Anti-glutamic acid decarboxylase antibody positive neurological syndromes

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ABSTRACT

A rare kind of antibody, known as anti-glutamic acid decarboxylase (GAD) autoantibody, is found in some patients. The antibody works against the GAD enzyme, which is essential in the formation of gamma aminobutyric acid (GABA), an inhibitory neurotransmitter found in the brain. Patients found with this antibody present with motor and cognitive problems due to low levels or lack of GABA, because in the absence or low levels of GABA patients exhibit motor and cognitive symptoms. The anti-GAD antibody is found in some neurological syndromes, including stiff-person syndrome, paraneoplastic stiff-person syndrome, Miller Fisher syndrome (MFS), limbic encephalopathy, cerebellar ataxia, eye movement disorders, and epilepsy. Previously, excluding MFS, these conditions were called ‘hyperexcitability disorders’. However, collectively, these syndromes should be known as “anti-GAD positive neurological syndromes.” An important limitation of this study is that the literature is lacking on the subject, and why patients with the above mentioned neurological problems present with different symptoms has not been studied in detail. Therefore, it is recommended that more research is conducted on this subject to obtain a better and deeper understanding of these anti-GAD antibody induced neurological syndromes.

GABA is an inhibitory neurotransmitter found in the CNS. It decreases neuronal excitability in the brain and plays an important role in muscle tone regulation. It is produced by cells in the nervous system known as GABAergic neurons that have an inhibitory action at receptors in an adult human or animal. In addition to inhibition, some GABAergic neurons, such as chandelier cells, are also capable of exciting their glutamatergic counterparts. Gamma aminobutyric acid is a known inhibitory neurotransmitter in the mature brain; however, its role changes from excitatory to inhibitory as the brain matures into adulthood.

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With abnormally low GABA, the firing frequency of nerve cells increases and leads to conditions like anxiety and seizure disorders. Various other neurological and cognitive problems are also associated with low levels of GABA including cerebellar ataxia and limbic encephalitis (LE) along with anxiety and epilepsy.\(^7,8\) Gamma aminobutyric acid is formed by the conversion of glutamate to GABA and carbon dioxide. This process is catalyzed by an enzyme called glutamate decarboxylase or glutamic acid decarboxylase (GAD).\(^9\) The GABAergic neurons in pancreatic cells usually expresses the GAD enzyme.\(^10\) Two major types of GAD enzyme exist, GAD65 and GAD67, which catalyze the formation of GABA at different locations in the cell and different time periods of development. The GAD67 enzyme is widely spread across the cell, while GAD65 is confined to nerve terminals. Gamma aminobutyric acid is synthesized by GAD67 for neuronal activity, which is not related to neurotransmission like synaptogenesis and injury protection of nerve cells. On the other hand, GAD65 produces GABA to neuro transmit and is required at synapse.\(^11\)

In some patients, however, a rare type of antibody is found, which is known as the anti-GAD antibody. These anti-GAD antibodies are usually formed against GAD 65.\(^11\) As the name implies, this antibody attacks the GAD65 enzyme, thus blocking the conversion of glutamate to GABA. Hence, the person is deprived of GABA, which leads to motor and cognitive problems associated with low GABA levels.\(^7,8\) Anti-GAD antibodies are produced by B cells, which cross the blood-brain barrier.\(^12-14\) Clonal expansion of B cells, anywhere in the body, along with autoantibodies plays an integral part in the pathology of many neurological disorders. Some of these neurological disorders are linked to GAD antibodies. These neurological diseases include subacute cerebellar ataxia, brainstem encephalitis, drug-refractory temporal epilepsy, and several forms of organ-specific autoimmune diseases.\(^10\) One such disorder is the rare condition known as anti-GAD positive antibody stiff-person syndrome (SPS). The SPS could be associated with the presence of various antibodies. However, this article focuses on all the possible neurological syndromes associated with positive anti-GAD antibodies.

