Successful Treatment of Anti-Caspr2 Syndrome by Interleukin 6 Receptor Blockade Through Tocilizumab

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Significant progress has been made in autoantibody-related neurological disorders.1 Typically, paraneoplastic syndromes are associated with tumors for which onconeuronal antibodies are directed against intracellular proteins. They appear to be mediated by cytotoxic T-cell responses and often display a limited treatment response.2 Interestingly, the newly described autoimmune synaptic or presynaptic disorders may occur without neoplasias.3 They appear to be directly mediated by autoantibodies targeting extracellular neuronal cell surface or synaptic proteins. These syndromes usually respond to immunotherapy better, although fatal courses have been reported.4 Among these recently characterized autoimmune diseases are the anti–voltage-gated potassium channel (VGKC)-associated syndromes.5 As the VGKC controls the axonal membrane in both the peripheral nervous system and central nervous system (CNS), patients may develop CNS dysfunction as well as peripheral nervous system symptoms. The combination of peripheral nervous system and CNS symptoms is called Morvan syndrome.6 Precisely, VGKC autoantibodies in Morvan disease are not primarily directed against the potassium channels themselves, but they often recognize a protein that is complexed with VGKC, the paranodal contactin-associated protein-like 2 (Caspr2).6

As the clinical presentation may vary greatly, it is likely that the syndromes often remain undetected and thus underdiagnosed. We report a case with an unusual clinical triad of epilepsy, dysarthria, and paroxysmal kinesigenic dystonia in which an anti-Caspr2-associated syndrome was eventually diagnosed.

Because these symptoms appear to be directly mediated by the presynaptic Caspr2 autoantibodies, we hypothesized that a B-cell–targeted immunotherapy may be more promising than traditional approaches.2 Using tocilizumab, a humanized monoclonal antibody against the interleukin 6 (IL-6) receptor, we have achieved complete and stable remission of symptoms.

Report of a Case

A 55-year-old man first presented to our department with a mild left-sided hemiparesis. The symptoms showed a quick and complete recovery. Besides these acute symptoms, the patient noted a fluctuating but progressive gait disturbance and dysarthria for several months. As a startle reaction, the patient showed a speech arrest for several seconds.

The onset of these symptoms was about 4 months prior to presentation. On referral to another neurological academic department, the symptoms were suspected to be psychogenic after extensive neurological investigations. Two months later, the patient had a generalized epileptic seizure,
and the anticonvulsive medication levetiracetam was started. Except smoking and latent hypertension, there was no other relevant medical history and no further medication was taken. The family history was unremarkable.

Neurological examination on admission revealed a mild left-sided hemiparesis with subsequent full remission. Examination findings of cranial nerves were normal, but fluctuating dysarthria was noted. There were no ataxia or sensory disturbances. Some rare muscle fasciculations were observed in all extremities. When starting to walk, the patient showed myocloniform movements in the lower limbs, partly with a slight dystonic posture (Video). This kinesigenic gait disturbance resulted in a short-term inability to walk; after a short resting period, however, the symptoms completely resolved. This gait disturbance was also accompanied by a subjective feeling of tightness and clumsiness in the left arm. Neuropsychological examination showed no evidence of significant depressive symptoms or cognitive deficits. The patient denied insomnia or vegetative symptoms like hyperhidrosis.

Cerebral magnetic resonance imaging revealed a subcortical lesion in the right hemisphere, without any signs of suspected vasculitis or encephalitis (Figure) and without evidence of microbleeds in the corresponding T2* sequence. Findings on neurosonological examination as well as electrocardiography and electroencephalography were normal. Extensive electromyographical analyses revealed some neuromyotonic discharges in the form of couplets.

Findings on general serological investigations including erythrocyte sedimentation rate and vasculitis typical parameters were normal. Also, blood serologies for viruses (hepatitis, human immunodeficiency virus) and Lyme disease were negative. Paraneoplastic antibodies including anti-glutamic acid decarboxylase, anti-Hu, anti-Ri, anti-Yo, anti-CV2/collapsin response mediator protein, anti-amphiphysin, and anti-Ma2 were negative. Antiphospholipid antibodies and anti–acetylcholine receptor antibodies were negative. Findings on thorough cerebrospinal fluid (CSF) examination were unremarkable.

