

Kathrin Doppler, MD
Barbara Schleyer
Christian Geis, MD
Benedikt Grünewald,
PhD
Evelyn Putz, MD
Carmen Villmann, PhD
Claudia Sommer, MD

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LOCKJAW IN STIFF-PERSON SYNDROME WITH AUTOANTIBODIES AGAINST GLYCINE RECEPTORS

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A 37-year-old man was admitted to our hospital in 1998 with severe contraction of both masseter muscles, which made him unable to open his mouth. He could only drink using a straw fitting through a tooth gap. Spasms of the facial and masseter muscles had started in 1993 and transiently improved after treatment with benzodiazepines. The patient's history included treatment of back and joint pain in 1990 and several admissions to psychiatry for "conversion neurosis." At one time, his wife was suspected of poisoning him with an insecticide because of residues of parathion in his serum.

Neurologic workup including brain and spinal cord MRI, lumbar puncture, extensive blood tests, and nerve conduction studies were normal. EMG showed profuse activity of the masseter muscle that increased when the mouth was passively opened. The masseter inhibitory reflex (MIR), performed according to Aramideh and Ongerboer de Visser,¹ revealed lack of the late silent period (SP2) even at high stimulus intensities, while the early silent period (SP1) was present (figure 1A).

With a tentative diagnosis of autoantibody-mediated stiff-person–like disorder, plasmapheresis was initiated. After the third treatment, the patient was able to open his mouth and to eat normally. EMG showed normal muscle activity. Both SP1 and SP2 of the MIR were now present (figure 1B).

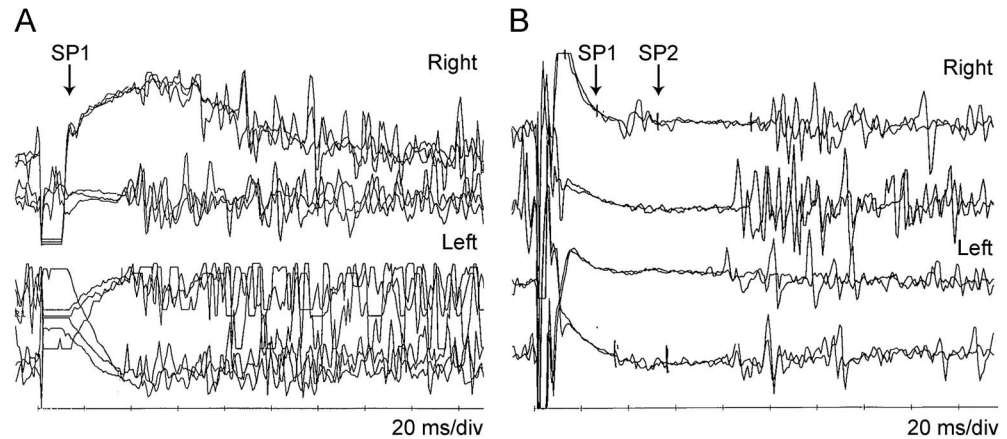
However, after 2 months, lockjaw reappeared. Again, plasmapheresis led to complete recovery. For 1 year, plasmapheresis was repeated every 6 weeks, because this was the interval when lockjaw recurred. Corticosteroids (methylprednisolone 1,000 mg/d for up to 5 days), azathioprine (150 mg/d), and IV immunoglobulins (Igs) (5×30 g, equaling 2 g/kg body weight) were ineffective and unable to prolong the intervals. In 1999, spasms of the right body and sudden falls occurred. Again, plasmapheresis led to fast improvement. Consecutive treatment with mycophenolate mofetil, cyclophosphamide, and rituximab was not effective. Immunoabsorption using a protein A-coated column was regularly performed since then,