It is known that anti-GAD antibodies lead to anti-GAD syndrome and related disorders. However, it is not completely understood why the presence of one antibody causes variable symptoms, and why different kinds of disorders rather than one particular disorder exist. Future research will uncover this mystery. However, the current review investigates the possible neurological syndromes associated with anti-GAD antibodies, and the mechanisms behind these associations. This review focuses on antibodies against GAD, which cause various neurological syndromes, to obtain a better understanding of these syndromes caused by lack of GAD enzymes.

**Stiff-person syndrome.** Patients with various neurological syndromes and positive anti-GAD antibodies in blood and CSF occasionally present in the neurological setting. One of the most commonly discussed and studied anti-GAD syndrome is SPS. Stiff-person syndrome was first studied by Moersch and Woltman in 1956.\(^15\) It is a rare immunological disorder characterized by progressive rigidity of the truncal muscles, painful spasms, continuous motor activity, and an exquisite sensitivity to external stimuli.\(^16-21\) Barker et al\(^22\) described persistent muscular stiffness due to a continuous co-activation of agonist and antagonist muscles, particularly the “core muscles” such as the paraspinal and abdominal muscles, as the hallmark of SPS. Some other common symptoms found in patients with SPS are rigidity and painful spasms of the lumbar paraspinal, abdominal, and occasionally proximal leg muscles associated with a lumbar hyperlordosis. In some patients, the upper limbs, distal lower limbs, or cranial nerves are not involved. A few patients have additional evidence of autoimmune disease. Continuous motor activity with abnormal exteroceptive reflexes, and normal interference pattern during spasms is observed.\(^22\) Meinck et al\(^23\) found some rare symptoms in some SPS patients: these symptoms consist of (1) an aura-like feeling preceding spontaneous spasmodic attacks; (2) a motor pattern observed during spasmodic jerks, with brief opisthotonos, stiffening of the slightly abducted legs and inversion of the plantar-flexed feet; (3) a paroxysmal fear while crossing a free space unaided, or even thinking about it.\(^23\) Stiff-person syndrome can also be found without anti-GAD antibodies,\(^24\) however, over 60% of SPS patients have these antibodies in the blood and the CSF,\(^25\) while some have other antibodies like anti-amphiphysin, anti-gephyrin, and anti-gamma-aminobutyric acid A receptor-associated protein (GABARAP) antibodies.\(^26\) Blood tests often contain anti-thyroid, anti-nuclear, anti-ribonucleoprotein (RNP), anti-gliadin, and anti-intrinsic factor.\(^27\)

**Subgroups of stiff-person syndrome - stiff-person syndrome-plus, and classic stiff-person syndrome.** Two main subgroups of SPS have been described so far. One is SPS-plus syndrome, which contains the stiff-limb subtype, in which only the lower limbs are affected, and jerking stiff-man syndrome, that contains progressive stiffness and myoclonus, and progressive and acute
onset encephalomyelitis with rigidity and myoclonus. This is also known as progressive encephalomyelopathy with rigidity and myoclonus (PERM). The PERM patients have more severe and progressive symptoms plus more attacks of autonomic dysregulation than SPS patients. The other is classic SPS, in which lumbar, trunk, and proximal limb muscles are affected. The variant of SPS, stiff-limb syndrome (SLS) is a rare focal variant condition in which rigidity and painful spasms of the distal limbs are observed, and abnormal fixed foot or hand postures are also evident. Anti-GAD antibodies are variably found in most clinical cases. Most SLS patients do not have cancer and respond to diazepam, baclofen, and steroids.

**Paraneoplastic SPS.** Paraneoplastic SPS accounts for approximately 59% of all cases of SPS, and is associated with anti-amphiphysin, anti-gephyrin, and anti-Ri antibodies. Patients positive for anti-GAD antibodies are also seen in the neurological setting who subsequently develop cancer. Carcinoma of the breast, small cell lung carcinoma, thymoma, and various other types of cancers like Hodgkin's lymphoma and colon cancer are found to be associated with paraneoplastic SPS. According to Tomioka et al., paraneoplastic SPS patients with breast cancer or small cell lung cancer have anti-amphiphysin antibodies. They also reported one case of mediastinal tumor with anti-gephyrin antibodies. However, the roles of these autoantibodies in the pathophysiology of SPS is still not clearly understood.

