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The neurological syndromes associated with glutamic acid decarboxylase antibodies

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ABSTRACT

A number of neurological syndromes have been described in patients with positive serum antibodies (Abs) against the enzyme glutamic acid decarboxylase (GAD), the rate limiting step in the synthesis of GABA (γ-aminobutyric acid). These disorders include: classical stiff-person syndrome and variants, cerebellar ataxia, limbic and extra-limbic encephalitis, nystagmus/oculomotor dysfunction, drug-resistant epilepsy, paraneoplastic stiff-person syndrome and progressive encephalopathy with rigidity and myoclonus (PERM), the latter two are mainly related to amphiphysin and the glycine receptor Abs respectively; but patients may also have positive GAD-Abs. Although observations are consistent with an autoimmune response in these patients and there is evidence of GABAergic dysfunction in some cases; the pathogenic role of GAD-Abs in the nervous system has not been clarified and it is a matter of debate. The diagnosis of these syndromes is based on clinical grounds plus the presence of GAD-Abs in serum and CSF with demonstration of intrathecal secretion. Although some presentations may be negative for GAD-Abs, such as stiff-person syndrome; positive GAD-Abs are required for the diagnosis in patients with cerebellar ataxia, encephalitis, and epilepsy. Immunotherapy is required for most patients. Intravenous immunoglobulins, oral or IV steroids and plasma exchange are considered the first line options, aimed to induce remission, but chronic immunosuppression is usually required. Symptomatic therapy should also be provided, aimed to control muscle spasms, seizures, delirium, etc. Prognosis varies among patients; but it is considered intermediate between that of patients with neurological syndromes associated with neural Abs against membrane antigens and those with onconeural Abs.

1. Introduction

The enzyme glutamic acid decarboxylase (GAD) provides neurons with γ-aminobutyric acid (GABA). This enzyme is the rate limiting step for the synthesis of GABA and is widely distributed within the central nervous system, pancreas and other organs [1]. Diabetes mellitus type 1 (DM1) is frequently associated with antibodies (Abs) directed against GAD. GAD-Abs are found in about 80–90% of patients with DM1; however, in most of these patients the titers are relatively low and the Abs have not shown to have a pathogenic role, representing rather an epiphenomenon [2]. Stiff-man syndrome was first described in 1956 by Moersch and Woltman in 14 patients with progressive but fluctuating rigidity [3]; however, a link with GAD-Abs was not discovered until 1988 by Solimena and colleagues [4]. More recently the name stiff-person syndrome (SPS) has been more frequently used, as the syndrome is more commonly seen in women. Syndromes with the combination of the typical rigidity and muscle spasms are known as SPS-spectrum disorders. Since the association of SPS with GAD-Abs; several other neurological disorders such as cerebellar ataxia, epilepsy, oculomotor dysfunction, limbic and extra-limbic encephalitis have been related with the presence of GAD-Abs (Table 1). These neurological syndromes are characterized by elevated titers of GAD-Abs in the serum and cerebrospinal fluid (CSF). However, there is controversial evidence that GAD-Abs have a direct pathogenic role in any of these disorders. Here, we review the clinical and immunological profile, diagnosis and treatment of these neurological disorders.

2. Clinical syndromes

2.1. Stiff-person syndrome

SPS has an estimated prevalence of 1–2 cases per million, women outnumber men by 2:1 and there is no racial predilection [5]. Most patients present between the third and sixth decades of life; children

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Table 1
Summary of clinical syndromes associated with anti-GAD antibodies.

GAD associated syndromes
Stiff-person syndrome (Classical)
Stiff-limb syndrome (also known as SPS focal or segmental)
Progressive encephalopathy rigidity and myoclonus (PERM)
Cerebellar ataxia (CA)
Brainstem attacks (BA)
Limbic encephalitis (LE)
Extra-limbic encephalitis
Epilepsy (drug-resistant without encephalitis)
Nystagmus and oculomotor dysfunction
Miller-Fisher-like syndrome
Palatal myoclonus
Peripheral neuropathy (?)
Most frequent overlap syndromes
SPS + CA
SPS + oculomotor dysfunction
CA + brainstem attacks
CA + oculomotor dysfunction
CA + epilepsy
LE + epilepsy

represented 5% of cases in a large series [6]. Classical SPS usually starts insidiously with axial muscle stiffness, that progress to involve the proximal and then the distal part of the limbs and even the cranial muscles in some patients; in other cases stiffness may start in the lower limbs and then involve the axial and trunk muscles [7–9]. This eventually leads to slow deliberated movements and abnormal axial postures, such as a thoracic kyphosis or the distinctive lumbar hyperlordosis, and muscle hypertrophy (Fig. 1A) [8,9]. Co-contractions of agonist and antagonist muscle underlie the stiffness which may have diurnal fluctuations. Additionally, patients develop episodic painful muscle spasm superimposed to the underlying rigidity; the spasms are usually precipitated by auditory, tactile or emotional stimuli; these paroxysms can be accompanied by dysautonomic symptoms such as hypertension, tachycardia, diaphoresis, hyperthermia that may lead to sudden death [10]. Disinhibition of exteroceptive and brainstem reflexes (including the startle response) are distinctive features of SPS [11,12]; along with psychiatric manifestations such as anxiety, depression, phobias and alcoholism [13]. Phobias represent realistic fears to fall rather than inherent phobic neurosis [14]. Stiff-limb syndrome, also known as focal or segmental SPS is a variant characterized by stiffness with superimposed muscle spasms restricted to one or two limbs, with preservation of the axial muscles [15–18]; these patients seem to have a lower rate of associated autoimmune disorders, but higher risk of underlying neoplasm compared with patients with classical SPS [19]. Other clinical variants include the jerking-SPS, if associated with prominent spontaneous or stimulus-sensitive myoclonus [20,21]; and paraneoplastic SPS (see below). The diagnosis of SPS is based on clinical demonstration of axial or limb stiffness with superimposed muscles spasms, along with EMG confirmation of continuous motor unit activity of agonists and antagonists muscles, plus the absence of other neurological disorder that can explain the symptoms; these features are considered the major diagnostic criteria [8]; whereas positive GAD-Abs is considered a minor criteria owing to the relative low sensitivity, as not all patients with SPS spectrum disorders have positive GAD-Abs, and they are not obligatory criteria for the diagnosis (Table 2). In a study of 121 patients with SPS-spectrum disorders; individuals with positive GAD-Abs were more likely to develop SPS, be females and had more frequently systemic autoimmune or endocrine disorders [22]. Besides GAD-Abs, other Abs may be positive in patients with SPS-spectrum disorders, such as anti-glycine-α1 receptor (*anti*-GlyR) Abs, which may have a higher potential pathogenic role as they recognize extracellular epitopes (Table 2). Most patients with SPS-spectrum disorders have a progressive course leading to impaired quality of life, severe limitations for walking, performing daily living activities and working [23].

