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HLA Markers DQ8 and DR53 Are Associated With Lymphocytic Hypophysitis and May Aid in Differential Diagnosis

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Importance: Lymphocytic hypophysitis (LH) is a poorly understood autoimmune disorder of the pituitary gland. Symptoms include headache, pituitary dysfunction, visual disturbances, and neurological deficits. The diagnosis can be made based on clinical and biochemical findings, but for atypical presentations, no circulatory diagnostic biomarkers exist, and a pituitary biopsy is necessary for diagnosis.

Objectives: We used high-resolution human leukocyte antigen (HLA) screening assays to investigate a relationship between specific HLA markers and LH.

Design: This was a retrospective analysis.

Setting: The study was conducted at a tertiary referral center.

Subjects: Fifteen patients with sporadic LH, 4 patients with melanoma who developed hypophysitis after administration of cytotoxic T lymphocyte antigen 4 (CTLA4) antibodies, and 1 patient with sarcoid-associated hypophysitis were evaluated.

Intervention: Clinical data, including endocrine function, were assessed, and HLA typing was performed in all 20 patients with hypophysitis, 50 control patients with other sellar abnormalities, and 4 CTLA4 antibody–treated patients without hypophysitis.

Results: Two major histocompatibility class II HLA markers, DQ8 and DR53, were found in 13 of 15 (87%) and 12 of 15 (80.0%) patients with sporadic LH, respectively. In contrast, none of the 4 patients who developed hypophysitis after administration of the CTLA4 antibodies exhibited the HLA-DQ8 marker and only 1 of 4 (25%) exhibited the HLA-DR53 marker. In a parallel group of 50 control subjects with sellar masses and 4 CTLA4 antibody–treated patients who did not develop evidence of pituitary failure, the candidate HLA subtypes were found in ~20% for DQ8 and ~48% for DR53, respectively.

Conclusion and Relevance: The HLA markers, DQ8 and DR53, were found to be commonly present in patients with LH. The odds ratio of a patient with LH expressing the HLA-DQ8 marker is 23.1-fold higher than that of a patient with another sellar mass. HLA-DQ8 testing may assist in diagnosis and avoid unnecessary biopsies in patients with atypical LH. (J Clin Endocrinol Metab 100: 4092–4097, 2015)

Abbreviations: CTLA4, cytotoxic T lymphocyte antigen 4; DI, diabetes insipidus; HLA, human leukocyte antigen; LAH, lymphocytic adenohypophysitis; LH, lymphocytic hypophysitis; LINH, lymphocytic infundibuloneurohypophysitis; LPH, lymphocytic panhypophysitis; MHC, major histocompatibility complex.
Pituitary inflammation may occur due to adjacent local lesions, including tumors (germinomas, craniopharyngiomas, and pituitary adenomas) or cysts (Rathke cleft cysts) (1–4) or as part of systemic diseases such as sarcoidosis, Wegener granulomatosis, syphilis, tuberculosis, and Langerhans cell histiocytosis (5–7). Primary pituitary inflammation is of 3 types: granulomatous in which the pituitary gland is infiltrated with multiloculated giant cells and histiococytes (8); xanthomatous in which the pituitary gland shows cystic areas of liquefaction infiltrated by lipid-rich foamy histiocytes and lymphocytes (9); or autoimmune hypophysitis or lymphocytic hypophysitis (LH). Although LH is rare with an annual incidence of 1 case per 9 million, the frequency of LH far exceeds those of the granulomatous or xanthomatous types (10). Described in 1962, it was initially believed to be confined to the anterior pituitary and was termed lymphocytic adenohypophysitis (LAH) (11). However, it can involve the stalk exclusively, termed lymphocytic infundibuloneurohypophysitis (LINH) (12), or both the anterior pituitary and stalk, called lymphocytic panhypophysitis (LPH) (13). It remains unclear whether the LAH, LINH, and LPH entities represent different diseases or different aspects of the same disease. LAH (6:1) and LPH (1.9:1) are more common in women, whereas LINH affects the two sexes equally (10, 14). Of cases of LAH, 57% present in the last month or within 2 months postpartum (15).

The clinical presentation of all forms of LH is variable, depending on whether the anterior lobe, the posterior lobe, or both are affected. Symptoms include those due to sellar compression, such as headache, visual disturbance (visual field defects or reduced acuity), and endocrine deficiency (mainly ACTH followed by TSH, gonadotrophins, and prolactin) (16). Diabetes insipidus (DI) due to a posterior pituitary deficit can also be seen. Occasionally, more widespread neurological symptoms and signs may occur, including cranial nerve palsies (13).

The defining pathological feature of LH is the infiltration of the pituitary gland with polyclonal T and B lymphocytes without a dominant subset as seen in other autoimmune diseases (10). Lymphocytes may aggregate to form true lymphoid follicles, often with germinal centers. Plasma cells, eosinophils, macrophages, histiococytes, and fibrosis can be found (17).

