



# Catatonic Schizophrenia Associated With Cerebrospinal GAD65 Autoantibodies: Case Report and Literature Review

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**Background:** GAD65 autoimmunity is reported to be associated with schizophrenia and bipolar disorder. However, there has been no evidence that glutamic acid decarboxylase 65 (GAD65) autoantibodies in cerebrospinal fluid (CSF) are associated with akinetic catatonia in schizophrenia patients.

**Methods:** We report the case of a 28-year-old man who underwent diagnostics including brain MRI, neuropsychological testing, and electroencephalography (EEG) as well as a tumor search *via* CT of the abdomen and thorax, as well as colonoscopy and gastroscopy. For clinical characterization, his patient files were retrospectively examined.

**Results:** Our patient presented catatonia that responded somewhat to benzodiazepines in combination with previously taken antipsychotics such as risperidone for prediagnosed paranoid schizophrenia. Diagnostics revealed GAD65 autoantibodies in his serum and CSF. MRI revealed no brain lesion, and the tumor search had no malignancy. We diagnosed catatonic schizophrenia. Furthermore, as he had not fully recovered, he was given immunotherapy entailing two cycles of intravenous immunoglobulins. Subsequent neuropsychological testing due to subjective cognitive complaints after immunotherapy revealed no objective cognitive deficits.

**Conclusions:** We present the novel finding of an association between GAD65 autoantibodies in the serum and CSF with catatonia in a patient suffering from prediagnosed chronic schizophrenia. Due to the presence of CSF GAD65 antibodies and the catatonia factor in prediagnosed schizophrenia, we suspect that his catatonia has an autoimmune origin. Immunotherapy stabilized the catatonia that had initially responded to lorazepam treatment. Further research should be done to characterize patients' responses to immunotherapy and standard treatment in a large cohort of patients with GAD65 antibody-associated catatonia and schizophrenia.

**Keywords:** catatonia, GAD65 autoantibodies, schizophrenia, autoimmunity, psychiatry

## INTRODUCTION

According to the latest *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM V), catatonia is considered an independent disease entity (1, 2). It is a clinical psychomotor syndrome manifesting in either an excited (hyperkinetic) or retarded (akinetetic) form. The latter is characterized by immobility, mutism, and rigidity, often coinciding with clinical features like abnormal posturing, echolalia or echopraxia, and waxy flexibility, whereas the hyperkinetic form reveals psychomotor agitation (1). Autoimmune catatonia is a catatonia subtype, recently characterized by Rogers et al. (3). Specific cell-membrane surface autoantibodies have been linked to catatonia, such as those against *N*-methyl-D-aspartate (NMDA) (4–14), gamma-aminobutyric acid A (GABAA) receptor (15–17) (**Table 1**), and voltage-gated potassium channels (8) or myelin (20) (for an overview, see **Table 1**).

Catatonia has not yet been described to be associated with glutamic acid decarboxylase 65 (GAD65) autoantibodies, but GAD65 antibodies are known to occur in schizophrenia. An analysis of pooled data from 9 different cohort studies revealed that GAD65 antibodies are detected in 4.6% of patients with schizophrenia compared with 2.7% in healthy controls with no relevant differences (21). However, our analysis also revealed that psychotic patients carry twice the risk of developing GAD65 autoantibodies than controls (21). GAD65 is a catalyzing enzyme in GABA synthesis. Its blockage by GAD65 antibodies led to motor dysfunction in an animal model, caused by impaired GABAergic transmission (22), and to motor dysfunction in stiff-person syndrome (23).