A normal brain and spinal MRI supports the diagnosis of SPS, along with EMG recordings showing low-frequency motor unit firing at rest, despite voluntary relaxation. Pathological studies in patients with classical SPS may show loss of anterior horn cells and spinal interneurons, and vacuolation in the soma of the motor neurons in the caudal spinal cord; but prominent inflammatory infiltrates in the nervous system are not characteristic of this disorder [24,25].

2.2. Progressive encephalomyelitis with rigidity and myoclonus (PERM)

Progressive encephalomyelitis with rigidity and myoclonus (PERM) was described the same year of SPS in 1956 by Campbell and Garland, under the term “subacute myoclonic spinal neuronitis” [26] Later, the term PERM was introduced by Whiteley and colleagues in 1976 [27]. Muscle stiffness, superimposed spasms, myoclonus and brainstem dysfunction such as oculomotor abnormalities, dysphagia and gait ataxia, are cardinal features of PERM [28]. Other prominent manifestations include: seizures, hypersomnia, behavioral changes, dysautonomia, corticospinal signs and somatosensory abnormalities indicating a clinical picture of diffuse encephalomyelitis [29–31]. Nonetheless neuroimaging studies are unremarkable in about two thirds of cases; in the remaining third; there may be diffuse, non-specific hyperintensities in the brain, brainstem and spinal cord, selective cases may have temporal lobe or longitudinally-extensive spinal cord lesions [28]. Although the disorder is named “progressive”, most patients usually have a relapsing-remitting course [30]. PERM presents equally in men and women, contrasting with what it is observed in classical SPS [28]. Although other autoimmune diseases are common in patients with PERM; DM1 is much less frequently observed than in classical SPS (Table 1). PERM is mostly related to *anti*-GlyR Abs, but in about 20% of cases GAD-Abs are detected [28]. On the other hand, about 10–15% of patients with classical SPS without overt PERM features harbor *anti*-GlyR Abs; these patients may have increased levels of emotional excitability and anxiety supporting a role of *anti*-GlyR Abs in some of the manifestations of classical SPS [32–34]. Moreover, SPS patients with *anti*-GlyR Abs seem to have higher rates of response to immunotherapy; but simultaneous test of serum and CSF may be necessary as some patients may have

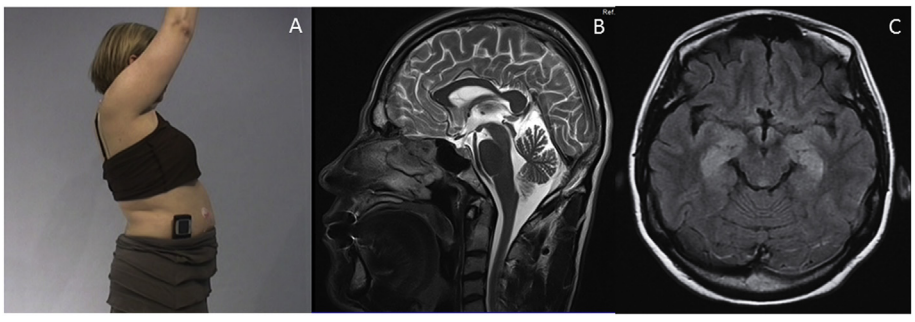

Fig. 1. A) Typical hyper-lordotic posture of classical stiff-person syndrome. B) Sagittal MRI shows mild cerebellar atrophy in a patient with GAD associated gait ataxia; C) Axial MRI shows bilateral hyperintensities restricted to both temporal lobes, consistent with limbic encephalitis [C is reproduced with permission from Oxford University Press].

Table 2
Summary of clinical features associated with anti-GAD related syndromes.

	SPS classical	SPS Focal[a]	PERM	CA	LE	Epilepsy[b]
Typical age at onset (years)	20-50 y	20-60 y	30-60 y	50-60 y	10-60 y	20-50 y
Gender F:M	2–3:1	2:1	1:1	~80% (female)	1:1	1:1
Frequency of serum anti-GAD antibodies	60–90%	~60%	~20%	100%[c]	100%[c]	100%[c]
Frequency of DM1	~30%	~20%	~5%	50–70%	Uncommon[d]	Uncommon[d]
Paraneoplastic disorder	~5%	~10–15%	~20%	~12%	~50%	Uncommon[d]
Other antibodies detected, some with potential pathogenic role	*Anti*-GlyR *Anti*-amphiphysin *Anti*-$GABA_AAPR$ *Anti*-gephyrin	*Anti*-amphiphysin	*Anti*-GlyR *Anti*-DPPX *Anti*-Ri	Anti-gliadin	*Anti*-$GABA_BR$ *Anti*-AMPAR *Anti*-LGI1 *Anti*-Hu Anti-Ma2	*Anti*-GlyR
Minimal elements necessary for diagnosis	Clinical manifestations only	Clinical manifestations + GAD-Abs	Clinical manifestations + GAD-Abs and/or GlyR-Abs	CA + serum and intrathecal GAD-Abs, (rule out other causes of CA)	Clinical manifestations + abnormal MRI + GAD-Abs	Clinical manifestations + GAD-Abs (rule out other causes of epilepsy)

AMPAR: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; GABA: γ-Aminobutyric acid-B; $GABA_AAPR$: $GABA_A$ receptor associated protein; GlyR: Glycine receptor; LGI1: leucine-rich glioma inactivated 1.
[a] Also known as stiff-limp syndrome or segmental stiff-person syndrome; b) Epilepsy without active brain parenchyma inflammation; c) These syndromes are defined by the presence of GAD-Abs therefore frequency is 100%; d) Frequencies are not well defined but probably "uncommon".

positive *anti*-GlyRα1-IgG Abs only in the serum or in the CSF [32].

An underlying tumor is detected in about 20% of patients with PERM; with thymoma and lymphoma being the most common [28]. Inflammatory infiltrates in pathological samples are common [27,35]; a particular involvement of Purkinje cells, hippocampal and pyramidal neurons, with relative preservation of the neocortex has been reported [35]; loss of spinal interneurons and ventral horn cells is another finding [36].

In summary, although part of the SPS-spectrum disorders, the clinical and immunological profile suggests that PERM is a distinct disorder associated with GlyR-Abs autoimmunity.

