

A case of hyperkinetic movement disorder associated with LGI1 antibodies

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Encephalitis associated with leucine-rich glioma inactivated 1 (LGI1) antibodies is often encountered in elderly male patients and may infrequently present with isolated syndromes. A 6-year-old boy was admitted with acute onset severe oral and facial stereotypic and choreiform movements. On his neurologic examination, he had repetitive and rhythmic movements in orolingual muscles including tongue protrusion, limb chorea and minimal facial stereotypic movements. Anti-streptolysin O (ASO) titers were found severely elevated in several measurements. Well-characterized antibodies against ion channels and synapse proteins were negative whereas LGI1 antibody was positive in both serum and CSF. Marked clinical improvement was observed after immunotherapy. Here, we present the first pediatric case with LGI1 antibody associated hyperkinetic movement disorders and emphasize the importance of investigating neuronal autoantibodies in patients with isolated and treatment resistant movement disorders.

Key words: hyperkinetic movement, autoimmune encephalitis, LGI1 antibody, Sydenham's chorea, immunoglobulin therapy.

Autoimmune encephalitis is characterized by seizures, memory dysfunction, behavioral changes and loss of consciousness that are related to neuronal antibodies against a variety of antigens including N-methyl-D-aspartate receptor (NMDAR), α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA), leucine-rich glioma-inactivated 1 (LGI1), contactin-associated protein like-2 (CASPR2), gamma-aminobutyric acid B receptor (GABA_BR) and glutamic acid decarboxylase (GAD) ¹⁻³.

Leucine-rich glioma-inactivated 1 (LGI1) is a secreted protein that interacts with post-synaptic A disintegrin and metalloproteinase (ADAM22) and presynaptic (ADAM23) and influences myelination and synaptic transmission by regulating voltage-gated potassium channels (VGKC) ^{4,5}. LGI1 gene mutations may result in autosomal dominant partial epilepsy with auditory features⁶, whereas autoimmune

encephalitis associated with LGI1 antibody is characterized with limbic symptoms (e.g., amnesia, confusion, hallucinations, seizures) as well as sleep disturbance, hyponatremia and faciobrachial dystonic seizures, which are frequent, brief dystonic jerks that typically affect the arm and ipsilateral face^{5,7}. Movement disorders are rarely related to LGI1 antibody and include parkinsonism, tremor, generalized chorea and stereotypies⁸⁻¹⁰.

Here, we present a child who had acute onset chorea accompanied by orolingual stereotypes associated with antibodies against LGI1 and increased anti-streptolysin O (ASO) titers.

Case Report

A 6-year-old boy was admitted to our hospital with a 2-day history of complex abnormal movements characterized by brief, non-rhythmic choreiform movements throughout his upper

extremities and irregular migrating contractions and writhing movements more prominent in his lower extremities. In the lower limb, slow, involuntary asynchronous (alternating flexion-extension) movements were observed. The patient also had repetitive, rhythmic oromandibular movements along with tongue protrusion and minimal facial stereotypic movements. His neurologic examination including mental state, orientation and speech was otherwise normal and his parents did not report any alterations in behavior and sleep. The patient had no antecedent infection, fever or any signs or symptoms of arthritis or skin lesions. There was no family history of autoimmune disease. Electroencephalography (EEG), magnetic resonance imaging (MRI), chest X ray and cerebrospinal fluid (CSF) analysis were all unremarkable.

The patient was admitted to intensive care unit because of his functional disability related to rapidly progressing movement disorder. Serum copper, ferritin, ceruloplasmin, thyroid hormone and electrolyte (Na, K, Ca, Mg) levels, sedimentation rate, blood biochemistry and complete blood count were within normal limits. ASO titers were found to be severely elevated in several measurements (1450–1500 IU/ml; normal <200 IU/ml). Throat culture was negative. Electrocardiography and echocardiography tests done to detect rheumatic carditis did not reveal any abnormal findings. Anti-nuclear antibody (ANA), thyroid antibodies, anti-Sm and anti-cardiolipin (IgG, IgM) antibodies were negative. Due to the acute-onset and rapidly progressive nature of clinical findings and exclusion of all other potential causes, an autoimmune encephalitis was suspected and antibodies against well-characterized ion channel and synapse antigens were investigated. While NMDAR, AMPAR, CASPR2, GABA_BR and GAD antibodies were negative, serum voltage-gated potassium channel (VGKC)-complex antibodies measured by radioimmunoprecipitation using ¹²⁵I-dendrotoxin (RSR Limited, Cardiff, UK) were found positive (820 pM; normal value <100 pM). To confirm the specificity of VGKC-complex antibodies, LGI1 antibody was investigated and found positive by a cell based-assay (Euroimmun, Luebeck, Germany) in both serum and CSF samples.

