

PATHCHAT

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Endorsed by the Ampath Infectious Diseases Peer Group

An Update on Autoimmune (Limbic) Encephalitis

Encephalitis (inflammation of the brain) is a pathological diagnosis, yet the diagnosis is made clinically. Diagnosis is made through the observation of neurologic dysfunction (e.g. depressed level of consciousness, seizures etc.) combined with corroborating findings of a cerebrospinal fluid (CSF) tap, EEG and neuroimaging studies.

Encephalitis syndromes are common medical emergencies requiring urgent attention for diagnosis and treatment, as a delay may cause irreversible brain injury and death.

Common causes include infections (mainly HSV and enteroviruses), seizures, metabolic encephalopathy, toxic (e.g. overdose) and cerebrovascular accidents.

A proportion of patients escape definitive diagnosis, however, and once systemic autoimmune disease and autoimmune thyroid disease have been excluded, autoimmune encephalitis needs to be considered.

What is autoimmune encephalitis, the burden thereof and why is it so important to identify?

Autoimmune encephalitis (AE) refers to *immune mediated* encephalitis, either via humoral or cellular pathways. It is a relatively complex group of disorders with new emerging entities.

Until recently, AE largely referred to rare cases of paraneoplastic neurological syndromes (PNS), in particular paraneoplastic limbic encephalitis (PLE). Of all the autoimmune encephalitides, limbic encephalitis (LE) is the most common and is the subject of this update. However other areas of the central nervous system may also be involved, e.g. spinal cord and brain stem.

While AE is rare, it is more common than previously thought and some types (e.g. N-methyl-D-aspartate Receptor (NMDAR) encephalitis) is being identified with similar frequency as HSV and enterovirus encephalitis. Since NMDAR encephalitis is amenable to treatment and with better outcomes the sooner the treatment is initiated, an early diagnosis is desirable.

T-lymphocyte mediated neurological syndromes:

This is the mechanism at play in PLE. In these patients, onconeural autoantibodies interact with intracellular localised autoantigens expressed in tumour and neuronal tissue. Antibodies directed against the **intraneuronal** target induces a CD8+ T-cell cytotoxic effect, which is believed to be responsible for the pathology.

PLE/PNS precedes cancer diagnosis in the vast majority of cases (70–80%), usually by weeks or months. It is often, but not invariably, associated with an

Definitions:

1. Paraneoplastic neurological syndromes (PNS) may affect any part of the central nervous system from cerebral cortex to neuromuscular junction and muscle. It refers to a neurological symptom complex that cannot be explained by local or distant spread of the tumour. It also excludes mechanisms other than metabolic and nutritional deficits, infections, coagulopathy or side effects of anti-cancer treatment.
2. Limbic encephalitis (LE) refers to inflammation of the rhinencephalon, characterised by degenerative changes of the hippocampus and amygdaloid nuclei, and present with a diversity of symptoms, including acute and sub-acute mood and behavioural changes, short-term memory problems and confusion, seizures and cognitive impairment with disordered perception and sleep disturbances.

identifiable onconeural antibody. Small cell lung carcinoma is the most common occult malignancy and is usually associated with anti-Hu (ANNA-1) and anti-CV2 (CRMP5) antibodies. Anti-CV2 antibodies may also indicate an underlying thymoma. Anti-amphiphysin antibodies are associated with paraneoplastic stiff-person syndrome. Anti-Ma2 antibodies indicate the presence of an underlying testicular seminoma.

PLE generally runs a severe clinical course which may stabilise with tumour resection and immunotherapy (which may include intravenous immune globulin (IVIG), corticosteroids or both), but neurologic deficits are usually irreversible.

Various other immune responses to intracellular antigens have been described and others have yet to be characterised. At Ampath, we offer immunofluorescence for anti-Hu, -Ri and -Yo (cerebellar degeneration) antibodies, a line immuno-assay for antibodies to Hu, Ri, Yo, Ma2, CV2 and amphiphysin, and an anti-GAD 65 ELISA assay. A request for neuronal antibodies on a clotted blood sample will cover all these tests, except anti-GAD 65, which needs to be ordered separately.

