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Autoimmune Parkinsonism: A Newer Manifestation of Contactin-Associated Protein-Like 2 Autoimmunity: A Case Report

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Abstract
Contactin-associated protein-like 2 (CASPR2) antibodies are part of an expanding spectrum of disorders. Although they were initially associated with Morvan's syndrome and peripheral nerve hyperexcitability, their clinical manifestations are more varied than previously recognized. In this report, we present a rare case of a middle-aged woman who experienced gait disturbances, sleep disturbances, behavioral changes, and postural abnormalities over a period of five months. A thorough examination revealed a Parkinsonian phenotype. Considering the timeline and symptomatology, an autoimmune work-up was conducted, which detected CASPR2 antibodies in the patient's serum. Treatment with high-dose intravenous Methylprednisolone followed by rituximab effectively reversed her clinical manifestations without residual neurological deficits.
Keywords: Potassium channels; Voltage-gated; Rituximab; Methylprednisolone; Autoimmune disease of the nervous system; Antibodies; CNTNAP2 protein; Human.

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Introduction

Over the last few decades, the identification of numerous antibodies has greatly aided in understanding the clinical syndromes linked to autoimmune disorders of the nervous system. In many of these conditions, movement disorders are frequently observed, and their gradual onset often provides valuable diagnostic information.[1] Contactin-associated protein-like 2 (CASPR2) is a membrane protein found in both the central nervous system (CNS) and the peripheral nervous system (PNS). Its primary function is to facilitate the positioning of voltage-gated potassium channels (VGKC) and other proteins within the juxtaparanodal region of myelinated axons, present in both the PNS and CNS.[2,3] Most studies concerning CASPR2 autoimmunity have centered on the patients' preselected clinical conditions such as Morvan's syndrome, epilepsy, and pain syndromes. The existing literature on CASPR2 autoimmunity mainly comprises a limited number of short case series. Furthermore, the recently identified autoimmune parkinsonism phenotype has only been documented once in medical literature. [2,4] We present a rare case of a 47-year-old female patient who presented with a five-month duration of involuntary jerking involving the upper and lower limbs, sleep and behavioral disturbances, and postural changes. Despite the initial indications of a rapidly progressing neurodegenerative disorder, a focused serological work-up unveiled CASPR2 autoimmunity alongside a clinical phenotype of Parkinsonism. Swift recognition of the condition, coupled with appropriate immunotherapy and supportive treatment, led to an exceptional outcome.

Case Report

A 47-year-old female presented to the neurology outpatient department with involuntary jerking movements for the past five months, initially involving both of her upper limbs. Over time, these jerks rapidly progressed to involve both her lower limbs, causing her walking to become erratic and requiring support to prevent falls. Her relatives reported that these jerks persisted even during sleep. They also noticed a change in her body posture while walking, characterized by stiffness in her back and a tendency to lean backward when standing or walking, although not while sitting. Additionally, there had been a recent change in her behaviour, with increased anxiety and frequent irritability. She reported a weight loss of approximately eight kilograms within the last five months. She denied any history of changes in

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smell, constipation, or urinary urgency. She was known hypertensive on regular medication. The relatives also mentioned that she had taken herbal remedies for body pains for two months the year before, after which the aforementioned symptoms started. She did not smoke nor drink. She was conscious and cooperative, and during a comprehensive mental status examination, she exhibited inattention while her other cognitive domains were intact. The motor examination revealed generalized bradykinesia, predominantly axial rigidity with mild appendicular rigidity, and multifocal stimulus-sensitive myoclonus. Extra-ocular movements appeared normal. Fasciculations, myotonia, or other extrapyramidal signs were not observed. There were no indications of weakness or sensory deficits. The patient's gait was slow and erratic, necessitating support even for short distances due to body bradykinesia and frequent leg myoclonus. While walking, a stiff neck and trunk were noted, and a tendency for retropulsion on the pull test was observed. Initially, the possibility of stiff person syndrome (SPS) and related disorders was considered.

A magnetic resonance imaging (MRI) of the brain, along with whole spine screening, yielded normal results. Due to the frequent myoclonus, completion of the contrast study was not feasible. Anesthesia support was avoided since the plain study showed normal findings. The cerebrospinal fluid (CSF) analysis revealed normal cell count, protein levels, and glucose concentration. The serum autoimmune profile exhibited a strong positive result for CASPR2, while the serological workup for SPS was negative. Whole-body PET/CT (Positron emission tomography/computed tomography) scanning for cancer screening yielded negative results.

