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ORIGINAL ARTICLE

Serum glutamate decarboxylase antibodies and neurological disorders: when to suspect their association?

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Abstract

Objectives To explore different neurological manifestations with suspicion of being associated to serum glutamate decarboxylase antibodies (GAD-Abs) in order to better characterize anti-GAD neurological syndromes.

Methods Observational retrospective study including all patients for whom GAD65-Abs titers in serum were requested by the Neurology Department at La Paz University Hospital between 2015 and 2019. GAD-Abs were measured by ELISA. Demographic data, neurological symptoms, comorbidity with diabetes mellitus (DM) or with another autoimmune disease, and GAD-Abs titers were studied. Stiff-person syndrome, ataxia, encephalitis, and epilepsy were considered typical anti-GAD neurological syndromes and were compared to other atypical manifestations.

Results A total of 173 patients (51.7% men, mean age 51.62) were included. A progressive increase in requests of serum GAD-Abs has occurred over the last 5 years, especially in patients with atypical neurological manifestations. GAD-Abs were found in the serum of 22 patients (12.7%); of those, 15 (68.18%) suffered a typical anti-GAD syndrome. Presence of DM or another organ-specific autoimmune disease was predictive of GAD-AB seropositivity ($p < 0.001$). 6.6% of requested patients with an atypical syndrome had GAD-Abs, but serum levels were significantly lower than those found in patients with a typical syndrome (706.67 vs 1430.23 UI/mL; Mann-Whitney U, $p = 0.034$), and were finally diagnosed with another neurological disease.

Conclusion Serum GAD-Abs were infrequently found in patients with clinical phenotypes other than those classically described as anti-GAD disorders, and with very low titers. In typical anti-GAD syndromes, there is a high comorbidity with DM and with other autoimmune diseases, and high serum GAD-Abs levels are usually present.

Keywords Glutamate decarboxylase · Autoantibodies (GAD) · Neurological autoimmune disorders

Introduction

Antibodies against glutamate decarboxylase (GAD-Abs) have been associated to diabetes mellitus (DM) and to different neurological disorders.

Stiff-person syndrome (SPS) was the first neurological disorder associated to GAD-Abs [1, 2]. Later, these antibodies were also found in some cases of cerebellar ataxia [3, 4] and epilepsy [5, 6]. In recent years, other related manifestations have been described, including limbic encephalitis [7], eye movement disorders [8], myoclonic jerks [9], Miller-Fisher syndrome [10], and inflammatory myopathies [11].

Glutamate decarboxylase (GAD) is a necessary enzyme for the formation of gamma aminobutyric acid (GABA) from glutamate. It is mainly expressed in central neural and pancreatic islet cells. There are two known isoforms (GAD65 and GAD67), but the main antibodies' target in the central nervous system (CNS) seems to be GAD65 [12]. GABA is a neurotransmitter with an important inhibitory role; therefore, a decrease in GABA concentrations, for example, by effect of GAD-Abs, might theoretically cause any kind of neuronal hyperexcitability disorders [13].

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However, the pathogenic role of GAD-Abs in neurological disorders remains a controversial issue. In vitro, inhibition of GABA production using serum from SPS patients with GAD-Abs has been demonstrated [14]. Also intrathecal injections of IgG from GAD65-Ab-positive patients [15] and monoclonal antibodies to GAD65 [16] have induced typical clinical symptoms in rats. However, GAD65 is an intracellular enzyme and antibody internalization and interaction with the GAD65 antigen has not yet been demonstrated in vivo [17]. Moreover, it is yet unknown why patients with GAD-Abs can present with such different, isolated, or overlapping neurological manifestations.

Serum GAD-Abs are present in 80% of patients with type 1 DM, and in 15–35% of patients with type 2 DM diagnosed before the age of 45 [18]. However, GAD-Abs do not have an apparent pathogenic role in DM [19]. According to experimental studies, GAD-Abs from patients with DM do not react against brain tissue [20] and have no effects on GABAergic neurotransmission [21]. However, neurological disorders associated with GAD-Abs usually coexist with DM, as well as with other organ-specific autoimmune disorders such as thyroiditis, vitiligo, pernicious anemia, or vitiligo. GAD-Abs have also been found in paraneoplastic neurological syndromes [22].

