PRESENTATION OF THE CASE

A 53-year-old woman complained in 2003 of breast pain, galactorrhea, and intense headache. A head tomography revealed hypophyseal microadenoma and a prolactin level of 65 ng/mL. Cabergoline (0.5 mg) every 24 hours was initiated, but she continued to complain of asthenia and headache. She subsequently noted hypopigmented macules on her face and extremities and experienced frequent diarrhea and vomiting. Table 1 presents the laboratory tests. Prednisone (5 mg every 24 hours) and levothyroxine (100 mcg daily) treatment was initiated, which normalized prolactin levels and abolished the galactorrhea. This treatment was maintained until admission to our hospital in December 2016 for follow-up and control.

The first evaluation in our hospital revealed stable vital signs. Her body mass index was 30.5 kg/m², and she exhibited hypopigmented macules on the face, neck, upper extremities, and armpits. The patient mentioned having first-degree relatives with a history of thyroid abnormalities, vitiligo, and adrenal diseases. We performed autoimmunity tests using glutamic acid decarboxylase 65 (GAD 65) and antibodies against parietal cells, which were negative. Her treatment was changed to 15 mg hydrocortisone daily. All of her children were examined for autoimmunity. Chemiluminescence measured the thyroid profile and prolactin and cortisol levels. Antithyroid and anti-GAD 65 antibodies were measured using radioimmunoassay (RIA). ACTH was measured using immunoradiometric analysis (IRMA). Anti-adrenal,
anti-endomysium and anti-gliadin antibodies were measured using ELISA.

ACTH levels in her 33-year-old daughter were above the normal range, with a cortisol level of 1.58 mcg/dL. She also exhibited subclinical hyperthyroidism and anti thyroperoxidase antibodies, anti-TG antibodies, and she was positive for Thyroid-stimulating immunoglobulin (TSI), anti-endomysial and anti-gliadin antibodies. The two boys, 37 and 33 years of age, were euthyroid and positive for antithyroid antibodies. The boys exhibited low cortisol levels of 3.4 and 3.6 mcg/dL, respectively. They were tested to confirm adrenal insufficiency using low-dose cosyntropin (1 mg) and exhibited positive results. Immediate substitution was initiated.

We investigated the genes of the human leukocyte antigen (HLA) class I system (HLA-A, HLA-B, HLA-C) and class II (HLA-DR, HLA-DQ) to examine the genetic basis of autoimmunity in this family, and Figure 1 shows the results. The genealogy revealed that all of the affected individuals were positive for the HLA DRB1*04, HLA DRB1*16, and HLA DRB1*14 alleles, which are associated with several forms of autoimmunity in the Mexican population. Some individuals were heterozygous HLA DRB1*04/DRB1*16 or homozygous for HLA DRB1*04, which suggests that susceptibility to autoimmunity was inherited via parental and maternal ancestries (Table 2).

**TABLE 1** Initial hormonal profile of the patient (2003)

| Parameter          | Value       | Reference ranges          |
|--------------------|-------------|---------------------------|
| TSH                | 6.59        | 0.35-4.94 mIU/L           |
| T3 total           | 1.08        | 0.58-1.59 ng/mL           |
| T4 total           | 5.61        | 4.87-11.72 μg/dL          |
| T4 free            | 0.68        | 0.70-1.48 ng/dL           |
| Up take            | 30.13       | 24%-39%                   |
| Anti-TPO           | 353         | Lower than 12             |
| Anti-Tg            | 72          | Lower than 34             |
| Prolactin          | 65.47       | 1.39-24.2 ng/mL           |
| Cortisol AM        | 0.6         | 6-22 mcg/dL               |
| Adrenal antibodies | Positive    | Negative                  |

Anti-Tg, anti-thyroglobulin antibodies; Anti-TPO, anti thyroperoxidase antibodies; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone.

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**FIGURE 1** Family pedigree. Note inbreeding meeting in the family because both monozygotic twin sisters had the same couple. In individuals III-1, IV-1, IV-2, IV-3 and IV-4 their human leukocyte antigen (HLA) haplotype is shown on their right side. Interesting, purpose and daughter IV-4, as well as both brothers share the same HLA haplotype, respectively. The rest affected individuals were diagnosed with some endocrinopathy but were not reviewed by us and did not accept the HLA test.
Polyglandular syndromes (PS) constitute a group of different autoimmune disorders that are characterized by the coexistence of at least two diseases mediated by endocrine glandular autoimmunity. Four major subtypes of APS are distinguished according to the age of onset, characteristic patterns of disease combinations, and different modes of inheritance. APS I is characterized by the occurrence of at least two of the following three components: Addison’s disease, hypoparathyroidism, and candidiasis. APS II is defined as a combination of Addison’s disease and autoimmune thyroid disease, with or without type 1 diabetes, and APS III summarizes a combination of autoimmune thyroid disease with autoimmune diseases other than Addison’s disease and hypoparathyroidism. APS IV includes all of the clinical associations not included in the other APS subtypes.