2.3. Cerebella ataxia

Cerebellar ataxia (CA) is one of the most common reported neurological syndromes associated with GAD-Abs, with prevalence similar to SPS [37–39]. Patients with anti-GAD CA usually present with a subacute or chronic evolution [40]. Gait ataxia is the most common manifestation, followed by limb ataxia, dysarthria, nystagmus and oculomotor dysfunction [41]. In about 25% of cases, the cerebellar syndrome may be preceded by transient brainstem dysfunction called "brainstem attacks" [42,43]. Clinical manifestations consistent with classical or focal/segmental SPS and drug-resistant focal epilepsy may also coexist with anti-GAD CA [39]. Moreover, a transition between SPS and CA has been observed, suggesting that both syndromes may also be part of a continuum. Cognitive impairment is occasionally observed [44]. As patients with SPS, extra-neurological autoimmune manifestations are common, including DM1, polyglandular autoimmune disease and autoimmune thyroiditis [41]. The classical presentation is associated with high serum titers of GAD-Abs and intrathecal production of such Abs; indeed, the detection of such Abs is necessary to define this syndrome. Neuroimaging studies usually show normal or mild to moderate cerebellar atrophy in 57% of cases, with preservation of the medulla oblongata (Fig. 1B) [38,45]. Pathological studies have demonstrated selective loss of Purkinje cells with diffuse proliferation of the Bergmann glia [46,47]. An intriguing relationship exists with patients with gluten sensitivity, characterized by positive anti-gliadin Abs without enteropathy, as a proportion of these patients present with GAD-Abs although with lower titers than in patients with SPS; It is unclear whether GAD-Abs in patients with gluten sensitivity have a pathogenic role or are just an epiphenomenon; however a strict gluten-free diet has been reported to improve ataxia and decrease the titer of GAD-Abs [48].

2.4. Limbic and extralimbic encephalitis

Limbic encephalitis (LE) can present as a pure autoimmune or as a paraneoplastic disorder [49]. LE has a subacute onset with progression in less than 3 months, characterized by impaired working memory, psychiatric symptoms and seizures [50]. Recent revised criteria requires the presence of bilateral T2-W/FLAIR MRI hypeintensities, highly restricted to the temporal lobes for the diagnosis of definitive autoimmune LE (Fig. 1C); if unilateral abnormalities are observed in the MRI, the presence of specific Abs is required [50]. In two large series of adult patients with LE, serum GAD-Abs were detected in between 7 and 17% of patients [51,52]. Most of these patients are women, with a mean age of 23 years [51]. Compared to patients with LE associated with voltage-gated potassium channel (VGKC) complex Abs (currently known to react with LGI-1 and CASPR-2 antigens), those with GAD-Abs were younger, presented seizures more commonly and had oligoclonal bands in the CSF, along with intrathecal secretion of GAD-Abs [51]. Rare cases may present without seizures or with prominent dysautonomic manifestations [53,54]. LE with GAD-Abs associated with underlying neoplasia, presented more frequently as a classic paraneoplastic disorder with rapid disease progression; the risk of cancer is particularly higher in patients older than 50 years of age with

concomitant $GABA_B$ receptor Abs [52,55]. Pathological specimens have shown acute necrosis with neuronal loss in the hippocampus of patients with active disease [56]. These inflammatory changes may evolve into hippocampal atrophy and chronic epilepsy [57].

Extralimbic encephalitis is also observed in patients with GAD-Abs [58]. These patients present with hyperintense cortical/subcortical lesions in T2W/FLAIR MRI sequences, usually without contrast enhancement [59–61]. The clinical manifestations may resemble those of LE, with some patients also developing status epilepticus [59]. PET scans may show hypermetabolism corresponding to the MRI lesions [62]. Histological samples of the lesions have revealed mild gliosis, microglial proliferation and perivascular lymphohistiocytic infiltrates [62,63]. Cases combining limbic and extralimbic encephalitis have also been described [60,61]. The evidence suggests that a cellular rather than a humoral immunological response is responsible for such foci of inflammation in the cerebral cortex, with an unclear role of frequently coexisting Abs (i.e. anti- $GABA_A$ receptor) [64]. GAD-Abs have been reported in few patients with Rasmussen's encephalitis (RE); a rare autoimmune encephalitis of unclear etiology with frequent neocortical focal seizures [65,66]. The role of GAD-Abs in RE should be further clarified.

2.5. Epilepsy

Besides the seizures observed during encephalitis; chronic epilepsy may present in patients with positive GAD-Abs without evidence of active brain inflammation in the MRI. Giometto and colleagues were the first to describe the presence of GAD-Abs in patients with pharmacoresistant temporal lobe epilepsy [67]. These patients usually present with drug-resistant focal epilepsy, frequently involving the temporal lobes (TLE) [68–70]. They may present with epilepsia partialis continua or refractory convulsive and non-convulsive status epilepticus [71–74].

Anti-GAD-Abs were detected in 2.6% of cases in a cohort of 233 patients with all types of epilepsy [75]. However, when considering only patients with localization-related epilepsy, GAD-Abs were present in 8 out of 51 (16%) patients, but in none with generalized epilepsy [76]. This percentage increased to 21.7% in patients with temporal lobe epilepsy of “unknown etiology” [77]. Among 80 children with epilepsy of undetermined etiology, GAD-Abs were the third most commonly observed Abs (8.75%), following antinuclear (18.8%) and *anti*-VGKC (16.25%) Abs [78]. Most studies assessing the frequency of serum GAD-Abs in epilepsy are limited by lack of CSF data. However, in a study of 112 patients, 6 (5.4%) with focal epilepsy had positive serum GAD-Abs, all of them had oligoclonal bands and positive GAD-Abs in the CSF [79]. Compared with patients with TLE without comorbid neural Abs, those with positive serology tend to be older and have a higher frequency of autoimmune comorbidity [69,70]. Moreover, some epileptic semiology such as musicogenic reflex seizures [80] and peri-ictal autonomic features seem to cluster in individuals with GAD-Abs; although the latter presentation may also be observed with other neural Abs [81].

In contrast with patients with acute encephalitis, neuroimaging studies do not show signs of active inflammation, although signs of hippocampal sclerosis are occasionally observed [79]. Pathological studies in these patients have shown the least common form of hippocampal sclerosis (HS) with predominant neuronal cell loss and gliosis in CA4 (International League Against Epilepsy –ILAE- HS type 3) [82,83]. In summary, the pathogenic role of GAD-Abs is unclear in encephalitis and chronic epilepsy; in some cases, these disorders seem to represent a continuum; although in most instances, they represent distinct disorders.

2.6. Oculomotor dysfunction and nystagmus

A wide range of oculomotor abnormalities have been described in single case reports and case series of patients with autoimmunity associated with GAD-Abs. These oculomotor abnormalities may be isolated or may be observed in patients with SPS, PERM, or CA. Ophthalmoparesis, nystagmus, saccadic intrusions/oscillations are among the most common oculomotor disorders. Downbeat nystagmus is perhaps the most frequent eye-movement abnormality in patients with GAD-Abs; it has been reported more frequently in patients with CA or with overlapping syndromes (i.e. SPS + CA) [84–87]. Downbeat nystagmus may result from a functional denervation of vestibular nuclei with increased drive to motor neurons of elevator muscles resulting in an upward slow phase followed by a quick compensatory downward phase [85,88,89]. Other forms of central nystagmus [90], fixed or alternating ocular misalignment can be observed in these patients [91,92]. Supranuclear vertical or horizontal gaze palsy may be a feature of SPS with GAD-Abs or PERM with GlyR-Abs [93,94]. Ophthalmoplegia with areflexia and ataxia resembling the Miller-Fisher syndrome (MFS) has been reported in few patients with GAD-Abs [95,96].