In cases of neurological disease related to GAD-Abs, immunotherapy seems to be at least partially effective, although there are few randomized trials and evidence comes almost entirely from small case series [23]. Early initiation of treatment apparently ameliorates the prognosis [23].

It is therefore important to improve our awareness about anti-GAD-related neurological manifestations, so as to make an early diagnosis and initiate treatment before irreversible damage has taken place.

However, the presence of these antibodies in serum could be only an epiphenomenon with no pathogenic significance. GAD-Abs can be present in healthy people or in patients with other neurological disorders [24] or with DM. Misdiagnosis of an autoimmune disorder related to GAD-Abs in these cases can lead to an unnecessary and potentially harmful treatment.

To establish the implication of GAD-Abs in a nervous system disorder, it is recommended that their presence in cerebrospinal fluid (CSF) is confirmed as well as intrathecal GAD-Abs synthesis [25]. However, before performing a lumbar puncture, it is mandatory to select patients with a high degree of suspicion.

This study aims to analyze the usefulness of determining serum GAD-Abs in patients with different neurological manifestations and to better characterize anti-GAD neurological syndromes considering GAD-Abs titers, clinical features, and comorbidities.

Methods

This is an observational retrospective study including all patients for whom titers of serum GAD-Abs were requested from the Clinical Analysis Laboratory by a Neurologist at La Paz University Hospital from 01 January 2015 to 31 December 2019. Patients under 14 years of age, or for whom clinical data was missing from their medical records, were excluded from the analysis.

Enzyme-linked immunosorbent assay (ELISA) technique was routinely used to detect and quantify GAD65-Abs in serum and CSF. Presence of GAD-Abs in serum was considered positive when levels were higher than 5 UI/mL. Levels higher than 2000 UI/mL could not be quantified and were reported as such.

Medical records of included patients were reviewed, and demographical data, comorbidities, neurological syndrome, diagnostic test results, treatment, and patient outcome were extracted to standardized tables.

In the absence of validated diagnostic criteria for neurological anti-GAD disorders, we have considered "typical anti-GAD neurological syndromes" those with a strong demonstrated association with GAD-Abs [23]: stiff-person syndrome, ataxia, epilepsy, and encephalitis. Other reported symptoms or syndromes were classified as "atypical anti-GAD neurological syndromes."

Statistical descriptive and comparative analysis was performed using the Statistical Package for the Social Sciences 22.0 (SPSS 22.0) software. Quantitative data are described using the mean ± standard deviation (SD). Qualitative data are described using absolute frequencies and percentages. The homogeneity of the groups was analyzed using Fisher's exact test and Mann-Whitney's test for quantitative data.

The study was approved by the Ethics Committee of La Paz University Hospital.

Results

Neurological syndromes suspected to be related to GAD-Abs

From 2015 to 2019, the Neurology Department at our tertiary hospital requested the determination of serum GAD-Abs in a total of 173 patients (51.7% men), mean age 51.62 (SD 15.58) years.

Demands for GAD-Ab detection in neurological patients progressively increased each year, while the percentage of positive results obtained per year fluctuates, decreasing in 2019 (Fig. 1).

GAD-Abs were requested for a wide variety of neurological manifestations (Table 1). The number of requests for serum GAD-Abs was higher in patients presenting syndromes atypically associated to GAD-Abs (60.6%). Trends over time in requests for GAD-Abs for patients with typical anti-GAD syndromes (SPS, ataxia, epilepsy, and encephalitis), and atypical ones, can be seen in Fig. 2.

