ABSTRACT

Objective: Neurologic autoimmune syndromes associated with anti-glutamate acid decarboxylase 65 antibodies (GAD65-Abs) are rare and mostly sporadic.

Methods: We describe a niece and her aunt with GAD65-Abs neurologic syndromes. High-resolution HLA typing of Class I and Class II alleles was performed using next-generation sequencing.

Results: The proband had cerebellar ataxia and probable limbic encephalitis features, whereas her niece had stiff-person syndrome. Both had a high titer of GAD65-Abs in serum and CSF and showed signs of inflammation in CSF. Both affected members carried the same rare recombinant DRB1*15:01:01–DQA1*01:02:01–DQB1*05:02:01 haplotype, which may or may not be involved in disease susceptibility. Of interest, other unaffected members of the family either had the same HLA haplotype but normal serum GAD65-Abs or had different HLA types but a high titer of serum GAD65-Abs without neurologic symptoms, suggesting cumulative effects.

Conclusions: This unique association strengthens the concept that hereditary factors, possibly including specific HLA haplotypes, play a role in neurologic syndromes associated with GAD65-Abs.

Glossary

GAD = glutamic acid decarboxylase; IgG = immunoglobulin G; SPS = stiff-person syndrome; T1DM = type 1 diabetes mellitus; TG = antithyroglobulin; TPO = antithyroperoxidase.

Glutamic acid decarboxylase (GAD) is the rate-limiting enzyme for the production of γ-aminobutyric acid, the main inhibitory neurotransmitter of the CNS. GAD is also expressed in pancreatic islet β-cells.1 Anti-GAD65 antibodies (GAD65-Abs) have been described as a biological marker in patients with type 1 diabetes mellitus (T1DM), but also in some patients with neurologic diseases, such as stiff-person syndrome (SPS), cerebellar ataxia, or limbic encephalitis.2–7 Although rare, the concept of neurologic syndromes with GAD65-Abs is now well established, most cases reported so far being sporadic.8 Few experimental studies suggest a possible pathogenic role of GAD65-Abs.9–11 We describe 2 members of the same family with GAD65-Abs neurologic syndromes in combination with a rare recombinant HLA haplotype and 2 other members without the same haplotype and with a high level of GAD65-Abs but no neurologic symptoms. These results suggest that there may be a genetic basis for susceptibility of the development of GAD-antibody autoimmunity.
samples named “Neurobietec” registered as the biobank of the Hospices Civils de Lyon. Full HLA next-generation sequencing–based typing was performed based on long-range PCRs detailed by Wang in 2012.12

RESULTS Cases reports. The first patient (II3, figure), a 68-year-old woman without a medical history, first developed acute dizziness and vomiting. Neurologic clinical examination revealed an ataxic gait with enlargement of the sustentation polygon and nystagmus. The rest of the physical examination was normal. Videonystagmography revealed a left vestibular deficit. Brain MRI showed no cerebellar atrophy, but hyperintensity on fluid attenuation inversion recovery sequences restricted to both hippocampi (nevertheless, no acute clinical signs of limbic encephalitis were observed). CSF examination showed elevated protein levels at 0.71 g/L without white blood cells and a normal immunoglobulin G (IgG) index (0.5; normal <0.7), but few oligoclonal bands (<5) were present. Antithyroid peroxidase (TPO) and antithyroglobulin (TG) antibodies were also positive (Varelisa; Thermo Fischer Scientific, Waltham, MA) (718 and 283 IU/mL, respectively, cutoff of positivity for both Abs: 60 IU/mL). No other biological abnormalities were detected. Body fluorodeoxyglucose–PET and mammography were also normal. A diagnosis of cerebellar ataxia with GAD65-Abs was

Figure Family tree with the HLA haplotyping of 6 members of the family

A

II

I

III

IV

○ Patient with anti-GAD antibodies without neurologic syndrome
Red circle: patient with anti-GAD antibodies and cerebellar ataxia
Blue circle: patient with anti-GAD antibodies and stiff-person syndrome
Green circle: patient with anti-TPO antibodies

