



RARE & SERONEGATIVE AUTOIMMUNE ENCEPHALITIS

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WHY WE DID THIS WORK

- **Autoimmune encephalitis (AE)** is a form of autoimmune disease whereby immune cells in the body inappropriately target components of the nervous system. This causes dysfunction of nerve cells, and in some cases death of these cells, and further produces different clinical symptoms that are reversible. Such symptoms include (but are not limited to) cognitive symptoms, such as difficulties with memory and language, seizures, movement disorders, and psychiatric symptoms.
- Antibodies are central to the diagnosis of many subtypes of autoimmune encephalitis. Generally, **antibodies** are proteins produced by the immune system to fight infections. In a proportion of patients with autoimmune encephalitis there can be an abnormal expression of antibodies, where, rather than targeting foreign molecules (e.g. viruses, bacteria), they mistakenly target self-proteins on nerve endings or self-proteins inside the nerve cell or neuron. In up to half of cases, an antibody is not detectable using current available tests or assays. This group of cases is called "**seronegative**" autoimmune encephalitis, i.e. denoting a lack of antibodies in the serum (a component of a patient's blood) or **cerebrospinal fluid** (a clear fluid that surrounds the brain and spinal cord, obtained via a lumbar puncture, a procedure involving a fine needle being inserted in the lower back). 'Seronegative' autoimmune encephalitis most likely represents a broader collection of disorders.
- Over the last two decades, antibody-mediated subtypes of autoimmune encephalitis continue to be discovered, with over ten such forms now recognised. Further, following the respective discovery of such new forms of autoimmune encephalitis, disease mechanisms and clinical features have been revealed.

However, seronegative autoimmune encephalitis remains less well characterised, possibly in part to because of its heterogeneous nature – meaning that a variety of disease forms may be included by the definition.

- The purpose of our review was to explore advances regarding five rare antibody-mediated forms of autoimmune encephalitis, namely, anti-g-aminobutyric acid B (GABAB) receptor-, anti- α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic receptor- (AMPA), anti-GABAA receptor- and anti-dipeptidyl-peptidase-like protein-6 (DPPX) encephalitis and IgLON5 disease.
- We also summarise current research and challenges in relation to 'seronegative' autoimmune encephalitis. For a detailed discussion of anti-NMDA autoimmune encephalitis, anti-LGI1 and anti-CASPR2 autoimmune encephalitis refer to (Contemporary advances in anti-NMDAR antibody (Ab)-mediated encephalitis - PubMed (nih.gov) (1) and Contemporary advances in antibody-mediated encephalitis: anti-LGI1 and anti-Caspr2 antibody (Ab)-mediated encephalitis - PubMed (nih.gov) (2).

