CASE REPORT

Down syndrome, insulin-dependent diabetes mellitus and hyperthyroidism: a rare association

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SUMMARY

The association between Down syndrome (DS) and autoimmune endocrinopathies is well established. These disorders become increasingly frequent as children grow older and the onset of one often predisposes to the development of others. However, there are few cases in the literature reporting the simultaneous onset of type 1 diabetes mellitus and hyperthyroidism in children with DS. We describe a case of an 8-year-old girl with DS who presented at the emergency department with hyperglycaemia and ketosis as a primary manifestation of type 1 diabetes mellitus. During the initial investigation, hyperthyroidism was detected, with thyroid-stimulating hormone <0.01 µU/mL, positive antithyroid antibodies and an increase in thyroid gland on ultrasound. The authors present this case to underline the usefulness of monitoring thyroid function at the diagnosis of diabetes, even without apparent clinical manifestations, and to alert for the possibility of autoimmune endocrine dysfunction in children with DS.

BACKGROUND

Down syndrome (DS) is the most common known genetic cause of moderate-to-severe intellectual disability and one of the most frequent chromosomal disorders in paediatric patients.¹ Its incidence varies between 1/449 and 1/800 of live births, across all races and socioeconomic levels.² Besides the typical phenotype and the main clinical signs (cognitive impairment, congenital heart disease and muscular hypotonia), children with DS have significant immunological changes determining increased predisposition to autoimmune diseases.^{3–4} Among those, endocrinopathies are the most common.^{5–7} The physiopathological bases for these changes are not fully understood, and studies suggest that endocrine dysfunction in DS may be multifactorial, explained not only by autoimmunity but also by cellular mechanisms.⁸

In the first decade of life, the incidence of type 1 diabetes mellitus (DM1) is four to six times higher in patients with DS than in the general population. In fact, children aged between 5 and 10 years are the ones who most often present the initial clinical manifestations of diabetes.⁹

Thyroid disturbances are also common in DS children.^{7–10–12} Hypothyroidism is the most frequent thyroid disorder and endocrine condition associated with DS.^{7–13–14} It can be found at any age and has an estimated prevalence of 30–40%.^{15–16} The most common aetiology is autoimmune with antithyroid antibodies being found in 13–34% of patients with DS.¹³ The symptoms of hypothyroidism can be

subtle and difficult to value, especially in people with DS. As for hyperthyroidism, despite being more prevalent among people with DS than in the general population,^{16–18} only sporadic cases have been described in the literature,^{6–7–11–13–19–22} and most studies show a low prevalence, generally under 3%.^{7–13} The principal cause is autoimmune and it manifests in the form of Graves' disease. Clinical characteristics are similar to those found in the general population and it rarely presents before 8 years of age.⁶

Children with DS are a population with special needs. The American Academy of Pediatrics recommends that thyroid function should be periodically evaluated in all children with DS⁸ due to the high prevalence of thyroid disturbances in this population, the adverse medical effects associated with these disorders, and the availability of safe testing and effective treatment.⁵ Some authors also suggest additionally conducting routine assessments for diabetes mellitus, since the clinical diagnosis is more difficult in these children, and their complications, such as hyperosmolar coma, are very common.^{23–24}

The authors present the case of a girl with DS who subsequently developed DM1 and hyperthyroidism, due to its clinical interest, and in order to emphasise the need for clinical suspicion and periodic laboratory monitoring for endocrine disorders in patients with this chromosomopathy.

CASE PRESENTATION

An 8-year-old girl diagnosed neonatally with DS (47,XX,+21), with no other relevant personal or family history, was brought to the emergency department for polyuria, change in behaviour, inattention, weight loss (3 kg) and vomiting; the parents also reported that the child had polydipsia, polyphagia and diarrhoea during the past three months. On physical examination, the girl appeared ill, was irritable and pale, and presented dried mucous membranes, sunken eyes, tachycardia, normal blood pressure, a systolic murmur grades III–IV/VI, a grade 1 goitre and slight exophthalmia. Her height was in the 50th centile and weight was <5th centile, as measured for age and sex according to DS growth charts.²⁵ No other changes were observed on systemic examination, except for the physical features of DS (slanting eyes, epicanthic folds, high-arched palate and protruding tongue).