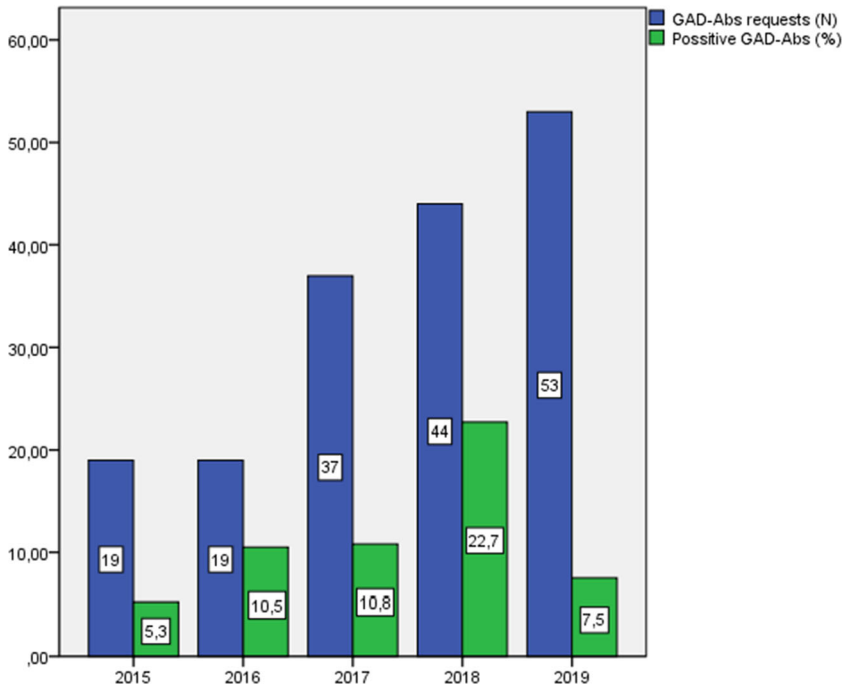

Fig. 1 Total number of serum GAD-Ab determinations requested and percentage of positive results per year

Table 1 Neurological syndromes suspected to be associated with GAD-Abs

Neurological syndrome	*N* of cases	GAD-Ab positivity in serum, *N* (%)	GAD-Abs titers, M (DS)	DM, *N* (%)*	Other autoimmune disorders, *N* (%)*
Anti-GAD typical syndrome					
Stiff-person syndrome	1	1 (100)	2000	0	1 (100)
Ataxia	47	3 (6.3)	1372 (1087.7)	2 (66.6)	2 (66.6)
Ataxia + epilepsy	4	4 (100)	2000	1 (25)	2 (50)
Epilepsy	14	5 (35.7)	1403.2 (517.2)	2 (40)	1 (20)
Encephalitis	2	2 (100)	114 (56.1)	0	1 (50)
	68	15 (22)	1430.2	5 (33.3)	7 (46.6)
Non anti-GAD typical syndrome					
Muscle hyperexcitability symptoms (spasms, cramps, fasciculations)	5	0			
Polyneuropathy	18	1 (5.6)	2000	1 (100)	0
Myopathy	4	0			
Neuron motor disease	10	1 (10)	87	0	0
Parkinsonism	3	0			
Cognitive disorder	14	2 (14.2)	120.5 (113.4)	2 (50)	0
Demyelinating disease	19	1 (5.2)	8	0	0
Chronic fatigue syndrome	2	0			
Tremor	3	0			
Nonepileptic paroxistic disorder	4	2 (50)	12 (4.2)	0	0
Myasthenia	2	0			
Dystonia	3	0			
Stroke	3	0			
Headache	3	0			
Myoclonus	3	0			
Rhombencephalitis	1	0			
Meningitis	1	0			
Abnormal ocular movements	4	0			
Dysautonomia	3	0			
	105	7 (6.6)	706.6	3 (42.8)	0