**Other conditions with high titers of anti-GAD antibodies.** Antibodies against GAD are associated with various autoimmune and neurological conditions. These conditions with high titers of anti-GAD antibodies include SPS, cerebellar ataxia, LE, or abnormal eye movements, and epilepsy. Anti-GAD antibodies are found in patients with all these conditions, and are considered to be important in diagnosis but does not correlate with disease severity, therapy response, or symptom variation. In in-vitro (enzymatic assays) and in vivo (animal models) systems, the pathophysiology of anti-GAD antibodies has not been proven for any specific condition. Some other antigenic targets have been studied, especially for SPS, in the pre- or postsynaptic neuronal synapses (inhibitory). These anti-GAD and related antibodies collectively form a group of syndromes known as ‘hyperexcitability disorders.’

**Non-paraneoplastic limbic encephalitis and glutamic acid decarboxylase.** Glutamic acid decarboxylase has been identified as a target of humoral autoimmunity in some patients with non-paraneoplastic LE. The condition is commonly referred to as LE. It affects the medial temporal lobe of the brain, occasionally involving hippocampal atrophy as well. Initially, it was believed to be only of paraneoplastic origin; however, later autoimmune (non-paraneoplastic) cases were also reported. Limbic encephalitis has also been associated with non-paraneoplastic antibodies such as voltage gated potassium channel antibodies, N-methyl-D-aspartate receptor receptor antibodies, and anti-GAD antibodies. Because the temporal lobe is involved in LE, temporal lobe epilepsy and psychiatric symptoms are also seen in the patients with LE. Various LE sub forms have also been studied. Volume changes of the amygdala and hippocampus are found on structural MRI findings. The complete pathophysiology of this encephalitis is not yet fully understood. The positron emission tomography scan demonstrates hyper metabolic lesions, while the biopsy shows nonspecific alterations. The treatment could be carried out successfully with immunosuppressant drugs, intravenous immunoglobulin, and plasma exchange. Autoimmune encephalitis can present with treatment-resistant partial seizures, plus other CNS symptoms. The presence of GAD antibodies is occasionally associated with status epilepticus. Cikrikçili et al. reported a 63-year-old woman initially admitted with sleep problems and psychiatric manifestaations. Generalized and rythmical slow spike-wave activity over the posterior regions of both hemispheres was found on EEG, and the patient was diagnosed with non-convulsive status epilepticus. Higher than normal levels of serum GAD antibody was found in the serum sample. The patient's neurological symptoms were resolved after methylprednisolone and intravenous immunoglobulin treatments. The EEG findings resolved, and the GAD antibody levels remarkably reduced. According to Cikrikçili et al., GAD antibodies should be included in the list of antineuronal antibodies associated with non-convulsive status epilepticus. Furthermore, the disappearance of clinical manifestations after immunotherapy indicated that GAD antibodies could be involved in seizure neuro-pathogenesis. Besides LE, epilepsy can be seen in some other anti-GAD positive patients. For example, in some patients of anti-GAD positive cerebellar ataxia, epilepsy and cerebellar ataxia can coexist.

**Dancing eye syndrome.** In addition to paraneoplastic SPS, among paraneoplastic neurologic disorders, opsoclonus-myoclonus syndrome, also known as “dancing eye syndrome,” has been found. It is a rare condition, which includes what is referred to as multifactorial eye movements by previous researchers, this multifactorial ocular movement is found with involuntary multifocal myoclonus, and cerebellar ataxia. It is found that various paraneoplastic antibodies against postsynaptic or cell-
surface antigens are present, however, most patients are serum anti GAD antibody negative. Laroumagne et al reported a 65-year-old patient with opsoclonus-myoclonus syndrome. The patient also had small cell lung carcinoma. Antineuronal antibody screening was conducted, except for anti-GAD antibodies, for which the patient was positive. Treatment was started with anticancer therapy and high dose corticosteroids, yet a severe and progressive encephalopathy developed and the patient died 10 days later. In addition to the non-paraneoplastic LE, paraneoplastic LE cases have also been found. Moreover, as discussed above, paraneoplastic SPS accounts for approximately 5% of all cases of SPS, with many antibodies including anti-GAD autoantibodies.

