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Recent Advance of Neuronal Cell Antigens and Autoimmune Encephalitis

Ekladious A[1,2,*]

[1]Associate professor of medicine, Faculty of health and medical sciences, University of Western Australia, 35/ Stirling Highway, Perth Western Australia

[2]Royal Hobart hospital 48 Liverpool Street , Hobart TAZ 7000

[*]**Corresponding author:**

Dr. Adel Ekladious,
1Associate professor of medicine, Faculty of health and medical sciences, University of Western Australia, 35/ Stirling Highway, Perth Western Australia
2Royal Hobart hospital 48 liverpool Street , Hobart , Tas 7000, Tel: 61499449905,
E-mail: ekladiou@gmail.com

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1. Abstract

Patients with autoimmune encephalitis rarely present to neurology clinic before presenting to memory, seizure, movement disorder, and psychiatry clinics, recent discovery of neuronal surface autoantibodies have shifted the balance towards the diagnosis of autoimmune encephalitis, patients with autoimmune encephalitis used to receive the diagnosis of infectious encephalitis, with poor response to antiseizure, antibacterial and antiviral therapy, autoimmune encephalitis has a fundamental phenotype which is very specific even if serology was negative, early diagnosis is of paramount importance due to starting immunotherapy and avoid mortality and significant morbidity.

1.1. Discussion

Discovery of pathogenic neuroglial surface antibodies has led to discovery of the main clinical manifestation of autoimmune encephalitis and immediate starting of immunotherapy in addition to treating the underlying malignancy [1] although most of autoimmune encephalitis present acutely with a nadir of 10 weeks, others present with a chronic course up to 4 years like Leucine-rich glioma inactivated protein 1(LG11), antibody Contact -Associated Protein 2 antibody (CASPR2) and Immunoglobulin -Like cell Adhesion Molecule 5 (IGLONA5) [2], most forms of autoimmune encephalitis had distinctive clinical manifestation. Which guide clinicians to choose the appropriate panel of autoantibodies, investigation of the causative malignancy and stratify the response to treatment and Prognosis [3]. Chronic progressive forms of autoimmune encephalitis often diagnosed late due to similarities to neurodegenerative diseases [4]. Other differential diagnosis which needed to be ruled out before starting immunotherapy except if the clinical suspicion is very high, included infectious encephalitis, Hashimoto encephalitis, metabolic encephalitis [5]. Temporal lobe Glioma, Creutzfeldt- Jacob disease and infectious encephalitis, it is currently a standard practice to observe patients with herpes simplex encephalitis for developing autoimmune encephalitis with preemptive treatment with steroid [6]. We will discuss core clinical manifestation of autoimmune encephalitis which should trigger, semi urgent clinical investigation and consider initiating first line immunotherapy after ruling out infectious cause, Psychiatric clinical manifestation which included hallucinations, sleep disorder, aggression is not uncommonly the presenting manifestation of NMDAR-antibody immune encephalitis. Usually, patients with NDMAR antibody encephalitis will not presented to neurologist until other symptoms occur like seizures, involuntary movements, and autonomic symptoms [7].

Patients with Gamma Aminobutyric Acid A Receptors (GABAaR) antibodies autoimmune encephalitis Have a specific psychiatric phenotype which included catatonia, depression, mania, inappropriate behavior, which makes the diagnosis very difficult in any patient with family history of mental illness. Some patients with systemic lupus can present with the above mentioned manifistations and will be misdiagnosed with autoimmune encephalitis rather than crebral lupus, low C4 and low to normal C3 support the diagnosis of active cerebral Lupus