Saccadic intrusions or oscillations are involuntary conjugate saccades that interrupt fixation; they may be sporadic (intrusions) or continuous (oscillations) [97]. Opsoclonus, either isolated or accompanied by ataxia and myoclonus has been reported in patients with GAD-Abs [98,99]. It has been theorized that certain saccadic intrusions such as square wave jerks emerge in a dysfunctional inhibitory system involving the cerebellum, superior colliculi and other structures that are not able to suppress unwanted saccades by reinforcing the inhibitory activity of omnipause neurons located in the medial pons [97]. These omnidirectional pause neurons, control saccadic eye movements by inhibiting the activity of all burst neurons with glycine; however, GlyR-Abs were not identified in patients with ocular flutter and opsoclonus-myoclonus syndrome in one case series, suggesting that other neurotransmitters may be implicated [100].

2.7. Paraneoplastic presentation

Patients with neurological syndromes associated with GAD-Abs, may have diverse types of cancer. This association was observed in 15 individuals among 106 patients with GAD syndromes; eight of these patients fulfilled diagnostic criteria for a definite paraneoplastic neurological syndrome (PNS) [55]. Small-cell lung cancer, followed by thymoma and breast cancer was the most commonly associated neoplasms [55]. Patients with PNS and GAD-Abs were older (60 vs. 48 years) with a much higher proportion of males affected and of coexisting Abs, mostly *anti*-$GABA_B$ receptor Abs than those without cancer [55]. However, the pathogenic role of such coexisting Abs is unclear. Encephalitis (n = 6) and CA (n = 4) were the most common syndromes presenting as PNS, contrasting with previous published reports, indicating that SPS is the most common anti-GAD syndrome associated with cancer [101–103]. In another study, which included 41 patients with anti-GAD CA, diverse types of cancer were identified in 22% of these patients [104]. Patients with anti-GAD CA usually have a slower progression, and better clinical responses to immunotherapy compared to patients with paraneoplastic CA and onconeural Abs [40,104].

A paraneoplastic SPS associated with *anti*-amphiphysin Abs is well recognized and is observed in about 5% of SPS cases [105]; these patients are usually women with breast cancer and may exhibit a different distribution of the stiffness with more prominent upper body involvement [106]. Perivascular and parenchymal infiltrates of cytotoxic $CD8^+$ lymphocytes have been reported in paraneoplastic SPS with *anti*-amphiphysin Abs [107]. Antibodies against gephyrin have been reported in a single patient with SPS and undifferentiated mediastinal tumor, although this observation has not been replicated [108]. Despite this evidence, it is currently not recommended to perform an extensive search for underlying cancer in these patients, unless *anti*-amphiphysin Abs are detected.

2.8. Other neurological manifestations and overlapping syndromes

Palatal myoclonus has been described combined with cerebellar ataxia [62,109], myoclonic tongue and hemifacial contractions [62,110]. Peripheral neuropathy and orthostatic tremor have been observed with or preceding SPS in few patients [19,111], but whether GAD-Abs have a pathogenic role is unclear.

Overlapping presentations among discussed syndromes are not quite uncommon. For example, 10 out of 121 (8.3%) patients with SPS-spectrum disorders were diagnosed with an overlapping syndrome, 6 had coexistent CA, 3 had epilepsy and 1 had LE [22]. In another study, muscle spasms and trunk rigidity were observed in up-to 26% of patients with anti-GAD CA [43]. Either syndrome may antedate the other by months or years [112,113]. Drug-resistant focal epilepsy may coexist in about 10% of patients with SPS and anti-GAD CA [114–116].

3. Pathogenesis

3.1. Characteristics of GAD proteins

The enzyme GAD is the rate limiting step in the decarboxylation of glutamate to γ-aminobutyric acid (GABA) [2]. Two isoforms are contained in neurons, a cytoplasmatic, constitutively active isoform of 67 kDa and a synaptic membrane-associated form of 65 kDa; the latter provides pulses of GABA under circumstances requiring fast post-synaptic inhibition [2,117]. The 65 kDa and 67 kDa isoforms are encoded by two different genes GAD1 and GAD2 located in chromosomes 2q31.1 and 10p12, respectively [118]. The GAD isoforms are divided into three functional domains: a middle segment and C-terminal for which both isoforms share 74% homology, and an N-terminal domain with 25% homology between the 65 and 67 isoforms (Fig. 2) [2]. As both isoforms share high similarity in the amino acid sequence, it was unclear why GAD67 alone is rarely if ever auto-antigenic. However, in 2007 the crystal structures of GAD enzymes were determined yielding important information about the antigenic characteristics of both isoforms [117]. GAD65 is highly charged and has increased flexibility in the C-terminal segment compared with GAD67; the increased mobility of the catalytic loop leads to easy access to the PLP-cofactor, permitting enzymatic activation, and auto-inactivation through loss of the PLP-cofactor and apo-GAD65 formation [119,120]. Distinct flexibility and charged properties of GAD65 have been suggested to explain its propensity for immunogenicity [117].

3.2. Differences in the immunological response between SPS and DM1

Several quantitative and qualitative immunological differences between SPS and DM1 have been observed. Patients with SPS and those with other anti-GAD syndrome usually have titers of serum GAD-Abs several hundred-fold higher than those with DM1: in addition, intrathecal secretion of GAD-Abs has been observed in patients with diverse neurological syndromes. Moreover, GAD-Abs in the CSF recognize different sets of epitopes than in the serum within the same patient [121]. Anti-GAD67-Abs have been mainly identified in patients with SPS [122], but rarely in those with DM1, although cross-reactivity of GAD65-Abs recognizing GAD67 has been reported in patients with DM1 [123].