Subjects

A/1

A/2

B/1

B/2

C/1

C/2

| Subjects | A/1 | A/2 | B/1 | B/2 | C/1 | C/2 |
| --- | --- | --- | --- | --- | --- | --- |
| II3 | A*24:02:01:01 | A*01:01:01:01 | B*39:06:02 | B*08:01:01 | C*07:01:01:01 | C*07:01:01:01 |
| II5 | A*24:02:01:01 | A*11:01:01:01 | B*39:06:02 | B*35:02:01 | C*07:01:01:01 | C*04:01:01:06 |
| II3 | A*11:01:01:01 | A*02:01:01:01 | B*52:01:01:02 | B*35:06:01 | C*12:02:02 | C*04:01:01:06 |
| II4 | A*11:01:01:01 | A*11:01:01:01 | B*52:01:01:02 | B*35:02:01 | C*12:02:02 | C*04:01:01:06 |
| II6 | A*24:02:01:01 | A*02:01:01:01 | B*39:06:02 | B*44:05:01 | C*07:02:01:01 | C*02:02:02:01 |
| II7 | A*24:02:01:01 | A*02:01:01:01 | B*39:06:02 | B*44:02:01:01 | C*07:02:01:01 | C*05:01:05:02 |
| II8 | A*24:02:01:01 | A*02:01:01:01 | B*39:06:02 | B*44:05:01 | C*07:02:01:01 | C*02:02:02:01 |
| II9 | A*24:02:01:01 | A*02:01:01:01 | B*39:06:02 | B*44:03:01:01 | C*07:02:01:01 | C*05:01:05:02 |

Subjects

DPA1/1

DPA1/2

DPB1/1

DPB1/2

DQA1/1

DQA1/2

| Subjects | DPA1/1 | DPA1/2 | DPB1/1 | DPB1/2 | DQA1/1 | DQA1/2 |
| --- | --- | --- | --- | --- | --- | --- |
| II3 | DPA1*01:03:01:05 | DPA1*02:01:02 | DPB1*04:02:01:02 | DPB1*01:01:01 | DQA1*01:02:01:03 | DQA1*05:01:01:02 |
| II5 | DPA1*01:03:01:05 | DPA1*01:03:01:03 | DPB1*04:02:01:02 | DPB1*04:02:01:02 | DQA1*01:02:01:03 | DQA1*05:05:01:01 |
| II3 | DPA1*02:02:02 | DPA1*02:02:02 | DPB1*04:01:01:01 | DPB1*04:01:01:01 | DQA1*01:03:01:01 | DQA1*05:05:01:01 |
| II4 | DPA1*03:01:03:03 | DPA1*03:01:03:03 | DPB1*04:01:01:01 | DPB1*04:01:01:01 | DQA1*01:03:01:01 | DQA1*05:05:01:01 |
| II6 | DPA1*01:03:01:05 | DPA1*03:01:03:02 | DPB1*04:02:01:02 | DPB1*02:01:02 | DQA1*01:02:01:03 | DQA1*01:02:01:02 |
| II7 | DPA1*01:03:01:05 | DPA1*02:01:01 | DPB1*04:02:01:02 | DPB1*14:01:01 | DQA1*01:02:01:03 | DQA1*01:03:01:02 |
| II8 | DPA1*01:03:01:05 | DPA1*03:01:03:02 | DPB1*04:02:01:02 | DPB1*02:01:02 | DQA1*01:02:01:03 | DQA1*01:02:01:03 |
| II9 | DPA1*01:03:01:05 | DPA1*03:01:03:02 | DPB1*04:02:01:02 | DPB1*14:01:01 | DQA1*01:02:01:03 | DQA1*01:03:01:02 |

Subjects

DQB1/1

DQB1/2

DRB1/1

DRB1/2

DRB5/1

DRB5/2

| Subjects | DQB1/1 | DQB1/2 | DRB1/1 | DRB1/2 | DRB5/1 | DRB5/2 |
| --- | --- | --- | --- | --- | --- | --- |
| II3 | DQB1*05:02:01 | DQB1*02:01:01 | DRB1*15:01:01:03 | DRB1*03:01:01:01 | DRB5*01:01:01 | DRB5*02:01:01 |
| II5 | DQB1*05:02:01 | DQB1*05:02:01 | DRB1*15:01:03:01 | DRB1*05:01:01 | DRB5*01:01:01 | DRB5*02:01:01 |
| II3 | DQB1*06:01:01 | DQB1*03:01:01:02 | DRB1*15:01:01:01 | DRB1*11:01:01 | DRB5*01:01:01 | DRB5*02:01:01 |
| II4 | DQB1*06:01:01 | DQB1*03:01:01:02 | DRB1*15:01:01:01 | DRB1*11:01:01 | DRB5*01:01:01 | DRB5*02:01:01 |
| II6 | DQB1*05:02:01 | DQB1*05:02:01 | DRB1*15:01:01:03 | DRB1*16:01:01 | DRB5*01:01:01 | DRB5*02:01:01 |
| II7 | DQB1*05:02:01 | DQB1*05:02:01 | DRB1*15:01:01:03 | DRB1*16:01:01 | DRB5*01:01:01 | DRB5*02:01:01 |
| II8 | DQB1*05:02:01 | DQB1*05:02:01 | DRB1*15:01:01:03 | DRB1*16:01:01 | DRB5*01:01:01 | DRB5*02:01:01 |
| II9 | DQB1*05:02:01 | DQB1*05:02:01 | DRB1*15:01:01:03 | DRB1*16:01:01 | DRB5*01:01:01 | DRB5*02:01:01 |