INVESTIGATIONS

Investigation performed at the emergency department revealed blood glucose 954 mg/dL, pH 7.34,

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HCO₃ 20 mmol/L, sodium 123 mmol/L, potassium 5 mmol/L and blood ketones 2 mg/dL.

TREATMENT

The child was admitted with the diagnosis of DM1 (first episode). Insulin therapy was started, with good clinical response and progressive metabolic control. Further laboratory investigation revealed: free thyroxine 4.08 ng/dL (reference value (RV): 0.8–2.0 ng/dL), free triiodothyronine 16.9 pg/mL (RV: 2–4 pg/mL) and thyroid-stimulating hormone (TSH) 0.01 mU/L (RV: 0.7–6.4 mU/L), positive antibodies to TSH receptor (thyrotropin receptor antibody) 39.4 IU/L and thyroid antimicrosomal 198.4 IU/mL, antithyroglobulin antibodies were negative, glycated hemoglobin was 11.5%, antglutamic acid decarboxylase (GAD) antibodies and anti-islets of Langerhans antibodies were positive.

Ultrasound showed thyroid with normal morphology and mobile with swallowing movements, with increased overall dimensions (right lobe: 36×15×13 mm, left lobe: 42×14×12 mm) and regular borders, and globally hypoechogenic, without evidence of intraglandular nodules.

The child was seen by a paediatric cardiologist, and despite the existence of a small muscular ventricular septal defect, thiamazole was started (0.25 mg/kg/day) with good clinical and laboratorial response.

During the hospital stay, the family was education about diabetes treatment and monitoring was started. The child was discharged after 14 days of hospitalisation, clinically stable and on intensive insulin treatment.

OUTCOME AND FOLLOW-UP

There were no other episodes of diabetic ketoacidosis or severe hyperglycaemia/hypoglycaemia. The child responded with clinical and biochemical remission after 12 months of treatment with thiamazole, which was maintained on subsequent follow-up for 6 months. The family eventually moved to another country and the patient was lost to follow-up.

DISCUSSION

The occurrence of DS and two clinically simultaneous endocrine diseases is rare. The association of DS, DM1 and hyperthyroidism has been reported in a few cases.^{18 21 22}

However, the isolated association between DS and each of these endocrinopathies is far more documented and studied. In fact, the first description of the association between DS and diabetes mellitus dates from 1968.²⁶ In 1973, Jeremiah *et al*²⁷ evaluated glycosuria in patients with DS reporting an increased prevalence of diabetes mellitus in this group. In 1997, Goor and Massa²³ assessed the prevalence of DM1 in patients with DS under the age of 9 years and found a rate of 335/100 000 cases, higher than the general population of this age group. The age of onset of diabetes in individuals with DS is lower than in the general population, with a peak incidence at the age of 8 years,⁹ which corresponds to the age of our patient at presentation. As in DS and diabetes mellitus, some isolated associations between DS and hyperthyroidism have also been described in the literature.^{6 7 11 13 19 22}

In our case, the presence of diarrhoea, change in behaviour, inattention, weight loss, tachycardia and goitre made us suspect the diagnosis. These symptoms could nevertheless have passed unnoticed within diabetic ketoacidosis in a patient with DS. Our patient's autoimmune antibody profile showed elevated thyroid antimicrosomal, TSH receptor, anti-GAD and anti-islets of Langerhans antibodies, meeting the literature's

data that patients with DS have a high prevalence of circulating autoantibodies.^{7 13 15 17}

The association between DS and autoimmune endocrine disorders, in spite of having been known for half a century, remains a focus of interest and research. The diagnosis is difficult, requiring a high index of suspicion. There are few reported cases documenting the simultaneous occurrence of DM1 and hyperthyroidism in children with this chromosomopathy. With this case, the authors emphasise the importance of diagnostic suspicion and laboratory evaluation for early diagnosis and treatment, crucial for the full development of these children.

Learning points

- ▶ Autoimmune endocrinopathies become more frequent with age, and the onset of one often predisposes to the development of others.
- ▶ Association between Down syndrome (DS) and autoimmune endocrine dysfunction is well established, although there are few cases in literature reporting the simultaneous diagnosis of type 1 diabetes mellitus and hyperthyroidism in these children.
- ▶ It is essential to monitor thyroid function at the diagnosis of diabetes, especially in children with DS.

Competing interests None declared.

Patient consent Obtained.

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