

LGI1/CASPR2-antibody encephalitis

(previously termed VGKC/voltage-gated potassium channel antibody encephalitis)

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What is LGI1 and CASPR2-antibody encephalitis?

Our immune system works to clear our bodies of foreign invaders such as infections. It does this, in part, by producing antibodies which attach to and help destroy the invaders. Instead of attaching to the invaders, occasionally the antibodies can mistake parts of the body as foreign and attach to these regions. If the brain is the mistaken region, the antibody attack leads to autoimmune encephalitis. When the antibodies target LGI1 (leucine-rich glioma inactivated 1) or CASPR2 (contactin-associated protein 2), they cause an encephalitis often termed 'limbic encephalitis' (LE).

Men are roughly affected twice as often as women by LGI1-antibodies, whereas in CASPR2-antibodies up to 90% of patients are male.

Symptoms

Initially, typically, family members notice seizures and/or that their relative becomes forgetful, confused, drowsy and withdrawn.

Seizures occur in almost all cases but can look very subtle. These may take the form of brief jerks of the face and arm (termed faciobrachial seizures) – this diagnostic sign is highly suggestive of LGI1-antibodies. Alternatively, they can appear as brief 'absences' when patients glaze over for a few seconds (also called 'temporal lobe epilepsy'), or full-blown arm and leg jerking which can be very disturbing for observers (also known as generalised seizures).

Patients can also develop mood disorders (like depression), atypical thoughts and behaviours and sleep disturbances.

Diagnosis

LGI1/CASPR2-antibody encephalitis can be mistaken for many other diseases, including viral encephalitis or other autoimmune conditions. Most patients are investigated with:

- blood tests (patients with LGI1 antibodies often have a low salt level in their blood)
- lumbar puncture (LP) to help exclude infection which is often normal in LGI1/CASPR2-antibody encephalitis
- electrical recordings of the brain (EEG) to look for seizure activity
- magnetic resonance imaging (MRI) scans which often show swelling and inflammation of the brain
- genetic testing; certain variants of an immune gene called human leucocyte antigen (HLA) are associated with these forms of encephalitis

Patients with both conditions may have tumours which are related to their condition. This is especially common in patients with CASPR2 antibodies.

To obtain a definitive diagnosis with the above clinical features, the LGI1/CASPR2-antibodies can be measured in blood and, often, spinal fluid.

Patients who have been tested for VGKC-antibodies should have additional LGI1 and CASPR2-antibody testing. These additional tests ensure the relevance of their antibodies to their condition and largely prevent misdiagnosis.

Treatments for LGI1/CASPR2-antibody encephalitis

LGI1/CASPR2-antibody encephalitis is a serious disease. Patients often spend some weeks in hospital receiving specialist treatment and assessment. If the antibodies are found in a patient with the recognised clinical features, LGI1/CASPR2-antibody encephalitis can be treated by dampening down the immune reaction that is causing the inflammation using immunosuppression.

However, no single set of medications is proven to be superior to others and research into new or optimal treatments is ongoing. Nevertheless, most clinicians opt to use immunosuppression with steroids (either taken as tablets or into a vein), intravenous immunoglobulin (a blood product given into the vein in a drip) and/or plasma exchange (when some of a person's blood is taken out from a vein, washed of various components including antibodies, and then put back into the vein in a drip). All these treatments have known side-effects and their benefits need to be weighed against possible side-effects in individual patients.

Typically, patients are given further tablet steroid treatments after discharge from hospital. Some patients (especially if only partial improvement after first round of treatment) receive Rituximab, a medication which targets antibody-producing B cells and is given as an infusion.

Treatment often results in fewer seizures and some improvement in confusion and memory problems. Improvements may be seen within a few days of treatment or in some cases only noticed after several months. Treatment, typically with steroid tablets and/or other immune therapies (steroid-sparing agents), may be continued for 1-2 years. In addition, patients may receive medications which suppress seizures (anti-seizure medications).

Relapses

In most cases (although the exact figures are not yet known) LGI1/CASPR2-antibody encephalitis will not recur. Unfortunately, in 10-30% of cases it may recur months or rarely years after initial disease, with many of the same symptoms as before (such as seizures, confusion or forgetfulness). It is not yet known what leads to this recurrence but it usually warrants repeat treatments that might range from steroids into the vein (intravenous methylprednisolone) through to plasma exchange and Rituximab.

Outcomes and future challenges

As this disease was only relatively recently described, there is still much to learn about what happens to patients in the long-term.

Almost all patients make some improvements but very few patients are left with no residual problems after treatments. Patients are left with problems in memory, fatigue, seizures and behaviour which may require medical and psychological input and, occasionally, may necessitate long-term placement in a home or other care facility. Other patients may return to their previous functioning, including getting back to work, some months or years after treatment. The time to treatment with immunosuppressive drugs is the main observed factor in determining outcome.

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