Patients with SPS and DM1 harbor Abs directed against conformational epitopes in the middle PLP and C-terminal segments of the GAD65 enzyme (Fig. 2) [122,124,125]. However, these Abs seem to recognize a different set of epitopes and have distinct biological effects in patients with SPS and DM1. For example, patients with SPS and CA show a strong recognition of b78 epitopes, whereas those with DM1

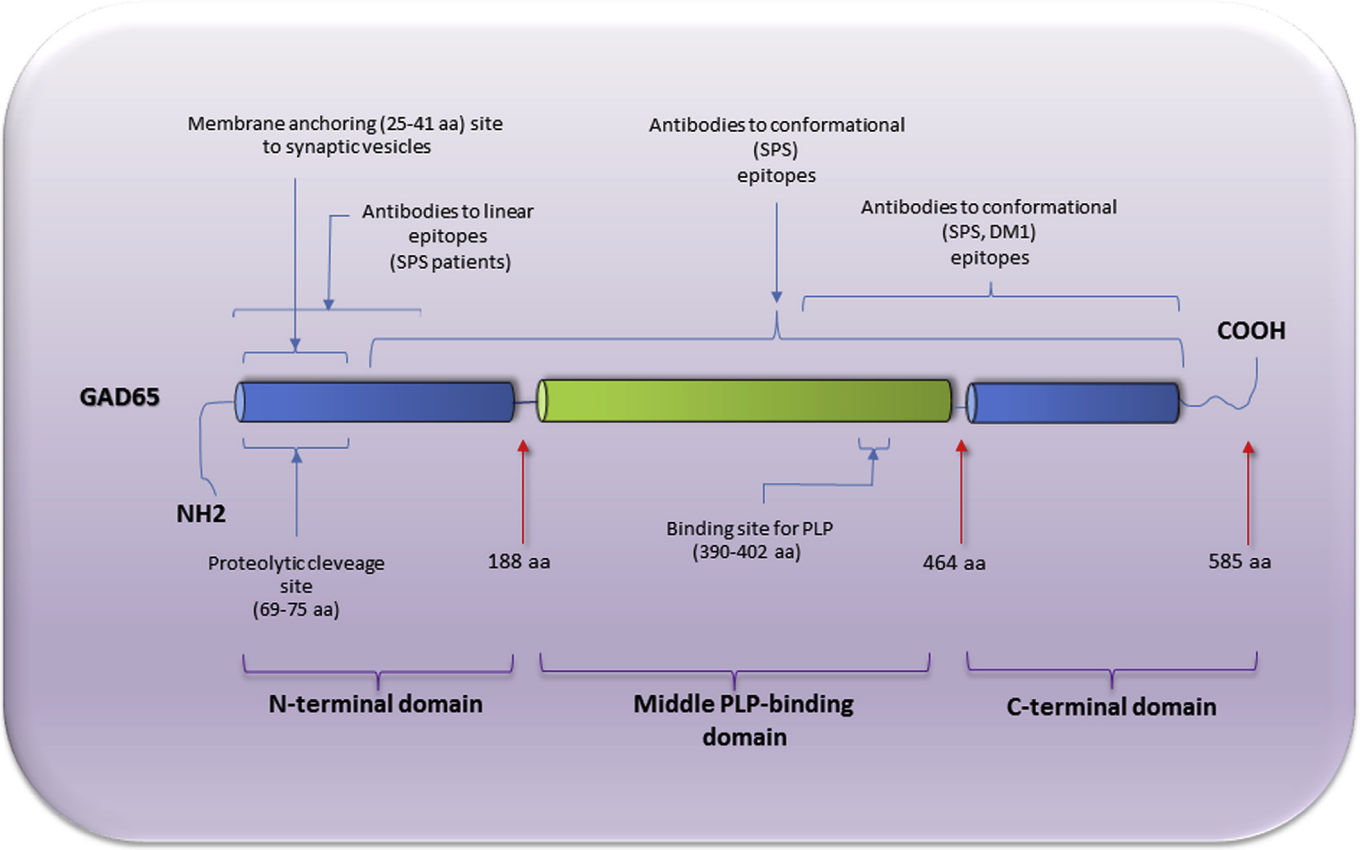

Fig. 2. A) GAD65 isoform form obligated functional dimers, each monomeric unit comprise three domains: N-terminal, PLP-binding, and C-terminal domain. The active site is located in the center of the PLP-binding domain.

recognize more commonly the b96.11 epitopes [121,126–128]. Antibodies against the b78 epitope have demonstrated to disrupt the link between GAD and GABA containing vesicles, inhibit the enzymatic activity of GAD65 and produce a gradual but sustained depression in the inhibitory synapsis in cerebellar rat slices; these effects were not observed with Abs against the b96.11 epitope [129]. Moreover, patients with SPS, but not with DM1, have linear Abs that bind the N-terminal and C-terminal segments of GAD65 [121,130]. More recent evidence shows that the N-terminal truncated GAD65 enzyme is less recognized by the anti-GAD-Abs of patients with SPS compared with those with DM1 [131]; adding evidence to GAD65 epitope specificities between both disorders.

Perhaps more importantly than the aforementioned differences, is that the serum or CSF containing GAD-Abs from patients with SPS inhibit the synthesis of GABA in rat cerebellar extracts, an effect not observed with human monoclonal GAD65-Abs and IgG purified from patients with DM1 or autoimmune polyendocrine syndrome [132]. An increase in the frequency of post-synaptic inhibitory potentials was registered on hippocampal cultured neurons following application of serum from epileptic patients with GAD-Abs but not from negative controls [133]. However, stereotactic injection of GAD-Abs into the hippocampus of rats in vivo did not alter spontaneous and evoked GABAergic synaptic transmission in two studies [134,135]. Despite these observations; there is controversial evidence regarding internalization of GAD-Abs into cultured cells with some experiments showing epitope-dependent pathogenic actions of GAD65-Abs in slice and in vivo preparations following internalization [129,136,137]; whereas another study showed lack of internalization of GAD-Abs into cultured hippocampal rat neurons [116]. If GAD-Abs do not internalize into neurons; it is unclear what would cause the GABAergic dysfunction of SPS. One study showed that GAD-Abs may coexist with Abs binding to cell surface of GABAergic neurons; although the underlying antigen was not identified and the pathogenic mechanisms of such Abs are unclear [137]. In summary, although GABAergic impairment has been demonstrated in experimental animals, the pathogenic role of GAD Abs in vivo is still debatable owing to the intracellular location of the antigen and controversial evidence of Abs internalization into neurons.

Increased genetic susceptibility related to HLA alleles has been observed in patients with SPS. The alleles DRB1*0301 and DQB1*0201 are more frequently found in patients with SPS and seem to increase the susceptibility to suffer other autoimmune disorders, including DM1 [138]. On the other hand the allele DQB1*0602 has been associated with lower risk of DM1 in patients with SPS [9]. Moreover, few familiar cases of patients with SPS or other GAD neurological disorders (CA and LE) sharing the same HLA alleles have been described [139], supporting an increased genetic susceptibility; however, it is unclear why these patients presented with diverse neurological syndromes or SPS phenomenology [140,141].

