Polyglandular autoimmune syndrome type 3 with pituitary involvement in a Latin American patient

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Abstract

Introduction: polyglandular autoimmune syndrome (PAS) is defined as the coexistence of at least two types of autoimmune endocrine diseases. Polyglandular autoimmune syndrome type 3 comprises autoimmune thyroid diseases and other autoimmune diseases not including Addison's disease. Up until now, there was only one case report of PAS type 3 in Asia, coupled with isolated reduction of gonadotropin releasing hormone (GnRH) caused by pituitary disease.

Case presentation: we present the case of a woman in her 20s with a one-year history of Hashimoto disease and type 1 diabetes, who presented with controlled hypothyroidism and hyperglycemia, but experiencing secondary amenorrhea. Following the GnRH stimulation test, she was diagnosed with secondary amenorrhea attributed to possible autoimmune hypothalamitis and PAS type 3. Our patient's HLA profile reported the DQB1*0201 allele and DRB1*0301 and *0803, DQ2 and DR8 gene sites.

Discussion: this is the first report in Latin American literature of PAS type 3 associated with pituitary involvement along with the other two diagnostic elements. A GnRH stimulation test is recommended for patients with PAS coupled with secondary amenorrhea which does not improve despite thyroid disease treatment. This case is anecdotal, with the description of this disease being relevant to our region. **(Acta Med Colomb 2024; 49. DOI: https://doi.org/10.36104/amc.2024.3013).**

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Introduction

Polyglandular autoimmune syndromes (PASs) are rare conditions characterized by autoimmune activity against multiple endocrine organs, although non-endocrine organs may also be affected (1). Typical endocrine diseases include type 1 diabetes mellitus (DM), autoimmune thyroid disease and Addison's disease. Other commonly involved conditions include celiac disease, alopecia, vitiligo, hypogonadism, pernicious anemia, etc.

The PASs are generally divided into four subtypes (2). Type 1 is characterized by the onset of at least two of the three cardinal components, consisting of chronic mucocutaneous candidiasis, hypoparathyroidism and Addison's disease. Type 2, also known as Schmidt syndrome, consists of Addison's disease, autoimmune thyroid disease and type 1 DM, all with an autoimmune component. Type 3 is defined by the presence of autoimmune thyroid disease and other autoimmune endocrine diseases other than Addison's disease. Finally, PAS type 4 refers to two or more specific autoimmune disorders of organs that do not fit the characteristics of PAS-1 or PAS-3.

Below we present the case of a patient with a rare combination of isolated GnRH deficiency and amenorrhea, which suggests autoimmune pituitary disease, and other characteristics of PAS type 3 associated with Hashimoto's disease and LADA. As far as we know, this is the first case described in Latin America, with only one report of this combination in Asia (3).

Case presentation

The patient was a woman in her twenties with amenorrhea, decreased libido, weight gain, and high blood sugar and glycosylated hemoglobin levels, as well as positive antimicrosomal, anti-thyroid peroxidase and anti-thyroglobulin antibody tests, confirming the diagnosis of Hashimoto's thyroiditis. Due to her abnormal carbohydrate metabolism, type 1 DM was suspected, and therefore glutamic acid decarboxylase antibodies (GADA), membrane phosphatase

anti-tyrosine (IA-2) and anti-insulin (IAA) antibody testing was carried out, which was positive. Therefore, she was also diagnosed with type 1 DM/LADA. The patient began once-daily basal insulin treatment, with significant improvement in her blood sugar levels; this occurred during 2021.

The patient was 12 years old at menarche, with regular menstrual cycles. She had a child via vaginal delivery and denied any miscarriages. However, during the last quarter of 2022, she had a new-onset menstrual cycle disorder characterized by amenorrhea along with significantly reduced libido. The patient had no history of autoimmune diseases nor was there a family history of endocrine or autoimmune problems.

She did not have adrenal insufficiency, with normal 8 a.m. and 4 p.m. cortisol levels. Likewise, there was no evidence of hypocalcemia in the 8 a.m. or 4 p.m. cortisol levels, with ionized calcium levels within normal limits. Pituitary magnetic resonance imaging with contrast showed no tumors or contrast uptake. She had lowered levels of estradiol, FSH and LH, with no response to human gonadotropic hormone (hCG) administration, which supported the diagnosis of hypogonadotropic hypogonadism. Based on these abnormalities, a genetic study was ordered, in which HLA class II genotyping showed the presence of DQB1*0201 and DRB1*0301-0803 alleles. Based on the clinical course and previous findings, the patient was diagnosed with isolated GnRH deficiency and polyglandular autoimmune syndrome type 3 associated with Hashimoto's disease and LADA.

