Case Report

# A unique combination of autoimmune limbic encephalitis, type 1 diabetes, and Stiff person syndrome associated with GAD-65 antibody

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**Abstract**

Antibodies to GAD-65 have been implicated in the pathogenesis of type 1 diabetes , limbic encephalitis and Stiff person syndrome, however these diseases rarely occur concurrently. We intend to present a rare case of 35 year old female who was recently diagnosed as having type 1 diabetes presented with 1½ month history of recurrent seizures, subacute onset gait ataxia, dysathria, psychiatric disturbance and cognitive decline. No tumor was found on imaging and the classic paraneoplastic panel was negative. Cerebrospinal fluid and blood was positive for GAD-65 antibodies.Patient showed significant improvement with immunomodulatory therapy. Association of GAD-65 antibodies has been found with various disorders including type 1 diabetes, limbic encephalitis, Stiff person syndrome,cerebellar ataxia and palatal myoclonus.This case presents with unique combination of type 1 diabetes, Stiff person syndrome and limbic encephalitis associated with GAD-65 antibodies that is responsive to immunotherapy. It also highlights the emerging concept of autoimmunity in the causation of various disorders and there associations.

**Key Words**

CSF-Cerebrospinal fluid, GAD-Glutamic acid decarboxylase

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*Ann Indian Acad Neurol 2016;19:146-149*

## Introduction

Limbic encephalitis (LE) is a rare disorder affecting limbic system mainly medial temporal lobe. Initially it was considered to be only of paraneoplastic origin, but now autoimmune (nonparaneoplastic) etiology had been identified. Most common autoantibodies associated with LE are voltage-gated potassium channel (VGKC) antibodies, N-methyl-D-aspartate (NMDA) receptor antibodies, and glutamic acid decarboxylase (GAD) antibodies.

LE was first described by Brierley *et al*., in 1960 when they reported three cases of subacute encephalitis involving limbic area.[1] Term "limbic encephalitis" was coined by Corsellis *et al*., in 1968,[2] and he established the relationship between LE and systemic cancer. Clinically, diagnosis of LE poses a challenge because of nonspecificity of signs and symptoms. It can present with seizures, memory problems, and psychiatric disturbance. Such a clinical syndrome can be seen in wide variety of disorders including viral encephalitis, autoimmune disorders as Hashimoto's thyroiditis, Sjogren's syndrome, systemic lupus erythematosis, and central nervous system (CNS) vasculitis. Many neuronal antibodies have been associated with LE. These can be either directed against intracellular antigen, including Hu, CV2/CRMP5, Ma2, and antiamphiphysin that is associated with classic paraneoplastic syndrome which is only partially responsive to immunomodulatory therapy. The other group includes either antibody directed against cell membrane antigen, including VGKC and NMDA receptor or against intracellular enzyme GAD and it shows significant response to immunomodulatory therapy.

Another disease associated with GAD-65 autoantibody is insulin-dependent diabetes mellitus (IDDM). A potential marker for prediabetics is the presence of autoantibodies to a 64,000 Mr protein detected in 70–80% of recent onset IDDM patients,[3] as well as several years before clinical onset of disease. This autoantigen was identified as gamma-aminobutyric acid and synthesizing enzyme GAD by Baekkeskov *et al*.[4] Subsequent cloning and sequencing revealed the existence of two GAD isoforms, GAD-65 and GAD-67. GAD-65 has been found to be target autoantibodies in the sera from recent onset IDDM patient.[4]

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**Website:** www.annalsofian.org

**DOI:** 10.4103/0972-2327.165462

Stiff person syndrome (SPS) is a rare autoimmune neurological disease that is characterized by rigidity, episodic spasm of musculature, and continuous motor activity.[5] It was first described by Moersch and Woltman after a review of 14 patients over 27 years. SPS may be associated with autoimmune diseases such as type 1 diabetes mellitus and pernicious anemia. This disorder is thought to be the result of an immune-mediated deficiency of gamma-aminobutyric acid, a major inhibitory neurotransmitter in the CNS. The majority of patients of SPS have high titers of GAD-65 antibodies.

Here we present a case of a 30-year-old female recently diagnosed diabetic presented with seizures, cognitive decline, psychiatric disturbance, rigidity, and cerebellar dysfunction and positive for GAD-65 antibody. This case shows classic but rare example of combination of autoimmune spectrum (LE, type 1 diabetes, and SPS) of disorders associated with GAD-65 antibodies. In addition to LE, SPS, and IDDM; other disorders described with GAD-65 antibodies are cerebellar ataxia with polyendocrine autoimmunity and epilepsy. Presence of cerebellar dysfunction in our patient points toward common etiology of spectrum of disorders associated with GAD-65 antibody.