The clinically manifested syndrome is considered only a fraction of the autoimmune background because latent forms are even more frequent. The combination of autoimmune adrenal insufficiency and autoimmune thyroid disease is known as Schmidt syndrome, which was the case in our patient. Notably, the prolactin elevation that the patient experienced at the beginning of her disease may be due to hyperprolactinemia, which causes hyperplasia and stimulation of the lactotroph cells in the anterior pituitary gland. This presentation explains the disappearance of hyperprolactinemia following treatment with thyroid hormone. Therefore, the abnormality seen in her initial tomography was a pituitary incidentaloma.

APS 2 primarily appears between 20 and 60 years of age, and subsequent generations are commonly affected. More than 20 years may elapse between the onset of one endocrinopathy and the diagnosis of the next episode, which means that 40%-50% of the subjects with Addison’s disease will develop an autoimmune endocrinopathy over time.

Carpenter reviewed 142 cases of Schmidt’s syndrome, and Hashimoto’s thyroiditis was the primary thyroid autoimmune disease. The remaining cases exhibited Graves’ disease. The complete triad of Addison’s disease, autoimmune thyroid disease, and DM1 is called Carpenter’s syndrome.

Patients will often not exhibit polyglandular failure at the onset of the clinical symptoms of autoimmune disease. Notably, the tests that should be used and the frequency with which they should be performed in anticipation of the occurrence of autoimmune diseases remain controversial.

APS 2 is primarily associated with HLA class II alleles, particularly DQ2 and DQ8, which is similar to many autoimmune diseases. APS 2 is strongly associated with HLA DR3/DQ2 (DQ2: DQA1*0501, DQB1*0201) and DR4/DQ8 (DQ8: DQA1*0301, DQB1*0302) and DRB1*0404. Other diseases associated with HLA-B8 and DR3 include IgA deficiency, juvenile dermatomyositis, dermatitis herpetiformis, alopecia, scleroderma, autoimmune thrombocytopenic purpura, hypophysitis, metaphyseal osteopenia, serositis, and premature ovarian failure.

Botta et al examined HLA in the members of two families with APS 2 and APS 3. The polymorphism DRB1*0301-DQB1*0201 was found in at least two of the members of each of these families, who were asymptomatic. Therefore, the identification of individuals carrying these polymorphisms may allow early intervention and reduce the chronic morbidity of these diseases, which are often subclinical or latent.

Mallea Gil et al reported the case of a man who was diagnosed with APS 2. He arrived at the emergency room in a state of shock, and they identified HLA DQB1*0302. This haplotype was described in previous cases, but the HLA DRB1 * 08 that was also found in this patient was not described in any other autoimmune disorder. These cases likely explain the variability of the affected locus. APS 2 is a polygenic disorder that produces polymorphisms that may increase the risk or protect against autoimmune diseases. For example, molecules of the major histocompatibility complex, such as DR and DQ, are associated with the development of the autoantibodies against hydroxylase that are associated with the clinical progression of adrenal failure, and HLA-B15 is associated with the protection of the progression of adrenal insufficiency in individuals with positive 21-hydroxylase autoantibodies.

Salinas-Santander et al evaluated 198 Mexican patients with vitiligo and found an association of it with the presence of autoimmune thyroid disease in 23% of these patients. To our knowledge, there is no report of an HLA association in a Mexican family with APS 2 in the literature. Therefore, this case may be the first presentation of the clinical manifestations, the biochemical determination of antibodies, and the HLA association.

### TABLE 2 Human leukocyte antigen (HLA) polymorphism of the members of the case family

| Subject | A          | C          | DR          | DQ          |
|---------|------------|------------|-------------|-------------|
| Mother  | A*11,A*24  | C*07,C*12  | DRB1*04,DRB1*16 | DQB1*03,DQB1*05 |
| Daughter| A*24,A31   | C*07,C*07  | DRB1*04,DRB1*04 | DQB1*03,DQB1*03 |
| Son 1   | A*02,A*11  | C*07,C*12  | DRB1*14,DRB1*16 | DQB1*03,DQB1*05 |
| Son 2   | A*02,A*11  | C*07,C*12  | DRB1*14,DRB1*16 | DQB1*03,DQB1*05 |
The treatment of APS generally consists of the adequate substitution of the compromised axes. This substitution is vitally important because it allows for the early detection of adrenal failure and avoids catastrophic outcomes.\textsuperscript{11}

3 | CONCLUSIONS

A polyglandular syndrome diagnosis should be suspected in patients with an autoimmune background. The presence of an endocrine disease suggests that other endocrine axes may be affected subsequently.

Antibody positivity and symptoms may manifest over time, and the identification of HLA polymorphisms, if available, could be useful in select patients with autoimmunity.

Examination of all of the patient’s children identified adrenal and thyroid autoimmunity to initiate timely treatment.

ACKNOWLEDGMENTS

We thank the index case of this family and her children for their cooperation and consent.

CONFLICT OF INTEREST

The authors declare no conflict of interests.

AUTHOR CONTRIBUTIONS

JB-C and AAR-A: evaluated the index case and planned patient management. JG: performed the HLA studies in the family. JJM, JAGG, SHD, and MGG: evaluated the genetics in the family.

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\textbf{How to cite this article:} Bermeo-Cabrera J, Reza-Albarrán AA, Granados I, et al. Polyglandular syndrome type 2 in a Mexican family and its association with human leukocyte antigen. \textit{Clin Case Rep}. 2019;7:79–82. \url{https://doi.org/10.1002/ccr3.1919}