The etiology of LH is unclear, but evidence indicates that it may have an underlying autoimmune origin. It cannot be directly transmitted through generations, as in classic autoimmune disorders such as Graves disease but hypophysitis has been induced in animals using emulsified pituitary tissue extracts combined with complete Freund adjuvant (18, 19). In addition, LH responds to immunosuppressive drugs, and pituitary antigen–directed autoantibodies to α-enolase have been found in some patients (20). In addition, LH is associated with other autoimmune diseases, such as Hashimoto disease, celiac disease, and diabetes (18).

To date, although isolated case reports have provided human leukocyte antigen (HLA) status in individual patients, insufficient data exist to link LH to any specific genes associated with autoimmunity, such as the major histocompatibility complex (MHC) locus and cytotoxic T lymphocyte antigen 4 (CTLA4) (21). In this study, we demonstrate that LH is strongly associated with the HLA subtype DQ8.

Materials and Methods

The primary aim of this study was to investigate the HLA status in a series of patients with sporadic LH to determine whether any association with an HLA allotype existed. We also examined the HLA status in other forms of pituitary inflammation, including the hypophysitis that occurs in ~1% to 8% of patients after administration of the CTLA4 antibodies, ipilimumab and tremelimumab, used to treat several solid cancers, and in a case of granulomatous hypophysitis in the setting of sarcoidosis (22). To identify patients, we reviewed extensive clinical and histopathological records and identified 15 patients with sporadic LH, 12 from histopathological records and a further 3 from clinical records who had not undergone surgical biopsy between 1995 and 2012. All histopathological specimens were carefully reviewed by a neuropathologist (W.Y.) to confirm the diagnosis. We also studied 4 patients who had developed anterior hypophysitis after administration of the CTLA4 inhibitors, tremelimumab (n = 2) or ipilimumab (n = 2), in addition to a patient who had sarcoid-associated hypophysitis (n = 1). As control subjects, we studied 50 patients with other sellar disorders and 4 CTLA4 inhibitor–treated patients (3 tremelimumab and 1 ipilimumab) who had not developed hypophysitis despite durations of drug treatment similar to those of the 4 patients who had exhibited hypophysitis.

Results

As depicted in Table 1, 20 patients with a constellation of symptoms suspicious of LH were evaluated. As the patients in this study span several years, most earlier patients with LH underwent surgical exploration of their pituitary masses. In more recent years, as knowledge of LH has increased, most patients suspected of having LH did not undergo pituitary biopsy. Nonetheless, as illustrated by one of our cases (case 7), although LH was initially suspected, due to a rapidly enlarging sellar mass over 3 to 4 months, a pituitary biopsy was performed. Thus, we were able to confirm LH histopathologically in 12 of 15 (80%) of the reported cases. In the remaining 3 cases (cases 1, 5, and 7), the presentation was fairly classic for LH and follow-up is now 3 to 6 years (median follow-up of 4.5 years).
In these patients, a response to immunosuppressive therapy (reduced mass in 2 and improved endocrine function in 1) was observed, supporting the clinical diagnosis.

Ten of the 15 subjects with LH presented with symptoms due to a mass effect, either headache (n = 10) and/or visual field restriction (n = 5), 8 had symptoms of DI, and 11 had symptoms of anterior pituitary dysfunction at presentation. On biochemical testing, 8 patients (53%) had evidence of infundibular and/or pituitary stalk involvement with DI. Eleven had variable degrees of hypopituitarism with central hypogonadism in all 11 patients, central hypothyroidism in 10, and hypotalamic-pituitary-adrenal axis dysfunction in 8 of the 11. Magnetic resonance imaging studies were available in all 15 patients. In 13 patients, a homogeneously enhancing enlarged pituitary gland was observed, the posterior pituitary bright spot was not visible in 4 patients, and some mass effect on the optic apparatus was apparent in 3 patients.

In the CTLA4 antibody–treated group, the onset of pituitary failure occurred quite rapidly between 4 and 7 months after the first dose of either ipilimumab or tremelimumab (mean, 4 months). The presenting clinical features that prompted testing of endocrine function were fatigue in 3 patients and syncope in the fourth patient. Similar to the presentation in the sporadic form, mass effect symptoms such as headache or visual symptoms were common in the CTLA4 antibody–treated cohort, and these have been observed in other studies (23). Magnetic resonance imaging in 3 of 3 CTLA4 antibody–treated patients showed stalk enlargement in one, a homogeneously enhancing enlarged pituitary in another patient, and a partially empty sella in the third patient.