WHAT WE FOUND

- GABAB, AMPAR and GABAA autoimmune encephalitis have common and distinguishing clinical features. These three forms of autoimmune encephalitis are diagnosed by the presence of antibodies found in the blood or cerebrospinal fluid of suspected patients. All three are relatively rare, compared to some other antibody-mediated forms of autoimmune encephalitis such as anti-N-methyl-D-aspartate receptor (NMDAR) and anti-leucine-rich glioma-inactivated 1 (LGI1) Ab-mediated encephalitis. GABAA encephalitis in particular is exceedingly rare, with approximately fifty cases reported overall as at a few years ago.
 - In these diseases, antibodies target the GABAB, AMPAR and GABAA receptors (proteins present on nerve cell endings), causing neuronal dysfunction. GABAB and GABAA receptors both attract an inhibitory neurotransmitter called GABA.
- A **neurotransmitter** is a signalling molecule that helps with communication and transmission of impulses between neurons, and inhibitory neurotransmitters reduce the likelihood a given neuron will generate an electrical signal called an action potential.
- Seizures in these diseases are a main feature, and may be particularly non-responsive to conventional anti-seizure treatment. Furthermore, cognitive and psychiatric symptoms are common in all three of these subtypes of autoimmune encephalitis. GABAB and AMPAR subtypes may have similar findings identified on MRI imaging of the brain, with inflammation and swelling seen in part of the brain called the **mesial temporal lobe** is an area of the brain important for memory, emotion and behaviour.
 - The diagnosis of autoimmune encephalitis invariably necessitates that clinicians investigate for the possibility of a tumour (e.g. lung cancer, thyroid cancer, breast cancer) that may have triggered the disease. Treating the tumour or cancer where feasible and as promptly as possible has been linked to improvements in autoimmune encephalitis symptoms. Similarly, the presence of neurological symptoms, if preceding a cancer diagnosis, may allow for this to be facilitated more quickly than might have been the case otherwise, which may help afford a better chance of more effectively treating the underlying cancer.
 - In approximately half of patients diagnosed with GABAB encephalitis, an underlying tumour is found, most often small-cell lung cancer. In AMPAR encephalitis, almost two-thirds of patients have an underlying tumour, with thymus tumours and lung cancer most common. In GABAA encephalitis, approximately one third of patients have also been shown to have an underlying tumour.
 - DPPX encephalitis and IgLON5 disease are two rare and somewhat clinically unique forms of autoimmune encephalitis. In DPPX encephalitis, patients commonly present with profound weight loss or diarrhoea and have features of central-nervous system **hyperexcitability**. This is a state where the brain has increased responsiveness to a variety of external stimuli.

In DPPX encephalitis, features attributed to CNS hyperexcitability include myoclonus, or rapid, involuntary muscle jerks, and tremor. IgLON5 disease on the other hand also has unique clinical features, such as a variety of sleep disturbances.

- Seronegative autoimmune encephalitis overall requires further study and description to identify potential antibodies which may be the cause. Seronegative limbic encephalitis is a form of seronegative autoimmune encephalitis, where the limbic structures in the brain are affected. In this subset of the disease inflammation is observed in the mesial temporal lobes using Magnetic Resonance Imaging (MRI). Seronegative limbic encephalitis is typically seen in older patients, with conventional antibody testing not revealing an antibody. Patients typically have memory impairment, with or without psychiatric symptoms and seizures, and are treated with medications that lower effects of the immune system, as in other forms of autoimmune encephalitis.

HOW CAN WE USE THIS RESEARCH

- These findings are intended to help researchers and clinicians better understand seronegative and rare forms of autoimmune encephalitis. By bringing this information together, it can assist with improving diagnosis and assisting with early treatment by clinicians.
- It should be noted that antibody-related forms of autoimmune encephalitis are usually diagnosed as “possible autoimmune encephalitis” prior to the availability of antibody results, which can take up to a period of weeks. A diagnosis of autoimmune encephalitis is based on broad criteria involving consideration of a patient’s symptoms and test results, including MRI, electroencephalogram (EEG – a measure of the electrical activity of the brain) and cerebrospinal fluid biopsy results, combined with the exclusion other diseases, for example, viruses that could mimic the observed symptoms.
- Prompt diagnosis of autoimmune encephalitis, and prompt exclusion of other causes such as viral encephalitis is very important, as there is a growing body of evidence indicating that earlier initiation of immune-lowering treatment for autoimmune encephalitis may be able to facilitate better recovery.
- The seronegative form of autoimmune encephalitis can represent a large proportion of autoimmune encephalitis patients overall so its understanding is crucial for improvements in clinical care.
- Regarding very rare subtypes of autoimmune encephalitis, an understanding of the characteristic features of these rare entities is crucial in forming a diagnostic workup plan. Further, awareness of the features of some of these rarer subtypes can ensure prompt and accurate investigation of underlying tumours. Knowledge of rarer subtypes may also be able to inform clinicians and patients about the possible outcomes of these conditions to inform day to day discussions with patients and their caregivers.

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References

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