Discussion

Polyglandular autoimmune syndrome type 3 is a type of adult PAS, defined as the combination of autoimmune thyroid disease and other autoimmune diseases, excluding Addison's disease and hypoparathyroidism. Our patient's clinical picture began in 2022 with biochemical abnormalities compatible with Hashimoto's hypothyroidism and autoimmune diabetes. Later, there were clinical findings compatible with hypogonadotropic hypogonadism.

Previous studies of this type of disease have confirmed the frequent coexistence of type 1 DM and autoimmune thyroid disease in patients with PAS (4). On the other hand, there is normally an interval of many years between the diagnosis of the first and second disease in patients with PAS (5, 6). Regarding the sequence of endocrine abnormalities manifested in PAS type 3, it has been reported that in 60% of patients with PAS type 3, the thyroid disorder is more likely to occur before type 1 DM, with an average time elapsed of seven years (3).

In the cohort of autoimmune disease components in patients with PAS established by Martin P Hansen et al. (7), the onset of type 1 DM was earlier (an average age of 27.5 years), while other diseases appeared within an age range of 36.5-40.5 years. Other studies have shown that the average age at onset of type 1 DM in patients with Hashimoto's disease is 34 years, with an incidence of 0.78% (8).

We must also consider that the patient's current diagnosis of PAS type 3 could be temporary. Patients with PAS type 3 may eventually develop Addison's disease and be reclassified as PAS type 2 (9). Furthermore, the association of autoimmune endocrine diseases is primary attributed to a common genetic susceptibility. Polyglandular autoimmune syndrome type 3 is often found in individuals within the same family. A study of 10 families with PAS found that one out of seven relatives had an undiagnosed autoimmune disease (9).

Based on the gonadotropin abnormalities found, our patient was considered to have secondary hypogonadism. To confirm whether the low GnRH level was due to pituitary dysfunction or secondary hypothalamic dysfunction, pituitary magnetic resonance imaging was ordered, which was normal. Thus far, secondary hypogonadism has been found in some patients with PAS, but most are thought to be caused by autoimmune hypophysitis (10-12) or poorly controlled Hashimoto's disease (13).

Clinical cases of amenorrhea due to hypothalamic dysfunction/GnRH deficiency are mostly triggered by gene mutations, tumors, infiltration, trauma, etc. (14). Clinically, it is difficult to determine if the secondary hypogonadism is due to hypothalamic or pituitary diseases, because it is difficult to directly detect the hormones secreted by the hypothalamus. Barran et al. reported two patients with isolated gonadotropin deficiency after puberty (10).

Ultimately, it was determined that the decreased gonadal hormone was due to autoimmune hypophysitis. In addition, there were no lesions on pituitary magnetic resonance imaging, such as a tumor, pituitary stalk deviation, inflammation or infiltration. Therefore, the lesion could be located in the hypothalamus, and it was reasonable to suspect that the isolated GnRH deficiency arose from the hypothalamus.

The isolated GnRH dysfunction in our case was probably due to autoimmunity. Given the multiple organ autoimmunity in PAS type 3, it is not surprising that patients with these diseases are prone to hypothalamic involvement. While anti-pituitary antibodies can contribute to the diagnosis of autoimmune lymphocytic hypophysitis, their use is still not routinely recommended. Anti-pituitary antibodies are not considered to be good disease markers because they are hard to detect with biochemical methods and the antigens involved have not been definitively identified.

It is well known that PAS type 3 is a type of HLA-related disease (15, 16). Many studies have indicated that HLA haplotypes DR3-DQB1*0201 and DR4-DQ*0302 contribute to PAS type 3 (17). Our patient's HLA profile showed the DQB1*0201 allele and gene sites DRB1*0301 and *0803, and the corresponding genotypes were DQ2 and DR8. It has been widely reported that DQ2 is correlated with PAS (15). As far as the HLA-DR8 haplotype, previous studies reported the potential relationships between primary biliary cirrhosis, autoimmune hepatitis and liver transplant outcomes (17, 18). It is also significantly related to patients with

Hashimoto's disease with thyrotropin-binding inhibitory immunoglobulins and possibly related to the susceptibility gene that produces TSH receptor blocking antibodies (18).

Conclusion

This is the first report of a patient with PAS type 3 complicated by isolated GnRH reduction possibly caused by autoimmune hypothalamic injury, which reminded us that the hypothalamus is not exempt from being affected in the general autoimmune process. Clinicians who examine patients with PAS who report secondary amenorrhea not explained by thyroid or adrenal dysfunction or diabetes should be alert to the new onset of other autoimmune endocrine disorders.

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