**Miller Fisher syndrome.** Miller Fisher syndrome (MFS) is a rare variant of Guillain-Barre syndrome (GBS). Approximately 5% of cases of GBS are actually MFS patients. The acute onset of external ophthalmoplegia is a cardinal, and differentiating feature between the 2 conditions. Ataxia is usually out of proportion to the degree of sensory loss. Patients occasionally also complain of ptosis, mild limb weakness, facial palsy, or bulbar palsy. Decreased or absent sensory nerve action potentials and absent tibial H reflex could also be seen in patients. Anti-GQ1b antibodies are prominent in MFS, and have a relatively high specificity and sensitivity for the disease. However, patients with MFS have also been reported to have anti GAD antibody positivity. The eye muscles are affected initially and later ophthalmoplegia, ataxia, and are flexia also develop. The ataxia mostly affects the gait and trunk, sparing the limbs. Anti-GQ1b antibodies are present in 90% of cases, and most of these cases are treated successfully just like GBS, with plasmapheresis.

**Glutamic acid decarboxylase antibodies and diabetes.** The GAD antibodies are present in 15-35% of patients with diagnosed type 2 diabetes mellitus at an age younger than 45 years, and only in 7-9% of older patients in the U.K. Prospective Diabetes Study. Autoantibodies to GAD are detected in around 80% of diabetes mellitus type 1 patients. The GAD antibodies are believed to play a part in the possible relationship between epilepsy and type 1 diabetes mellitus. Epilepsy and type 1 diabetes mellitus can be seen together in one patient, or can be seen separately in anti-GAD antibody positive patients.

**Neuropathophysiology of the neurological disorders associated with anti-GAD antibodies.** To comprehend the pathophysiology of all the possible neurological disorders associated with anti-GAD antibodies, it is imperative to understand the pathophysiology of SPS, because the basics of the pathophysiologic mechanism of all the neurological disorders are similar to SPS. Three forms of SPS are described pathophysiologically; autoimmune, paraneoplastic, and idiopathic SPS. In the autoimmune form of SPS, the antibodies are specific for GAD. The paraneoplastic form has antibodies specific for presynaptic protein amphiphysin, or the postsynaptic protein gephyrin. Two mechanisms have been proposed to explain how anti-GAD and amphiphysin antibodies impair GABAergic neurotransmission. Primarily by the inhibition of GABA synthesis and secondarily by interference with the exocytosis of vesicles containing GABA.

Antibodies against GAD could be used as a diagnostic marker; however, their exact role in the pathophysiology of the disease is not yet clear. The GABARAP present in the postsynaptic regions of GABAergic synapses, are usually targeted. Circulating anti-GABARAP antibodies inhibit GABA (A) receptor expression in around 65% of SPS patients. Autoantibodies to GAD are linked with other antibodies that bind to the GABAergic neurons. The association of SPS with major histocompatibility-II alleles and the response of immunoglobulin point toward its autoimmune nature. The GABAergic pathways impairment and decrease in GABA leads to stiffness, spasms, and phobias. Furthermore, autoantibodies against GAD are seen in 60-80% of patients with SPS. This combined evidence is sufficient to conclude that SPS is immunological in nature.

