Original Article

Neurological Manifestations of Glutamic Acid Decarboxylase Autoimmunity in Indian Patients

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Abstract

Objective: To study the neurological manifestations of glutamic acid decarboxylase (GAD 65) autoimmunity in Indian patients. **Methods:** Retrospective study conducted in a tertiary care referral hospital in South India. Patients who tested positive for GAD 65 antibodies from February 2013 to July 2019 were included. **Results:** We identified 922 patients who underwent GAD 65 testing, of which 81 tested positive (8.78%) [mean age 55.42 years (SD 17.39, range 9–86 years, median age 57 years)]. Males (n = 47) outnumbered the females (n = 34). All the GAD values measured were <5000 IU/ml. There were 34 cases (42%) of atypical parkinsonism (16/34, 47% fulfilled the diagnostic criteria for autoimmune atypical parkinsonism) in our series forming the most common group with GAD 65 positivity, followed by autoimmune encephalitis (8 cases, 9.88%). Men were more affected with atypical parkinsonism (22/34; 64.70%), stiff person syndrome (2/3; 66.66%), and neuropathy (4/7; 57.1%) while women were more with autoimmune encephalitis (6/8; 75%). Eighteen (22.6%) had underlying autoimmunity (three had type 1 diabetes mellitus). Six (7.4%) had underlying neoplasm. Thirty-three out of 43 patients responded to immunotherapy (76.74%). Five had spontaneous improvement. **Conclusion:** Glutamic acid decarboxylase65 antibody values were much lower in our study population. Male-dominant autoimmunity was seen unlike that in Western literature. The most striking was the high preponderance of atypical parkinsonism in GAD 65-positive patients. We also found that GAD 65 positivity is a useful marker for a positive response to immunotherapy in suspected autoimmune neurological syndromes irrespective of their titers.

Keywords: Atypical parkinsonism, autoimmune atypical parkinsonism, autoimmune encephalitis, glutamic acid decarboxylase65 antibody

Introduction

Glutamic acid decarboxylase (GAD) is the rate-limiting enzyme to produce gamma-aminobutyric acid, which is the main inhibitory neurotransmitter in the central nervous system. It has 2 isoforms GAD 65 and GAD67, of which GAD 65 is used more extensively as a clinical biomarker due to its greater autoantigenicity.[1] It is widely used as a biomarker for type 1 diabetes mellitus, but relatively lately, it is also being used as a marker of neurological autoimmunity.[2] Stiff-person syndrome, limbic encephalitis, epilepsy, cerebellar ataxia, isolated cases of palatal tremor, and paraneoplastic neurological syndromes are some of the neurological diseases in which GAD 65 positivity is described.[3-6] GAD 65 positivity has also been described in multiple system atrophy and some patients with cognitive decline.[7,8] Most of the literature on GAD 65 neurological autoimmunity is from the West. There are only a few studies from Asia on the neurological manifestation of the GAD 65 antibody.[7–11] Sparse data is available on neurological manifestations of GAD 65 autoimmunity in Asians and no data on Indian patients. We present a retrospective case series of GAD 65-positive patients with an intent of identifying the neurological phenotypes in the Indian population. The previous studies in the Western population show that very high values of GAD 65 were seen in neurological autoimmunity compared to endocrine autoimmunity and low values were seen in the normal population as well.[2,3,12–14]

Methods

The study was conducted in the department of neurology and biochemistry in Amrita Institute of Medical Sciences, Kochi, Kerala, which is the tertiary care post-graduate teaching hospital in South India. Inclusion criteria–Those patients who were tested positive for GAD 65 antibody were included in the study if the request was made for diagnosis of neurological disease from February 2013 to July 2019. Exclusion criteria—Patients referred from other countries were excluded. We retrospectively identified patients, who were tested for GAD 65 antibody as per the request of neurologists from February 2013 to July 2019 by reviewing electronic medical records (EMR). Clinical and treatment details of positive patients were extracted from EMR.

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Levels of GAD 65 antibody were detected using enzyme-linked immunosorbent assay (ELISA) using commercial kits and following manufacturer's instructions. Two ELISA diagnostics kits were used to detect levels of GAD 65 antibody during the period between February 2013 to July 2019. Medizym anti-GAD ELISA, (MEDIPAN GMBH, Berlin, Germany) was used from 2013 February to 2016 June; Anti-GAD ELISA (EUROIMMUN AG, Luebeck, Germany) was used from 2016 June to 2019 July. For the first ELISA kit >5.0 IU/ml was considered as positive and for the second ELISA kit >10 IU/ml was considered as positive. Clinical outcomes were measured with 9-question modified Rankin Scale (mRS-9Q) (reduction in score by a score of one is considered as improvement), Unified Parkinson Disease Rating Scale (UPDRS) and Glasgow Coma Scale (GCS). All consecutive GAD 65 patients were included in the study. cerebrospinal fluid (CSF) GAD 65 assay was not performed. Tissue-based assay was performed in all patients to detect neuronal antibodies.

Statistical analysis was performed using IBM SPSS version 20.0 software. Categorical variables were expressed using frequency and percentage. Numerical variables were presented using mean and standard deviation (SD). To test the statistical significance of the association of two categorical variables, Chi-square test was used. A *P*-value of <0.05 was considered statistically significant.

Standard protocol approvals, registrations, and patient consents

This retrospective study was approved by the Institute ethics committee. Ethics committee determined that participant consent was not required.

Data availability - The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary material.

Results

We identified 922 patients who had undergone GAD 65 testing, out of which 81 tested positive (8.78%). The mean age was 55.42 years (SD 17.39, range 9–86 years, median age 57 years). Males ($n=47$) outnumbered the females ($n=34$) [Refer Table 1]. All the GAD values measured were below 5000 IU/ml. Thirty-four patients had a clinical diagnosis of atypical parkinsonism (two with coexisting autoimmune encephalitis, one with coexisting myasthenia), eight had autoimmune encephalitis, three had the stiff-person syndrome, seven had neuropathy (including two with atypical GBS and one with CIDP), two had Creutzfeldt Jakob disease, two had cervical demyelinating myelopathy, two had motor neuron diseases, two had epilepsy one had aquaporin 4 IgG-positive neuromyelitis optica syndrome, one had myasthenia gravis, one lambert eaton myasthenic syndrome (LEMS), one had vasculitis affecting CNS and peripheral nervous system, one myoneuropathy, one myeloneuropathy, one cerebellar ataxia, one post-infectious extrapyramidal syndrome, one had a single episode of seizure and one frontotemporal dementia. Of the 81 cases, there were alternate diagnoses in 12 cases, which were unrelated to GAD 65 autoimmunity (Creutzfeldt-Jakob disease-2, motor neuron disease-2, vascular parkinsonism-1, tuberculous meningitis-1, metabolic encephalopathy-1, macular degeneration-1, viral encephalitis-1, suspected transient ischemic attack-1, severe anxiety with depression-1, partially treated meningitis-1). Please refer to the supplementary data for full clinical details. Follow-up period ranges from 1 month to 6 years.