## Case Report

A case of 30-year-old, right-handed female who was recently diagnosed diabetic 3 months back presented with 1.5 month history of recurrent episodes of GTCS; cognitive decline in the form of decreased memory; behavioral changes in the form of apathy; and brief episodes of disorientation with ataxia, diplopia, slurring of speech, generalized rigidity, and spasm of limbs. Higher mental functions testing revealed cognitive decline in the form of loss of immediate and recent memory and cerebellar dysarthria. Cranial nerve examination showed slowing of saccades and broken pursuit and rest was normal. Motor system examination revealed generalized rigidity, power was 5/5 in all four limbs, deep tendon reflexes were normal, and plantars were bilaterally flexor. Sensory examination was normal and there were positive cerebellar signs on both sides with ataxic gait.

Fasting, postprandial, and random blood sugar were found to be raised on several occasions. Magnetic resonance imaging (MRI) was suggestive of hyperintensities in bilateral medial temporal lobes [Figure 1] and electroencephalogram (EEG) done was showing slowing of background. Lumber puncture done was suggestive of normal cells, sugar, protein, and polymerase chain reaction (PCR) for herpes simplex virus (HSV) was negative. Contrast computed tomography (CT; thorax + abdomen) and mammography were normal and serological studies for various tumor markers were negative. Evaluation of typical antibodies (Hu, CV2/CRMP-5, Ma2, and antiamphiphysin) present in paraneoplastic panel was also found to be negative. Autoantibody markers in cerebrospinal fluid (CSF) and serum showed presence of GAD-65 antibody, but evaluation of NMDA receptor antibodies and VGKC antibody (CASPR2 and LGI1) was negative. Method used for autoantibody testing was indirect immunofluorescence test. Electromyography showed continuous motor unit activity in agonist and antagonist muscles.

In view of above clinical syndrome and investigational findings, possibility of autoimmune LE with type 1 diabetes and SPS was considered. Patient was managed with intravenous immunoglobulin at total dose of 2 g/kg over 5 days, insulin, baclofen 10 mg, antiepileptics (levitracetam and clobazem), and other supportive medications. Patient was discharged on azathioprine (1.5 mg/kg/day) and rest treatment. At 3-month follow-up, patient showed significant improvement in cognitive status, rigidity, cerebellar signs and symptoms, and also requirement of insulin has been decreased. No fresh episode of seizure occurred during this period.

## Discussion

LE typically presents with amnesia, behavioral disturbance, psychiatric symptoms, seizures, and altered consciousness. Although the etiology was historically considered as paraneoplastic, now it is well-known that it could result from autoimmune processes. Besides there are also case reports pertaining to noninfective, antibody negative LE.[6] Clinical signs and symptoms are nonspecific and they can also be seen in other conditions such as viral infections, inflammatory or autoimmune disorder (lupus, Sjogren's, Hashimoto's encephalopathy, and vasculitis), and toxic and metabolic encephalopathies. This creates a diagnostic challenge to label a patient as LE. So other condition must be ruled out before diagnosing LE.

Two set of criteria are used for diagnosis of paraneoplastic LE. First criterion was proposed by Gultekin *et al*., in 2000 [Table 1], which was revised by Graus and Saiz in 2005 [Table 2].[7,8]

Forty to fifty percent of patient with LE do not have any of the classic paraneoplastic or antineuronal antibody.[9] Therefore, two broad categories of autoimmune LE were formulated:

1. One associated with antibodies to intracellular neuronal antigens including Hu, Ma2, CV2/CRMP5, and amphiphysin (classic paraneoplastic).
2. One associated with either antibodies to cell membrane antigens, including VGKC and NMDA receptor or intracellular enzyme like GAD.

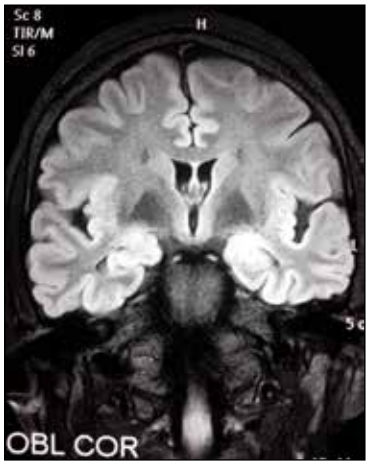


**Figure 1: T2 FLAIR image showing bilateral medial temporal hyperintensity. FLAIR = Fluid-attenuated inversion recovery**

