AMPATHCHAT no. 81

AN APPROACH TO AUTOIMMUNE ENCEPHALITIS

Dr Lizelle Nagel, Dr Mark da Silva

KEY MESSAGES

- The phenotype does not predict the antibody that will be detected. All three neural antibody profiles should be tested to avoid missing an important diagnosis.
- Both cerebrospinal fluid (CSF) and serum should be tested for optimal sensitivity and specificity.
- If the clinical picture does not correlate with the antibody detected, the possibility of a false positive antibody should be considered.
- If the patient tests positive for an onconeuronal antibody like anti-Hu, an intensive cancer investigation is required. Negative cancer screens should be repeated six monthly for a period of two years.
- Negative results do not exclude autoimmune encephalitis (AE) as testing is not available for all possible antigens. Furthermore, a significant proportion of patients are sero-negative.
- Ampath's neural antibody tests can be found on the Immunology Autoimmunity request form under Central Nervous System.

Please select the following options:

Neuronal antibodies (Serum + CSF)	**NEUR + NEURC**
Anti-NMDA and other glutamate receptors (Serum + CSF)	**NMDA + NMDAC**
Aquaporin and anti-MOG (Serum + CSF)	**NMO + NMOC**

BACKGROUND

Autoimmune encephalitis is caused by autoantibodies against intracellular, membrane or synaptic neuronal proteins.[1] The prevalence and incidence of AE is comparable to infectious encephalitis, and its detection is increasing over time. Several clinical syndromes and diagnostic variants have been described. The nomenclature may be confusing since the clinical spectrum is wide, and all presentations have underlying autoimmune insults to neurons.[2]

Limbic encephalitis is the most frequent clinical manifestation.[1] It refers to the autoimmune inflammation of limbic structures (hippocampus, amygdala, hypothalamus, cingulate gyrus and limbic cortex) that presents as acute or subacute mood and behavioural changes, short-term memory problems, complex partial seizures, cognitive dysfunction and hypothalamic dysfunction evolving over days to weeks. Autoimmune encephalitis can also be linked to cancer (paraneoplastic encephalitis) and may present as limbic or brainstem encephalitis, or encephalomyelitis developing weeks to months before a cancer diagnosis. Early recognition and treatment with anti-cancer therapy, immunosuppression, apheresis or intravenous immunoglobulins are important for stabilising or improving the outcome.[2]

DIAGNOSTIC APPROACH

A definitive clinical diagnosis can be made when all diagnostic criteria are met and alternative diagnoses have been adequately excluded.[3] Suggestive MRI findings include signal hyperintensities on FLAIR or T2-weighted images in regions like the medial temporal lobes (limbic encephalitis) or subcortical regions (brainstem or cerebellum). Electroencephalography (EEG) is used to exclude non-convulsive seizures and is mostly non-specific.

CEREBROSPINAL FLUID FINDINGS

Cerebrospinal fluid examinations include cell count, protein, glucose, IgG index, oligoclonal bands, viral PCR studies, bacterial and fungal cultures, VDRL and cytology. Patients with AE have a normal or an inflammatory CSF picture. Inflammatory findings include mildly increased protein (<1 g/L), pleocytosis, elevated IgG index or oligoclonal bands.[3]

SEROLOGICAL FINDINGS

The detection of specific antibodies within the appropriate clinical context confirms the diagnosis. Autoantibodies can be produced intrathecally or systemically. The diagnostic sensitivities and specificities differ between the compartments. For optimal sensitivity and specificity, antibodies should be tested in both CSF and serum. High titres are more likely to be neurologically relevant than low titres. Negative results do not exclude AE since commercial testing is not available for all possible antigens.[3]