Mean GAD value was 206.31 IU/ml (SD 685.45), median value 6.83 IU/ml. Most patients had low values of GAD titer. Only two had a value above 2000 IU/ml. Mean GAD 65 values in the atypical parkinsonism group was 183.73 IU/ml (SD 757.77, median value 6.07 IU/ml), autoimmune encephalitis group was 42.75 IU/ml (SD 53.66, median 17.14), and stiff person group was 1240.85 IU/ml (SD 1524.24, median 328 IU/ml) [Refer Table 2]. Eighteen (22.2%) had underlying autoimmunity. Three patients had type 1 diabetes mellitus. Six (7.4%) had underlying neoplasm: carcinoma breast and carcinoma ovary (1), diffuse large B cell lymphoma (1), endometrial hyperplasia with atypia (1), carcinoma ovary (1), adrenal adenoma (1), thymoma (1). Thirty-three out of 43 patients with treatment details responded to immunotherapy (76.74%). Five patients had spontaneous improvement (Suspected myelopathy-1, atypical parkinsonism-1, autoimmune encephalitis-2, GBS-1). One stiff person syndrome with a high value (3388.43 IU/ml) showed a poor response to immunotherapy. Four patients died of infection. Four patients discontinued immunosuppression due to infection and four lost follow up [Refer Table 3].

There were 34 cases (42%) of atypical parkinsonism in our series forming the most common significant diagnostic entity with GAD 65 positivity, followed by autoimmune encephalitis (8 cases, 9.88%). Fourteen of the atypical parkinsonism (14/34, 41.2%) fulfilled the criteria for autoimmune atypical parkinsonism (AAP) proposed by Kannoth *et al*.[15] Regarding the sex distribution, men were more affected with

Table 1: Demographic data

Characteristic	Number ($n=81$)
Age (mean±SD, range)	55.42±17.39 (9–86 years)
Gender	Male-47, female-34
Underlying autoimmunity	18 (22.22%)
Atypical parkinsonism	34 (2 had additional autoimmune encephalitis)
Autoimmune encephalitis (AE)	8
Stiff-person syndrome	3
Neuropathy	7 (including 2 atypical Guillain barre syndrome, 1 CIDP)
Myelopathy	2
Cerebellar ataxia	1
Epilepsy	1
Lambert Eaton syndrome	1
Myasthenia	1
Myasthenia with parkinsonism	1
Neuromyelitis optica	1
Others	21
Immunotherapy attempted	43 cases
Improvement with immunotherapy	33 cases (76.74%)

atypical parkinsonism (22/34; 64.70%), stiff-person syndrome (2/3;66.66%), and neuropathy (4/7;57.1%) while the neurological phenotype of women was more consistent with autoimmune encephalitis (6/8;75%).

The levels of antibodies did not cross 10000 IU/ml to qualify it as high as per the literature in our study population.[13] To determine any possible correlation of GAD 65 levels with diagnosis and treatment response, we arbitrarily classified GAD levels up to 5 times the upper limit of normal as low and those above 5 times as high. As per this classification, 68 patients (86%) had low GAD levels and 13 had high GAD levels. Low GAD 65 levels were more frequent in atypical parkinsonism (31/33; 91.2%), autoimmune encephalitis (7/9; 77.8%), and neuropathy (5/7;71.4%), while high GAD level (i.e., >5 times the upper limit of normal) was seen in stiff-person syndrome (2/3;66.7%) and myelopathy (2/3;66.66%). In the low GAD group, 11/68 (16.17%) had associated autoimmune disorders while in the high GAD group, 7/13 (53.84%) had associated autoimmune disorders (P = 0.003). As regards response to immunotherapy, 28/35 (80%) in the low GAD group improved with immunotherapy while in the high group, 5/8 (62.50%) improved with immunotherapy (P = 0.38). In the low GAD group, 62/68 (91.17%) had other antibodies detected in abnormal levels, while in the high GAD group, all 13 (100%) had other antibodies detectable in abnormal levels (P = 0.59). This included neuromyelitis optica IgG, contactin-associated protein-like 2 (CASPR2) antibodies, voltage-gated calcium channel antibody, anti-Factor XIII antibody, antinuclear antibody, anti-double stranded DNA, antiphospholipid antibodies, anticardiolipin antibodies, acetylcholine receptor antibody, anti-thyroid peroxidase antibody, anti-thyroglobulin antibody, and multiple neuronal antibodies, which are yet to be characterized, termed as unclassified neuronal antibodies.[15–17] Low complement levels were detected in 8/25 (32%) in the low GAD group, while in the high GAD group, it was 2/3 (66.66%) (P = 0.28).

Discussion

This case series highlights the diverse spectrum of neurological diseases associated with GAD 65 autoimmunity. In most of the previously published series, women were more affected.[2,7,8,10–14,18-21] Male preponderance was reported in the paraneoplastic subgroup, low concentration subgroup, and pediatric limbic encephalitis subgroup.[6,13,22] Unlike the other series, men dominated in our series. The male preponderance in our series can be explained by the predominance of atypical parkinsonism. Autoimmune atypical parkinsonism is a male-dominant disease.[15] The other male-predominant autoimmune diseases include myasthenia in the elderly, CASPR2, and Leucine-rich glioma-inactivated 1 (LGI 1) antibody-mediated autoimmune encephalitis. Apart from this, most of the patients in our series had low GAD 65 values. In a study by Muñoz-Lopetegi *et al*.,[13] in the low GAD 65 antibody group, males were more commonly affected.

Atypical parkinsonism was the most common single disease entity in our series. GAD 65 autoimmunity in association with extra pyramidal manifestation was reported by Pittock *et al*.[2] in 16% cases of which, 4 were atypical parkinsonism. Eight cases of atypical parkinsonism fulfilling the diagnosis criteria of multiple system atrophy (MSA) were found to have low GAD 65 values in the study by Kuo *et al*.,[8] which amounted to 29.6% of cases with neurological symptoms in their series. One of the patients with MSA phenotype in this series improved with immunotherapy. A case of low positive CSF GAD 65 was reported with atypical parkinsonism from Italy without serum positivity.[23] Glutamic acid decarboxylase 65 autoimmunity presenting as hemiparkinsonism has also been reported.[24] In our series, 14 out of the 34 atypical parkinsonism (41.17%) fulfilled the diagnostic criteria for AAP- i.e., had the presence of neuronal antibodies and responded to immunotherapy. In the rest of the cases, either immunotherapy was not attempted due to various reasons or did not respond to first-line immunotherapy making it difficult to ascertain whether they are all AAP. The high prevalence of atypical parkinsonism is attributed to the fact that our group has described the syndrome of autoimmune atypical parkinsonism. This led to careful evaluation and investigation of cases of atypical parkinsonism for autoimmune etiology.