3.3. Differences in immunological profile between neurological syndromes

If GAD-Abs are pathogenic in patients with neurological syndromes, a key question is what differences in the immunological response would result in diverse neurological syndromes. In one study, which analyzed staining patterns, they were different among patients with SPS, CA and epilepsy related to GAD-Abs, using immunofluorescence on cultured hippocampal neurons, suggesting different epitope recognition [142]. In that study, GAD-Abs from patients with DM1 did not react with brain tissue [142]. In another study, serum GAD-Abs from patients with LE were more likely to react with the N-terminal domain of GAD, compared to patients with SPS, CA or epilepsy: 69% vs. 29% ($P = 0.002$); whereas GAD-Abs from patients with epilepsy showed more reactivity to the C-terminal domain of the enzyme, compared to patients with SPS, CA or LE: 67% vs. 38% ($P = 0.04$); however, no differences in epitope recognition was observed with GAD-Abs from the CSF [116]. A recent study showed different GAD65-Abs pattern recognition in patients with epilepsy, compared with those with SPS and DM1 [143]. Moreover, patients with epilepsy and DM1 may have different set of GAD65-Abs, in some cases with epitope specificity similar to patients with DM1 only and in others with epilepsy only, suggesting that epilepsy is related to an autoimmune process in a subset of these patients [143]. In another study, epitope recognition differed between patients with LE and those with SPS and CA [129]. Despite this evidence, another study of 27 patients with diverse neurological syndromes associated with GAD-Abs did not find differences in epitope specificities, except for 3 patients with epilepsy [144]. Another possibility is whether associated pathogenic Abs may explain the different clinical presentations; other Abs such as *anti*-$GABA_AR$, *anti*-$GABA_{AP}R$, *anti*-gephyrin or *anti*-GlyR did not consistently distributed within a particular presentation [116]. *Anti*-$GABA_{AP}R$-Abs were reported in about 70% of cases in a series of 25 patients with SPS [145]; however, this finding has not been replicated in other studies. Furthermore, low serum levels of $GABA_AR$ and GlyR-Abs have been observed in a similar proportion in healthy controls and patients with SPS-spectrum disorders; therefore, its presence should be interpreted cautiously [22]. In summary, current evidence is insufficient to fully explain the diverse clinical presentations by different epitope binding of GAD-Abs and associated pathogenic Abs such as *anti*-GlyR-Abs are observed in SPS and PERM, but their frequency in other neurological syndromes is unknown.

Quantitative differences in serum GAD-Abs secretion have also been observed in these patients. In a study of 106 patients with neurological syndromes associated with GAD-Abs; higher GAD65-Abs were present in patients in CA and LE compared to patients with SPS in the serum, this difference was even higher in the CSF. Patients with CA showed higher median index of intrathecal anti-GAD65-Abs synthesis compared with SPS patients: 9.7 vs. 5.3 [116]. In summary, although some quantitative and qualitative differences in the humoral profile have been reported among different neurological syndromes; these are not specific enough to fully explain why patients present with isolated or overlapping neurological syndromes.

3.4. Cellular responses and potential triggers of autoimmunity

Peripheral activation of T-cells reacting to GAD epitopes has been observed in patients with SPS; although detection of such lymphocytes in peripheral blood is difficult [146]. Although overlap in epitope recognition by T-cells of peripheral blood exists between patients with SPS and DM1, lymphocytes from the former mostly recognize GAD regions 81–171 and 313–403, whereas those from patients with DM1 mainly recognized GAD regions 161–243 and 473–555 [147]. Moreover, lymphocytes isolated and cloned from the CSF of 3 patients with SPS recognized several GAD65 epitopes unique in each patient, including a critical region for enzymatic function (474–484) [148].

T-cells from patients with SPS produce high levels of Th2 cytokines such as IL-4, IL-5, and IL-13 [149]. It is unclear, however, what activates lymphocytes. A single study showed that GAD65-specific T-cells cross-react with a peptide expressed in the human cytomegalovirus major DNA-binding protein, following processing by dendritic cells [150]; certain infections, including coxsackievirus, cytomegalovirus and West Nile virus have been observed preceding SPS [151]; but whether these infections are the triggers of SPS or other neurological disorders associated with GAD-Abs is unclear.

3.5. Effects of antibodies on experimental animals

A number of experimental studies based on passive transfer of Abs from patients with neurological disorders associated with GAD-Abs into rats or mice have shown diverse findings. Stiffness-like behavior with impaired walking, continuous motor activity with repetitive muscle discharges, and abnormally enhanced exteroceptive reflexes with increased excitability of anterior horn cells have been reported only in few of these studies [152–154]. Other studies have reported a trend

