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CLINICAL CASE

Type 1 diabetes mellitus and Graves Basedow's disease, a case of Autoimmune Polyglandular Syndrome

Diabetes mellitus tipo 1 y enfermedad de Graves Basedow, un caso de Síndrome Poliglandular Autoinmune

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What do we know about the subject matter of this study?

The Autoimmune Polyglandular Syndrome (APS) is a group of heterogeneous disorders that combines several autoimmune diseases, classified into four types. Type 1 is the most frequent in childhood, type 2 in adolescence and adults, and type 3 and 4 more frequent in adults.

What does this study contribute to what is already known?

We present the case of an adolescent with APS type 3A caused by Diabetes Mellitus I and Hyperthyroidism with Graves-Basedow Disease. In Chile, DM1 has increased in recent years, so it is important to look for other autoimmune diseases in this group of patients.

Abstract

Type 1 diabetes mellitus (T1DM) is one of the most frequent autoimmune diseases in childhood. Its diagnosis requires the search for other autoimmune diseases**. Objective:** to present the case of a pediatric patient with two rare concomitant autoimmune endocrine diseases. **Clinical Case:** A 12-year-old male with no significant morbid history, is hospitalized due to a 3-month clinical picture of fatigue, eye pain, intermittent eyelid edema, goiter, polyphagia, polydipsia, polyuria, and weight loss (12 kilograms), compatible with T1DM and Graves-Basedow disease. It was confirmed by laboratory tests which showed elevated glycemia (207 mg/dL, HbA1C 10.9%), suppressed TSH (< 0.01 uIU/mL), elevated FT4 (6.99 ng/dL), and the presence of anti-autoantibodies thyroid peroxidase, antithyroglobulin, and anti-TSH receptor, along with suggestive ultrasound findings. Therefore, we established the diagnosis of autoimmune polyglandular syndrome (APS) 3A and initiated treatment with insulin, propranolol, and thiamazole. The patient evolved satisfactorily and was discharged with outpatient follow-up. **Conclusion:** We present the case of an adolescent who presented APS due to T1DM and hyperthyroidism. This APS may be more common than is reported in clinical practice. The alteration of two or more endocrine glands or other autoimmune diseases should make us suspect its diagnosis, with important clinical implications, such as comorbidity and quality of life prognosis.

Keywords:
Type 1 Diabetes Mellitus; Hyperthyroidism; Autoimmune Polyglandular Syndrome; Adolescent

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Introduction

Diabetes mellitus 1 (DM1) is one of the most common chronic diseases in childhood. The highest peak presentation occurs between 5-7 years of age and around puberty, occurring earlier in females (between 5-9 years) compared with males (10-14 years)[1]. In recent years, its incidence has been increasing and varies according to region. In China, an incidence of 0.1/100,000 inhabitants has been described, while in Finland more than 60 cases per 100,000 persons/year[2]. In Chile, the incidence of DM1 in children under 20 years of age increased from 10.1/100,000 in 2006 to 16.5/100,000 in 2014[3].

DM1 is frequently associated with other endocrine and non-endocrine autoimmune diseases, including hyper- or hypothyroidism, celiac disease, adrenal insufficiency, inflammatory bowel disease, collagen vascular disease, among others[4].

Thyroid diseases are a public health problem that can significantly impact patient well-being, especially in pregnancy and childhood[5]. Of these, the most common is hypothyroidism, with a prevalence in the general population between 0.2-5%[5]. The main causes of primary hypothyroidism are iodine deficiency and autoimmune diseases (Hashimoto's thyroiditis). Worldwide, the prevalence of hyperthyroidism is between 0.2-1.3% with Graves-Basedow disease (GBD) as the main cause in 50-80% of cases[5]. Frequently, certain syndromes have been related to thyroid diseases, such as Down syndrome and Turner syndrome[5]. Likewise, a patient with a thyroid disease due to an autoimmune disorder is more at risk from other autoimmune diseases such as diabetes, alopecia, vitiligo, and celiac disease[6].

The coexistence of more than one autoimmune disease in a patient has been called autoimmune polyglandular syndrome (APS). APSs are a group of heterogeneous disorders, combining several autoimmune diseases. They are characterized by lymphocytic infiltration that can affect both endocrine and non-endocrine organs, the presence of organ-specific autoantibodies, and a defect in the cellular and humoral immune response[7]. APSs have been classified into four types, with type 1 as the most frequent in childhood, type 2 in adolescence and adults, and types 3 and 4 more frequent in adults[8].

The prevalence of autoimmune disorders has been increasing over the last decades[7]. In many cases, they are often considered as two isolated entities instead of comorbidities, therefore, their true prevalence is still unknown since there is a large underreporting of them[7].

The objective of this report is to present the case of a pediatric patient with two rare concomitant autoimmune endocrine diseases.