In our series, only 17.3% (14/81) presented with the core manifestations of the GAD 65 syndrome—stiff-person spectrum, limbic encephalitis, ataxia, and epilepsy. It is interesting to note that even patients with the classical syndrome had low GAD 65 values compared to the literature, i.e., <10,000 IU/ml.[17,18] Only five cases had multifocal manifestations/overlap syndrome. Isolated peripheral

Table 2: GAD 65 subgroups

Subgroup	No. of cases	Mean age±SD (years)	Sex ratio (Male: Female)	Mean±SD GAD value (IU/ml)	Median GAD value[IU/ml]	Improvement with immunotherapy
Atypical parkinsonism	34	65.71±10.97	22:12	183.73±757.77	6.07 IU/ml	14/18 (77.77%)
Autoimmune encephalitis	8	42.65±20.48	2:6	42.75±53.66	17.14 IU/ml	5/6 (83.33%)
Stiff person syndrome	3	57±3.74	2:1	1240.85±1524.24	328 IU/ml	0/2 (0%)
Demyelinating myelopathy	2	44.5±20.5	1:1	219.52±52.82	219.52 IU/ml	2/2 (100%)
Cerebellar ataxia	1	20	1:0	6.07		1/1 (100%)
Epilepsy	2	24±12	1:1	6.81±1.24	6.81 IU/ml	Not attempted
Neuropathy	7	42±8.38	4:3	121.70±240.99		3/3 (100%)

Table 3: GAD 65 immunotherapy response

Age/Sex	GAD value (IU/ml)	Diagnosis	Associated diseases	Immunotherapy responses
49/M	15	Atypical parkinsonism	Rheumatoid arthritis, psychosis	Improved with immunotherapy. Treated with intravenous methylprednisolone 1 gm x 5 days, azathioprine 50 mg 1-0-1×5 months. Symptom onset was 7 years ago –parkinsonim followed by psychosis. Not fulfulling the criteria for PSP, MSA, CBS. Patient was on levo dopa 1100 mg/day with mild improvement in symptoms. After starting immunotherapy levodopa was stopped. CSF showed no cell, protein 43.5 mg/dl, glucose 65.8 mg/dl. MRI brain was normal. Followed up for six years.
50/M	30.62	Chronic inflammatory demyelinating polyradiculoneuropathy	Type 2 Diabetes mellitus	Improved with immunotherapy. Treated with intravenous methylprednisolone and mycophenolate mofetil 500 mg 1-0-1 for one year
52/F	17.09	Atypical parkinsonism	Systemic hypertension	Onset with slowness and imbalance three years. No response to syndopa. Not fulfilling the diagnostic criteria of PSP, MSA, CBS. MRI brain no significant abnormality. CSF cell count 5/cmm, protein 38.8 mg/dl, glucose 91.5 mg/dl No improvement with immunotherapy with intravenous methylprednisolone and mycophenolate mofetil 500 mg 1-0-1×2 weeks. Therapy stopped after 2 weeks as patient did not report any benefit. Patient developed brain abscess with listeria monocytogens. Improved with antibiotics. Followed up for six more years
65/F	166.7	Chronic Demyelinating myelopathy	Type 2 Diabetes mellitus, systemic hypertension subclinical hypothyroidism	Improved with immunotherapy- intravenous methylprednisolone 1 gm daily infusion for 5 days followed oral prednisolone 1 mg/kg/day tapered after 4 months and azathioprine 1-0-1×4 years. 9 qmRS improved from 5 to 3.
43/M	10.68	Atypical parkinsonism	Nil	Tremor, slowness nad imbalance of 3 year duration. No response to levo dopa. MRI brain normal. CSF No cells, protein 38.5 mg/dl, glucose 65.2 mg/dl No improvement with immunotherapy with intravenous Methylprednisolone 1 gm daily for 5 days and oral prednisolone 1 mg/kg/day for 3 months and mycophenolate mofetil 1 gm twice daily for 3 months
15/F	19.7	Autoimmune encephalitis	Nil	Improved with intravenous methylprednisolone 1 gm daily for 5 days followed by oral prednisolone 1 mg/kg for 1 month. GCS improved from 9 to 15.
86/M	40.5	Atypical parkinsonism	Acid peptic disease	PSP phenotype x 6 months MRI brain age-related atrophy CSF protein 57.2 mg/dl glucose 68.2 mg/dl improved with intravenous methylprednisolone 1 gm for 5 days. 9 qmRS improved from 3 to 2, UPDRS motor score improved from 26 to13. Follow-up 1 month. Discontinued immunotherapy due to family issues.
37/M	89.09	Guillain Barre Syndrome	Type 2 Diabetes mellitus	Improved with immunotherapy-Intravenous Immunoglobulin 2 gm/kg over 5 days. 9 qmRS improved from 5 to 2 at discharge and 1 month later to 0.
45/F	135.2	Autoimmune encephalitis	Non- Hodgkin's lymphoma	No improvement with immunotherapy-intravenous methylprednisolone 1 gm/day for 5 days, intravenous Immunoglobulin 2 gm/kg over 5 days. Died of infection- 9 qmRS worsened from 5 to 6.
39/F	5.85	Neuromyelitis optica (NMO) spectrum disorder- brainstem presentation	Nil	Improved with immunotherapy-intravenous methylprednisolone 1 gm/day for 5 days followed by azathioprine 50 mg 1-0-1 being continued-Improvement measured as complete resolution of ophthalmoplegia and gait ataxia.
42/F	24.02	Lambert Eaton Myasthenic syndrome	Nil	Improved with intravenous immune globulin 2 gm/kg over 5 days and azathioprine 50 mg 1-0-1 on last follow-up at 6 months. Improvement is measured as need for less help in getting up form chair.
56/M	328	Stiff person syndrome	Autoimmune diabetes mellitus	No response to immunotherapy-Intravenous immune globulin 2 gm/kg over 5 days, mycophenolate mofetil 1 gm twice daily for 3 months. Lost follow-up.

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Table 3: Contd...