**TABLE 1** | Overview of the diversity of neural autoantibody-associated catatonia.

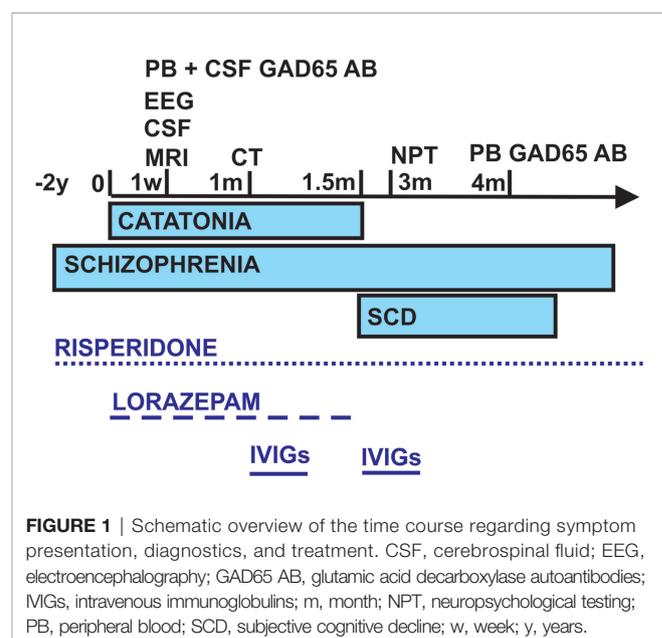
Number of patients	Psychiatric disease	Auto-antibodies	References
189/347	Depression,	NMDAR	(5)
	psychosis		(6)
	Anxiety		(7)
	Cognitive dysfunction		(8)
	Delirium		(9)
	Behavioral		(10)
	abnormalities		(11)
	Mania		(12)
			(4)
			(18)
			(13)
			(14)
	3/41		Behavioral changes
1/12	Depression	VGKC	(8)
	Anxiety		
	Suicidality		
1/1	Psychosis	Unknown epitope, somatodendritic staining	(19)
10/20	Schizophrenia	Myelin	(20)

GABAAR, gamma-aminobutyric acid receptor A; NMDAR, *N*-methyl-D-aspartate receptor; VGKC, voltage-gated potassium channel.

GAD65 antibodies are thus likely to cause motor dysfunction manifesting as catatonia, although there is no evidence to date that GAD65 autoantibodies play a causal role. Here, we present the first case of GAD65 antibodies in the serum and cerebrospinal fluid (CSF) of a patient with schizophrenia who suffered catatonia responding to benzodiazepine and later immunotherapeutic treatment with intravenous immunoglobulins (IVIgs).

## CASE REPORT

We present the case of a 28-year-old male who presented for the first time in our Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, with akinetic catatonia initially presenting as a stupor and immobility (**Figure 1**). The patient has a master's in bioengineering after studying for 5 years in India. He is a native Hindi and English speaker and migrated to Germany in 2020 to start a PhD in neuroscience. He attended school for 12 years in India. His roommate found him immobile on the floor, failing to respond to any speech. The roommate called the emergency medical services to have him transported to our department. After being given midazolam, he was able to start speaking. Midazolam has been given in addition to the antipsychotic medications he was already taking [risperidone (4 mg/day)]. He was later treated with 5.5 mg/day of lorazepam, and his stupor resolved somewhat within hours after taking lorazepam. He reported that he had paranoia (being watched) before the catatonia started, indicative of psychotic symptoms of his pre-diagnosed paranoid schizophrenia 2 years ago in India (treated with risperidone) (**Figure 1**). Apart from his risperidone therapy, he had undergone no medical interventions in the past. Furthermore, his psychosocial history revealed no abnormalities. No somatic comorbidities were reported.



His psychopathology revealed a growing sensation of being watched by other people (mild delusions of reference). We were unable to explore any delusions or hallucinations or ego disturbances. The sensation of being observed by other people became weaker within 2 weeks. His neurological examination was unremarkable, and no paresis was apparent. However, he did describe a feeling of stiffness that was less pronounced at night and not present in the neurological examination. His patient history revealed a prior episode of catatonia in 2014 while traveling by train. At that time, he was also hungry and stressed out.