Clinical Case

A 12-year-old adolescent, with no significant history of morbidity, consulted a primary health care center due to a 3-month clinical picture consisting of fatigue, eye pain, and intermittent eyelid edema, associated with polyphagia, polydipsia, polyuria, nocturia, and weight loss (around 12 kg), without fever, gastrointestinal, and respiratory symptoms. Laboratory tests were requested, highlighting hyperglycemia, increased glycosylated hemoglobin, and altered thyroid tests including decreased thyroid-stimulating hormone (TSH), elevated free thyroxine (FT4); glycosuria 200 mg/dL, normal hepatic and renal profile as well as electrolyte and acid-base profile (Table 1). With these results, the patient was referred to the emergency department of the *Hospital Luis Calvo Mackenna*.

On physical examination, the patient presented tachycardia (140 beats/minute), hypertension 130/79mmHg (95th percentile), weight 37 kg, height 1.62 mt, BMI 14.14, BMI/A -3.13 (Z), H/A -0.15 (Z). In addition, it was observed exophthalmos (Figure 1a), bilateral enlarged thyroid of about 3 cm in diameter (Figure 1b and 1c), non-painful, smooth, without nodules, no thyroid murmur on auscultation but a collapsing pulse was observed. Fine tremor was observed in the hands when extending the arms and warm skin. Admission tests confirmed hyperglycemia, increased HbA1C levels, without ketonemia but with ketonuria, suppressed TSH level, and elevated triiodothyronine (T3) and FT4. Blood count, renal function, venous blood gases, and electrolytes without alterations (table 1)

Further studies showed increased anti-thyroid peroxidase antibodies (anti-TPO), slightly elevated anti-thyroglobulin antibodies (anti-TG), positive TSH receptor antibody (TRab) of 35.4 IU/l (table 1), and negative antibodies for celiac disease (anti-endomysial, anti-transglutaminase). The electrocardiogram showed no alteration. Neck ultrasound showed a thyroid with lobulated margins and increased size, right lobe 23 x 22 x 22 x 62 mm, and left lobe 22 x 20 x 20 x 60 mm in transverse, anteroposterior, and longitudinal diameters, respectively. Slightly hypoechogenic parenchyma, heterogeneous echotexture, and pseudonodular appearance, with increased vascularization, no solid or cystic focal lesions; compatible with signs of chronic thyroiditis (Figure 2a and 2b).

Based on the physical and laboratory findings, the patient was diagnosed with DM1 and Graves-Basedow disease and was managed with a diabetic diet and insulin. In addition, propranolol and thiamazole were prescribed for treating hyperthyroidism.

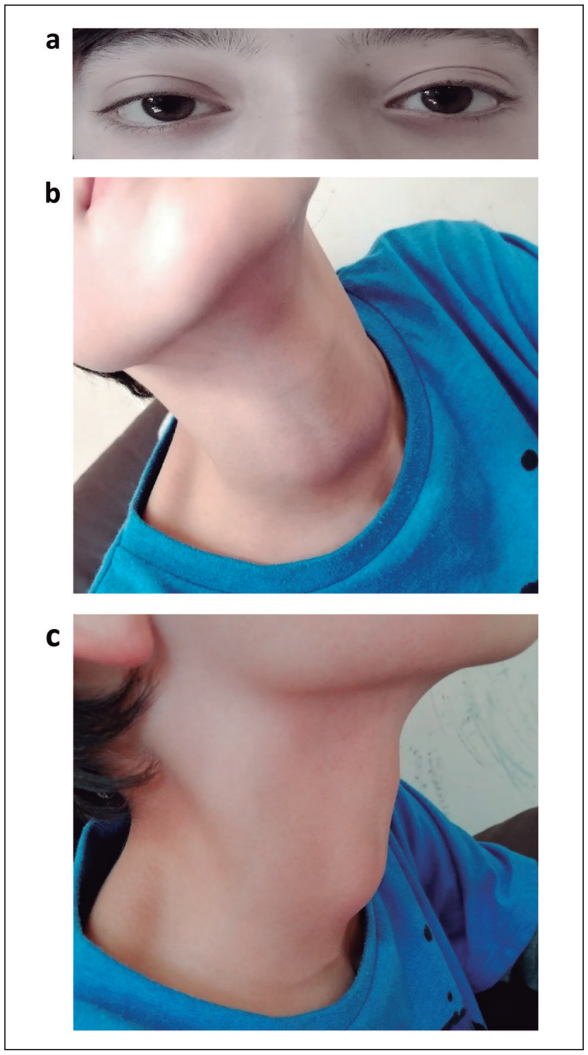

Figure 1. a. frontal photo shows exophthalmos and enlarged thyroid; **b** and **c**, oblique and lateral photos showing the marked enlargement of the thyroid.