Age/Sex	GAD value (IU/ml)	Diagnosis	Associated diseases	Immunotherapy responses
24/M	272.34	Demyelinating myelopathy	Autoimmune diabetes mellitus	Improved with intravenous Immune globulin 2 gm/kg over 5 days. 9 qmrs improved from 4 to 2 at discharge and 1 at one month after discharge.
71/F	5.4	Atypical parkinsonism	Systemic hypertension, dyslipidemia	Slowness, imbalance, and tremoer of one-year duration, Not responding to levo dopa.o/e vertical gaze restricted with mild symmetric parkinsonism, axial rigidity more than appendicular rigidity. Improved with immunotherapy-intravenous methylprednisolone 1 gm per day for 5 days and mycophenolate mofetil 1 gm twice daily, but died of infection after 4 months. 9 qmRS improved from 3 to 2, UPDRS motor improved from 26 to 20
68/M	5.3	Atypical parkinsonism with autoimmune encephalitis	Autoimmune thyroiditis	Improved with immunotherapy-intravenous methylprednisolone 1 gm per day for 5 days followed by myophenolate mofetil 1 gm twice daily for 6 months. Improvement was noted as fluctuations in sensorium disappeared and independent in activities of daily living. 9 qmRS improved from 2 to 1.
20/M	6.07	Autoimmune cerebellar ataxia	Nephrotic syndrome	Ataxia 2 weeks O/e Pan cerebellar signs MRI brain normal. CSF TC 35 cells/cmm, protein 235 mg/dl gluoce 68 mg/dlImproved with intravenous methylprednisolone 1 gm daily for 5 days, followed by injection cyclophosphamide 750 mg/m2/month for 9 doses followed by oral methotrexate 20 mg/week for 2 years. 9 qmRS improved from 3 to 1 to 2 with steroid and 0 at the end of 6 months
9/M	19	Autoimmune encephalitis	Nil	Improved with immunotherapy-intravenous methylprednisolone 1 gm per day for 5 days and intravenous immune globulin 2 gm/kg over 5 days. GCS improved from 7 to 15.
32/F	6.84	Post-infectious extrapyramidal syndrome	Nil	Improved with immunotherapy-intravenous methylprednisolone 1 gm per day for 5 days followed by oral steroids 1 mg/kg for 2 weeks and then tapered over 1 month. 9 qmRS improved from 4 to 1 at discharge and 0 at 1 month.
32/M	5.87	Autoimmune encephalitis	Nil	Improved with immunotherapy- intravenous methylprednisolone 1 gm/per day for 5 days followed by oral prednisolone 1 mg/kg for 2 weeks and then tapered over 1 month. Improvemenmt is measured as normalization of orientation and memory at the end of the treatment.
56/M	5.61	Atypical parkinsonism	Systemic hypertension, coronary artery disease. Ischemic stroke	Improved with immunotherapy-intravenous methylprednisolone 1 gm per day for 5 days followed oral prednisolone 1 gm/kg followed by oral prednisolone 1 mg/kg and injection cyclophosphamide 750 mg/meter square for 1 dose. Treatment discontinued after 3 months due to infection. 9 qmRS improved from 5 to 4 to 4 after steroid therapy
63/F	6.13	Possible Amyotrophic lateral sclerosis	Nil	No response to immunotherapy- intravenous methyl prednisolone 1 gm iv daily for 5 days followed by oral prednisolone 1 mg/kg for 2 weeks tapered over next 1 month due to lack of response.
67/M	6.96	Atypical parkinsonism	Coronary artery disease, Systemic hypertension	Improved with immunotherapy- intravenous methylprednisolone 1 gm daily for 5 days followed by oral prednisolone 1 mg/kg. Patient continued the same dose without follow up for 16 months and developed disseminated tuberculosis despite good improvement in parkinsonism. 9 qmRS 3 at admission and improved to 1.
81/F	6.13	Atypical parkinsonism with autoimmune encephalitis	Autoimmune hypothyroidism, type 2 Diabetes mellitus, systemic hypertension, chronic kidney disease	Improved with immunotherapy- intravenous methylprednisolone 1 gm daily for 5 days followed by oral prednisolone 1 mg/kg followed by injection cyclophosphamide 750 mg/meter square for 1 dose. Treatment continued for 3 months and discontinued after infection. 9 qmRS improved from 3 to 2.

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Table 3: Contd...

Age/Sex	GAD value (IU/ml)	Diagnosis	Associated diseases	Immunotherapy responses
70/M	6.91	Atypical parkinsonism- Probable progressive supranuclear palsy like phenotype	Nil	Improved with immunotherapy- intravenous methylprednisolone 1 gm daily for 5 days followed by oral prednisolone 1 mg/kg/day followed by intravenous Cyclophosphamide 750 mg per square meter once a month for 3 doses 0.9 qmRs improved from 4 to 3.
53/M	7.13	Atypical parkinsonism- probable progressive supranuclear palsy phenotype	Chronic liver disease	Improved with immunotherapy- intravenous methylprednisolone 1 gm per day for 5 days followed by oral prednisolone 1 mg/kg per day and intravenous cyclophosphamide 750 mg per square meter once amonth for doses. 9 qmRs improved from 4 to 3 and UPDRS motor score improved from 28 to 16.
68/F	6.96	Atypical parkinsonism- probable multiple system Atrophy- cerebellar type	Dyslipidemia	No response to immunotherapy-Intravenous methylprednisolone 1 gm infusion daily for 5 days
65/F	6.08	Autoimmune encephalitis	Systemic hypertension	Improved with immunotherapy- intravenous methylprednisolone 1 gm per day for 5 days. - GCS improved from 7 to 15.
56/M	6.17	Myasthenia gravis	Parapsoriasis, hypothyroidism	Improved with immunotherapy-intravenous immune globulin 2 gm/kg over 5 days, plasma exchange 7 cycles, oral steroids 1 mg/kg/day, and rituximab1 gm infusion 2 doses. 9 qmrs improved from 4 to 2 but later died of infection at 7 months.
64/M	6.67	CNS vasculitis with peripheral neuropathy	Nil	Improved with immunotherapy- intravenous methylprednisolone 1 gm per day for 5 days followed mycophenolate mofetil 1gm twice daily.
75/M	6.73	Atypical parkinsonism	Systemic hypertension, ischemic stroke	1 ½ years duration. MRI brain chronic small vessel ischemic change. CSF no cells protein 36.7 mg/dl, glucose 63.6 mg/dl Improved with immunotherapy- intravenous methylprednisolone 1 gm daily for days followed bu oral prednisolone 1 mg/kg followed by intravenous cyclophosphamide 750 mg/square meter per month for 4 doses. 9 qmRS improved form 4 to3, UPDRS motor improved from 27 to 17
72/M	6.83	Atypical parkinsonism -probable multiple system Atrophy	Systemic hypertension	Improved with immunotherapy-intravenous methylprednisolone 1 gm daily for 5 days followed by oral prednisolone 1 mg/kg per day followed by intravenous cyclophosphamide 750 mg/suare meter per month for 7 doses. UPDRS motor score improved from 43 to 20 and 9 qmRS from 5 to 3. Died of infection after 7 months.
55/M	5.69	Creutzfeldt Jakcob disease	Type 2 Diabetes mellitus, systemic hypertension	No response to immunotherapy with intravenous methylprednisolone 1 gm daily for 5 days.
65/F	5.53	Creutzfeldt Jakob disease	Type 2 Diabetes mellitus, systemic hypertension, dyslipidemia	No response to immunotherapy with intravenous methylprednisolone 1 gm daily for 5 days.
69/F	5.38	Atypical parkinsonism- probable progressive supranuclear palsy like phenotype	Hypothyroidism, vitamin B12 deficiency	CSF 2 cells/cmm, protein 89.9 mg/dl, glucose 139 mg/dl. MRI brain normal. No response to levo dopa. Improved with immunotherapy-intravenous methylprednisolone 1 gm daily for 5 days followed by oral prednisolone 1 mg/kg/day and inj cyclophosphamide 750 mg/square meter/month one dose given. UPDRS motor score improved from 31 to 25, 9 qmRS improved from 3 to 2. Treatment discontinued after 1 month due to infection
57/M	5.4	Atypical parkinsonism-possible progressive supranuclear palsy	Type 2 Diabetes mellitus	No response to immunotherapy with intravenous methylprednisolone 1 gm daily for 5 days and oral prednisolone 1 mg/kg/day and mycophenolate mofetil 500 mg 1-0-1 for 5 months
52/F	5.53	Myeloneuropathy	Type 2 Diabetes mellitus	Improved with intravenous methylprednisolone 1 gm daily for 5 days followed by oral prednisolone 1 mg/kg/day for 1 month. 9 qmR improved from 4 to 3. Treatment discontinued as patient had significant concerns about infection.

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Table 3: Contd...