and a Cimino fistula was installed in the patient's left forearm for reliable vascular access. Still, lockjaw was the main symptom, remitting rapidly after immunoabsorption and recurring a few weeks later (video at Neurology.org/nn). If an interval of 4 weeks for immunoabsorption was maintained, lockjaw could be prevented. Whenever the interval was prolonged—like most recently because of a strike of train drivers in May 2015, which made it impossible for the patient to attend our department for immunoabsorption—lockjaw and falls reoccurred. Limb spasms and dystonic malposition of the right fingers 3 to 5 are present most of the time, but myoclonus, other brainstem symptoms, and hyperekplexia have not occurred so far. Assays for autoantibodies against anti-glutamate decarboxylase or anti-amphiphysin were negative, as was tumor screening. Patient serum did not bind to sections of human, rat, or mouse nervous tissue but did bind to freshly dissociated mouse hippocampal neurons.

In 2014, anti-glycine receptor (GlyR) α autoantibodies were detected in the patient's serum and purified IgG by binding assays using unfixed human embryonic kidney 293 cells transfected with GlyR $\alpha 1$, $\alpha 2$, and $\alpha 3$ (figure 2). Binding to $\alpha 1$, $\alpha 2$, and $\alpha 3$ subunits suggests that GlyR autoantibodies recognize an epitope common to all α subunits. Similar reactivity to all α subunits that, however, did not relate to the overall autoantibody titers has been described in a recent study.² In fact, the use of unfixed cells has been reported to be more sensitive compared to fixed cells in the detection of GlyR $\alpha 1$ autoantibodies.³ GlyR $\alpha 1$ autoantibodies have been described in patients with progressive encephalomyelitis with rigidity and myoclonus (PERM),^{4–6} a more severe variant of stiff-person syndrome, and also in 12% of patients with stiff-person syndrome.⁷ In a larger cohort of GlyR α antibody–positive patients, the majority showed the typical clinical picture of PERM; only 2 patients had stiff-person syndrome.² Trigeminal, facial, and bulbar symptoms, including trismus, were reported at the onset of disease in 47% and in 57% during the course of disease.² Trismus was also predominant in an adult in this study, resulting in an inability to eat.⁶ However, all patients described so far presented with additional signs and symptoms,