A possible mechanism explaining how antibodies come to recognize GAD and other intracellular antigens is that some peptide fragments could be expressed temporarily at the cell surface during exocytosis and are presented to T-cell receptors by the antigen-presenting cells. Studies have shown that T-cell mediated processes are observed in insulin-dependent diabetes mellitus patients. In these patients the type 1-Hyper T cells response is observed with upregulation of interleukin-1 and interferon-gamma, and generation of cytotoxic T cells against the enzyme GAD (of the pancreatic beta cells). Whereas in SPS patients, the very high anti-GAD titers are found with a type-2 helper T cells response. This leads to the release of cytokines like interleukin-4 and interleukin-6, hence suppressing a T-cell-mediated cytotoxicity. On the other hand, Burton et al, using a mouse model demonstrated that the monoclonal GAD65-specific CD4(+) T cell population (4B5, PA19.9G11, or PA17.9G7) response caused SPS-like encephalomyelitis by altering the GABAergic neurons' functionality. An active T-cell response plays a key role in driving humoral autoimmune processes, but T-cell infiltration is not commonly observed in the nervous
system of SPS patients.\textsuperscript{76} The observation of SPS patients responding to immunomodulatory therapies further supports the notion of humoral autoimmune involvement.\textsuperscript{70} GAD ANTI BODY \( \rightarrow \) GAD \( \rightarrow \) No GABA \( \rightarrow \) no inhibition \( \rightarrow \) symptoms

In some patients, a rare kind of antibody is found, which is called as anti-GAD antibody, these anti-GAD antibodies are usually formed against GAD 65.\textsuperscript{11} As the name implies, this antibody attacks GAD enzyme (GAD65), thus blocking the conversion of glutamate to GABA. Hence the person is deprived from GABA which leads to motor and cognitive problems associated with low levels.\textsuperscript{7,8}

\textbf{Diagnosis.} To correctly diagnose SPS and anti-GAD syndromes, neurological problems like dystonias, myelopathies, primary lateral sclerosis, spinocerebellar degenerations, neuromyotonia, tetanus, neuroleptic malignant syndrome, malignant hyperpyrexia, chronic spinal interneuronitis, serotonin syndrome, Isaac’s syndrome, multiple sclerosis, Parkinson’s disease, and some psychogenic disorders that behave in a similar fashion as SPS and anti-GAD syndrome\textsuperscript{25,27,77} should be excluded. Stiff-person syndrome is diagnosed by evaluating clinical findings and excluding other conditions.\textsuperscript{27} There is no specific laboratory test that confirms its presence.\textsuperscript{78} Under diagnoses, and misdiagnosis are common.\textsuperscript{25} Therefore, the presence of antibodies against GAD is the best indication of the condition, which can be detected by blood and CSF testing. Anti-GAD65 is found in around 80\% of SPS patients. Anti-thyroid, anti-intrinsic factor, anti-nuclear, anti-RNP, and anti-gliadin are also often present in blood tests. Electromyography (EMG), can also be carried out to differentiate between anti-GAD antibody positive neurological syndromes. The EMG demonstrates involuntary motor unit firing in SPS patients,\textsuperscript{27} and can confirm the diagnosis by noting spasms in distant muscles as a result of subnoxious stimulation of cutaneous or mixed nerves.\textsuperscript{25} Responsiveness to diazepam helps confirm that the patient is suffering from SPS, as this decreases stiffness and motor unit potential firing.\textsuperscript{27}

\textbf{Treatment.} All anti-GAD antibody positive neurological syndromes are treated in a similar fashion. GABAergic drug therapy does not completely eradicate the problem.\textsuperscript{58} Therefore, symptomatic treatment is the best approach to date, and is achieved with high doses of baclofen, diazepam, and immunomodulation by intravenous immunoglobulin and plasmapheresis. Studies also support the use anticonvulsants, and botulinum toxin as a mode of treatment for SPS and related disorders,\textsuperscript{25} whereas refractory cases are suggested to be managed with rituximab.\textsuperscript{37,79-82} Furthermore, cases refractory to baclofen are treated with steroids.\textsuperscript{83} Regarding the use of immunoglobulins, the European Federation of Neurological Sciences recommends that it must only be used when the patients do not respond to diazepam and baclofen.\textsuperscript{78} This review shows that the anti-GAD antibodies are found in SPS, cerebellar ataxia, epilepsy, LE or abnormal eye movements,\textsuperscript{38} and also paraneoplastic syndromes linked with these conditions. Paraneoplastic anti-GAD positive syndromes are also associated with other autoantibodies similar to other