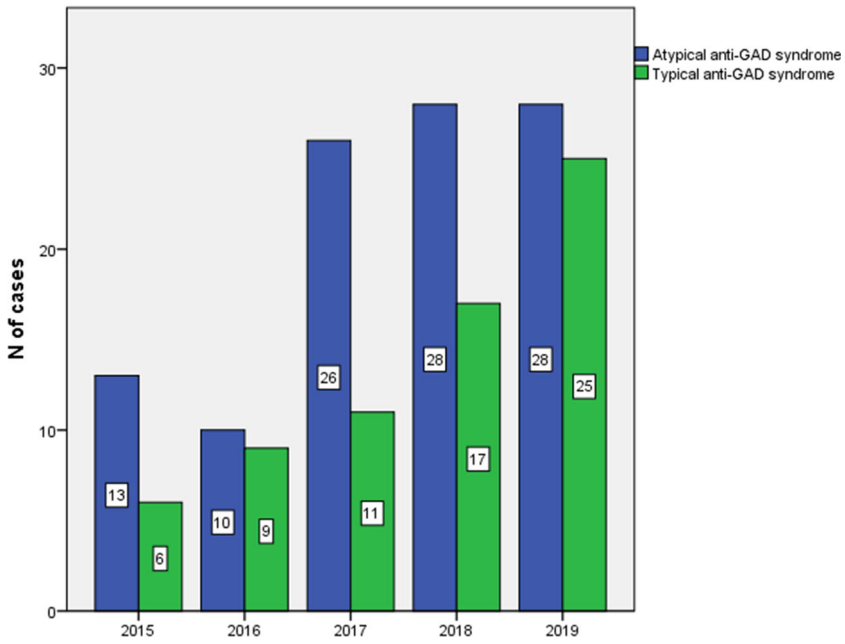

Fig. 2 Number of GAD-Ab requests per year in patients with an atypical or a typical anti-GAD syndrome

Predictive factors of GAD-Ab seropositivity

Serum GAD-Abs were positive in only 7 (6.66%) cases of atypical anti-GAD syndromes, while they were positive in 15 (22.05%) patients with typical syndromes (chi-square, $p = 0.060$).

Patients for whom GAD-Ab determination was positive were significantly younger (44.33 (SD 17.2) years) than seronegative patients (52.57 (SD 15.4) years) (Mann-Whitney U, $p = 0.029$), and there was a slightly higher proportion of males among patients in whom GAD-Abs were found, albeit not significant (chi-square, $p = 0.647$).

In our cohort, only 11 (6.4%) patients for whom serum GAD-Abs were requested also suffered DM. GAD-Abs were positive in the serum of 63.6% of diabetic patients, while this was the case in only 9.3% of non-diabetics (chi-square, $p < 0.001$). Comorbidity with other organ-specific autoimmune diseases was also predictive for GAD-Ab positivity (58.3% vs 9.3%; $p < 0.001$).

Main features of patients with GAD-Abs in serum

GAD-Abs were found in 22 patients (12.7% of total), 12 (54.54%) were male, and the mean age was 44.33 (SD 17.2) years.

In Table 1, differences with regard to GAD-Abs titers and to DM or other autoimmune disorder comorbidities are detailed in patients with typical and atypical neurological syndromes.

A lumbar puncture was performed in only 7 cases to assess for GAD-Abs in CSF. All of them suffered ataxia and/or epilepsy. GAD-Abs were present in the CSF of 5 patients, whereas in only 2 patients a high index GAD-Abs CSF/GAD-Abs serum was confirmed. Titers of GAD-Abs in CSF varied from 25 to 6885 UI/mL.

DM and other autoimmune disorder comorbidities

Out of all positive GAD-Ab patients, 36.36% suffered DM (33.33% with typical and 42.86% with atypical neurological presentation). In the typical anti-GAD disorder group, 31.81% of patients had other organ-specific autoimmune diseases (5 thyroiditis, 1 pernicious anemia, and 1 had antibodies against the NMDA receptor), while none in atypical group. Of note, two cases of pulmonar neoplasm were found in anti-GAD positive patients.

Onconeuronal antibodies were also studied in 43 patients (23 with a typical anti-GAD neurological syndrome) and only one patient was positive for anti-Hu antibody as well as for anti-GAD. Moreover, 30 patients were also assessed for cell surface antibodies (of which 16 with a typical syndrome), with only one case positive for NMDA. Another 13 cases were studied for the presence of aquaporin-4 and MOG antibodies; however, all were seronegative.