Supplemental data
at Neurology.org/nn

Figure 1 Masseter inhibitory reflex

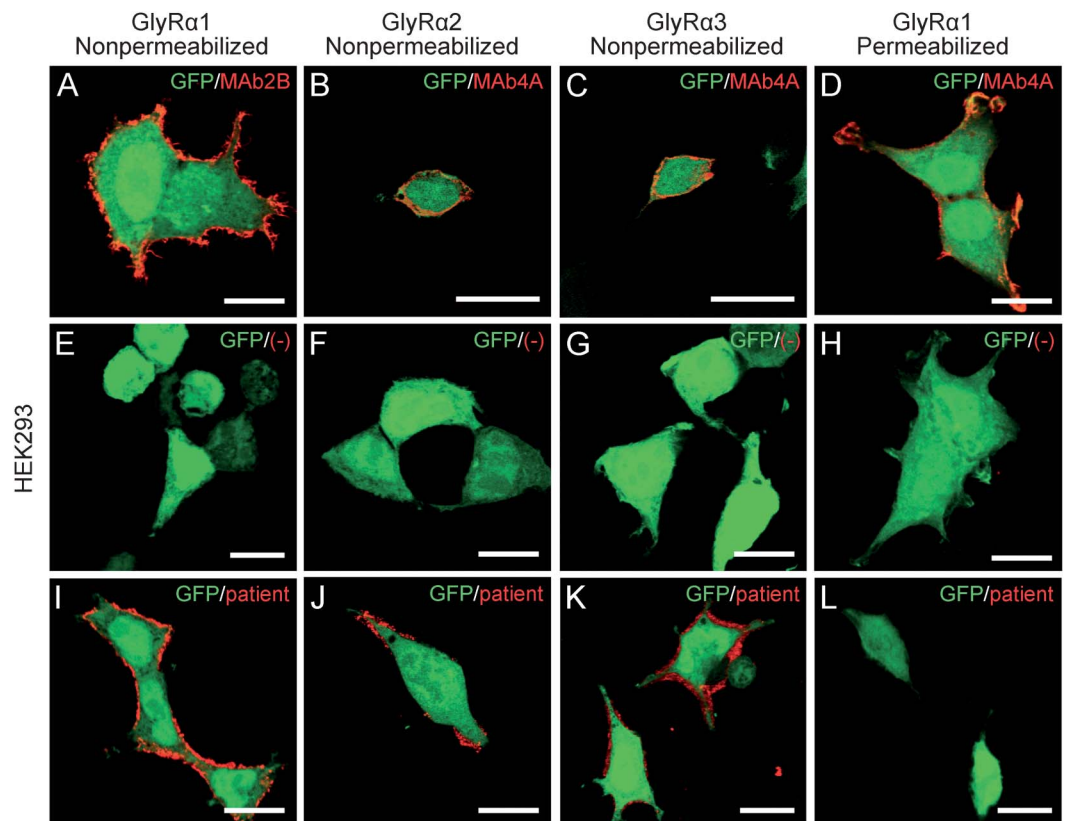


The masseter inhibitory reflex revealed lack of the late silent period (SP2) even at high stimulus intensities, while the early silent period (SP1) was present (A). After treatment, both silent periods (SP1 and SP2) were present (B).

facilitating diagnosis of stiff-person syndrome or PERM. Several studies aimed to determine the clinical syndrome of anti-GlyR antibody-related disease,

but concluded that it comprises a wide range of symptoms, mostly summarized as PERM.^{2,6} Brainstem symptoms are often reported, and binding assays with

Figure 2 GlyR antibody binding



Antibodies bind to extracellular domain of glycine receptor subunits. HEK293 cells were cotransfected with GFP and with different glycine receptor subunits 1, 2, 3. Cells were incubated with purified patient IgG (I-L) and IgG from a healthy control (E-H) in a 2 mg/mL concentration. The GlyR 1-specific antibody MAb2B was used as a positive control, as well as the pan-antibody MAb4A to stain 2 and 3 (A-D). Of note, the surface staining of all GlyR subunits upon incubation with the patient's IgG is only present in live cells (A-C, E-G, I-K), not in fixed and permeabilized cells (D, H, L), while the control antibodies bind in both conditions. This shows that the antibodies in patient serum bind only to the glycine receptors in their native state. White bar = 10 μ m. GFP = green fluorescent protein; GlyR = glycine receptor; IgG = immunoglobulin G; MAb = monoclonal antibody.

patients' sera on brainstem showed distinctive binding,² which is in line with the predominant distribution of GlyR in the brainstem.⁸ GlyR mediate inhibitory neurotransmission and dysregulation may induce uncontrolled excitation resulting in muscle spasms.⁸ The lack of the MIR SP2 in contrast to the preserved SP1 underscores a deficit in inhibitory neurotransmission at the level of the pontomedullary junction.¹ Of note, in GAD antibody-positive stiff-person syndrome, the MIR can be elicited with high stimulus intensities, in contrast to the glycine receptor disorder familial hyperekplexia,⁹ which supports the glycine-related pathophysiology in our patient.

We conclude that stiff-person syndrome and especially anti-GlyR-mediated disease needs to be considered in cases of severe lockjaw even if there are no other relevant symptoms of stiff-person syndrome or PERM at the onset of disease as the clinical presentation is heterogeneous. Appropriate treatment needs to be initiated to prevent disease progression. In our case, plasmapheresis was started before the detection of autoantibodies. An unequivocal response to plasmapheresis can be of diagnostic value in suspected autoantibody-mediated disease and can significantly improve patients' quality of life.

From the Department of Neurology (K.D., C.G., B.G., C.S.), Institute for Clinical Neurobiology (B.S., C.V.), and Department of Transfusion Medicine (E.P.), University Hospital Würzburg; and Hans Berger Department of Neurology and Center for Sepsis Control and Care (C.G., B.G.), Jena University Hospital, Jena, Germany.

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Correspondence to Dr. Sommer: sommer@uni-wuerzburg.de

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