\begin{table}
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\caption{Neurological syndromes with positive anti-glutamic acid decarboxylase antibodies.}
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\textbf{Disorder} & \textbf{Symptom} \\
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Stiff-person syndrome (SPS)\textsuperscript{15-21} & Progressive rigidity of the truncal muscles, painful spasms and continuous motor activity and an exquisite sensitivity to external stimuli

Continuous co-activation of agonist and antagonist muscles, particularly “core muscles” - paraspinal and abdominal muscles

Rigidity and painful spasms of the lumbar paraspinal, abdominal, and occasionally proximal leg muscles associated with a lumbar hyperlordosis

Classic SPS, which affects the lumbar, trunk, and proximal limb muscles

SPS-plus syndrome, which consists of (a) the stiff-limb subtype, in which symptoms are limited to the lower limbs; (b) jerking stiff-man syndrome, characterized by chronically progressive stiffness and myoclonus; and (c) acute onset and progressive encephalomyelitis with rigidity and myoclonus

Cerebellar ataxia\textsuperscript{39} & Lack of voluntary coordination of muscle movements

Epilepsy\textsuperscript{39} & Seizures - violent shaking and loss of alertness

Limbic encephalitis\textsuperscript{41-43,44} & Short-term memory deficits, headache, irritability, sleep disturbance, delusions, hallucinations, agitation, seizures and psychosis

Dancing eye syndrome\textsuperscript{40-45} & Multivectorial eye movements, involuntary multifocal myoclonus, and cerebellar ataxia

Miller Fisher syndrome\textsuperscript{46} & Acute onset of external ophthalmoplegia, ataxia, mild limb weakness, ptosis, facial palsy, or bulbar palsy. Patients have reduced or absent sensory nerve action potentials and absent tibial Hoffmann’s reflex
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neurological conditions. However, the paraneoplastic version is the most dangerous of all types because of its association with different kinds of cancers, which could culminate in death of the patient. Collectively, all these conditions are termed hyperexcitability disorders.\(^9\) However, this comprehensive review has shown that anti-GAD antibodies are also found in a rare variant of GBS, known as MFS, which is comprised of the acute onset of external ophthalmoplegia,\(^{48}\) ataxia, mild limb weakness, ptosis, facial palsy, or bulbar palsy. Patients with MFS have reduced or absent sensory nerve action potentials and absent tibial Hoffmann’s reflex. Anti-GAD antibodies are also found in both type 1 and 2 diabetes; however, diabetes is not primarily a neurological disease. Therefore, the collective term for all these neurological conditions including SPS, cerebellar ataxia, epilepsy, LE or abnormal eye movements, paraneoplastic variants, and MFS, should be “anti-GAD positive neurological syndromes” (Table 1).

In conclusion, in some patients a rare kind of antibody is found, known as the anti-GAD autoantibody; this antibody attacks the GAD enzyme, hence blocking the formation of GABA from glutamate. The patient ultimately develops motor, and cognitive problems due to low levels, or lack of GABA.\(^{7,8}\) The conditions with these motor and cognitive symptoms are, SPS, cerebellar ataxia, epilepsy, LE or abnormal eye movements, and MFS. Previous authors have not considered MFS a part of the hyperexcitability disorders, probably because of the lack of similarity in the symptoms between MFS and other hyperexcitability disorders. However, evidence indicates that anti-GAD antibodies are associated with MFS as well. Therefore, a new collective name for these neurological syndromes including MFS should be considered, such as ‘anti-GAD positive neurological syndrome’. Due to a lack of understanding of the pathophysiological mechanisms, and a lack of awareness of MFS, more research on the subject is recommended to obtain a better and deeper understanding of anti-GAD antibody induced neurological syndromes.

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