Administration of pimozide (0.75 mg 2 times a day) and tetrabenazine (25 mg 3 times a day) induced only a minimal improvement. Marked clinical improvement was observed after a 7-day (25 mg/kg per day) course of intravenous corticosteroid treatment followed by tapered oral doses. A month later, he had a relapse, demonstrating moderate generalized choreiform movements with mild upper throat infection symptoms. Therefore, an additional intravenous immunoglobulin (IVIG) therapy was administered at a dose of 0.4 g/kg/day for 5 days.

A repeat assay showed mildly increased ASO titer (450 IU/ml) and a whole-body fluorodeoxyglucose positron emission tomography (FDG-PET) scan showed no change of activity in the brain or in other tissues. Throat culture was negative and no malignant cells were found in the peripheral blood smear. The LGI1 antibodies were also found to be negative in serum and CSF after the treatment. Treatment with IVIG and tetrabenazine (25 mg 2 times a day) resulted in complete resolution in his involuntary movements in the second month of follow-up.

Discussion

Sydenham's chorea (SC) is the most common cause of acute, isolated chorea in children, and is characterized by tics, oculomotor abnormalities, dysarthria, motor imperistence, gait disturbance and emotional lability. Anti-basal ganglia antibodies are expected to be found positive especially in patients with streptococci and movement disorders¹³. The medical conditions that should be taken into account in the differential diagnosis of patients with chorea, especially in the pediatric population are SC, autoimmune encephalitis, systemic lupus erythematosus, antiphospholipid antibody-mediated chorea and vascular diseases such as Moyamoya syndrome^{11–13}.

We initially diagnosed our patient as SC because of choreiform movements and severely elevated ASO titers. However, the presence of treatment resistant progressive symptoms and the need for ICU, which is unusual for SC, led us to consider autoimmune encephalitis. Antibody-mediated encephalopathies present with acute-onset amnesia, confusion, seizures, psychiatric symptoms and movement disorders

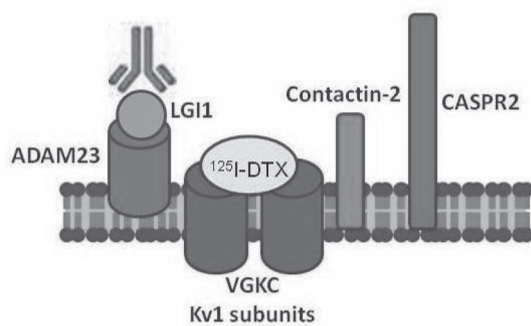


Fig. 1. Schematic illustration of voltage-gated potassium channel (VGKC)-complex proteins [Kv1 subunits of VGKC, leucine-rich glioma inactivated 1 (LGI1), contactin-associated protein-2 (CASPR2) and contactin-2] that are co-immunoprecipitated in the ^{125}I - α -dendrotoxin (DTX) radioimmunoassay. Antibodies of VGKC-complex antibody positive patients are primarily directed against LGI1 within the complex. LGI1 antibody is detected with a cell based assay utilizing human embryonic kidney cells transfected with LGI1 cDNA.

associated with serum and/or CSF antibodies directed against ion channels, receptors and associated membrane proteins and are now well known in adults^{2,3}. However, autoimmune encephalopathies are also increasingly being recognized in children with antibodies to NMDAR and VGKC-complex proteins. While around 40% of NMDAR encephalitis patients present in childhood or adolescence, VGKC-complex antibodies are very rarely detected in pediatric patients. Around 40-50% of NMDAR encephalitis patients present with an underlying ovarian teratoma, whereas thymoma and lung cancer are the leading accompanying tumors in VGKC-complex antibody associated encephalitis and is found in less than 20% of the cases. Adult and pediatric autoimmune encephalitis patients with or without tumors usually respond favorably to immunosuppressive treatments (steroids, IVIg and plasma exchange)^{2,5,9,12}.