Differential diagnosis (**Figure 1**) *via* brain MRI revealed no pathological brain lesions. Electroencephalography (EEG) early in his time course exhibited no epileptic potentials or focal or multifocal slowing. No continuous EEG monitoring was done. CSF analysis *via* lumbar puncture showed no pleocytosis or elevated protein levels. Furthermore, we detected no intrathecal IgG synthesis. CSF analysis also yielded anti-GAD65 autoantibodies in immunoblots (1:100), and his blood analysis revealed GAD65 autoantibodies in immunoblots (1:3,200) and rodent immunohistochemistry (**Table 2** and **Figure 1**). We searched for anti-Zic4, anti-TR, anti-SOX1, anti-Ri, anti-Yo, anti-Hu, anti-amphiphysin, and anti-CV2/CRMP5 antibodies *via* immunoblots. Cell-based assays involving indirect immunohistochemistry were done to search for anti-NMDAR, anti-Leucin Rich Glioma Inactivated Protein 1 (LGI1), anti-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor 1/2 (AMPA1/2), anti-gamma-aminobutyric acid receptor 1/2 (GABABR1/2), anti-dipeptidyl-peptidase-like 6 protein (DPPX), and anti-contactin associated protein 2 (CASPR2) antibodies.

Three weeks after his initial presentation, he was sent to the Neurology Department, University Medical Center Göttingen, and given IVIGs (160 g) because of incompletely resolved symptoms and remaining stiffness, psychotic symptoms, and spatial disorientation. During the 3 weeks in the Department of Psychiatry and Psychotherapy (with his first stay in a protected and later non-protected setting), lorazepam was slowly reduced and finally stopped after IVIG application because his symptoms were alleviated on a psychiatric ward after his stay in the Department of Neurology, University Medical Center Göttingen (**Figure 1**). IVIGs were chosen for this patient as his initial treatment regimen because corticosteroids would have had the potential to exacerbate psychotic symptoms or induce depressive symptoms. CT of the thorax and abdomen performed during his stay in the Department of Neurology, University Medical Center Göttingen, revealed no malignancy, nor did the colonoscopy and gastroscopy (**Figure 1**). His gastroscopy showed a reflux esophagitis grade A (Los Angeles classification). One and a half months later, he received IVIGs again to stabilize his current status, as his symptoms had not disappeared entirely (**Figure 1**). Immediately after his catatonic episode terminated, he reported persistent cognitive decline at regularly scheduled outpatient visits, namely, difficulty finding words and memory deficits, especially recalling conversations. He also complained of losing things and felt like he was losing control of his own actions. We therefore had him undergo extensive neuropsychological testing 3 months after his initial

**TABLE 2 |** Laboratory and clinical parameters.

Laboratory parameters	First presentation	Follow-up
<b>Antibodies</b>		
GAD65 serum	1:3,200	1:3200
GAD65 CSF	1:100	–
<b>Cells CSF</b>		
Cells/ $\mu$ l (<5 $\mu$ g/L)	0	–
Lymphocytes %	80	–
Monocytes %	14	–
Lactat mmol/L	1.4	–
<b>Proteins CSF</b>		
Total protein mg/L	319	–
Albumin mg/L	216	–
IgG mg/L	29.4	–
IgA mg/L	2.2	–
IgM mg/L	0.17	–
QAlb %	5.3	–
QIgG %	3	–
QIgA %	1.6	–
QIgM %	0.3	–
<b>CSF blood–brain barrier disturbance</b>	No	–
<b>CSF intrathecal IgG synthesis</b>	No	–
<b>Neuropsychological and clinical parameters</b>		
MMSE (screening) orientation	10/10	–
CDT (screening)	01	–
TMT Part A (processing speed)	50–50	–
WAIS-IV Coding (processing speed)	25	–
TAP Alertness (phasic alertness) Index	58	–
TAP Divided Attention (divided attention), Omissions	24	–
TAP Go/NoGo (selective attention), errors	58	–
TMT Part B (flexibility)	40–50	–
RWT semantic fluency—alternating (flexibility)	29	–
RWT letter fluency—alternating (flexibility)	52	–
RCFT Copy (visual functions)	$\geq$ 16	–
WAIS-IV Block Design (visuoconstruction)	63	–
WAIS-IV Digit Span forward (memory span)	91	–
WAIS-IV Digit Span backward (working memory)	50	–
RAVLT Sum trials 1–5 (verbal learning)	50	–
RAVLT trial 7 (verbal delayed recall)	70–85	–
RAVLT trials 5–7 (verbal long-term memory/retention)	65–85	–
WMS-IV Visual Reproduction I (visual immediate recall)	16	–
WMS-IV Visual Reproduction II (visual delayed recall)	35	–

For neuropsychological parameters starting from TMTA to WMS-IV, percentage ranges are indicated.