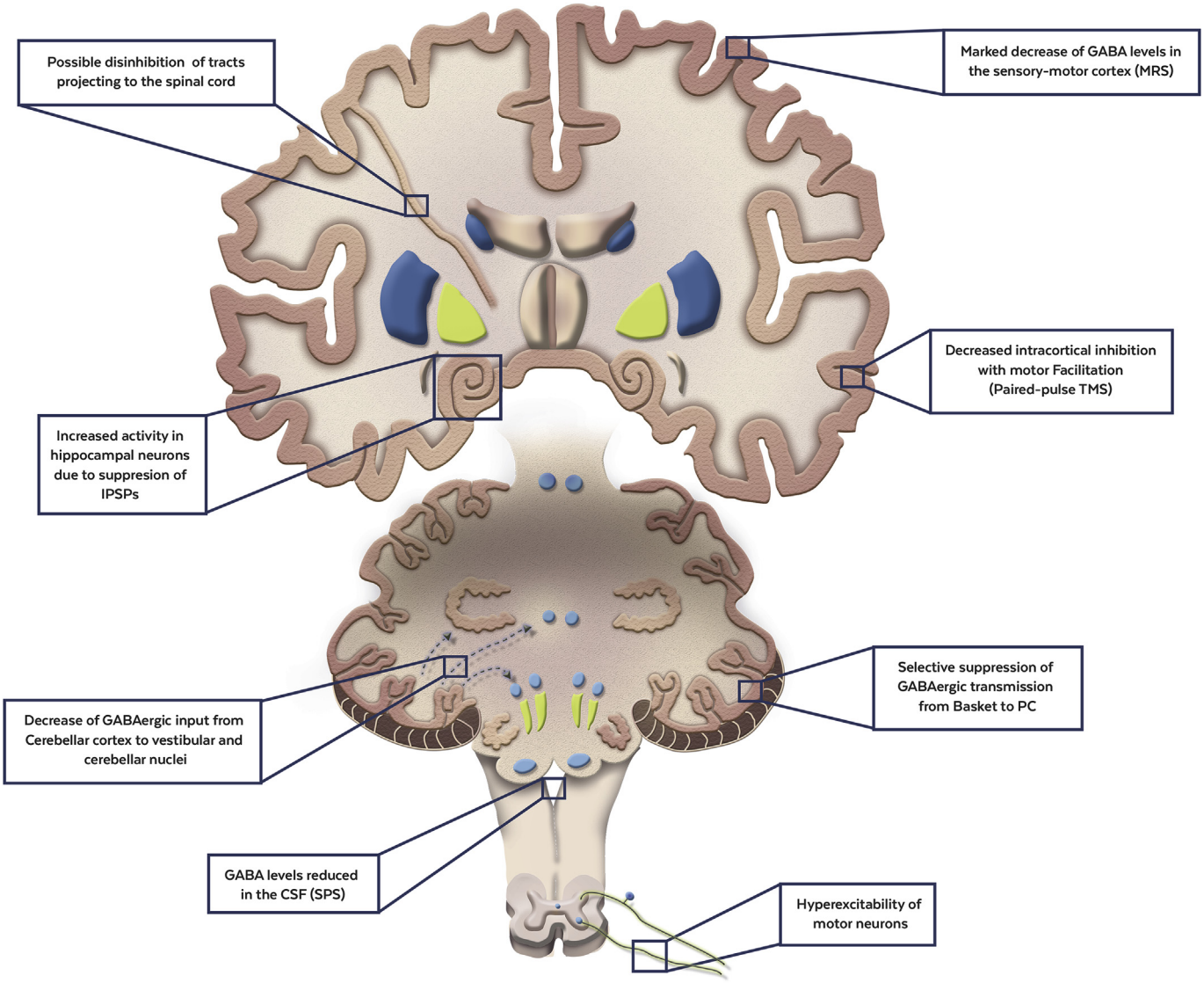

Fig. 3. Imaging summarizing the functional abnormalities leading to disinhibition detected in patients with GAD-Abs associated neurological disorders.

toward reduced activity in mice [155], impaired procedural spatial functions [156] and anxiety behavior [157]; or no distinct effect when mice are exposed or immunized with GAD [137]. However, in pathological studies a trend toward loss of GABAergic neurons in the brainstem has been observed [155]. It remains to see if other neurological syndromes such as myoclonus and ataxia can be transferred by systemic or CNS delivery of GAD-Abs to experimental animals [158]. This inconsistent induction of SPS-like manifestations to mice cast doubts about the pathogenic role of GAD-Abs and contrasts with the more consistent induction of stiffness and muscle spasms when experimental animals are exposed to purified IgG *anti*-amphiphysin Abs either by intraperitoneal [159] or intrathecal injection [160]. Furthermore, IgG *anti*-amphiphysin Abs have been demonstrated to internalize into neurons by an epitope-specific mechanism and disrupt the mechanism involved in neural endocytic pathways [161,162].

In patients with cerebellar ataxia, functional impairment of GABAergic Purkinje cells projecting to deep cerebellar and vestibular nuclei has been proposed to explain oculomotor dysfunction, nystagmus and cerebellar manifestations observed in these patients (Fig. 3) [39]. In this case, rat cerebellar slices exposed to the serum or CSF of patients with SPS or CA produce a gradual but lasting decrease of the inhibitory postsynaptic currents of Purkinje cells contrasting with the lack of effect when using Abs from ataxic patients without GAD-Abs [84,163,164]. The effect of GAD-Abs in the cerebellum may also interfere with motor learning [152,156]; and disrupt *in vitro* association of GAD with GABA [129].

3.6. Possible clinical effects of GAD-Abs and GABAergic deficits in humans

Patients with neurological syndromes associated with GAD-Abs usually have clinical manifestations reflecting widespread disinhibition within the central nervous system (Fig. 3). Patients with SPS have co-contraction of agonist and antagonist muscles, suggesting lack of reciprocal inhibition; along with exaggerated responses to exteroceptive stimuli, particularly somatosensory and acoustic [165,166], the latter feature clearly differentiates SPS from spasticity. Enhanced H-reflex recovery and decreased vibration-induced H-reflex inhibition suggests altered GABAergic inhibition in the spinal cord [11,166]; peripheral nerve stimulation in patients with SPS leads to synchronous spasmodic reflex myoclonus [11]. Hyperexcitability of brainstem reflexes with increased startle responses [167,168] clearly points to a contribution of supraspinal disinhibition. Excessive facilitation of motor evoked potentials and shorter intracortical silence periods assessed by TMS, indicate cortical disinhibition [169,170], which is supported by decreased cortical levels of GABA assessed by high resolution magnetic resonance spectroscopy in patients with SPS and chronic epilepsy with

GAD-Abs [171,172].

4. Diagnosis

Except for SPS (classical and focal/segmental variants) and PERM where the diagnosis does not necessarily require positive GAD-Abs, the other syndromes are defined by their presence (Table 2). GAD-Abs can be measure with radioimmunoassay (RIA) or enzyme-linked immunosorbent assay (ELISA) with titers expressed in IU/ml; these techniques can be useful for patients with neurological disorders and DM1 as they can detect low titers of GAD-Abs. High serum titers of GAD-Abs are usually defined as values ≥ 2000 U/ml by radioimmunoassay (RIA), as levels above this threshold produce the characteristic GAD-Abs pattern by immunohistochemistry [41]; the latter technique can be used for screening in patients with neurological disorders [41,173]. Levels below 2000 U/ml are detected in patients with DM1 but rarely in those with neurological manifestations.

The intrathecal synthesis of GAD-Abs in the CSF support the diagnosis of a neurological disorder associated with GAD, particularly in those cases when a patient has low serum titers of GAD-Abs and associated DM1. On the other hand, rare patients with DM1 or polyendocrine syndrome may also have high serum levels of GAD-Abs [38,41]. In the latter case, measurement of CSF GAD-Abs is also useful in case of comorbid neurological manifestations, as it clarifies the origin of them.

The differential diagnosis of SPS is wide and included disorders with increased muscle activity such as dystonia, spasticity, tetanus, neuromyotonia or disorders with slow movements such as those presenting with parkinsonism; some SPS patients may be misdiagnosed with multiple sclerosis [174]. For the other neurological syndromes a case by case analysis should be done depending on the presentation.

5. Treatment

Treatment should be directed to 3 lines of action: 1) immunotherapy, 2) symptomatic treatment, and 3) detection and treatment of associated autoimmune disorders and/or underlying cancer. There are few randomized trials assessing the effect of diverse drugs in patients with these syndromes, and most of the evidence comes from small case series. In a randomized-crossover trial, IVIg was compared against placebo in 16 patients with SPS [175], a significant decrease in stiffness and heightened-sensitivity scores was observed in patients while they were receiving IVIg, and a substantial proportion had improvement in gait with a decreased number of falls and titer of GAD-Abs [175]. However, not all patients with SPS seem to respond to IVIg; and a partial response is frequently reported in patients with anti-GAD CA [176–178]. A recent trial showed no benefit with the chimeric (mouse-human, IgG1) monoclonal anti-CD20 antibody, rituximab [179]; however, it is unclear why some patients with SPS seem to respond to this drug; even after failure of first line immunotherapy [180–182]. Although the role of B-cell depletion remains controversial in SPS, research using newer therapeutic anti-CD20 and anti-CD19 agents deserves further exploration as partial responses are frequently observed with first line immunotherapies, along with a high rate of side effects; moreover, data regarding treatment of disorders associated with Abs reacting to cell surface antigens (i.e. PERM with *anti*-GlyR Abs) is lacking. Second generation anti-CD20 monoclonal Abs show differences compared with rituximab; for example the humanized ocrelizumab and obinutuzumab have enhanced antibody-dependent cellular cytotoxicity (ADCC) compared with rituximab; whereas veltuzumab and the fully human ofatumumab have greater complement-dependent cytotoxicity than rituximab [183]. Although there are no reports of these Abs in GAD-neurological syndromes, they are potential therapeutic options along with anti-CD19 monoclonal Abs such as inebilizumab; another potential target to reduce the B-cell pool.