The colors indicate the bioclinical characteristics of the patients. Black circle: patients with GAD65-Abs without neurologic syndromes (II3 and II4). Red circle: patient with GAD65-Abs and cerebellar ataxia (II3). Blue circle: patient with GAD65-Abs and stiff-person syndrome (II5). Green circle: patients with TPO-Abs (II3, II3, and II5).
DRB5 typing revealed that this patient also carried the unusual haplotype and experienced only partial recovery. HLA later, no diabetes mellitus was observed and no cancer was noted. Five years after activity and cocontraction of agonist and antagonist muscles of the thigh, hip, and back muscles. The father of II3 developed dementia and diabetes mellitus, and his HLA haplotype was not characterized.

DISCUSSION Very little is known regarding genetic predisposition to autoimmune neurologic syndromes with GAD65-Abs. HLA genetic predisposition to SPS has been studied only in 1 large study of 18 patients, with unremarkable findings, although weak association with DQB1*02 (DQB1*02:01 and DQB1*02:02) was suggested.13 In this study, however the presence of DQB1*06:02, a strong protective allele for type 1 diabetes, was present in some patients with SPS without type 1 diabetes but in none with cooccurring diabetes.13,14 However, a few familial occurrences of neurologic conditions associated with GAD65-Abs have been previously described, 2 families with multiplex familial SPS15,16 and 1 family with 2 sibling sisters with cerebellar ataxia and GAD65-Abs, suggesting that genetic factors may be involved (HLA typing was not performed in these cases).

In our 2 cases, DQB1*02 was present only in 1 affected case, but both carried an unusual haplotype. HLA-DRB1*15:01~DQA1*01:02~DQB1*05:02. This haplotype is likely the result from recombination of HLA-DRB1*15:01~DQA1*01:02~DQB1*06:02:01 with DRB1*16:01:02~DQA1*01:02:02~DQB1*05:02:01, 2 common Caucasian haplotypes. We can also speculate that the father of II3 who developed dementia and diabetes mellitus may also have had this rare haplotype. Although reported rarely in the literature, except in a few patients of Romani people, Northern Indian, and Chinese origin,18-20 this haplotype is extremely rare in US and French Caucasians (<0.1%)21 and thus unlikely to be present by chance in these 2 affected patients.20 The rare haplotype, if involved, is however not the sole determinant of disease, as 4 relatives (II 6, 7, 8, and 9) with the haplotype do not have neurologic symptoms or GAD65-Abs.

Surprisingly, we also found 2 other relatives (II3 and III4) having high GAD65-Abs titers without neurologic symptoms. This is also unlikely to be a chance phenomenon, as GAD65-Abs are found only in around 1.7% of the general population with or without neurologic disorders.22,23 Of interest, the...

Familial history. After identification of these 2 index cases, we reviewed the entire family history and extended HLA typing to 6 other members of the family (figure). The entire family is of Caucasian ethnicity. The father of II3 developed dementia and diabetes mellitus, but we have no more information. Of interest, 2 relatives (II3 and III4) without the rare haplotype had serum GAD65-Abs titer higher than 250 IU/mL. One (III3), the sister of the patient III5 with SPS, developed pernicious anemia with intrinsic antibodies, breast cancer, and thyroiditis, and her brother (III4) had no particular medical history. All the members of the family were examined by JH and had no abnormalities on neurologic examination. No other disease was reported in the other members of the family. Conversely, 4 other members of the family (II 6, 7, 8, and 9) shared the rare DRB5*01:01:01~DRB1*15:01:01~DQA1*01:02:01~DQB1*05:02:02, but had no GAD65-Abs and no neurologic symptoms. The father of II3 developed dementia and diabetes mellitus, and his HLA haplotype was not characterized.