The treatment approach commenced with a 5-day course of intravenous methylprednisolone at a dosage of 30 mg/kg/d, followed by two doses of Rituximab (1 g) administered two weeks apart. The patient's regimen included oral prednisolone (1 mg/kg/d) with a tapering dosage, as well as levetiracetam (500 mg twice daily) and clonazepam (0.5 mg daily) for managing her myoclonus. Within one month, the patient reported a notable reduction in myoclonus and rigidity and regained the ability to walk independently. After three months, the use of steroids was discontinued, and the patient remained in remission. A second and third cycle of rituximab was administered after a six-month and 12-month interval correspondingly. Levetiracetam and clonazepam were also tapered and stopped. The plan is to maintain the patient on Rituximab for two years. Throughout the 18-month follow-up period, the patient remained in remission without any recurrence of symptoms.

Discussion

VGKC are a diverse collection of tetrameric signaling proteins, typically structured with alpha-subunits possessing 6-transmembrane domains, and often accompanied by a range of auxiliary proteins. These channels have a crucial role in generating cellular action potentials, which makes them extremely important in the functioning of neurons and muscles. They also have the potential to be significant in the context of autoantigens.[5] Initially, anti-VGKC antibodies were implicated in several autoimmune conditions, including epilepsy, acquired neuromyotonia, limbic encephalitis, Morvan syndrome, gastrointestinal dysmotility, and dysautonomic phenomena such as hyperhidrosis. Nonetheless, recent findings indicate that only certain variants of anti-VGKCs are associated with disease.[2,5,6]

It was later discovered that the antibodies were not directly attacking the VGKC subtypes; instead, they were targeting associated proteins. In 2010, two of these proteins were identified: leucine-rich gliomainactivated1 (LGI1) and CASPR2. Antibodies directed against LGI1 are mainly associated with limbic encephalitis and faciobrachial dystonic seizures. In contrast, the clinical conditions related to CASPR2 antibodies show greater variability.[2]

In their study, Tan et al uncovered a wider array of neurological symptoms linked to VGKC autoantibodies, surpassing prior expectations.[5] CASPR2 antibodies fall under the category of VGKC antibodies and are primarily tied to manifestations in the PNS. The main symptoms include peripheral nerve hyperexcitability, autonomic dysfunction (as seen in Morvan's syndrome), encephalopathy, and insomnia. The spectrum of clinical manifestations associated with CASPR2 antibodies is continually expanding. Subsequent reports have shown connections with myoclonus, orthostatic myoclonus, myoclonic status epilepticus, dyskinesia, cerebellar ataxia, seizures, chronic pain, chorea, Guillain-Barre syndrome, Creutzfeldt-Jakob disease, amyotrophic lateral sclerosis, fronto-temporal dementia-like syndrome, and eyelid tremors.[4]

However, the core clinical features include cerebral symptoms (cognition, epilepsy), cerebellar symptoms, peripheral nerve hyperexcitability, autonomic dysfunction, insomnia, neuropathic pain and weight loss.[2]

The precise pathogenesis of this range of disorders are still not well understood. Nonetheless, the consistent positive therapeutic response to treatments like intravenous immunoglobulins (IVIg) and plasmapheresis, along with other forms of immunotherapies reported in the literature, supports the idea that a humoral immune-driven mechanism is at play.[7] It is important to note that this does not mean VGKC autoantibodies are solely responsible for all neurological manifestations. They actually function as an underappreciated indicator of autoimmune neurological disorders, possibly influenced by accompanying autoantibodies (including some yet

unidentified) or cytotoxic T-lymphocytes.[5]

The CASPR2 protein is widely found throughout the CNS, including regions like the frontal lobes, perisylvian areas, and Broca's area. Furthermore, this protein is notably expressed in subcortical structures, which encompass the dorsal thalamus, putamen, caudate, and amygdala. The presence of CASPR2 protein in the basal ganglia could potentially offer insights into the development of parkinsonism.[4,8]