Titers of serum GAD-Abs

In anti-GAD positive patients, mean GAD-Ab serum titer was 1134.23 UI/mL (SD 972.67, range 7–2000). In 12 patients (54.5%), titers were above 2000 UI/mL.

Repeated determinations of GAD-Ab titers in serum were done in 15 cases at different times. A change in Ab titers occurred in only 4 cases (25%), with small variations (58 to 41 UI/mL; 116 to 105 UI/mL; 0 to 42 to 0 UI/mL; 0 to 6 UI/

mL). No positive patient with GAD-Ab titers > 2000 UI/mL showed variation over time (Figs. 3 and 4).

No difference in GAD-Ab titers between sex was found (Mann-Whitney U, $p = 0.318$) and there was no correlation with patients' age.

Serum titers of patients with typical anti-GAD syndromes (M: 1430.23 UI/mL) were significantly higher than those of patients with atypical manifestation (M: 706.67 UI/mL) (Mann-Whitney U, $p = 0.034$) (Fig. 5). Only 4/15 patients with a typical syndrome had serum GAD-Ab titers lower than 2000 UI/mL (from 58 to 249 UI/mL). And in 4/7 patients with atypical manifestation, serum GAD-Ab levels were very low (< 20 UI/mL).

Comorbidity with DM was not predictive of GAD-Ab titers (Mann-Whitney U, $p = 0.166$), but these were higher if other autoimmune disorders, not DM, were also present (M 1749.86 vs 846.93 UI/mL; $p = 0.028$).

Clinical phenotype and treatment response of anti-GAD typical syndromes

A stiff-person syndrome (SPS) was diagnosed in a median-aged patient with history of positivity for many other systemic antibodies (anti-thyroid, anti-parietal cells and intrinsic factor, anti-acetylcholine receptor, and cryoglobulins). Clinical stability was obtained with intravenous immunoglobulins (iv Igs) treatment.

Among epileptic patients ($n = 9$), focal seizure of temporal origin was the most frequently described, in 4 cases. Two patients debuted with epileptic state. Neuroimaging defects were observed in only one patient, with hyperintense signal of the temporal lobe in T2/flair magnetic resonance sequences.

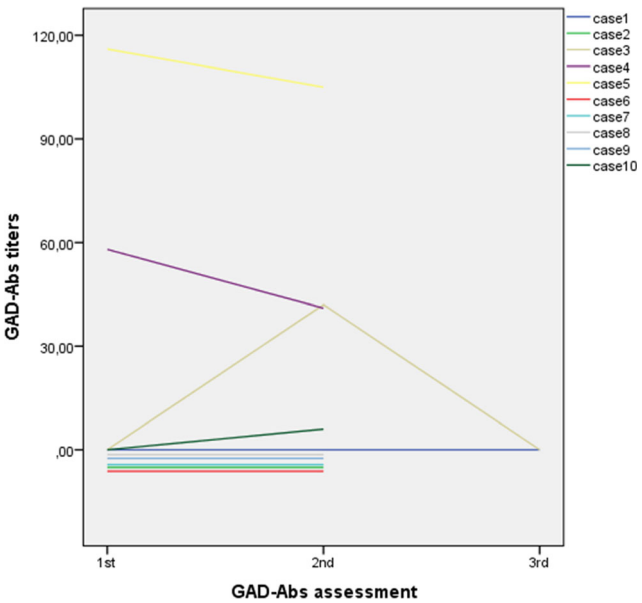

Fig. 3 Cases with low GAD-Ab serum titers (< 120 UI/mL) showed small variations in titers over time