Age/Sex	GAD value (IU/ml)	Diagnosis	Associated diseases	Immunotherapy responses
41/F	5.51	Chronic axonal neuropathy	Nil	Improved with immunotherapy-intravenous methylprednisolone 1 gm daily followed by oral prednisolone 1 mg/kg/day tapered after one month and injection cyclophosphamide 500 mg per square meter per month one dose was given. Total 3 months of treatment, further immunosuppression could not be done due to recurrent infection Reported significant improvement in symptoms.
70/F	5.35	Atypical parkinsonism-probableprogressive supranuclear palsy like phenotype	Nil	Symptomatic for 1 year. MRI brain age-related atrophy. CSF no cells. Protein 49.4 mg/dl. Glucose 89.4 mg/dl. Improved with immunotherapy intravenous methylprednisolone 1 gm daily for 5 days followed by oral prednisolone 1 mg/kg/day and injection cyclophosphamide 750 mg/square meter per month 1 doase. UPDRS motor score improved from 24 to 17,9 qmRs remained the same 3. Treatment was discontinued by the patient after 4 months.
73/M	6.02	Atypical parkinsonism-overlapping phenotypes of multiple system atrophy and progressive supranuclear palsy	Type 2 Diabetes mellitus, systemic hypertension, dyslipidemia	MRI brain small vessel ischemic changes, CSF not done. Improved with immunotherapy -intravenous methylprednisolone 1 gm daily for 5 days followed by oral prednisolone 1 mg/kg/day. 9 qmRS improved from 4 to 3 after 1 month of therapy. Lost follow up.
81/M	1692.71	Myasthenia gravis with atypical parkinsonism	Thymoma, systemic hypertension, coronary artery disease.	Improved with immunotherapy- oral prednisolone, pyridostigmine and neostigmine. Underwent thymectomy
66/F	15.29	Autoimmune encephalitis	Systemic hypertension, depression	Improved with immunotherapy-intravenous immunoglobulin 2 gm/kg over 5 days.
53/F	3388.43	Stiff person syndrome	Hypothyroidism	No response to immunotherapy with intravenous immune globulin 2 gm/kg over 5 days and intravenous methylprednisolone 1 gm daily for 5 days
54/M	1376.52	Brainstem demyelination	Type 2 Diabetes mellitus, systemic hypertension, Fuchs endothelial dystrophy	Improved with immunotherapy-intravenous methylprednisolone 1 gm followed by oral prednisolone 1 mg/kg

nervous system manifestations were noted in nine cases (one myasthenia, one LEMS, seven neuropathies of which two were atypical AIDP and 1 CIDP). Peripheral nervous system manifestation of GAD 65 autoimmunity is described in multiple studies.[25]

The most striking finding was the low level of GAD 65 in our population. In most series from the West, GAD 65 levels, more than >10,000 IU/ml have been reported in those with neurological manifestations.[2,3] In contrast, a couple of previous studies from Asia have shown the presence of low titers in neurological syndromes associated with GAD autoimmunity when compared to similar diseases from the West.[8,11] Glutamic acid decarboxylase 65 titers were low in series reported by Kuo *et al*.,[8] Wang *et al*.,[11] and Sriwastava *et al*.[18] These three studies were from Taiwan, India, and China, and indicate an ethnic variation—a tendency for low titers in Chinese and Indian population. In all the three studies, tests were conducted with commercial kits, which were used widely across the globe. In another study, African Americans were found to have greater severity of the disease when compared to Caucasians and another study showed more brainstem involvement with African Americans.[2,18] This exemplifies the role of ethnicity in GAD 65 autoimmunity, and this remains to be explored.

The immunotherapy response in our series was good—76.74%. This is in striking contrast to the previous reports where only 50% responded to immunotherapy.[1] The poor response is attributed to the intracellular location of the antigen, autoimmunity, which is usually mediated by T cells.[1] This mechanism causes more neuronal damage than that occurs with B cell or antibody-mediated disease as in the case of antibody to synaptic protein. But, immunotherapy response in our group was 76.74%, which is comparable with that of high GAD 65 (>10,000 U/ml) series by Muñoz-LopetegiA *et al*. (77%).[13] Since our series did not show high GAD values as found in previous literature (>10,000 U/ml), we arbitrarily classified values upto five times the normal limit as low, and more than five times as high to compare the treatment responses in both the groups. We found that many patients with low positive values also showed a good response to immunotherapy. There was no significant difference in the treatment response between the low positive (80%) and high positive (62.5%) group of patients (*P*-value - 0.386). This finding is similar to a study by Wang *et al*. in which it was found that in neurocritical patients with GAD positivity, all patients responded well to immunotherapy irrespective of their GAD titers.[11]

Analyzing the clinical diagnoses and treatment response, we found that the clinical phenotype determines the treatment outcome, e.g., Those with myasthenia, demyelinating myelopathy, immune-mediated neuropathies, autoimmune encephalitis, and AAP responded well to immunotherapy in our treatment group when compared to stiff person syndrome, though the latter had higher GAD 65 values. This goes well with the current literature where treatment response depends on the phenotype of the classical syndromes—stiff person (77%), limbic encephalitis (71%), overlap syndrome (70%), cerebellar ataxia (58%), epilepsy (50%).[14]

The good immunotherapy response in low positive GAD 65 in our series can be attributed to the fact that GAD 65 may be acting only as a marker of underlying autoimmunity rather than mediating the disease. This is very evident in some of the cases with NMO spectrum disorder, LEMS, LGI1, and acetylcholine receptor antibody positivity. In others, there were other pieces of evidence for antibody-mediated disease-ten patients had low complement in our series indicating an antibody-mediated disease (nine of them had unclassified neuronal antibody to unknown target epitope, as evidenced by immunofluorescence in the monkey brain, and one had CASPR 2 antibody positivity). Antibodies other than GAD 65 were detected in 92.6% of cases and most of them were neuronal antibodies. In our series, 22.2% had an underlying autoimmune disease which again points that GAD 65 positivity at low titers itself could be just an indicator of underlying autoimmunity. Our study brings out an important finding, a low positive GAD 65 antibody in the right clinical setting can be used as a good marker for a positive response to immunotherapy. In a suspected autoimmune neurological disease, the presence of GAD 65 antibody positivity whether low or high, is a marker of potentially good immunotherapy response, which should prompt the clinician to look for the coexistence of other antibodies. If other diagnostic possibilities are excluded, then it may be worthwhile attempting a trial of immunosuppression. A similar view has been expressed by Gaspard.[26]

Glutamic acid decarboxylase 65 antibody-associated diseases are often reported to have coexisting antibodies. Gamma-aminobutyric acid antibodies were reported in 70% of cases, glycine receptor antibodies were reported in 15% cases, amphiphysin antibody was reported in 5% and rarely, gephyrin in GAD-associated stiff-person syndrome.[27] Though T cell-mediated disease mechanism is experimentally proven and GAD antigen is located intracytoplasmic, IVIgG is the mainstay of treatment of GAD 65-associated disease.[27] A transient moonlighting antigen to the synaptic cleft is the paradigm that is used to explain the pathogenicity of the GAD 65 antibody.[28] In a recent study by Czempik *et al*.,[29] they reviewed the literature from 1989 regarding the effect of plasma exchange in stiff-person syndrome and who found that 23 out of 30 GAD-positive patients (76.67%) underwent plasma exchange showed marked improvement. Though the randomized controlled trial of rituximab on stiff-person syndrome did not reveal any positive response, it is still a therapeutic option in patients who are not responding to other therapy.[28] Multiple studies have revealed GAD titers have no correlation with the severity of disease and also that, there is no correlation between a fall in titer and improvement of disease. Even after plasma exchange, the antibody levels were not falling but patients were improving clinically (Czempic).[29] The good response to treatment modalities that work well on antibody-mediated disease like IVIgG, plasma exchange, and rituximab (rituximab effect on refractory cases), heterogenicity in clinical manifestations, lack of correlation of titers with severity and presence of multiple coexisting antibodies made many experts view the pathogenic role of GAD 65 antibody skeptically.[27,30] Our series also questions the pathogenic role of GAD 65 antibodies as mentioned in the previous paragraph.