Inconsistent benefit with plasma exchanges (PE) is reported in most patients with SPS, CA, LE and refractory epilepsy failing to steroids and IVIg [92,184–186]. There are few reports reporting benefit with steroids in SPS and CA, but these drugs are limited by their side effects, particularly when there is comorbid DM1 [187–190]. Patients with epilepsy associated to GAD-Abs are usually resistant to antiepileptic drugs; and partial responses are observed with steroids, IVIg and plasma exchange [191]; therefore, aggressive, prolonged treatment with rituximab and/or cyclophosphamide has been proposed [74,192]; in these cases, early initiation of immunotherapy (in less than 10 months) seems to improve the prognosis [70]. Outcomes of epilepsy surgery seem to be worse than with other epileptic etiologies [70,193]. Aggressive immunosuppressive therapy is also recommended in patients with encephalitis, combination of steroids and IVIg has been suggested in patients with LE [194]. Rescue therapy with basiliximab, a chimeric monoclonal Abs to CD25 (interleukin-2 receptor) has been used with partial success, highlighting the role of cell-mediated autoimmunity in these patients [195]. More recently, the humanized anti-CD25, daclizumab, has been used with success in other autoimmune disorders [196]. The use of monoclonal Abs directed against interferon (IFN)-gamma has not been tested in patients with SPS, but is a theoretical therapeutic target considering the increment of the Th1-response cytokine in the CSF of patients with SPS [148]. Other experimental therapy such as transplantation of hematopoietic stem cells [197] has been tested with relative success, but it requires confirmation. If GAD-Abs are produced intrathecally; it is unclear why immunotherapies are effective in some patients.

Symptomatic treatment of stiffness, muscle spasms and epilepsy can be tried with medications with GABAergic effect such as benzodiazepines, baclofen, and anticonvulsants (Table 3) [8,114,198]. Patients with SPS usually require progressively higher doses of benzodiazepines; therefore a combination with muscle relaxants is not uncommonly required. In case of comorbid anxiety and depression, tricyclic antidepressants should be avoided as they can potentially exacerbate the motor symptoms of SPS [165]. Patients with chronic epilepsy or LE usually require a combination of various anticonvulsants, although clinical responses are mostly unsatisfactory if immunotherapy is not used [199,200].

6. Conclusions

A number of neurological disorders have been identified in patients with GAD-Abs. These Abs are directed against the rate limiting enzyme for the synthesis of the main inhibitory neurotransmitter: GABA; evidence suggests that GAD-Abs are produced within the CNS, rather than produced in the periphery and crossing the blood brain barrier. Evidence suggesting a pathogenic role of GAD-Abs, include: 1) clinical features of most of these syndromes suggesting a state of decreased inhibition with low levels of GABA in the CNS, 2) inhibition of GABA production in some experimental models using serum from patients with positive GAD-Abs and 3) a clinical response observed to GABAergic drugs; however, other observations argue against a pathogenic role of these Abs such as the intracellular location of GAD enzyme making it inaccessible to Abs, the clinical features of SPS and other neurological disorders have not been reliably transferred to experimental animals and there is a poor correlation between the clinical manifestation, response to immunotherapy and the titers of GAD-Abs; moreover, some patients with SPS are negative for GAD-Abs, suggesting that these Abs are not necessary to cause this phenotype. Although the role of cellular autoimmunity is yet to be defined; at least a partial response is expected in the majority of these patients following immunotherapy, supporting an autoimmune mechanism underlying these syndromes; however, further studies should characterize better the immunological profile in each syndrome in order to provide the best therapy to improve the prognosis.

Table 3
Pharmacological therapies for patients with neurological disorders associated with anti-GAD antibodies.

Immunotherapy (1st line)	Recommended dose	Major or common side effects
IVIg	2 g/kg in 2–5 days	Anaphylactic reactions (IgA-deficient patients) renal failure, thromboembolic events, hemolytic anemia, aseptic meningitis
IV methylprednisolone	1 gr/day for 3–5 days	
Oral steroids (prednisone)	50–60 mg/day	Hyperglycemia, weight gain, hypertension, osteoporosis
Rituximab	375 mg/m^2 weekly	Same as other steroids Allergic infusion reactions, infections, late-onset neutropenia, PML
Immunotherapy (2nd line)		
Azathioprine	1–2.5 mg/kg/day	Nausea, diarrhea, fatigue, lymphopenia, infections, liver toxicity
Mofetil mycophenolate	2000 mg/day	GI, Hypercholesterolemia, liver toxicity, myelotoxicity, PML
Cyclophosphamide	1–5 mg/kg/day	Ovarian failure, neutropenia, infections, hemorrhagic cystitis
Symptomatic therapy for muscle spasms		
Diazepam	5–100 mg/day	Drowsiness, lethargy, fatigue, hypotonia, ataxia, dependence
Clonazepam	2.5–6 mg/day	Same as Diazepam
Baclofen (oral)	10–60 mg/day	Drowsiness, dry mouth, decreased cardiac output, nausea, ataxia.
Baclofen (Intrathecal)	50–150 μg/day	Risk of severe withdrawal with catheter dysfunction
Tizanidine	6–36 mg/day	Dry mouth, sedation, fatigue, dizziness, bradycardia, ataxia
Dantrolene	50 mg, qid	Drowsiness, dizziness, malaise, liver injury
Symptomatic therapy for abnormal ocular movements		
Baclofen (oral)	10–60 mg/day	Drowsiness, dry mouth, decreased cardiac output, nausea, ataxia
3,4-Diaminopiridine	10–20 mg tid	Dizziness, hypoesthesia, paresthesia, hyperhidrosis, cold sweat
Symptomatic therapy for epilepsy and muscle spasms		
Levetiracetam	500–1500 mg bid	Irritability, nervousness, mood swings, headache, ataxia
Gabapentin	300–600 mg tid	Somnolence, dizziness, ataxia, peripheral edema
Pregabaline	75–150 mg bid	Drowsiness, dry mouth, blurred/double vision, weight gain, numbness
Vigabatrine	500–1500 mg bid	Somnolence, incoordination, peripheral edema, visual field changes
Valproate	300–600 mg tid	Drowsiness, weight gain, tremor, teratogenic

IVIg: Intravenous Immunoglobulins; PML: Progressive Multifocal Leukoencephalopathy.

Competing interest related to this project

None.

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Dr. Baizabal-Carvallo gathered the data, conceptualized, drafted and reviewed the manuscript.

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Appendix A. Supplementary data

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