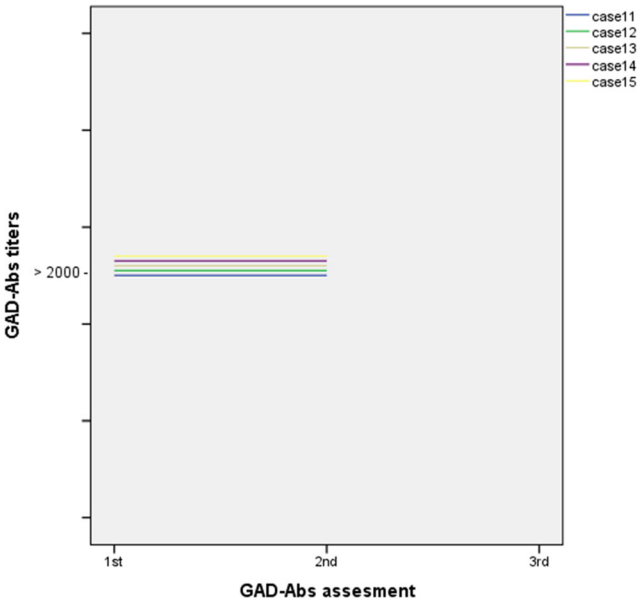

Fig. 4 Cases with high GAD-Ab serum titers (> 2000 UI/mL) did not show titer variation over time

Outcome was good after immunotherapy in 5/8 treated patients who suffered epilepsy (2 patients received plasmapheresis, 1 methylprednisolone plus iv Igs, and 2 rituximab).

Regarding clinical features described in 7 patients with ataxia, two patients associated ocular movement disorders (all directional nystagmus and oscillopsia). Coexisting alternative causes of ataxia (B_{12} vitamin deficit and sensitive polyneuropathy) were found in two cases. In another patient, anti-Hu antibodies and a pulmonary neoplasm were detected. Cerebellar atrophy was the only radiological finding when results of magnetic resonance imaging (MRI) were available in the clinical history ($n = 3$). Immunosuppressant treatment was prescribed in 5/7 patients (3 plasmapheresis, 1 iv Igs, and 1 rituximab) without clinical improvement in any of them.

Epilepsy and ataxia coexisted in 4 cases. In two patients, epilepsy manifested before ataxia (14 and 20 years before), in one patient both coincided in time, and in the other case ataxia initiated 6 months before epilepsy.

Two patients presented with autoimmune encephalitis, in both GAD-Ab serum levels were quite low (58 and 170) and determination of GAD-Abs in CSF could not be made due to hematic CSF. None of these patients had DM. Other infectious and autoimmune etiologies for encephalitis were ruled out. Both cases had a normal cranial MRI and improved with iv Igs.

Atypical neurological presentations with GAD-Ab seropositivity

Five of the seven patients with atypical anti-GAD clinical manifestations met diagnostic criteria of other well-defined diseases that explained neurological symptoms (motorneuron

