported significant weight loss from 18 kg to 14 kg despite increased appetite, along with frequent palpitations and night sweats. Additional complaints included mood swings, behavioral disturbances, speech and language delays, as well as a two-year history of excessive thirst and frequent urination. Her medical history revealed a prior diagnosis of congenital heart disease, a first visit to endocrinology in 2019, and poor follow-up due to financial constraints, with a background of familial diabetes and advanced maternal age at birth.

On physical examination, the patient had a blood pressure of 105/75 mmHg, pulse rate of 120 bpm, respiratory rate of 22 breaths per minute, temperature of 36.3°C, and oxygen saturation of 98% on room air. Characteristic phenotypic features of Down syndrome were noted, including slanted epicanthal folds and a transverse palmar crease. Neck examination revealed a diffuse goiter that moved with swallowing, while cardiac auscultation detected a diastolic murmur at the second left intercostal space. Anthropometric assessment based on the Down syndrome growth chart showed a weight of 16 kg and height of 120 cm, placing her below the 5th percentile for weight-for-age and between the 5th–10th percentile for height-for-age, with an ideal body weight attainment of only 59.2%.

Laboratory evaluation showed low TSH 0.01 µU/mL (ref range: 0.7-5.7 µU/mL) and high FT4 5.3 ng/dL (ref range: 0.8-1.9 ng/dL), fasting plasma glucose was elevated at 293 mg/dL, with a two-hour postload glucose of 615 mg/dL and an HbA1c of 12.9%, consistent with poorly controlled diabetes mellitus. Thyroid function and autoimmunity tests revealed markedly elevated thyroglobulin (277 ng/mL) and anti-thyroid peroxidase (anti-TPO) antibodies (1,070.84 IU/mL), suggestive of autoimmune thyroiditis. In addition, there was a decreased c-peptide level of 0.2 ng/mL (reference range: 0.5–2.0 ng/mL) indicating impaired endogenous insulin production. The presence of glutamic acid decarboxylase 65 (GAD65) antibodies at 11 IU/mL and a negative Mantoux test supported the diagnosis of autoimmune diabetes without evidence of tuberculosis.

The ultrasound of the upper and lower abdomen revealed normal findings for the liver, spleen, gallbladder, pancreas, kidney, bladder, uterus, and adnexa. The chest x-ray suggested the presence of congenital heart disease with a left-to-right shunt (VSD). The echocardiography showed a large perimembranous VSD, large tricuspid regurgitation (TR), pulmonary hypertension (PHT), and an ejection fraction (EF) of 73.5%. She got Lisinopril 1 x 1.5 mg per orally and sildenafil 4 x 8 mg.

Based on clinical presentation and diagnostic findings, the patient was diagnosed with a combination of type 1 diabetes mellitus (T1DM), hyperthyroidism, and Down syndrome. She was hospitalized for initiation of insulin therapy and blood glucose monitoring, receiving long-acting insulin (0-0-8 IU) and short-acting insulin adjusted according to the insulin-to-carbohydrate ratio (ICR) and insulin sensitivity factor (ISF). In addition, she was prescribed metformin 2 × 250 mg orally and thiamazole 1 × 5 mg daily for hyperthyroid management. During hospitalization, the patient remained clinically stable without signs of diabetic ketoacidosis, and her family received structured education on diabetes care, with a recommendation for monthly follow-up in the endocrinology clinic.

3. DISCUSSION

The coexistence of Down syndrome (DS), type 1 diabetes mellitus (T1DM), and hyperthyroidism is an uncommon clinical presentation, particularly in early childhood. While autoimmune thyroiditis is the most prevalent autoimmune disorder in children with DS, with a reported prevalence of 16–28%, the incidence of T1DM in this population ranges from 1.4–10.6%. Although there have been documented cases of adolescents with DS presenting with multiple autoimmune diseases, including thyroiditis and T1DM, the simultaneous onset of two autoimmune endocrinopathies in a younger child remains rare. To date, only a few such cases have been reported in the literature, making this clinical presentation significant in understanding autoimmune disease clustering in DS [4]. This case demonstrates the simultaneous manifestation of two autoimmune endocrinopathies in a child with DS, which is not only rare but also points to the importance of a deeper understanding of immunogenetic interactions in trisomy 21. The presence of both T1DM and early hyperthyroidism highlights how autoimmune diseases can group together, making it harder to diagnose and speeding up the onset of these conditions in this population.