Alb, albumin; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; CDT, Clock Drawing Test; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; LTM, long-term memory; M, memory; MMSE, Mini Mental Status Examination; P-Tau 181, phosphorylated tau protein 181; Q, quotient; RCFT, Rey Complex Figure Test; RWT, Regensburg Word Fluency Test; TAP, test of attentional performance; TMT, Trail Making Test; WAIS-IV, Wechsler Adult Intelligence Scale, fourth edition; WMS-IV, Wechsler Memory Scale, fourth edition.

presentation (done in English) (**Figure 1**). In all cognitive tests, including screening tests and tests of attention, executive, visuoconstructive/visual, and memory functions, his performance was normal (**Table 2**). Only the immediate recall of visual stimuli was weaker than could be expected from his premorbid level but was still within the normal range (low average). Therefore, we classified his cognitive complaints as subjective cognitive decline. Additional autoantibody testing 4 months later revealed again anti-GAD65 autoantibodies in

serum (1:3,200) (**Figure 1**). Our patient is still taking risperidone regularly at a dosage of 4 mg/day. Stupor together with rigidity and immobility that responds to benzodiazepine is diagnosed as akinetic catatonia most likely caused by an underlying chronic paranoid schizophrenia; his illness is thus referred to as catatonic schizophrenia associated with serum and CSF GAD65 autoantibodies. We assumed that his catatonia had an immune origin, as we had detected CSF GAD65 autoantibodies in a psychotic patient in conjunction with a hypokinetic movement disorder symptom like catatonia, which was in line with autoimmune catatonia or autoimmune psychosis with catatonia according to recent guidelines from Pollak et al. (24) and Hansen et al. (25). As another supporting criterion for a catatonia's autoimmune origin, we detected responsiveness to immunotherapy. We had originally suspected stiff-person syndrome as the differential diagnosis, but he failed to meet the criteria for that diagnosis, such as a hyperlordosis or pronounced stiffness. Due to his normal EEG, a persistent non-convulsive status is unlikely, although we cannot rule it out entirely as he did not undergo continuous EEG monitoring. Moreover, we observed no indications of temporal lobe seizures or other seizure types like musicogenic epilepsy, which is reportedly associated with GAD65 autoantibodies (26–28). His EEG revealed no epileptic potentials, making seizures of a temporal origin or otherwise unlikely, although they cannot be fully excluded. As no bitemporal signal abnormalities were found in MRI, his EEG was unremarkable, no temporal lobe epilepsy was diagnosed, and a definitive GAD65-positive limbic encephalitis is highly unlikely.

## DISCUSSION

To our knowledge, it is a novel finding that we detected CSF GAD65 antibodies in association with catatonia, in particular, catatonic schizophrenia. GAD65 antibodies have been reported by many investigators in conjunction with schizophrenia (21), at a higher frequency than in control subjects. GABAergic signaling might be implicated in schizophrenia, as studies have shown weaker GAD67 (29) and GAD65 expression (30) in the brain tissue of schizophrenic patients. Another hint originates from evidence showing that a GABA-related protein like GAD65 is known to be downregulated in the MK-801 schizophrenia-like model in mice, with consequences for GABA metabolism and homeostasis (31). It is thus likely that GAD65 antibodies that impair GABAergic neuronal signaling might affect the disease activity in patients with schizophrenia. Furthermore, catatonia might originate from heightened neuronal activity in premotor regions, as Walther et al. reported (32). They showed that it is unclear whether such increased activity in premotor regions is attributable to locally heightened neural activity *via* cortico-cortical inhibition or inhibitory transmission in cortical-basal ganglia circuits. GAD65 antibodies might conceivably disturb GABAergic signaling in both neuronal loops, resulting in catatonia. A recent study (33) revealed that catatonia correlated with increased functional connectivity in