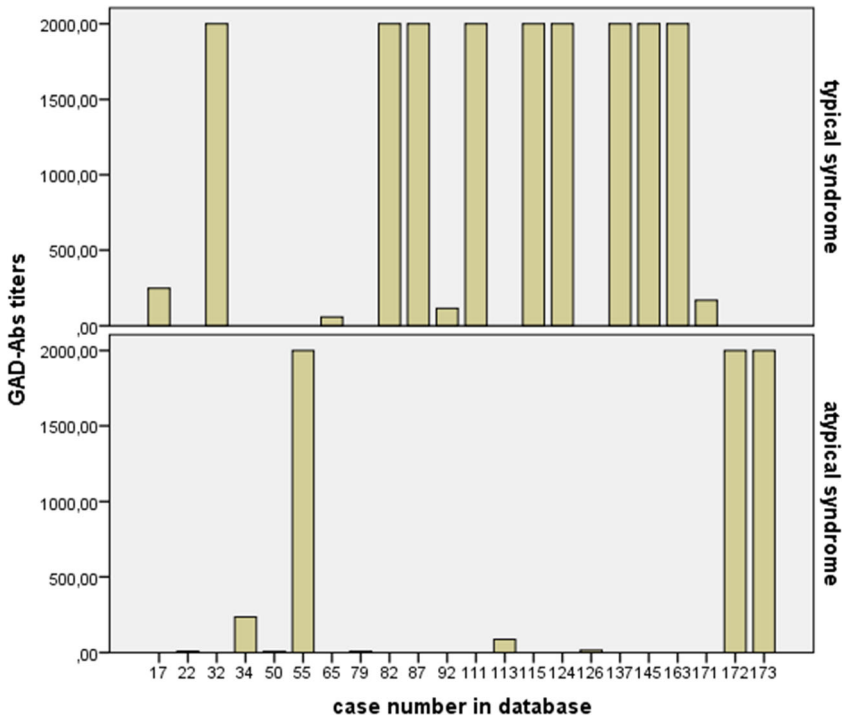

Fig. 5 Different GAD-Ab titers in patients with typical and atypical syndromes

disease, Alzheimer disease, Creutzfeldt-Jakob disease, chronic inflammatory demyelinating polyneuropathy (CIDP), and multiple sclerosis). The other two cases were classified as "non-epileptic paroxistic disorder" (NEPD), due to a probably functional neurological disorder. Only three patients showed serum GAD-Ab levels higher than 20 UI/mL: one with motorneuron disease (87 UI/mL), one with Alzheimer disease and DM (234 UI/mL), and one with CIDP (> 2000 UI/mL) who also suffered DM.

Discussion

In recent years, many new different neurological syndromes have been found associated with GAD-Abs [7–10, 26]. This fact may have increased clinicians' suspicion of the possible implication of GAD-Abs in other neurological manifestations. In our study, we certainly have seen a progressive increase in serum GAD-Ab requests since 2015. Patients for whom serum GAD-Abs were requested presented mostly a neurological disorder different to those classically described related to anti-GAD (SPS, ataxia, epilepsy, and encephalitis). The decision to request GAD-Ab titers in serum was apparently not conditioned by the presence of DM comorbidity as it is present in only 6.4% of patients in our cohort.

Meinck et al. have studied the prevalence of GAD-Abs in 279 patients with neurological diseases other than SPS, observing presence of GAD-Abs in serum in 5% of them and in 1% of healthy controls [24]. We have found 12.1% of GAD-Ab positivity in our study from real-life clinical practice. There is still no clear evidence that GAD-Abs are pathogenic in any of the associated neurological syndromes described [25]; their presence could represent just an epiphenomenon of neuronal damage, or even a risk marker for other immunological disorders, and should be interpreted with caution.

Our small sample size, coupled with the great diversity of syndromes in which GAD-Abs were requested, represents a limitation when attempting to establish a possible association between any of the atypical anti-GAD syndromes found in our cohort and the presence of GAD-Abs. However, although a confirmatory CSF study ruling out intrathecal anti-GAD synthesis was not performed, there are reasons to rule out a causality, as GAD-Ab levels were very low and many met diagnostic criteria of an alternative neurological disease.

When a patient presents with a suggestive neurological disorder and has high serum GAD-Ab titers, but also suffers DM, one could think that the GAD-Abs are only related to DM and do not have a pathophysiological role in neurological syndrome, as is the case in many diabetic patients without neurological symptoms. However, coexistence of DM and neurological syndromes is frequent in GAD-Ab-positive patients. Saiz et al. found type 1 DM in 59% of patients with anti-GAD SPS, with a variable diabetic debut occurring before or even years after (46%) neurological manifestations [4]. In our series, 33.33% of patients with a typical anti-GAD neurological syndrome also have DM.

We also found that suffering an organ-specific autoimmune systemic disease was also predictive for GAD-Ab positivity. Thyroiditis and pernicious anemia were the most frequently associated disorders. In the literature,

other antibodies, such as anti-thyroid, anti-intrinsic-factor, anti-nuclear, anti-RNP, anti-gliadin, anti-NMDA, and anti-acetylcholine-receptor, have been described coexisting with GAD-Abs in the serum of SPS patients. This fact could represent a deregulated immune system targeting different organs [13]. The challenge is to discern which antibody has a pathogenic role in each individual case.

Patients with typical anti-GAD neurological syndromes rarely have cancer [22]. Cancer risk increases with age, male sex, and a classic paraneoplastic clinical presentation, with most frequently diagnosed tumors being lung and thymic neoplasms. In our series, pulmonary neoplasm was found in two (9.09%) GAD-Ab-positive patients, who suffered from epilepsy and ataxia (Hu-Abs +).