Nine of the 15 patients with sporadic LH were treated with immunosuppressive therapy in the form of a steroid taper with prednisone. In 7 of these 9 patients, a potential response was seen as gauged by an improvement in endocrine function, a reduction in sellar mass size, or improved visual symptoms. However, in 3 of these 7 patients, the improvement was temporary and ultimately the presteroid baseline state in regard to endocrine dysfunction was reestablished. In the subjects who developed hypophysitis after CTLA4 antibodies, this treatment was replaced with glucocorticoids (n = 4), thyroid hormone (n = 3), and androgens (2 of 2 men).

Our hypothesis was that LH is an autoimmune disease, and therefore people with certain HLA types may be predisposed to it. Based on this theory, we first used high-resolution HLA typing to screen both MHC class I and class II markers in an initial series of 5 patients with LH. In this pilot phase, the HLA-DQ8 and -DR53 markers were both present in all of the initial 5 subjects with LH

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**Table 1.** Clinical and Biochemical Characteristics and HLA DQ8 and DRWS5 Subtype in Patients With Sporadic and CTLA4 Antibody–Mediated Hypophysitis

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Abbreviations: A, Asian; Ab, antibody; B, black/African American; F, female; HA, headache; HLA-DQ8, human leukocyte antigen serotype; HLA-DR53, human leukocyte antigen serotype; HPA axis, hypothalamic-pituitary-adrenal axis; M, male; MR Abn, magnetic resonance imaging abnormality; N, no; NA, not available; ND, not determined; Pres, presentation; PRL, prolactin; VF Abn, visual field abnormality; W, white.

a Hashimoto thyroiditis.
b Polyendocrine autoimmune syndrome type 1.
tested but were not demonstrated in the 5 control subjects. Therefore, we then used PCR-based sequence-specific oligonucleotide probe hybridization to test for the HLA-DQ8 and -DR53 markers in an additional 10 subjects. Results of this analysis are depicted in Table 1. It can be seen that 13 of 15 (87%) subjects exhibited positivity for DQ8, 12 of 15 (80.0%) were positive for the DR53 locus, and 11 of 15 (73%) were positive for both alleles. We did not perform allele-level typing as the LH association appeared to be with the DQ8 and DR53 molecules. As a specific allele, DQB1*03:02 encodes the DQ8 molecule; the serotype DQ8 is equivalent to the DQB1*03:02 allele. The DRB4 gene limited alleles (DRB4 01:01–01:09) to encode DR53.

In contrast to the patients in the sporadic LH group, none of the 4 patients who developed hypophysitis after administration of the CTLA4 antibodies exhibited the HLA-DQ8 marker and 1 of 4 (25%) exhibited the HLA-DR53 marker. DQ8 was present in 1 and DR53 in 2 of an additional 4 CTLA4 antibody–treated patients who did not develop hypophysitis. Neither the HLA-DQ8 or -DR53 marker was present in the patient with sarcoidosis-associated hypophysitis.

In a parallel group of 50 control subjects with sellar masses (38 pituitary adenomas, 5 Rathke cleft cysts, 3 craniopharyngiomas, 1 glioneuronal neoplasm, 1 ganglioneuroma, 1 empty sella, and 1 epidermoid cyst) and 4 CTLA4 antibody–treated patients who had not developed any evidence of pituitary failure, the frequencies of the candidate HLA subtypes were 20% for DQ8 and 48% for DR53, respectively. We also reviewed the reported frequencies of the DQ8 and DR53 allotypes in a database of donors being screened for renal transplantation (24). The frequencies of DQ8 and DR53 in this latter population were 33% and 51%, respectively.

**Discussion**

Although the diagnosis of LH can sometimes be made based on the presenting clinical symptoms and signs in conjunction with biochemical evaluation, there are occasional patients in whom the diagnosis remains in question and pituitary biopsy is considered to clarify the diagnosis. Therefore, any serological biomarker that would assist in evaluating these more challenging cases would be helpful. Prior studies have described antibodies to pituitary antigens such as α-enolase in some patients with LH (20). However, although initial studies indicated high specificity for these tests, subsequent studies reported the presence of α-enolase antibodies in patients with other sellar disorders, including pituitary adenoma (46% of patients), similar to that in LH. Likewise, given that the HLA haplotypes are ubiquitous, these markers are not specific to LH, and a significant percentage of patients with other non-LH sellar disorders such as pituitary tumors or cysts may exhibit the HLA markers DR53 and DQ8. This frequency of the HLA-DQ8 haplotype varies widely in different populations, ranging from 1% to 10% in parts of Asia, 5% to 10% in Europe, 50% in central America, and up to 80% in Venezuela and parts of Mexico (25). Most of our patients with LH and control subjects were of European and Asian ethnicities (LH: 73% white, 1.3% Asian; control: 73% white, 8% Asian), and therefore the expected frequency of the HLA-DQ8 serotype in these ethnic groups is in the 1% to 10% range.