Medullary and brain MRI were normal. The CSF study revealed a normal IgG index (0.61; normal < 1 for 5,000 patients). The frequency of this haplotype in France must be less than 1 in 100 French people. In our estimation, the frequency of this haplotype in France must be less than 1 in 5,000 patients.

Her niece (III5, figure) developed signs of progressive muscular rigidity with superimposed spasms at the age of 42 years. The right leg was first affected, followed by the trunk and the left leg. Her medical history was notable for Hashimoto thyroiditis (with anti-TPO at 1,966 IU/mL and anti-TG-Abs at 12,786 IU/mL). Medullary and brain MRI were normal. The CSF globulin was initiated. After 6 months, the patient stabilized, while still exhibiting a mild cerebellar syndrome. GAD65-Abs remained positive during 15 years of follow-up. Brain MRI performed 4 years after onset showed cerebellar and diffuse brain atrophy. The patient developed late-onset T1DM and a progressive dementia without significant clinical progression of cerebellar ataxia. HLA typing revealed the presence of an unusual haplotype DRB5*01:01:01~DRB1*15:01:01~DQA1*01:02:01~DQB1*05:02:01, together with a classical type 1 diabetes–associated haplotype DRB1*03:01:01~DQA1*05:01:01~DQB1*02:01:01 (figure). DRB5*01:01:01~DRB1*15:01:01~DQA1*01:02:01~DQB1*05:02:01 is very unusual. In large samples from north European countries, the frequency is typically below 1 for 1,000 patients. We identified no patient with this haplotype in more than 100 French people. In our estimation, the frequency of this haplotype in France must be less than 1 for 5,000 patients.

T h e p a t i e n t d e v e l o p e d l a t e - o n s e t T 1 D M a n d p r o -

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Surprisingly, we also found 2 other relatives (II3 and III4) having high GAD65-Abs titers without neurologic symptoms. This is also unlikely to be a chance phenomenon, as GAD65-Abs are found only in around 1.7% of the general population with or without neurologic disorders.22,23 Of interest, the...
In our family, the 2 asymptomatic patients with high GAD65-Abs do not share the same extended HLA subtypes with both affected patients, suggesting that GAD65-Abs are unlinked with HLA alone and that the sole presence of high titers of GAD65-Abs is insufficient to develop neurologic symptoms. One reason could be that GAD65-Abs in affected vs unaffected patients target different epitopes, as has been shown for type 1 diabetes vs SPS.\textsuperscript{25–27} Of interest, a recent study in 6,556 type 1 diabetes cases has shown strong genetic association for the presence of GAD65-Abs not with an HLA region, but with other genes, notably in \textit{IFIH1}, a locus associated with positivity for TPO and GAD65-Abs\textsuperscript{28} and involved in other immune phenotypes.\textsuperscript{29,30}

A similar complex genetic susceptibility has already been discussed in neuromyelitis optica (NMO), another autoimmune neurologic disorder associated with antineural antibodies.\textsuperscript{31} In NMO, around 3% of patients have a familial occurrence of the disease, and familial NMO is indistinguishable from sporadic NMO.\textsuperscript{31} Furthermore, the association with a specific HLA haplotyping is also highly debated.\textsuperscript{32} Our family with GAD65-Abs and all the data of the literature suggest that coincident complex genetic factors in the HLA and non-HLA regions should be carefully studied in autoimmune neurologic disorders associated with antineural antibodies.

**AUTHOR CONTRIBUTIONS**

Aude Belbezier contributed to the acquisition of data, analysis, interpretation of the data, drafting the manuscript for intellectual contents. Bastien Joubert contributed to the acquisition of data, analysis, interpretation of the data, critical revision of the manuscript for intellectual content. Gonzalo Montero-Martin contributed to the acquisition of data, analysis, interpretation of the data, critical revision of the manuscript for intellectual content. Marcelo Fernandez-Vina contributed to the acquisition of data, analysis, interpretation of the data, critical revision of the manuscript for intellectual content. Nicole Fabien contributed to the acquisition of data. Yéronique Rogemond contributed to the acquisition of data. Emmanuel Mignot contributed to the interpretation of the data and critical revision of the manuscript for intellectual content. Jérôme Honnorat contributed to the study concept and design of the study, critical revision of manuscript for intellectual content, study supervision.

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**DISCLOSURE**

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