GAD-Ab titers in patients with neurological disorders are known to be higher than those found in patients with only DM [20, 27]. In a preliminary study [28], we collected data from 184 patients with serum GAD-Abs detected in our hospital in the last 5 years. A total of 168 (91.3%) patients suffered DM and only 14 (7.6%) had a neurological syndrome. Antibody serum titers in neurological patients were 1225.1 UI/mL in average (SD 955.2), against 626.4 UI/mL (SD 825.31) in diabetic patients without neurological manifestations.

In the present study, we have also found significatively higher serum GAD-Ab titers in patients with typical anti-GAD syndromes compared to patients with atypical anti-GAD syndromes. 11/15 (73.33%) patients with typical anti-GAD syndrome had serum titers > 2000 UI/mL. Even though most authors [29] consider only high serum levels as an indicator of a neurological syndrome associated to GAD-Abs, it has not yet been clarified what quantitative level of GAD-Abs should be considered pathogenic for each individual patient. Threshold may also depend on type of laboratory testing. At our hospital, titers > 2000 UI/mL were considered the highest level. No patient with neurological symptoms in our series had titers between 250 and > 2000 UI/mL. However, we have noticed 6 patients with GAD-Ab titers < 250 UI/mL who suffered a typical anti-GAD neurological syndrome, without any other known cause and without coexisting DM.

Recently, a decrease in GAD-Ab titers after immunotherapy has been seen in patients with high GAD-Ab concentrations (> 10.000 IU/mL) [25]. In our study, only 4 cases showed small variations in GAD-Ab titers over time. Clinical correlation with active or inactive phase or with treatment response was not investigated. However, none of the cases with GAD-Ab titers > 2000 UI/mL showed variations, even after treatment.

Typical anti-GAD neurological disorders are unspecific and can be also due to many other conditions, which should be excluded. Our small sample size did not allow for further characterization of these patients to help improve our clinical suspicion. However, it is important to note that coexistence of ataxia and epilepsy was found in a high proportion of anti-GAD positive patients [30], and focal temporal seizure was the most frequent finding in patients with epilepsy. The limbic region is typically the most affected region in encephalitis, so both entities (epilepsy and encephalitis) could be part of the same spectrum of clinical manifestations of temporal damage due to GAD-Abs. In addition, cognitive decline in epileptic anti-GAD patients has also been seen and may be related to this possible tropism [31, 32].

This study has important limitations as follows: (1) It is a retrospective study reviewing medical records; (2) GAD-Abs were studied in CSF of low number of patients; and (3) a small sample size and a great diversity of symptoms complicate the analysis of variables. Prospective experimental studies would be advisable; however, they would have many design methodological problems, with the necessity of a large sample size and long recruitment time, as anti-GAD neurological syndromes are infrequent, and have an unpredictable time of clinical onset. Moreover, analysis of CSF would be desirable; however, ethical considerations must be overweighed. In the meantime, observational studies such as this one may help to shed light on the changing landscape of GAD-Abs related to neurological syndromes.

From our observational study, we may conclude that serum GAD-Ab detection in atypical anti-GAD neurological manifestations is very infrequent and that low Ab titers can be found in many other diseases and could be predictive of casual association rather than pathogenic implication. In typical anti-GAD syndromes, there is a high comorbidity with DM and with other autoimmune diseases, and high serum GAD-Ab levels are usually, but not always, present. In order to demonstrate the pathogenic link of a neurological manifestation with GAD autoimmunity, it is mandatory to demonstrate intrathecal GAD-Ab production by performing a lumbar puncture and comparing serum/CSF antibodies. Analysis of CSF seems mandatory in patients with a high clinical suspicion of an immunomediated cause for the neurological syndrome but with low titers of GAD-Abs in serum.

Declarations

Informed consents are not required in view of the retrospective nature of the study and all the procedures being performed were part of the routine care, and as long as information is anonymized and the submission does not include images that may identify the person.

Ethical approval Ethical approval was obtained from the Local Ethics Committee of La Paz University Hospital (Date 8/10/2019; N° PI-3818).

Conflict of interest The authors declare no competing interests.

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