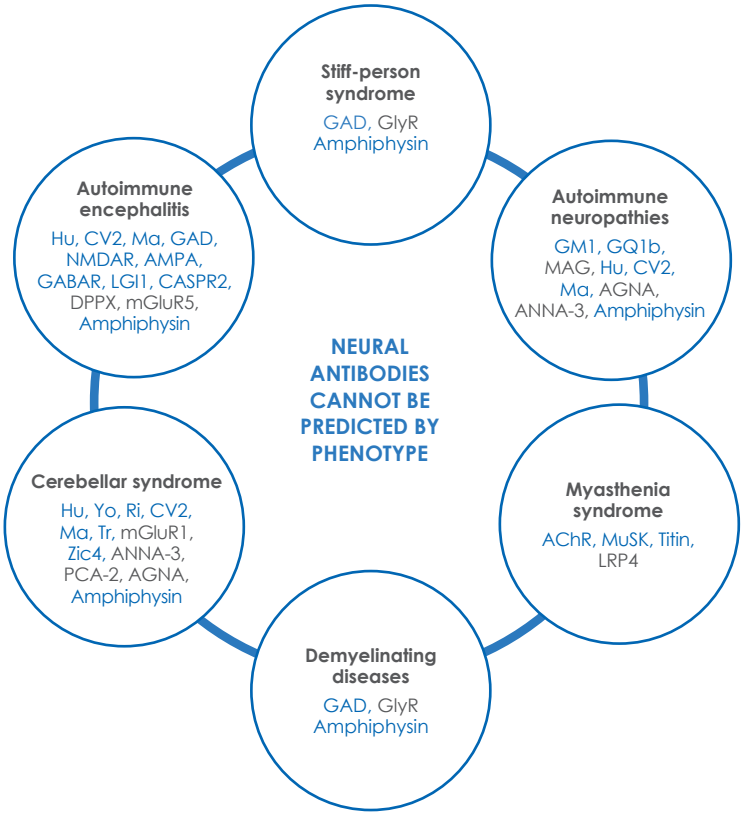
Paraneoplastic encephalitis is diagnosed when high-risk (>70%) or intermediate-risk (30 to 70%) onconeuronal autoantibodies test positive. In patients with positive results for one or more onconeuronal antibodies and

no known cancer diagnosis, an intensive cancer investigation is required to search for an occult tumour. The most frequent cancers are lung cancer, breast cancer, thymoma, Hodgkin's lymphoma, ovarian cancer and testicular cancer.[3]

One should guard against the over-interpretation of non-specific antibody reactions. The following general principles should guide the interpretation[3]:

- Test for antibodies in both CSF and serum.
- If the clinical picture does not fit the antibody that was detected, it may be false-positive, particularly if only serum was tested or if the CSF is negative.
- Clinical decisions should be based on clinical assessment since titres do not always correlate with clinical disease status.

Ampath offers testing for several neural antibodies (Figure 1). Dual platform testing is offered routinely for Hu, Yo and Ri antibodies to improve sensitivity and specificity.



Source: Euroimmun (www.euroimmun.com)

FIGURE 1: ANTIBODIES IN BLUE ARE ROUTINELY AVAILABLE THROUGH AMPATH. ANTIBODIES IN GREY MAY BE TESTED ON REQUEST FOR INDIVIDUAL CASES THROUGH A PARTNERING RESEARCH LABORATORY.

PAEDIATRIC VERSUS ADULT AUTOIMMUNE ENCEPHALITIS

Immune-mediated encephalitis is the second-largest group of childhood encephalitides beyond viral etiologies.[4,5] Anti-N-methyl-D-aspartate receptor (anti-NMDAR) and anti-GAD65 encephalitis are the most common, but adult-type AE can also occur. Similarly, some traditional paediatric AEs also occur in adults. Since the phenotype does not predict the antibody, all three neural antibody profiles should be assayed in both children and adults in the event of an atypical diagnosis being made.

Please do not hesitate to contact a pathologist in the Immunology Laboratory on 012 678 0613/4/31 for assistance.

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REFERENCES

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3. Graus F, Vogrig A, Muñiz-Castrillo S, Antoine JG, Desestret V, Dubey D et al. Updated diagnostic criteria for paraneoplastic neurologic syndromes. Neurology, Neuroimmunology and Neuroinflammation 2021; 8(4).
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