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Novel clinical features of glycine receptor antibody syndrome

A series of 17 cases

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Abstract

Objective

To describe novel clinical features of GlyRα1-IgG–positive patients.

Methods

Patients with a positive serum GlyRα1-IgG were identified during a 2-year period from July 2016 to December 2018 at 2 academic centers and followed prospectively. All patients in this series were evaluated in the Neuroimmunology and Autoimmune Neurology clinics at the University of Utah or the University of Colorado.

Results

Thirteen of 17 patients had phenotypes more typically associated with glutamic acid decarboxylase (GAD65) antibody syndromes, consisting of stiff-person syndrome (SPS) with parkinsonism or cerebellar signs. One patient with parkinsonism had a presentation similar to rapidly progressive multiple system atrophy with severe dysautonomia. Ten of 17 patients had various visual symptoms including visual snow, spider web–like images forming shapes and 3-dimensional images, palinopsia, photophobia, visual hallucinations, synesthesia, and intermittent diplopia. Three of 17 patients presented with primarily autoimmune epilepsy accompanied by psychiatric symptoms.

Conclusions

Clinicians should consider testing for GlyR antibodies in GAD65 antibody–negative or low-positive GAD65 antibody patients with SPS-like presentations, especially in the setting of atypical features such as visual disturbances, parkinsonism, or epilepsy.

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Glossary

DaT = dopamine transporter; **ERG** = electroretinogram; **GAD** = glutamic acid decarboxylase; **MSA** = multiple system atrophy; **PD** = Parkinson disease; **PERM** = progressive encephalomyelitis with rigidity and myoclonus; **SPS** = stiff-person syndrome; **SPSD** = stiff-person spectrum disorder.

Stiff-person syndrome (SPS) is a rare neurologic disorder characterized by progressive muscle stiffness and painful spasms. Several variants have been described, with severity ranging from isolated stiff-limb symptoms to progressive encephalomyelitis with rigidity and myoclonus (PERM) to other neurologic manifestations collectively described as stiff-person spectrum disorder (SPSD). Autoantibodies identified in association with SPSD include glutamic acid decarboxylase (GAD65),[1,2] glycine receptor alpha-1 subunit (GlyRα1),[1,3,4] amphiphysin[1], dipeptidyl peptidase-like protein 6,[5] and gephyrin.[6]

Glycine receptors (GlyRs) are highly expressed in the ventral and dorsal horn of the spinal cord; motor, auditory, vestibular, and sensory nuclei of the brainstem; superior colliculus; granular cell layer of the cerebellum; retina; olfactory bulb; and hippocampus.[7] GlyRs have also been identified in various regions of the basal ganglia, including lower concentrations in the striatum and globus pallidus and larger concentration in the substantia nigra.[8] The GlyRs are formed by the association of any of 4 alpha subtypes (α1-4) and a beta subunit.[9]

GlyRα1 autoantibodies have been recognized in SPSD cases, particularly in patients with PERM.[1,4] Mutations in GlyRα1 and beta subunits are well known in their involvement in hyperekplexia, a paroxysmal motor disorder, and thus, the well-described presence of a hyperstartle reflex is not surprising in PERM and SPSD.[4] GlyRα1 plays an integral role in motor neuron excitability in the brain stem and spinal cord[3] and has also been demonstrated as a key inhibitory receptor in the inner plexiform layer of the retina.[10,11]

We provide a comprehensive evaluation of an expanded neurologic phenotype in all patients identified with GlyR autoantibodies at 2 large academic referral centers over a 2-year period.

Methods

Patient subjects and ascertainment

The study was approved by the Institutional Review Board of the University of Colorado, Aurora, CO, and the University of Utah, Salt Lake City, UT. Patients were identified through keyword search of stiff-person syndrome, GAD65 antibodies, and GlyR antibodies in the medical record from July 2016 to July 2018. Patients were included in this series if they met the following 2 criteria: (1) positive GlyRα1 autoantibody testing in the serum and (2) underwent evaluation in the Neuroimmunology/Autoimmune Neurology clinics.

Autoantibody testing

GlyRα1-IgG binding antibody using cell-based assay testing was performed at Mayo Clinic Laboratories on a research basis. This method of antibody testing has been reported to improve specificity[12] with serum testing.

Data availability

Seventeen patients met the inclusion criteria, and deidentified patient data were collected and summarized in e-tables 1 and 2 (links.lww.com/NXI/A127).