**Table 1: Gultekin diagnostic criteria for limbic encephalitis**

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| Either histopathological evidence of limbic encephalitis or presence of following |
| Psychiatric symptoms, short-term memory loss, or temporal lobe seizures suggestive of limbic system involvement |
| Time period between onset of neurological symptoms and cancer diagnosis <4 years |
| Exclusion of other etiologies causing limbic encephalopathy: Infection, metastases, metabolic causes, stroke, and medication side-effects |
| At least one of |
| Inflammatory findings in cerebrospinal fluid (CSF) |
| Magnetic resonance imaging (MRI) fluid-attenuated inversion recovery (FLAIR) or T2 showing bilateral medial temporal hyperintensity |
| Electroencephalogram (EEG) showing focal temporal lobe changes either epileptic discharges or slowing |

**Table 2: Graus and Saiz diagnostic criteria for limbic encephalitis**

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| Subacute onset (few days to 12 weeks) of short-term memory loss, seizures, confusion, and psychiatric symptoms and |
| Evidence of limbic system involvement (radiologic or neuropathologic) and |
| Time period between onset of neurological symptoms and cancer diagnosis <5 years or development of limbic dysfunctions symptomatology in association with a well-defined paraneoplastic antibody (amphiphysin, CV2, Hu, Ma2, and Ri) and |
| Exclusion of other etiologies explaining above symptoms |

Mata *et al.*,[10] showed association between GAD antibody and nonparaneoplastic LE. In addition to LE it is also described in other conditions such as SPS, cerebellar ataxia, type 1 diabetes mellitus, generalized and focal epilepsy, and palatal myoclonus and pernicious anemia. Corticosteroids, intravenous immunoglobulin, and plasma exchange are most frequently used as therapeutic options. Other immunosuppressive agents like cyclophosphamide and rituximab can also be utilized as a therapeutic option.[9,11] GAD antibody associated LE patients are far more resistant to methylprednisolone treatment compared to VGKC antibody LE patients. But these patients have responded well to intravenous immunoglobulin and plasma exchange.[12] A study conducted by Saidha *et al*., also shows promising results with decrease in seizure frequency and improvement in behavior and memory testing in these patients with use of mycophenolate mofetil.[13]

SPS is a condition characterized by progressive muscle rigidity and stiffness with concurrent painful spasm of axial musculature and continuous motor activity.[5] It affects females more than males and the age of onset is in 3$^{rd}$–6$^{th}$ decade. Gamma-amino butyric acid (GABA) is an inhibitory neurotransmitter in brain and spinal cord. Impairment of GABAergic pathway with deficiency of brain GABA leads to continuous firing of spinal motor neuron, with resultant stiffness and spasms, which are the hallmark of SPS. It has been demonstrated that antibodies to GABA A receptor association protein (GABARAP) play role in SPS pathogenesis. Antibodies to GAD are excellent diagnostic marker in SPS and later linked to its pathogenesis.[14] SPS is associated with autoimmune diseases as type 1 diabetes mellitus (60% of cases), (10) thyroiditis, vitiligo, myasthenia, adrenal insufficiency, and pernicious anemia. For treatment part, benzodiazepines and baclofen are considered as initial therapy for SPS.[2] Corticosteroids, intravenous immunoglobulin are other therapeutic options.

Here we found a case of 30-year-old female with LE in association with type 1 diabetes mellitus and SPS. In our patient, another finding was cerebellar ataxia and this might be another manifestation of GAD spectrum disorder. Treatment with diazepam, baclofen, intravenous immunoglobulin, insulin, and antiepileptic was given. Patient was then continued on azathioprine. At 3 months follow-up, we found significant improvement in cognitive status, decrease in rigidity, and ataxia. No fresh episode of seizure occurred during this period and her blood sugar level showed progressively decreasing requirement of insulin.

## Conclusion

LE is a rare disorder affecting mainly medial temporal lobe. Initially it was considered to be paraneoplastic, but autoimmune (nonparaneoplastic) cases have also been found. Anti-GAD antibodies have been described in many conditions in addition to autoimmune LE. Here we are presenting a case of autoimmune LE in association with type 1 diabetes mellitus and SPS along with cerebellar ataxia. Since it is therapeutically responsive, so timely diagnosing and proper intervention will prevent permanent neurologic damage.

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**How to cite this article:** Sharma CM, Pandey RK, Kumawat BL, Khandelwal D, Gandhi P. A unique combination of autoimmune limbic encephalitis, type 1 diabetes, and Stiff person syndrome associated with GAD-65 antibody. Ann Indian Acad Neurol 2016;19:146-9.

**Received:** 08-02-15, **Revised:** 01-03-15, **Accepted:** 28-04-15

**Source of Support:** Nil, **Conflicts of Interest:** None declared.