Six patients in our series had neoplasm in association with GAD 65 positivity and neurological syndrome. Though they did not fulfill all the criteria for paraneoplastic neurologic syndromes, this pattern is in concordance with the study by Saiz *et al*. from Barcelona and distinctly different from the Mayo clinic series where there was no malignancy associated with the GAD 65.[2,3] We would like to stress the fact that a positive GAD 65 antibody should not prevent a neurologist from looking for an underlying malignancy.

Being a retrospective study, it has its own limitations. Glutamic acid decarboxylase 65 was tested in all suspected autoimmune neurological disorders and not only in the published phenotypes, so chances of false positivity cannot be ruled out. However, this kind of extensive testing is needed to reveal the expanding clinical spectrum of GAD autoimmunity as has been the case with other antibodies. Since, we identified the cases from the laboratory register, chances for clinical false positivity also are there. Another significant limitation was that CSF GAD 65 test was not performed in our laboratory.

This study brings out some important observations regarding the ethnic variability of the neurological manifestations of the GAD 65 antibody. Glutamic acid decarboxylase 65 antibody values were much lower in our population among patients with neurological disorders, even in published phenotypes. Male-dominant autoimmunity was seen unlike that in Western literature. A higher frequency of malignancy was noted in our series. Most striking was the high preponderance of positive GAD 65 in atypical parkinsonism. We also found that GAD 65 positivity is a useful marker for a positive response to immunotherapy in suspected autoimmune neurological syndromes, irrespective of their titers. Even though it has been observed that low GAD positivity might not be mediating the disease, the presence of GAD antibodies, even in low titers may be considered as one of the criteria to investigate for other coexisting antibodies as well as to offer trial immunotherapy to patients in the absence of an alternate diagnosis.

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Conflicts of interest

There are no conflicts of interest.

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GAD 65 Supplementary data						
Age/ Sex	**GAD value (IU/ml)**	**Diagnosis**	**Associated diseases**	**Immunotherapy responses**	**Other antibodies**	**Serum Complement (C3/C4)**
47/F	11.07	Suspected myelopathy	Hypothyroidism, dyslipidemia	spontaneous improvement	Thyroglobulin and TPO antibodies elevated, Unclassified neuronal antibody detected by immunofluorescence,	Not done
81/M	5.4	atypical parkinsonism	Type 2 Diabetes mellitus, subdural hematoma	No treatment given	Unclassified neuronal antibody detected by immunofluorescence,	Not done
85/M	5.85	atypical parkinsonism	Coronary artery disease (CAD)	No treatment given	Unclassified neuronal antibody detected by immunofluorescence,	Not done
49/M	15	atypical parkinsonism	Rheumatoid arthritis, psychosis	Improved with immunotherapy. Treated with intravenous methylprednisolone, azathioprine	Unclassified neuronal antibody detected by immunofluorescence,	Not done
71/F	13.12	atypical parkinsonism	Type 2 Diabetes mellitus, subdural hematoma, Bullous pemphigoid	spontaneous improvement	Unclassified neuronal antibody detected by immunofluorescence,	Not done
50/M	30.62	Chronic inflammatory demyelinating polyradiculoneuropathy	Type Diabetes mellitus	Improved with immunotherapy. Treated with intravenous methylprednisolone and mycophenolate mofetil	Anti Sm antibody positive, Unclassified neuronal antibody detected by immunofluorescence,	Not done
31/M	26.5	Motor neuron disease	Nil	No treatment given	Unclassified neuronal antibody detected by immunofluorescence,	Not done
70/M	22.6	atypical parkinsonism	Type 2 Diabetes mellitus, systemic hypertension, cervical compressive myeloradiculopathy	No treatment given	Unclassified neuronal antibody detected by immunofluorescence	Not done
66/M	5.05	Cystoid macular edema	Nil	No treatment given	Unclassified neuronal antibody detected by immunofluorescence	Not done
52/F	17.09	atypical parkinsonism	Systemic hypertension	No improvement with immunotherapy with intravenous methylprednisolone and mycophenolate mofetil	Elevated thyroglobulin antibody and unclassified neuronal antibody detected by immunofluorescence	Not done
60/F	9.03	Myoneuropathy	Systemic hypertension	No immunotherapy given	ANA positive and Unclassified neuronal antibody detected by immunofluorescence	Not done
48/M	10.2	atypical parkinsonism	Nil	No treatment given	Unclassified neuronal antibody detected by immunofluorescence	Not done
65/F	166.7	Demyelinating myelopathy	Type 2 Diabetes mellitus, systemic hypertension subclinical hypothyroidism	Improved with immunotherapy- intravenous methylprednisolone and azathioprine	Anti SSB antibody elevated, Unclassified neuronal antibody detected by immunofluorescence	Not done
43/M	10.68	atypical parkinsonism	Nil	No improvement with immunotherapy with intravenous methylprednisolone and mycophenolate mofetil	Anti SSB antibody elevated, Unclassified neuronal antibody detected by immunofluorescence	Not done
15/F	19.7	autoimmune encephalitis	Nil	Improved with intravenous methylprednisolone followed by oral steroids	Not detected	Not done