Type 1 diabetes mellitus is a chronic autoimmune condition marked by the destruction of insulin-producing β-cells in the pancreas, leading to absolute insulin deficiency [5]. The pathogenesis of T1DM involves complex interactions between genetic predisposition, environmental exposures, and immune dysregulation. The presence of islet cell antibodies, such as anti-GAD, often precedes the clinical onset of diabetes, and symptoms typically emerge once β-cell destruction exceeds 90%. In DS patients, the autoimmune basis of T1DM is supported by the frequent presence of circulating autoantibodies, indicating a heightened immunological vulnerability likely influenced by trisomy 21 [4], [6].

Recent epidemiological studies have shown an increasing global incidence of T1DM in children, estimated to rise by 2–5% annually, with over 100,000 new diagnoses each year among those under 15 years old. In Indonesia, the reported prevalence of pediatric T1DM has surged significantly, although underdiagnosis remains a concern. Children with DS are diagnosed

with T1DM at younger ages compared to the general population, possibly due to immunogenetic factors associated with chromosome 21. These observations underscore the need for vigilant screening and early diagnosis of autoimmune disorders in children with DS, particularly when multiple endocrinopathies are suspected, providing a state-of-the-art context for the present case [7].

T1DM progresses through identifiable stages, beginning with the appearance of islet autoantibodies, often in genetically predisposed individuals. The presence of two or more autoantibodies marks Stage 1, followed by asymptomatic dysglycemia in Stage 2, and eventual clinical onset in Stage 3 or established disease in Stage 4. New-onset T1DM in children typically presents with classic symptoms such as polyuria, polydipsia, polyphagia, and weight loss, though diabetic ketoacidosis (DKA) may also be the first presentation. In this case, the patient presented with a history of significant weight loss, increased thirst, and frequent urination, without signs of acute complications like DKA [8], [9].

Autoantibodies such as insulin (IAA), glutamic acid decarboxylase (GADA), islet antigen-2 (IA-2A), and ZnT8A are key markers in the diagnosis and progression of autoimmune diabetes. Children with Down syndrome (DS) have a significantly higher prevalence of multiple islet autoantibodies compared to the general population, supporting an increased risk of autoimmune diabetes. Evidence suggests accelerated onset of T1DM in children with DS, with some studies showing peak onset as early as 2 years old. This pattern is further supported by large-scale longitudinal studies, confirming that T1DM in DS manifests earlier and more frequently than in the general pediatric population [10].

Type 1 diabetes mellitus (T1DM) is often associated with other autoimmune disorders, including thyroid disease. In this case, the patient presented with an enlarged thyroid gland, heat intolerance, sweating, fatigue, weakness, and unexplained weight loss, which are characteristic signs of both T1DM and hyperthyroidism. Laboratory results confirmed hyperthyroidism with elevated FT4 (5.3 ng/dL) and suppressed TSH (<0.01 μIU/mL). Thyroid function tests should be performed once metabolic stability and good glycemic control are achieved, as abnormal thyroid function can be diagnosed with simple blood tests and managed effectively [4], [11]. In clinical practice, delay in detecting these two diseases together may increase the risk of acute complications and worsen the patient's metabolic status. Therefore, in DS children with non-specific metabolic symptoms such as weakness, fatigue, or weight changes, blood glucose and thyroid function should be considered as part of the initial evaluation.

Thyroid antibodies, such as anti-microsomal peroxidase (TPOAb) and antithyroglobulin (TG-Ab), are commonly found in T1DM patients, with prevalence rates ranging from 15% to 30%. In this patient, the thyroglobulin level was high (277 ng/dL), and the anti-TPO level was significantly elevated (1,070.84 IU/mL). Autoimmune thyroid disorders tend to increase with the duration of diabetes and age, and in female patients, sex hormones may influence the development of thyroid antibodies. The patient’s undernourished status, rapid weight loss, and typical symptoms of T1DM further support the diagnosis of T1DM, which often presents in lean children with impaired insulin secretion [3], [4].

