Seronegative Autoimmune Encephalitis – A Diagnostic and Therapeutic Dilemma

Autoimmune mechanisms causing diverse neuropsychiatric symptoms are increasingly recognized and brought about a paradigm shift in the understanding of Autoimmune Encephalitis (AE).[1] They are a group of autoantibody-mediated encephalitis[2] that responds well to immunotherapy. They have a varied clinical presentation that includes cognitive impairment, behavioural changes, personality changes, seizures, abnormal movements, autonomic disturbances and decreased level of sensorium. The initial diagnostic criteria were very much reliant on antibody testing and response to immunotherapy.[3] But, these criteria may always not be realistic as antibodies may not be detectable.[3] Diagnostic challenge occurs when there are no detectable auto-antibodies in serum or CSF; these subgroup of patients are termed Seronegative (or antibody-negative) autoimmune encephalitis (SAE) with suspected immunological origin based on clinical and imaging features.

In recent years, there is increased description of antibodies associated with AE. These are[4]: (i) *Intraneuronal antigens* (onconeural antibodies): AGNA, ANNA, CRMP-5. GAD-65, GFAP, anti-Ma, PCA. (ii) *Cell-surface antigens*: AMPAR, CASPR2, DPPX, GABA, GlyαR, IgLON5, mGluR1, mGluR5, NMDAR, VGKC, VGCC (iii) *Extracellular location*: LGI-1. MRI brain is usually normal or show abnormalities in 40% patients affecting the temporal lobe, cortical, subcortical and basal ganglia. CSF analysis may be normal or show pleocytosis.[5] EEG may be normal or show background slowing, delta brush pattern, electrodecremental response, focal epileptiform discharges or triphasic waves.[6] Early immunotherapy may result in complete reversibility of the neurological disorder.

Sahoo *et al*.[7] evaluated seven pediatric SAE patients with similar clinical presentation and therapeutic response as in antibody-positive AE. CSF studies in their patients found mild pleocytosis with normal protein. But they did not have a comparative group. Dr Pradhan *et al*.[8] prospectively evaluated SAE over two years and compared seropositive and seronegative AE. Previously there have been few case reports and case series describing SAE; but none of them compared with seropositive cases. Pradhan *et al*. found similar clinical features in both seropositive and seronegative AE. MRI and EEG were comparable in both; CSF showed pleocytosis with increased protein in the antibody-positive group. All the patients showed adequate response with immunotherapy.

Auto-antibodies that bind to extracellular or intracellular epitopes have provided neurologists with essential biomarkers in diagnosis of AE. But, a large proportion of patients with suspected immune-mediated disorders do not have detectable auto-antibodies, resulting in diagnostic and therapeutic challenges. This is the first article highlighting the importance of diagnosing seronegative autoimmune encephalitis which lacks a diagnostic biomarker but has similar demographic, imaging and therapeutic response as in seropositive AE.

The field of autoimmune encephalitis is rapidly expanding with the advent of many newer auto-antibodies; the real life clinical experience of evaluation of AE without diagnostic biomarkers results in diagnostic and therapeutic challenges which has been addressed in this article. However, overdependence on antibody testing may delay diagnosis as it is not readily accessible and sometimes results can be delayed. This article raises the question about the importance of the diagnosis of autoimmune encephalitis in the absence of a biomarker and the need for revised guidelines in the diagnosis and treatment of seronegative autoimmune encephalitis.

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Conflicts of interest

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References

1. Dale RC, Church AJ, Surtees RAJ, Lees AJ, Adcock JE, Harding B, *et al*. Encephalitis lethargica syndrome: 20 new cases and evidence of basal ganglia autoimmunity. Brain 2004;127:21-33.
2. Ramanathan S, Mohammad SS, Brilot F, Dale RC. Autoimmune encephalitis: Recent updates and emerging challenges. J Clin Neurosci 2014;21:722-30.
3. Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Cellucci T, *et al*. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol 2016;15:391-404.
4. Bradshaw MJ, Linnoila JJ. An overview of autoimmune and paraneoplastic encephalitides. Semin Neurol 2018;38:330-43.
5. Irani SR, Bien CG, Lang B. Autoimmune epilepsies. Curr Opin Neurol 2011;24:146-53.
6. Kamble N, Netravathi M, Saini J, Mahadevan A, Yadav R, Nalini A, *et al*. Clinical and imaging characteristics of 16 patients with autoimmune neuronal synaptic encephalitis. Neurol India 2015;63:687-96.

7. Sahoo B, Jain MK, Mishra R, Patnaik S. Dilemmas and challenges in treating seronegative autoimmune encephalitis in Indian children. Indian J Crit Care Med 2018;22:875-8.
8. Pradhan S, Das A, Das A, Mulmuley M. Antibody-negative autoimmune encephalitis – Does it differ from definite one? 2019;22:401-8. AIAN. doi: 10.4103/aian.AIAN_206_19.

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