Table 1. Laboratory test

Laboratory test	Primary care center	HLCM
Glycemia (mg/dL) (random < 140)	155	207
HbA1C (%) (5.7)	12	10.9
TSH (uUI/mL) (0.36-6.00)	< 0.085	0.01
FT4 (ng/dL) (0.78-2.49)	6.82	6.99
T3 (ng/dL) (86-199)	-	436
Anti-TPO (IU/mL) (< 5.61)	-	64.16
TgAb (IU/mL) (< 4.11)	-	4.58
TSHR-Ab (IU/l) (< 1)	-	35.4

HbA1C glycosylated hemoglobin; TSH thyroid stimulating hormone; FT4 free tetraiodothyronine; T3 triiodothyronine; Anti-TPO anti-peroxidase antibody; TgAb thyroglobulin antibody; TSHR-Ab Autoantibodies against the TSH recepetor; HLCM Hospital Dr. Luis Calvo Mackenna.

During hospitalization, the patient evolved favorably, with a decrease in blood pressure, heart rate, and tremor in the limbs, requiring adjustments to his insulin regimen, thus achieving therapeutic goals. The patient was diagnosed with APS type 3A and subsequently, after informing both patient and family members about his base diseases, was discharged in good clinical condition, and with indication of outpatient follow-up with the endocrinology team.

The publication of this case was approved by the Ethics Committee of the University of Chile.

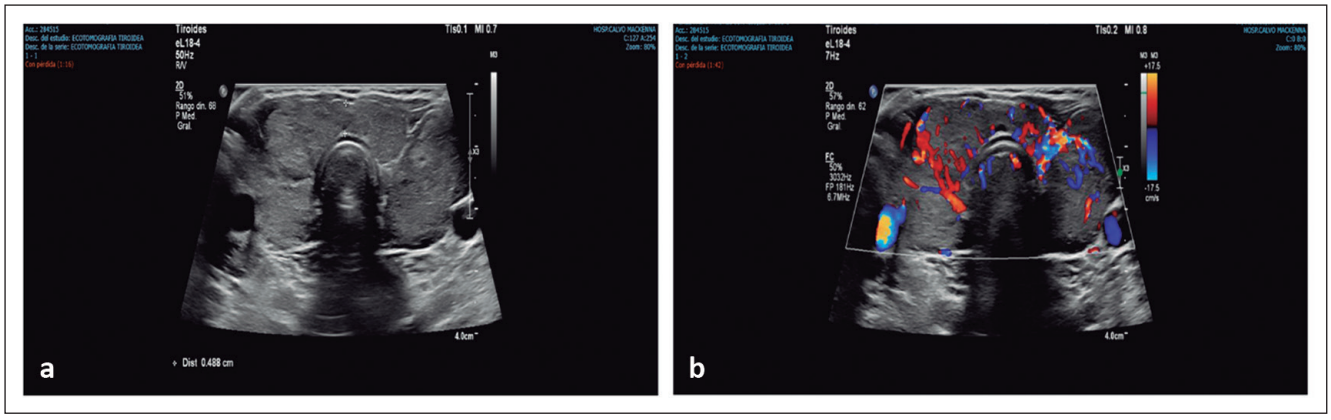

Figure 2. a. Thyroid gland ultrasound, grayscale linear transducer: thyroid gland enlarged, margins lobulated; **b.** linear transducer with color Doppler application: increased vascularity throughout the gland.

Discussion

We present the case of an adolescent patient with APS type 3A determined by the presence of hyperthyroidism and DM1. APS is a complex and heterogeneous disorder, often underdiagnosed due to its wide variety of presentations[1]. The underlying condition is a loss of immune tolerance leading to impaired polyglandular function[1].

APS was first described in 1929 by Thorpe et al.[9] who established the association between hypoparathyroidism and mucocutaneous candidiasis, and as a greater number of associations of other affected glands were described, the spectrum of this syndrome increased[8]. According to the endocrine glands involved, it was classified into 4 types[8,10].

APS type 1 is characterized by the presence of chronic mucocutaneous candidiasis, hypoparathyroidism, and adrenal insufficiency. A chronological sequence has been described for this syndrome, where candidiasis is present before 5 years of age, hypoparathyroidism between 5 and 10 years of age, and Addison's disease before 15 years of age[8,10]. The cause of this syndrome is monogenic due to AIRE gene mutations[8,10]. It usually manifests in pre-school age (3-5 years) or early adolescence, and although it is considered one of the rarest APSs (1:100,000), it presents a high prevalence in certain population groups such as Finland (1:25,000) and Sardegna (1:14,000)[11,12].