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Age/ Sex	GAD value (IU/ml)	Diagnosis	Associated diseases	Immunotherapy responses	Other antibodies	Serum Complement (C3/C4)
86/M	40.5	atypical parkinsonism	Acid peptic disease	improved with intravenous methylprednisolone	Unclassified neuronal antibody detected by immunofluorescence	Not done
37/M	89.09	Guillain Barre Syndrome	Type 2 Diabetes mellitus	Improved with immunotherapy-Intravenous Immunoglobulin	Unclassified neuronal antibody detected by immunofluorescence	Not done
45/F	135.2	autoimmune encephalitis	Non- Hodgkin's lymphoma	No improvement with immunotherapy-intravenous methylprednisolone, intravenous immunoglobulin	Anti SSA antibody positive, Unclassified neuronal antibody detected by immunofluorescence	Not done
39/F	5.85	Neuromyelitis optica (NMO) spectrum disorder- brainstem presentation	Nil	Improved with immunotherapy- intravenous methylprednisolone and azathioprine	NMO IgG antibody positive,	Not done
36/F	8.05	Migraine, seizure disorder	Immature squamous metaplasia of cervix, leiomyoma, and adenomyosis	No immunotherapy warranted	Unclassified neuronal antibody detected by immunofluorescence	Not done
42/F	24.02	Lambert Eaton Myasthenic syndrome	Nil	Improved with intravenous immune globulin and azathioprine	Voltage-gated calcium channel antibody P/Q and N-type	Not done
57/F	135.27	autoimmune encephalitis	Hypothyroidism, Autoimmune diabetes	Spontaneous improvement	Thyroglobulin and TPO antibodies elevated, Unclassified neuronal antibody detected by immunofluorescence,	Not done
62/M	6.13	stiff person syndrome	Nil	No immunotherapy was attempted	Unclassified neuronal antibody detected by immunofluorescence	Not done
56/M	328	stiff person syndrome	Autoimmune diabetes mellitus	No response to immunotherapy-Intravenous immune globulin, mycophenolate mofetil	Unclassified neuronal antibody detected by immunofluorescence	Not done
24/M	272.34	demyelinating myelopathy	Autoimmune diabetes mellitus	Improved with intravenous Immune globulin	Thyroglobulin antibodies elevated. Unclassified neuronal antibody detected by immunofluorescence	Not done
80/M	9.47	Vascular parkinsonism	Type 2 Diabetes mellitus, ischemic stroke	No immunotherapy attempted	Unclassified neuronal antibody detected by immunofluorescence	Not done
71/F	5.4	atypical parkinsonism	Systemic hypertension, dyslipidemia	Improved with immunotherapy- intravenous methylprednisolone and mycophenolate mofetil, but died of infection	Thyroglobulin and TPO antibodies elevated, Unclassified neuronal antibody detected by immunofluorescence	Normal
68/M	5.3	atypical parkinsonism with autoimmune encephalitis	Autoimmune thyroiditis	Improved with immunotherapy-intravenous methylprednisolone followed by oral steroids	Unclassified neuronal antibody detected by immunofluorescences	Low C3, normal C4
20/M	6.07	Autoimmune cerebellar ataxia	Nephrotic syndrome	Improved with intravenous methylprednisolone, followed by injection cyclophosphamide followed by oral methotrexate	Unclassified neuronal antibody detected by immunofluorescence	Normal
70/M	5.5	atypical parkinsonism	Nil	Immunotherapy was not attempted	Unclassified neuronal antibody detected by immunofluorescence	Normal

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Age/ Sex	GAD value (IU/ml)	Diagnosis	Associated diseases	Immunotherapy responses	Other antibodies	Serum Complement (C3/C4)
53/F	5.73	Guillain Barre Syndrome	Autoimmune thyroiditis, carcinoma ovary, and breast	Spontaneous improvement	Thyroglobulin and TPO antibodies elevated, Unclassified neuronal antibody detected by immunofluorescence	Not done
9/M	19	autoimmune encephalitis	Nil	Improved with immunotherapy- intravenous methylprednisolone and intravenous immune globulin	Thyroglobulin and TPO antibodies elevated,	Not done
57/F	5.27	atypical parkinsonism-probable progressive supranuclear palsy	Dyslipidemia	Not attempted on immunotherapy	Lupus anticoagulant positive, Unclassified neuronal antibody detected by immunofluorescence	normal
67/M	5.16	atypical parkinsonism -possible dementia with Lewy body	Type 2 Diabetes mellitus, dyslipidemia, systemic hypertension	Immunotherapy not attempted	Unclassified neuronal antibody detected by immunofluorescence	Not done
60/M	5.49	atypical parkinsonism-probable Progressive supranuclear palsy	Systemic hypertension	Immunotherapy not attempted	Unclassified neuronal antibody detected by immunofluorescence	normal
66/F	5.76	atypical parkinsonism	Carcinoma ovary, type 2 diabetes mellitus	No immunotherapy given	Unclassified neuronal antibody detected by immunofluorescence	Not done
32/F	6.84	Post-infectious extrapyramidal syndrome	Nil	Improved with immunotherapy-intravenous methylprednisolone followed by oral steroids	No antibodies detected	Normal
65/F	6.34	Severe anxiety with depression	Systemic hypertension	No immunotherapy attempted	NMDA receptor antibody NR 1 subunit positive in serum	Not done
52/F	5.61	autoimmune encephalitis	Autoimmune hypothyroidism	Spontaneous improvement	Thyroglobulin and TPO antibodies elevated, Unclassified neuronal antibody detected by immunofluorescence	Not done
38/M	6.4	Suspected trigeminal neuropathy	Nil	No immunotherapy attempted	TPO antibody elevated, Unclassified neuronal antibody detected by immunofluorescence	normal
12/M	5.57	Seizure disorder	Nil	No immunotherapy was attempted	No antibodies detected	Not done
49/M	7.11	chronic axonal neuropathy	Nil	No immunotherapy attempted	Unclassified neuronal antibody detected by immunofluorescence	Normal
56/M	6.34	Seizure secondary to hyponatremia, Syndrome of Inappropriate ADH secretion	CAD, adrenal adenoma	No immunotherapy attempted	Thyroglobulin antibody elevated, Unclassified neuronal antibody detected by immunofluorescence	Not done
32/M	5.87	autoimmune encephalitis	Nil	Improved with immunotherapy- intravenous methylprednisolone	Thyroglobulin antibody elevated, Unclassified neuronal antibody detected by immunofluorescence	Not done
58/M	7.59	Dementia- probable frontotemporal	CAD	No immunotherapy done	Thyroglobulin and TPO antibodies elevated, Unclassified neuronal antibody detected by immunofluorescence	Not done

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Age/ Sex	GAD value (IU/ml)	Diagnosis	Associated diseases	Immunotherapy responses	Other antibodies	Serum Complement (C3/C4)
56/M	5.61	atypical parkinsonism	Systemic hypertension, CAD, Ischemic stroke	Improved with immunotherapy- intravenous methylprednisolone followed injection cyclophosphamide	Unclassified neuronal antibody detected by immunofluorescence	Low C3 with normal C4
63/F	6.13	Possible Amyotrophic lateral sclerosis	Nil	No response to immunotherapy	Unclassified neuronal antibody detected by immunofluorescence	Low C3 with normal C4
36/M	5.91	inflammatory neuropathy	Nil	Immunotherapy not attempted	Unclassified neuronal antibody detected by immunofluorescence	Not done
67/M	6.96	atypical parkinsonism	CAD, Systemic hypertension	Improved with immunotherapy- intravenous methylprednisolone followed by oral prednisolone	ANA positive and Unclassified neuronal antibody detected by immunofluorescence	Low C3 with normal C4
81/F	6.13	atypical parkinsonism with autoimmune encephalopathy	Autoimmune hypothyroidism, type 2 Diabetes mellitus, systemic hypertension, chronic kidney disease	Improved with immunotherapy- intravenous methylprednisolone followed by injection cyclophosphamide	Thyroglobulin and TPO antibodies elevated, Unclassified neuronal antibody detected by immunofluorescence	Low C3 with normal C4
70/M	6.91	atypical parkinsonism-Probable progressive supranuclear palsy	Nil	Improved with immunotherapy- intravenous methylprednisolone followed by intravenous cyclophosphamide	Unclassified neuronal antibody detected by immunofluorescence	normal
68/M	5.74	atypical parkinsonism	Type 2 Diabetes mellitus, systemic hypertension	No immunotherapy tried	Thyroglobulin antibody elevated, Unclassified neuronal antibody detected by immunofluorescence	Normal
67/F	7.22	atypical parkinsonism-possible multiple system atrophy	CAD, Type 2 Diabetes mellitus, Dyslipidemia	No immunotherapy was attempted	Unclassified neuronal antibody detected by immunofluorescence	Normal
53/M	7.13	atypical parkinsonism-probable progressive supranuclear palsy	Chronic liver disease	Improved with immunotherapy- intravenous methylprednisolone followed by intravenous cyclophosphamide	Unclassified neuronal antibody detected by immunofluorescence	Not done
68/F	6.96	atypical parkinsonism-probable multiple system atrophy (MSA)-cerebellar	Dyslipidemia	No response to immunotherapy-Intravenous methylprednisolone	Thyroglobulin antibody elevated, Unclassified neuronal antibody detected by immunofluorescence	Low C3 with normal C4
65/F	6.08	autoimmune encephalitis	Systemic hypertension	Improved with immunotherapy- intravenous methylprednisolone	Unclassified neuronal antibody detected by immunofluorescence	Not done
56/M	6.17	Myasthenia gravis	Parapsoriasis, hypothyroidism	Improved with immunotherapy-intravenous immune globulin, plasma exchange, steroids, and rituximab. Died of infection	TPO antibody elevated, Unclassified neuronal antibody detected by immunofluorescence	Normal
64/M	6.67	CNS vasculitis with peripheral neuropathy	Nil	Improved with immunotherapy- intravenous methylprednisolone followed mycophenolate mofetil	Unclassified neuronal antibody detected by immunofluorescence	Normal
28/M	7.25	Tuberculous meningoencephalitis	Nil	No immunotherapy attempted	Unclassified neuronal antibody detected by immunofluorescence	Not done