T1DM in prepubertal children is primarily diagnosed as Type 1, but distinguishing it from Type 2 in overweight or obese adolescents can be challenging. Diagnosis in these cases requires evaluating family history, islet autoantibodies, and C-peptide levels. The main objectives of diabetes management are achieving optimal metabolic control, preventing complications, and supporting the psychological well-being of both patients and families. Management relies on five pillars: insulin administration, blood glucose monitoring, nutrition, physical activity, and education, with an integrated healthcare team essential for optimal care [12].

Insulin regimens should be tailored based on factors like age, weight, disease duration, and comorbidities, typically following a basal-bolus approach using both basal and rapid-acting insulin. The basal insulin dose typically comprises 30% to 50% of the total daily requirement, and adjustments are made according to blood glucose levels, especially around meals. Blood glucose monitoring, HbA1c tracking, and, when necessary, continuous glucose monitoring, are key for managing T1DM, with regular adjustments based on readings and specific guidelines for different blood glucose levels [6].

Proper nutrition and physical activity are integral to managing T1DM. A balanced diet, including vegetables, fruits, whole grains, dairy, and lean meats, is recommended, with daily physical activity of at least 60 minutes to improve insulin sensitivity and overall health. Education is also vital, focusing on self-management skills for insulin use, diet, and responding to acute complications like diabetic ketoacidosis or hypoglycemia. This comprehensive approach ensures effective long-term management and minimizes complications for children with T1DM [13] .

Early detection of endocrine disorders in patients with Down Syndrome (DS) is an important step in preventing more severe multisystem complications. DS patients have a higher risk of various autoimmune endocrinopathies, especially type 1 diabetes mellitus (T1DM) and autoimmune thyroid disease, even from an early age. Studies show that the prevalence of thyroid disorders in children with DS is as high as 30-40%, while the risk of T1DM increases 4-6 times compared to the general population [1], [7]. Early evaluation allows for more targeted interventions, prevents delays in diagnosis, and reduces the risk of acute complications such as diabetic ketoacidosis or thyrotoxic crisis. This report is also addressed to general practitioners as the first line in the healthcare system.

In daily clinical practice, general practitioners are expected to recognise prodromal symptoms of endocrine disorders that are often atypical in paediatric patients, especially with comorbidities such as DS. Thyroid function tests and autoantibody screening (such as anti-GAD and anti-TPO) should be performed in DS patients who present with metabolic symptoms,

mood or developmental changes, or growth disturbances, as recommended by the International Society for Pediatric and Adolescent Diabetes.[7] By increasing awareness and clinical knowledge of the relationship between DS and endocrinopathies, GPs have an important role to play in expediting diagnosis and referral to relevant specialists.

This case report has limitations in terms of long-term monitoring of the patient. Information on the possibility of developing other autoimmune disorders, such as celiac disease or adrenal insufficiency, is not available. In fact, individuals with Down syndrome are known to have a higher risk of developing more than one autoimmune disorder, and the onset of one autoimmune disease may predispose them to the occurrence of another disease with age [4]. In addition, the patient's response to long-term therapy could not be thoroughly evaluated due to limited follow-up. Therefore, longitudinal studies are needed to understand the natural course of autoimmunity and the effectiveness of long-term therapy in children with Down syndrome.

4. CONCLUSION

In conclusion, this case underscores the importance of early detection and management of autoimmune conditions in children with Down syndrome, particularly when diagnosing Type 1 diabetes (T1DM). The patient's presentation of hyperthyroidism and T1DM emphasizes the increased risk of autoimmune endocrinopathies in this population. Monitoring thyroid function, including TSH and TPO antibodies, at the time of T1DM diagnosis is essential for preventing complications. Early diagnosis and intervention are key to ensuring optimal health outcomes and supporting the overall development of affected children.

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