Autoantibody mediated neurological syndromes:

With the recent characterisation of antibodies to cell **surface antigens/synaptic proteins**, new entities of immune mediated limbic encephalitis and other encephalitic syndromes have been described. These target antigens play a critical role in neuronal transmission and plasticity. The association with underlying malignancy/tumour is more variable, but there is a greater likelihood of recovery with immunotherapy/tumour removal and with less/limited neurological sequelae. Of these, anti-NMDAR encephalitis deserves special mention.

N-methyl-D-aspartate Receptor encephalitis:

Anti-NMDAR encephalitis presents with a characteristic syndrome that is preceded by a prodromal viral-like illness that progresses to prominent

psychiatric manifestations, insomnia, memory deficits, seizures, decreased level of consciousness, dyskinesias, autonomic instability and language dysfunction.

It occurs mainly in women under the age of 30, although men may also be affected. Two thirds of cases occur in individuals under the age of 18. This disorder may occur as a paraneoplastic manifestation of ovarian teratomas, seen in approximately 50% of female patients older than 18. When identified in patients over 45 years, there is usually an underlying carcinoma. The diagnosis is confirmed by detecting antibodies to the NR1 subunit of the NMDAR in serum or CSF.

In a recently published study, the California Encephalitis Project (CEP) found the relative frequency of NMDAR encephalitis in patients ≤ 30 years to be more common than the most common infectious aetiologies, notably HSV1 and enterovirus. This study points out that the characteristic symptoms, together with EEG and MRI changes (not converging on the temporal lobe), lower levels of CSF pleocytosis and protein can help distinguish it from key viral entities. It is their opinion that NMDA antibody testing should be requested together with HSV and enteroviral PCR.

Treatment:

Therapeutic strategies include resection of the underlying tumour (if present) with immunotherapy, IVIG, corticosteroids or both. Patients treated earlier appear to be more likely to make a complete recovery, and up to 80% of patients respond. In non-responders, second-line immunotherapy with rituximab, cyclophosphamide or both is recommended. Considering this diagnosis early may also save a considerable amount of money on other diagnostics, treatments and hospital stay.

Other autoimmune encephalitides and associated antibodies:

These include LGI1, AMPA receptor, GABA receptor and CASPR2. Both LGI1 and CASPR2 were previously attributed to antibodies to voltage gated potassium channels (VGKC) and are

least likely to be paraneoplastic in origin. Similar to NMDAR encephalitis, clinical recovery is significant with LE associated with LGI1 antibodies.

Tests for these antibodies can be done at Ampath, using both CSF and serum. Please request NMDA antibodies, which will include tests for the abovementioned antibodies. In NMDAR encephalitis, antibodies may be present in CSF and absent in serum. The titres of CSF antibodies appear to correlate more closely with the clinical outcome. In non-paraneoplastic LGI1 – associated LE, antibody titres are usually higher in the serum and may be negative in the CSF.

In a nutshell:

- Autoimmune encephalitis should be considered in the differential diagnosis of encephalitis syndromes.
- Patients with suspected/proven limbic encephalitis should undergo an intensive tumour screen, even in the absence of onconeural antibodies.
- Some encephalitides are responsive to treatment and outcomes are better if treatment is initiated sooner, e.g. NMDAR and LGI1.
- Antibody tests to cell surface antigens, e.g. NMDAR, should be considered when requesting HSV and enteroviral PCR, particularly in patients presenting with characteristic symptoms.
- Tests should be ordered as **neuronal antibodies** and **GAD 65 antibodies** on **serum** samples. For antibodies against cell surface antigens, **both CSF and serum** samples are recommended and the test ordered should be **NMDAR antibodies**.

References

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