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Age/ Sex	GAD value (IU/ml)	Diagnosis	Associated diseases	Immunotherapy responses	Other antibodies	Serum Complement (C3/C4)
75/M	6.73	atypical parkinsonism	Systemic hypertension, ischemic stroke	Improved with immunotherapy- intravenous methylprednisolone followed by intravenous cyclophosphamide	Unclassified neuronal antibody detected by immunofluorescence	Low C3 and low C4
72/M	6.83	atypical parkinsonism -probable MSA	Systemic hypertension	Improved with immunotherapy-intravenous methylprednisolone followed by intravenous cyclophosphamide and oral steroids, died of infection	CASPR 2 antibody positive, Thyroglobulin antibody positive, anti-factor XIII antibody positive	Low C3 with normal C4
55/M	5.69	Creutzfeld Jacob disease	Type 2 Diabetes mellitus, systemic hypertension	No response to immunotherapy with intravenous methylprednisolone	Thyroglobulin antibody elevated, Unclassified neuronal antibody detected by immunofluorescence	Not done
65/F	5.53	Creutzfeld Jacob disease	Type 2 Diabetes mellitus, systemic hypertension, dyslipidemia	No response to immunotherapy with intravenous methylprednisolone	Thyroglobulin and TPO antibodies elevated, Unclassified neuronal antibody detected by immunofluorescence	Not done
69/M	5.2	atypical parkinsonism	Benign prostatic hyperplasia	No immunotherapy was attempted	Unclassified neuronal antibody detected by immunofluorescence	Normal
26/M	5.34	Partially treated meningitis	Nil	No immunotherapy tried	Unclassified neuronal antibody detected by immunofluorescence	Not done
69/F	5.38	atypical parkinsonism-probable supranuclear palsy	Hypothyroidism, vitamin B12 deficiency	Improved with immunotherapy- intravenous methylprednisolone followed by oral prednisolone and intravenous cyclophosphamide	Thyroglobulin and TPO antibodies elevated, Unclassified neuronal antibody detected by immunofluorescence	Not done
57/M	5.4	atypical parkinsonism-possible progressive supranuclear palsy	Type 2 Diabetes mellitus	No response to immunotherapy with intravenous methylprednisolone and mycophenolate mofetil	Thyroglobulin antibody elevated, Unclassified neuronal antibody detected by immunofluorescence	Not done
52/F	5.53	myeloneuropathy	Type 2 Diabetes mellitus	Improved with intravenous methylprednisolone followed by oral prednisolone	Unclassified neuronal antibody detected by immunofluorescence	Normal
41/F	5.51	Chronic axonal neuropathy	Nil	Improved with immunotherapy- intravenous methylprednisolone followed by oral prednisolone and injection cyclophosphamide.	Unclassified neuronal antibody detected by immunofluorescence	Normal
70/F	5.35	atypical parkinsonism-probable progressive supranuclear palsy	Nil	Improved with immunotherapy intravenous methylprednisolone followed by injection cyclophosphamide	Thyroglobulin and TPO antibodies elevated, Unclassified neuronal antibody detected by immunofluorescence	Not done
73/M	6.02	atypical parkinsonism-the overlap of multiple system atrophy and progressive supranuclear palsy	Type 2 Diabetes mellitus, systemic hypertension, dyslipidemia	Improved with immunotherapy -intravenous methylprednisolone followed by oral prednisolone	Unclassified neuronal antibody detected by immunofluorescence	Not done

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Age/ Sex	GAD value (IU/ml)	Diagnosis	Associated diseases	Immunotherapy responses	Other antibodies	Serum Complement (C3/C4)
61/M	5.86	atypical parkinsonism	Type 2 Diabetes mellitus, systemic hypertension, dyslipidemia, CAD	No immunotherapy attempted	Unclassified neuronal antibody detected by immunofluorescence	Normal
58/M	1833.75	Suspected brainstem TIA	Chronic liver disease, bipolar disorder, hypothyroidism	No immunotherapy attempted	ANA positive, Unclassified neuronal antibody detected by immunofluorescence	Not done
81/M	1692.71	Myasthenia gravis with atypical parkinsonism	Thymoma, systemic hypertension, CAD	Improved with immunotherapy- oral prednisolone	acetylcholine receptor antibody positive, antiphospholipid antibody positive, Unclassified neuronal antibody detected by immunofluorescence	Low C3 with normal C4
28/F	707.94	Mononeuritis multiplex.	Autoimmune diabetes mellitus	No immunotherapy attempted	Thyroglobulin and TPO antibodies elevated, Unclassified neuronal antibody detected by immunofluorescence	Low C3 with normal C4
66/F	15.29	autoimmune encephalitis	Systemic hypertension, depression	Improved with immunotherapy-intravenous immunoglobulin	Anti SSA positive, Unclassified neuronal antibody detected by immunofluorescence	Not done
40/F	4179	atypical parkinsonism	Nil	No immunotherapy attempted	Unclassified neuronal antibody detected by immunofluorescence	Not done
53/F	3388.43	stiff person syndrome	Hypothyroidism	No response to immunotherapy with intravenous immune globulin and intravenous methylprednisolone	Unclassified neuronal antibody detected by immunofluorescence	Not done
74/F	1789.66	atypical parkinsonism, myasthenia gravis	Type 2 Diabetes mellitus, systemic hypertension, ischemic stroke	Immunotherapy not attempted	acetylcholine receptor antibody positive, Unclassified neuronal antibody detected by immunofluorescence	Not done
54/M	1376.52	Brainstem demyelination	Type 2 Diabetes mellitus, systemic hypertension, Fuchs endothelial dystrophy	Improved with immunotherapy- intravenous methylprednisolone followed by oral prednisolone	ANA positive, Unclassified neuronal antibody detected by immunofluorescence	Normal
76/F	13.78	viral encephalitis	Systemic hypertension, paroxysmal atrial fibrillation	Immunotherapy not attempted	Unclassified neuronal antibody detected by immunofluorescence	Not done