Serum VGKC-complex antibody titers were measured by radioimmunoassay and were present at a titer of 381 pmol/L (reference range, 0-85 pmol/L; Labor Krone, Bad Salzuflen, Germany). Further investigation using immunohistochemistry and cell-based assays then revealed that the patient had autoantibodies targeting Caspr2 at an IgG titer of 1:500 000 (range, <1:10; laboratory of Christian G. Bien, MD, Epilepsy Center Bethel, Bielefeld, Germany), while the serum Caspr2-IgA titer was 1:10 (normally negative). Further analysis of CSF revealed the presence of Caspr2 antibodies with an IgG titer of 1:4000, resulting in a CSF Caspr2-IgG antibody index of 2.46 (CSF Caspr2-IgA was negative). Other targets known to be complexed with VGKC in peripheral nerves and CNS such as Lgi1 were negative.

A 3-day course of methylprednisolone sodium succinate (1 g/d) was initiated. The patient then showed full remission after alternate treatment with plasma exchange and immunosorption. To further suppress B-cell activation, treatment with the IL-6 receptor–blocking antibody tocilizumab was initiated at a standard dosage of 8 mg/kg every 4 weeks.

At the last visit (7 months after initiation of IL-6 receptor-blocking therapy with tocilizumab), he was still seizure free and was able to fluently converse, even in situations in which he was startled. No gait disturbances have occurred and walking distance is not limited. Repeated extensive tumor screening after 6 months did not reveal a neoplasia; in particular, there were no signs for an underlying thymoma.

The serological follow-up examination revealed moderately decreased titers (VGKC-complex antibody at a titer of 243 pmol/L and Caspr2-IgG titer of 1:100 000). This is in accordance with the observation that in contrast to other autoantibody-related neurological diseases, in Caspr2 antibody-associated syndromes the serology does not necessarily reflect the clinical course (Christian G. Bien, MD, written communication, January 3, 2013). The probably more relevant follow-up analysis of CSF was not approved by the patient.
Discussion

Herein, we describe the successful treatment of anti-Caspr2 syndrome with the B-cell-directed monoclonal antibody tocilizumab. Recently, the number of antineuronal antibodies reported in the context of autoimmune neurological disorders as well as the number of clinical vignettes has increased significantly. In this context, one of the latest discoveries has been antibodies directed against the paranodal Caspr2, a transmembrane protein with a large extracellular domain previously attributed to VGKC. It is essential for the clustering of VGKC subunits Kv1.1 and Kv1.2 at juxtaparanodal regions of myelinated axons. The presence of Caspr2 antibodies is associated with a subgroup of autoimmune-mediated neurological disorders, including encephalitis, peripheral nerve dysfunction, or a combination of both, called Morvan syndrome.

We report a case with an atypical combination of mild peripheral nerve symptoms and dominant CNS dysfunction with kinesigenic dystonia and epileptic seizures in which a high titer of Caspr2 antibodies was detected. As the most frequently reported neuropsychiatric features and dysautonomia in Morvan syndrome did not occur in our case, it is unclear whether our patient should be classified as having an atypical Morvan syndrome or has a completely different disease entity additionally accompanied by cerebrovascular events. It could be hypothesized that antibodies binding to the VGKC complex in the brain microvessels (here the Caspr2 autoantibodies) may induce a perturbation of vascular homeostasis leading to vasocostriction or that direct activation of the complement cascade leads to endothelial damage. This hypothesis has been expressed as the underlying course in a recently published case with VGKC antibody-associated cerebral microbleeds. Of course, this hypothesis will require further investigations to be confirmed. Our case demonstrates that the clinical presentation of autoantibody-mediated neurological disorders may vary widely and that Caspr2 antibodies may be associated with a broader clinical spectrum than yet described.