Results

Patients ranged in age from 17 to 75 years. Twelve of 17 patients (71%) had phenotypes typically associated with GAD65 antibody syndromes as part of their presentation, including muscle cramping, spasticity, hyperekplexia, and gait disturbance. Eight of the 17 patients (47%) had significant cerebellar and/or parkinsonian signs on examination. One patient with parkinsonism had a presentation similar to rapidly progressive multiple system atrophy (MSA) complicated by significant dysautonomia (patient 9, table e-1, links.lww.com/NXI/A127). Another patient carried a diagnosis of idiopathic Parkinson disease (PD) 10 years before the discovery of the positive GlyR antibody, tested in the setting of new-onset temporal lobe epilepsy and personality changes (patient 12, table e-1). Both of these patients had cardinal features on examination consistent with PD including resting and postural tremor, postural instability, and bradykinesia, as well as supportive imaging features with a positive dopamine transporter (DaT) scan. With the positive DaT scan results, there is a degree of uncertainty whether the parkinsonism features are related to the GlyR antibody syndrome or a sign of concomitant PD. In patient 9 there were no prior signs of PD reported prior to his progressive, subacute presentation over 2 months, whereas patient 12 had long-standing signs of PD before the onset of his temporal lobe epilepsy, personality changes, and muscle spasms. Patient 12 also had EMG findings supportive of SPS, arguing that SPSD was contributing to his clinical presentation.

Ten of the 17 patients (59%) had prominent visual disturbances including visual snow, spider web–like images forming shapes and 3-dimensional images, palinopsia, photophobia, visual hallucinations, synesthesia, and intermittent diplopia. Although the visual symptoms were similar to those seen with visual aura of migraine, one distinguishing feature seen in our cohort was the persistence of the disturbance, rather than an intermittent visual disturbance as commonly

seen in association with migraine headache. Patient 1 (table e-1 links.lww.com/NXI/A127) presented with several years of visual distortions including palinopsia worsened by light and sound, consistent with synesthesia, with later progression to cognitive symptoms, epilepsy, and muscle spasms. Thirteen years after her initial presentation, she developed a more classic SPS phenotype with progressive full-body stiffness and spasms including diaphragmatic and laryngeal involvement. Her GAD65 antibody was repeatedly negative, and ultimately, a positive GlyR antibody was discovered after the advent of testing. Patient 11 (table e-1) presented with typical features of SPSD and similar visual symptoms of palinopsia, intermittent diplopia, and photophobia. On objective testing, she had automated visual field testing with profound constriction and an abnormal electroretinogram (ERG).

Three of 17 patients had a diagnosis of autoimmune epilepsy, all of which had additional psychiatric symptoms (see summary in table e-1, links.lww.com/NXI/A127). All of these patients had evidence of temporal lobe seizures on EEG. Patient 10 had an initial EEG with higher amplitude delta waves with superimposed fast activity suggestive of extreme delta brush pattern, in addition to multifocal seizures with bitemporal onset. Notably, her NMDA receptor antibody was negative in the CSF.

Only 1 patient in this series (0.06%) had a history of malignancy (patient 7, papillary thyroid cancer); otherwise, no other patients were found to have either a history of malignancy or concurrent malignancy suggestive of a paraneoplastic etiology associated with GlyR autoantibody positivity. A prior published series noted malignancies most commonly presenting in the PERM/SPS phenotypes including thymomas, B-cell lymphoma, Hodgkin lymphoma, breast cancer, and small cell lung cancer.[4]

In this series, 53% of patients with glycine receptor autoantibodies were identified to also have coexisting GAD65 autoantibodies, most of which were considered low titer (41%). We also report a variable response to immunotherapy including steroids, IV immunoglobulin, plasma exchange, and rituximab in this series (table e-2, links.lww.com/NXI/A127). Unlike other published series, which predict greater immunotherapy responsiveness in GlyR patients compared with GAD65 patients, some of our GlyR autoantibody patients demonstrated a progressive course.

Discussion

This series adds to the growing phenotypic spectrum of glycine receptor autoimmunity. GlyR antibodies have recently been described as strongly associated with spinal and brainstem disorders and SPS-spectrum phenotype. The clinical features of GlyR-associated SPSD continue to evolve. Martinez-Hernandez et al.[1] described a cohort of 121 patients with SPS in which those with GlyR antibodies were found to develop SPS-plus phenotypes (defined by all or partial elements of PERM with brainstem dysfunction, myoclonus, upper or lower motor neuron symptoms, sensory and/or autonomic dysfunction, seizures, and cognitive changes) compared with those isolated GAD65-seropositive or GAD65-seronegative patients. In this series, all patients had a positive GlyR autoantibody in the serum. One limitation of the study, due to the lack of CSF availability, was that most patients did not have testing for CSF antibodies (table e-1, links.lww.com/NXI/A127). Documentation of CSF GlyR antibody positivity has been well described in PERM phenotypes[4]; however, GlyR antibodies in the sera have been reported in patients with a more diverse neurologic phenotype including oculomotor disturbance,[4] encephalopathy,[4] SPSD,[4,12] and epilepsy in the absence of CSF positivity.[13] The presence of sera positivity in these more diverse neurologic phenotypes and in other immune-mediated neurologic diseases (e.g., seen concurrently with other autoantibody syndromes including aquaporin-4 or myelin oligodendrocyte glycoprotein antibody syndromes and MS controls)[1,14,15] and in control samples found to have underlying cancer,[15,16] suggests that the specificity of serum GlyR is likely not as strong compared with CSF testing. Previous literature suggests that CSF testing might improve specificity,[12] whereas another study has supported the use of serum antibody testing as sufficient to support diagnosis in the proper clinical context.[4] Here, we expand on the SPS-plus phenotypes to include novel visual symptoms, autoimmune epilepsy, a cerebellar syndrome, and atypical SPS phenotypes with parkinsonian features including a presentation of MSA in patients with antiglycine receptor antibody disease.