APS type 2 has a prevalence of 1:20,000 people, especially in women (male:female ratio 1:3), with the highest incidence between the third and fourth decade of life[13]. It is characterized by the deficiency of two or more glands, mainly the adrenal and thyroid ones (Schmidt's syndrome) and/or DM1[14]. This syndrome is related to alterations in genes encoding key regulatory proteins in the innate and adaptive immune system, mainly with the human leukocyte antigen (HLA) as the DR3 and DR4 allele, as well as genes encoding CTLA-4[8,11].

APS type 3 is the most frequent, it can occur even in the pediatric age, especially during adolescence, as the case described. It has a wider spectrum of presentation and is related to HLA, CTLA-4, and protein tyrosine phosphatase non-receptor type 22 (PTPN22) genes involvement, in different ethnic groups, especially Asians[15]. The main organ affected by autoimmune disorder is the thyroid, associated with other autoimmune diseases, excluding Addison's disease[8,16].

Due to its broad spectrum of presentation, it has been subdivided as follows[16]: A. Associated with other endocrine diseases (DM1, Hirata's disease); B. Associated with autoimmune gastrointestinal diseases (atrophic gastritis, pernicious anemia, celiac disease, inflammatory bowel disease, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis); C. Associated with skin, neuromuscular, and hematopoietic diseases (vitiligo, alopecia, autoimmune thrombocytopenia, autoimmune hemolytic anemia, antiphospholipid syndrome, myasthenia gravis, multiple sclerosis); and D. Associated with collagen and vasculitis diseases (lupus, rheumatoid arthritis, reactive arthritis, scleroderma, Sjögren's syndrome, vasculitis).

Finally, *APS type 4* is a rare syndrome, which includes all clinical combinations that are not classified in previous APSs[16].

The actual prevalence of APS type 3 is unknown. A study[4] conducted in 461 Polish children with DM1 found a prevalence of 14.5% and 11.1% in type 3A. Of all diabetic children, 10.4% presented Hashitoxicosis and 0.7% Graves' disease, with a greater incidence in girls than in boys (3:1 ratio)[4]. In the United States, hyperthyroidism was detected in 0.5% of children with DM1[17]. According to age group, APS type 3A has been identified in 19% of children under 5 years old, 5.1% between 6-10 years old, 6.2% between 11-15 years old, and 22.7% between 16-18 years old[4].

In our case, given the presence of DM1 and GBD, an adolescent patient was diagnosed with APS type 3A. Due to the simultaneous diagnosis of both entities, we cannot state which one presented first, however, in patients with DM1, the association of other autoimmune diseases such as thyroid disease is frequent (15-30%); among them, hypothyroidism is the most frequent (25%), and hyperthyroidism accounted for 0.5-0.7% of cases[4].

Another disease related to DM1 has been celiac disease (1.6-16.4%)[18]. A higher prevalence of this association has been found in the Japanese population where more than 90% of patients with DM1 have autoimmune thyroid disease, and specifically, in a group of 30 patients with DM1 and GBD, 60% of them developed GBD before the onset of DM1, and 10% had DM1 and GBD concurrently, which could be the case of our patient. On the other hand, based on pediatric patients with autoimmune thyroid disease, it has been found that 30% of them present involvement of another endocrine gland, with DM1 as the most frequent (61%), followed by celiac disease (22.2%)[19]. Therefore, when one of these autoimmune diseases is diagnosed, it is necessary to look for other diseases, as we did in our patient.

The diagnosis of DM1 is based on clinical and laboratory criteria, without requiring the detection of autoantibodies[20]. Similarly, the diagnosis of GBD can be established quickly by clinical signs, history of symptoms in the last few months in a patient with any sign of Graves' orbitopathy, diffuse goiter, and altered thyroid hormones levels (increased FT4, suppressed TSH).

The predominance of hyperthyroid symptoms and the presence of orbitopathy suggest that this case is Graves-Basedow disease, and the presence of autoantibodies further strengthens the diagnosis. For example, in Hashitoxicosis anti-TPO and anti-TG antibodies are common, while in GBD the presence of TRab and anti-TPO is more frequent[21]. In the case presented, the presence of TRab, anti-TPO, and anti-TG was demonstrated, which individually can be positive in up to 10% of patients with Graves' disease[21].

Accordingly, this case is exceptional, not only due to the concomitance of DM1 and hyperthyroidism, but also because it is an adolescent male patient and the presence of positive antibodies against several thyroid antigens. As stated in the national and American guidelines, patient management should be focused on treating the underlying pathologies[20,22,23].

Conclusion

We present the case of an adolescent with APS due to the simultaneous occurrence of DM1 and GBD. These APSs may be more common than what is reported in clinical practice. The alteration of two or more endocrine glands or other autoimmune diseases should lead us to suspect the diagnosis. Given the frequent association reported between DM1 and thyroid disease in pediatric patients, it is very likely that APS type 3A is underdiagnosed, which has important clinical implications, such as comorbidity and quality of life prognosis.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the parents (tutors) of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

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