cerebellum-dependent networks and decreased oscillations in a low-frequency band in basal ganglia networks. Interestingly, the same study demonstrated that motor functions (evident in motor scores correlating strongly with functional network activity in cortico-striatal connections) add support to the second hypothesis of Walther et al. (32) with the most prominent anomalies in neural activity occurring in cortico-basal ganglia loops. The planning and generation of movements are triggered by a complex interplay between excitatory (mostly glutamatergic) and inhibitory GABAergic signaling in motor regions. It is therefore not surprising that autoimmune catatonia might be associated with neural autoantibodies against the two most involved receptors, such as excitatory glutamatergic NMDAR on the one hand (4–14) and inhibitory GABAAR on the other (15–17) (**Table 1**). Immunotherapy *via* corticosteroids, immunoglobulins, and rituximab alleviated catatonia in these patients (4, 15). In GABAAR-positive catatonia, immunotherapy proved effective in treating catatonia, unlike lorazepam and antipsychotics (15). In our case, his catatonia had already responded to benzodiazepine application, which was supplemented by adding IVIGs, underlying the possibility of different response patterns depending on the type of associated antibody. GAD65 antibodies target an intracellular epitope, making it less probable that these autoantibodies mediate the catatonia, as a T cell-driven pathomechanism is often detected in GAD65 autoimmunity (i.e., limbic encephalitis) (34). In contrast, GABAAR antibodies are more probably involved in the pathogenesis of catatonia, as they are antibodies against extracellular targets. In addition to GABAAR and NMDAR antibodies, novel neural autoantibodies (against an unknown epitope in granule cells in cerebellar and hippocampal interneurons) were identified in a patient suffering from psychosis and severe chronic catatonia (19). That patient responded to immunotherapy, but not to standard treatment with antipsychotics and benzodiazepines, supporting the relevance of taking CSF and blood samples to look for both known and novel autoantibodies in order to treat these patients adequately. The strength of our case is that we have expanded the phenotypic spectrum of GAD65 autoimmunity. Limitations concern the evidence level of a case report and the absence of additional CSF parameters underlying an immunogenic origin of catatonia in our patients such as pleocytosis of intrathecal IgG synthesis. Furthermore, long-term EEG monitoring would have facilitated an epilepsy-related GAD65 autoimmunity phenomenon if present. As GAD65 antibodies are not themselves pathogenic, a more straightforward approach would have helped us detect *via* cell flow cytometry immune cell subsets such as T cells in GAD65 autoimmunity or other inflammation parameters like neopterin. We believe that our findings deserve attention, as they provide evidence toward a novel path for investigating psychotic disorders *via* biomarkers like GAD65 autoantibodies, known to be the second most frequently detected serum autoantibody, i.e., in a large cohort of 22,472 suspected paraneoplastic and autoimmune encephalitis patients (35).

We report the case of a schizophrenic patient suffering from akinetic catatonia associated with CSF GAD65 antibodies

responsive to immunotherapy. Our case reveals the possibility that GAD65 antibodies are involved in catatonia's pathogenesis and highlights the urgency of seeking antibodies in these patients, keeping in mind its rarity, as reported in a recent study by Hoffmann et al. (36), and especially atypical GAD-related syndromes (37) as our patient's. A positive response to standard treatment and immunotherapy has the potential to enable a good long-term outcome and maintain the alleviation of symptoms.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the corresponding author.

## ETHICS STATEMENT

Ethical review and approval were not required for the study on human participants in accordance with the local legislation and

institutional requirements. The patient provided their written informed consent for publication.

## AUTHOR CONTRIBUTIONS

NH wrote the manuscript. CB, JW, and BM have revised the manuscript for important intellectual content. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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**Conflict of Interest:** BT was employed by Euroimmun Reference Laboratory.

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