Among autoimmune encephalitis', NMDAR encephalitis is most frequently related with movement disorders. Although orofacial dyskinesia is often the initial movement disorder, chorea, dystonia, catatonia, and stereotypical movements may also be encountered in early childhood^{14,15}. Stereotyped movements (85%) and orofacial dyskinesia (45%) are the most common movement disorders in NMDAR encephalitis seen during the childhood¹².

However, our patient was positive for LGI1 and VGKC-complex antibodies which are

less frequently associated with movement disorders and pediatric disease onset. The VGKC-complex is made up of four Kv1 subunits embedded in neuronal membrane and tightly associated proteins such as LGI1, CASPR2 and contactin-2, which regulate the expression and functions of VGKCs. LGI1 is a neuronal secreted protein that interacts with presynaptic ADAM23 and postsynaptic ADAM22⁴⁻⁶ (Fig. 1). Around 80-90% of VGKC-complex antibody positive patients have antibodies to LGI1, whereas rest of the patients display antibodies to CASPR2, contactin-2, Kv1 subunits and to as yet undetermined VGKC-complex proteins. LGI1 antibodies are predominantly detected in patients with limbic encephalitis and faciobrachial dystonic seizures and CASPR2 antibodies in Morvan's syndrome and neuromyotonia^{1,5,7}. LGI1 antibodies are exclusively found in autoimmune encephalitis patients, whereas in patients with VGKC-complex antibodies that do not react with LGI1 and CASPR2, the syndrome association is not specific and response to immunotreatment is uncertain (i.e. these antibodies can be detected in patients without autoimmune encephalitis and patients that are resistant to immunotherapies)^{2,5}. Therefore, following the initial detection of serum VGKC-complex antibodies by a radioimmunoassay during autoimmune encephalitis screening, serum and CSF samples were investigated for LGI1 antibodies and found positive confirming that our case had autoimmune encephalitis. Although absence of other limbic symptoms (e.g. confusion, seizures) contradicted this diagnosis, similar monosymptomatic encephalitis patients with isolated movement disorders and normal cognitive functions have been described⁸. Rapid response to immunosuppressive treatments also supported the diagnosis of autoimmune encephalitis.

To our knowledge, only three cases of chorea associated with LGI1 encephalitis have been reported so far. Tofaris et al¹⁰ reported two patients with subacute chorea as the initial feature of LGI1 encephalitis. These cases are distinctly different from our case in that the onset of symptoms were observed at an older age (after 60), and they had isolated chorea (no other movement disorders) and additionally epileptic seizures or hyponatremia¹⁰. Another reported case of isolated mild chorea associated

with LGI1 antibody also differed from our case in displaying late onset (at the age of 53), mild symptoms, and immediate response to steroid therapy⁸. Our case indicates that LGI1 encephalitis should also be considered in pediatric patients and in patients with isolated chorea with or without stereotypes.

Another intriguing finding of our case was the highly elevated ASO titers despite the absence of rheumatic fever or streptococcal pharyngitis. Patients with autoimmune encephalitis often display prodromal symptoms in the form of upper respiratory infection^{2,15}. A recently established link between herpes simplex virus and NMDAR encephalitis has brought forward the possibility that autoimmune encephalitis might be triggered by microorganisms¹⁶. Whether or not the molecular mimicry between streptococcal antigens and VGKC-complex proteins might initiate the LGI1 encephalitis requires to be investigated.

In conclusion, the herein presented pediatric patient with hyperkinetic movement disorders and LGI1 antibody has allowed us to emphasize the importance of investigating neuronal autoantibodies in patients with isolated and treatment-resistant movement disorders. Together with other similar cases recently published in the literature, the presence of our case implies that isolated movement disorders should be included in the diagnostic and treatment algorithms of autoimmune encephalitis.

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