CASPR2 autoimmunity has been reported to predominantly affect men (89%) with a median age of 66 years.[2] However, our patient, a middle-aged woman, represents a notable deviation from the typical demographic profile observed in CASPR2 autoimmunity cases. Based on her medical history, our patient had been using native herbal medicine for two months prior to the onset of her symptoms. An estimated four billion people across the globe, especially in developing nations, depend on various herbal remedies for their healthcare. Yet, the herbal medicine industry lacks proper regulation, leading to limited or even absent patient oversight. It is not unusual for some plant species used in these remedies to carry natural toxicity or to be contaminated with excessive or prohibited pesticides, harmful microbes, heavy metals, chemical toxins, conventional medications, and other impurities.[9] The exposure to heavy metals is believed to have the potential to play a role in the development of autoimmune conditions and the emergence of CASPR2 antibodies, either directly or indirectly.[4,10,11]

In our case, the initial consideration was given to the possibility of a spectrum of disorders related to SPS. SPS is an uncommon disorder marked by a gradual increase in muscle stiffness, rigidity, and spasms, mainly impacting the core muscles of the trunk and the proximal muscles of the limbs. Muscle spasms in SPS are often triggered by stimuli like touch, noise, or emotional stress. Conditions related to SPS include progressive encephalomyelitis with rigidity and myoclonus (PERM), which shares SPS-like symptoms and may also involve brainstem dysfunction, seizures, or encephalopathy. Additionally, there's stiff-limb syndrome, where one or more limbs display rigidity primarily at the distal ends.[1] However, the serological workup yielded negative results for GAD65 (glutamic acid decarboxylase 65-kilodalton isoform) antibody, which is the classical marker for SPS/PERM. It was also negative for other autoantibodies associated with the SPS/PERM spectrum, such as Anti Ri (Anti-neuronal nuclear autoantibody type 2), Anti-glycine receptor antibodies, and Anti-amphiphysin antibodies.

Our patient exhibited a combination of bradykinesia and rigidity, which are essential criteria for diagnosing parkinsonism according to the Movement Disorder Society clinical diagnostic criteria for Parkinson's disease.[12] Furthermore, there were noticeable features such as prominent myoclonus, behavioral changes, and predominant axial rigidity, accompanied by early gait abnormalities. These signs collectively indicate the likelihood of atypical or secondary parkinsonism. Given the subacute onset and relatively rapid progression of symptoms, we pursued a comprehensive evaluation for reversible causes. Considering the timeline of the evolution of the clinical features, an autoimmune etiology was deemed a probable possibility.[1,2,4-6]

The MRI results were unremarkable, and the whole-body PET/CT scan for cancer screening yielded negative results, effectively excluding paraneoplastic movement disorders.[1] Furthermore, additional autoimmune investigations revealed strong positivity for CASPR2. In our case, if we had limited the testing to a narrow range of defined neurological syndromes, the diagnosis would have been overlooked.

The patient started to show clinical improvement after receiving steroid pulse therapy, which strongly supports an autoimmune etiology. Similar results have been observed in a study conducted by Tan et al, where immunotherapy resulted in benefits for 89% of the participants, with 50% of them reporting marked improvement.[5] In another short case series by Kannoth and colleagues, all three patients with CASPR2 autoimmune manifestations responded well to immunotherapy.[4] Following the administration of steroids, Rituximab was initiated, which is one of the most commonly used second-line agents for autoimmune encephalitis. Rituximab has shown particular effectiveness in patients who did not respond to conventional immunotherapies such as pulse steroid therapy, IVIg, or plasmapheresis.[2,4,13,14] The existing literature strongly supports the use of rituximab in CASPR2 autoimmunity. Thaler and co-workers reported that early and short-term rituximab therapy could be an effective and safe treatment option for most patients.[15] As our patient fulfilled the clinical criteria for parkinsonism and also tested positive for CASPR2 antibodies she fits into the newly described entity of autoimmune parkinsonism. To the best of our knowledge, this represents a highly uncommon manifestation of CASPR2 autoimmunity, thus adding valuable evidence to the existing literature.

Conclusion

Parkinsonism syndrome is an important manifestation of CASPR2 autoimmunity. When the clinical phenotype resembles that of a neurodegenerative disease, it is crucial to investigate potential treatable causes, especially when the symptoms have recently appeared. In today's age of accelerated understanding of autoimmune diseases, conducting a targeted serological workup aids in achieving an accurate diagnosis. This, in turn, plays a significant role in minimizing long-term disability for both the patient and reduces the burden of the caregivers.

Authors' Contribution

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Competing Interests

None declared.

Ethical Approval

All the authors declare that they have adhered to the following principles of ethical consideration in research: voluntary participation, informed consent, anonymity, confidentiality, potential for harm, and results communication.

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