Although previous studies have described GlyR antibody patients with optic neuropathy and progressive vision loss[3] and ocular dysmotility,[4] positive visual phenomena or palinopsia have not been previously described. Patients 1 and 2 presented with several years of visual symptoms before the onset of progressive lower extremity stiffness and cramping. Patient 3 had evidence of retinal dysfunction with an abnormal full-field ERG. Therefore, visual disturbances may be an early hint to the GlyR autoimmunity in the appropriate clinical setting. Because GlyRα1 is a major inhibitory neurotransmitter of the human retina,[10] dysregulated signaling may result in positive visual phenomena and unformed visual hallucinations. Further neuro-ophthalmologic investigations are needed to clarify potential retinal and cortical contributions.

GlyRs have been identified in various regions of the basal ganglia, including lower concentrations in the striatum and globus pallidus and higher concentration in the substantia nigra.[8] Given the presence of these GlyRs in the basal ganglia, it is hypothesized that GlyRs may form another inhibitory mechanism modulating basal ganglia function. This is relevant, as it may suggest that parkinsonism present in a subset of patients could be related to GlyR autoimmunity. Glycine stimulates striational and mesolimbic dopamine release.[17] Notably, 42% of patients in this series had evidence of

parkinsonian features on their neurologic examination, and 2 patients had a positive DaT scan.

GlyRα1-IgG, like other cell surface antibodies, targets membrane neuronal surface receptors and alters synaptic transmission. The mechanism for hereditary hyperekplexia inspired the discovery of mutated GlyR resulting in muscle stiffness and an exaggerated hyperstartle response. GlyR antibodies have been described to activate complement and cause receptor internalization via lysosomal pathways,[4] which would be compatible with the clinical signs of decreased glycinergic neurotransmission and the loss of brainstem and spinal inhibition seen in hyperekplexia.[18] The GlyR antibody–mediated pathology could be similar in the basal ganglia and retina, and direct study may provide novel insights into GlyR antibody immunopathophysiology.

GlyR antibodies can coexist with variable titers of GAD65 antibodies. In this study, 53% of patients were identified to have coexisting GAD65 antibodies, most of which were considered low titer (41% of the total cohort). Other prior published reports have seen a similar coexistence of these antibodies.[3,4,12] The coexistence of GAD65 and GlyR is unlikely explained on the basis of cross-reaction alone, given the difference in testing methods—specifically cell-based assay for GlyR and radioimmunoassay for GAD65 testing. Prior published studies have suggested that coexpression of GAD65 and GlyR antibodies portent a good clinical response to immunosuppression.[4,12] Our experience with immunotherapy in this series, however, was not as promising. Although patients may have experienced an initial response to immunosuppression, many developed a relapsing or progressive course. These differences could be due to the longer follow-up time in our study (range 2 months to 17 years) or small sample size.

Clinicians should consider testing for GlyR antibodies in negative or low-positive GAD65 autoantibody patients with SPS-like presentations, especially in the setting of atypical features such as visual disturbances or parkinsonism. Our observation broadens the spectrum of clinical presentations associated with GlyR antibodies and emphasizes clinical presentations outside of the classic SPS and PERM phenotypes. Furthermore, although some patients responded quite well to immunomodulation initially, many had a more progressive, immunotherapy-refractory course, especially when followed over time.

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Appendix Authors

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Amanda L. Piquet, MD	University of Colorado School of Medicine, Aurora, CO	Author	Drafted and revised the manuscript for intellectual content and direct patient care.
Murtaza Kahn, MD	University of Colorado School of Medicine, Aurora, CO	Author	Revised the manuscript for intellectual content and direct patient care.
Judith Warner, MD	University of Utah, Salt Lake City, UT	Author	Revised the manuscript for intellectual content and direct patient care.
Matthew P. Wicklund, MD	University of Colorado School of Medicine, Aurora, CO	Author	Revised the manuscript for intellectual content and direct patient care.
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Appendix *(continued)*

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Teri L. Schreiner, MD, MPH	University of Colorado School of Medicine, Aurora, CO	Author	Revised the manuscript for intellectual content and direct patient care.
Lauren Seeberger, MD	University of Colorado School of Medicine, Aurora, CO	Author	Revised the manuscript for intellectual content and direct patient care.
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