Therefore, use of these HLA markers as a diagnostic aid must take into account their frequency in the patients’ ethnic background, as a significant false-positive rate may be encountered. However, although the HLA-DQ8 and -DR53 haplotypes may be quite common in some ethnic groups, only 10.5% of white control subjects (including Hispanic groups) from a very large dataset of bone marrow transplant donors carry the DQ8 or DR53 haplotype (26). In contrast 11 of the 15 patients with LH (73%) carried both the DQ8 and DR53 haplotypes. In addition, in a patient who presents with a symptom complex that raises suspicion of LH, the presence of the HLA-DQ8 allotype alone or in combination with DR53 may serve to either substantiate that suspicion or direct investigation toward ultimately determining the correct diagnosis. Based on our data, the odds ratio of expressing the HLA-DQ8 marker in LH is 23.1 (95% confidence interval, 5.24–181; P < .0001) compared with that of a patient with a sellar mass who does not have LH. For the DR53 marker, the odds ratio is 3.5 (95% confidence interval, 0.96–17.1; P < .059).

Although our numbers are small, in contrast to its presence in primary LH, the HLA-DQ8 marker was present in only 1 of 4 patients with metastatic melanoma with anterior pituitary dysfunction after treatment with the CTLA4 antibodies, tremelimumab or ipilimumab, and was not present in a patient with granulomatous LH associated with sarcoidosis. In CTLA4 antibody–induced hypophysitis, DI is comparatively uncommon, unlike for the sporadic form of LH where DI occurs in 10% to 15% of patients. The histopathology of CTLA4 antibody–induced hypophysitis in humans is unclear, as no pituitary biopsy has been reported. However, mice injected with a CTLA4-blocking IgG1 exhibited pituitary gland infiltration with hematopoietic mononuclear cells, CD45+ lymphocytes, and F4/80+ macrophages and developed antibodies against the anterior pituitary hormones prolactin and ACTH (27).
Ipiilimumab and tremelimumab are fully humanized monoclonal antibodies that block CTLA4 and enhance T-cell activation. Both activate the classic complement pathway, although IgG1 in more potent than IgG2. Ipiilimumab is of the IgG1 subclass, whereas tremelimumab is of the IgG2 subclass (28), and hypophysitis due to treatment is more common with ipilimumab (106 of 2853 [4%]) than with tremelimumab (10 of 917 [1%]) (27).

Several endocrine abnormalities have been described in patients treated with ipilimumab and tremelimumab, including hypophysitis, primary thyroid disorders (hyper- or hypothyroidism), and adrenal insufficiency. The antigenic targets of the CTLA4 antibodies have not been fully defined. Typically, CTLA4 is expressed on T lymphocytes, although it has also been demonstrated on murine embryonic stem cells, human muscle cells, placental fibroblasts, monocytes, leukemia cells, and dendritic cells. CTLA4 expression on pituitary endocrine cells has also been reported (27). However, the thyroid gland, which can also be involved with thyroiditis after CTLA4 antibody therapy, was devoid of CTLA4 expression, suggesting that other antigens are involved. Our data raise the possibility that the mechanisms or immune targets may differ between the sporadic form of LH and the CTLA4 antibody–induced form. However, further cases of both the sporadic and CTLA4 inhibitor–induced forms of LH need to be studied before firm conclusions can be drawn.

As discussed in the Introduction, several lines of evidence indicate that sporadic LH is an autoimmune disease. It is not uncommon for several organ-specific autoimmune diseases to occur in the same patient. One of our patients had polyendocrine autoimmunity type 1 with type 1 diabetes mellitus, primary hypothyroidism before presentation, and subsequent DI, amenorrhoea, hypocortisolism, and GH deficiency consistent with LH. One prior study reported a 14-fold increased risk of type 1 diabetes mellitus in patients carrying the HLA-DQ8 marker (29). A second group of our patients had a history of Hashimoto thyroiditis and had commenced thyroid replacement therapy 12 years before presenting with LH. Our finding of the HLA markers DQ8 and DR53 in 87% and 80% of patients with LH, respectively, adds further support to the concept that LH is primarily an autoimmune disease.

It must also be acknowledged that some of our more recent patients (3 of 15) did not undergo pituitary biopsy, and therefore it is possible that some of these patients could have an alternate pituitary inflammatory disorder besides LH and simply be a false-positive case for the DQ8 marker. However, even if we eliminate this subgroup, the frequency of the DQ8 marker in patients with biopsy-proven LH is still 10 of 12 (83%). In summary, we have observed the HLA-DQ8 allotype in 87% of patients with sporadic pituitary LH in comparison to 21% of a control group with other sellar disorders and to up to 33% in a normal population derived from a renal transplantation database. Our study suggests that evaluation of HLA status and specifically the HLA-DQ8 biomarker may be helpful in aiding in the diagnosis of LH, and potentially spare patients from unnecessary pituitary biopsy.

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**References**