Kinesigenic dyskinesia may include dystonia, athetosis, ballism, or chorea. It is induced by sudden voluntary movement and may occur as a result of a wide variety of conditions, including trauma, metabolic abnormalities, CNS infections, or an autoimmune origin. Owing to the heterogeneous causes of this syndrome, the recommended therapeutic regimens include both anticonvulsants and immunosuppressants.

The exact mechanism of the paroxysmal kinesigenic dyskinesia in our patient is probably based on Caspr2 autoantibody-mediated dysfunction of the VGKCs with an increase of excitability finally resulting in hyperpolarization of neurons. Recently, Aradillas and Schwartzman reported a case of paroxysmal dystonias associated with VGKC-complex antibody encephalitis. Even if it has been initially referred to as paroxysmal kinesigenic dyskinesia, the described movement disturbance is very different from the dyskinesia in our patient. There, the paroxysmal dystonic face and limb movements in their 38-year-old male patient were very frequent (about 50 per day) and each episode lasted only for seconds (Video). Interestingly, Sarosh R. Irani, MD, DPhil, indicates in his online comment to the article by Aradillas and Schwartzman that these paroxysmal dystonias were identical to the episodes recently described in 29 patients by him and his colleagues, and thus it may rather be classified correctly as faciobrachial dystonic seizure. Faciobrachial dystonic seizure was found to be consistently in association with autoantibodies targeting Lgi1 and not Caspr2, even though both antigens were previously attributed to the VGKC complex.

The plethora of immunotherapeutic approaches against Caspr2 syndrome is described in a recently published case series of 8 patients with Caspr2 antibody-associated disorders. Corticosteroids and plasma exchange are the established therapy in the acute phase. Three of the 8 patients were subsequently treated with rituximab. In 1 patient, intravenous immunoglobulin was used both as initial treatment as well as maintenance immunotherapy. Seven of the 8 patients responded to immunotherapy (median follow-up in this case series, 8 months). Nevertheless, in a recent large report of clinical and serological observations in 29 cases of Morvan syndrome, even fatal courses were reported. Most of these patients had antibodies to many of the tested VGKC-complex components (Caspr2, Lgi1, and contactin 2). Only 6 of them had only Caspr2 antibodies, as in our case. Interestingly, the therapeutic responses in this group were poorest, as 4 of these 6 patients died. The mortality in this subgroup was associated with thymoma recurrence.

The inconsistent data about the responsiveness to immunotherapy in patients with Morvan syndrome with isolated Caspr2 antibodies indicated to us that further optimization of therapy may be necessary. As the pathophysiology in this presynaptic disorder appears to be directly mediated by antibodies directed toward the extracellular neuronal cell surface, B-cell-depleting or B-cell-paralyzing therapy might present the most promising immunotherapeutic approach. In this context, tocilizumab, a chimeric monoclonal antibody against CD20, primarily found on the surface of B cells, has shown positive effects in a few cases of patients with Caspr2 antibodies. Nevertheless, owing to the long-lasting effect of rituximab and the absence of the CD20 antigen on mature plasma cells and plasmablasts, it is more difficult to handle possible adverse effects. Thus, B-cell-energizing therapy using tocilizumab, a humanized monoclonal antibody against the IL-6 receptor, might be more advantageous. Furthermore, our experience has shown that tocilizumab was also effective in neuromyelitis optica cases nonresponsive to rituximab therapy. Following a similar approach in our patient with Caspr 2 autoantibodies, a full and stable remission of symptoms has been achieved over a follow-up period of 7 months so far. Tocilizumab has been well tolerated ever since.

Conclusions

Autoantibodies to Caspr2 may induce a various combination of peripheral nerve symptoms and CNS dysfunction. To our knowledge, this is the first report of a symptom triad with epilepsy, dysarthria, and paroxysmal kinesigenic dyskinesia.
In our patient, implementation of a B-cell–anergizing therapy using tocilizumab, a humanized monoclonal antibody against the IL-6 receptor, has shown an excellent response. Larger case series or even controlled studies are needed to confirm the efficacy of tocilizumab in autoimmune synaptic and presynaptic diseases.

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