2. Seizures

Seizure is a cardinal symptom in autoimmune encephalitis which usually the main reason that patients will be referred to neurologist [8]. Phenotype of seizure can give clue to diagnosis, for example CASPR2 -antibody autoimmune encephalitis is charscterized with frequent focal seizures, Patients with LG11- antibody encephalitis has a pathognomonic faciobrachial dystonic seizures, Commenly due dystonic posture of the ipsilateral arm and face, frequent falls

to leg spasm, paroxysmal dizzy spells with negative EEG, temporal lobe seizures, frequent piloerection seizures [9]. Status epilepticus are common presentations in GABAaR and GABAbR antibody autoimmune encephalitis, the latter is commonly associated with small cell lung cancer, some guidelines advise to investigate. All patients with status epilepticus for autoimmune encephalitis [10]. Myelin Oligodendrocyte Glycoprotein (MOG) antibodies autoimmune encephalitis can present with seizure before other manifestation like optic neuritis and transverse myelitis, seizure usually respond promptly to steroid [11].

Patients with recent diagnosis of epilepsy who have neuronal surface autoantibodies and Autonomic manifistation like tachycardia, Bradycardia, orthostatic hypotension, constipation, diarrhea, steroid responsive seizure, MRI changes in the Limbic system, should be diagnosed and treated as autoimmune encephalitis [11].

3. Movement Disorders

Glycine Receptor (GlyR)and Dipeptidyl Peptidase like Protein 6(DPPX) are characterized by myoclonus and startle syndrome (eye blinking, body spasm in response to unexpected noise, movement or touch) [12] in addition to diarrhea. IgLON5 antibodies due to autoimmune encephalitis is characterized by axial rigidity, supra nuclear gaze paly and sleep disturbance [13]. CASPR2 antibody autoimmune encephalitis is characterized by episodic or persistent gait ataxia [14], frequent falls are common.

4. Disturbance in Autonomic Nervous System

Dysautonomia is common feature in most of autoimmune encephalitis specially in NMDAR antibody autoimmune encephalitis and can lead to death due to tach or brady arrythmia and hypotension, few patients need to be treated with pacemaker and vasopressors due to symtomatic bradycardia and hypotension respectively).

5. Cognition

Acute confusion, disorientation are frequent initial manifestation followed by anterograde amnesia in LG11 autoimmune encephalitis, most of limbic autoimmune encephalitis patients experienced marked cognition impairment due to involvement of the Hippocampus, neuropathic pain is common in CASPR2 encephalitis, pruritus is common in Glycine receptor antibody autoimmune encephalitis, pain is less common in LG11antibody autoimmune encephalitis and usually responds to immunotherapy. Clinicians should have a low threshold to iniate immunotherapy once infectious encephalitis had been ruled out and clinical manifestation is consistent with phenotype syndrome of autoimmune encephalitis. Paired simultaneous autoantibodies from serum and CSF should be ordered, fixed cell-based cell serology should be done first, live cell-based assay should be done only once the former came negative and the clinical suspicious still high. NMDAR serology is more sensitive in CSF than serum, LG11 antibodies are sensitive in serum than CSF.

6. Common Manifestations of Autoimmune Encephalitis

6.1. DPPX Autoimmune Encephalitis

Tremors, Diarrhea, weight loss, myoclonus, and hyperekplexia, normal brain MRI, association with B cell lymphoma, leukemia, gastrointestinal follicular lymphoma.

6.2. IGLONS5

Axial rigidity, Supranuclear palsy, chorea, sleep apnea, disordered REM and NREM sleep, impaired Cognition, bulbar symptoms.

6.3. GLYR Glycin Receptor Antibody

Axial rigidity, myoclonus, limbic encephalitis, impaired

REM and NREM sleep.

6.4. MOG (Mylene Oligodendrocyte Glycoprotein Antibody)

young females, optic chiasma involvement, optic neuritis, transverse myelitis, steroid responsive.

6.5. NMDA Receptor Antibody Autoimmune Encephalitis

Manifested initially with psychiatric symtoms, movement disorders, dysautonomia, Ovarian teratoma in 60% of females.

6.6. LG11

Frequent faciobrachial seizures, dystonia of ipsilateral face and arm, spasm in legs causing falls, temporal lobe seizures, piloerection seizures.

6.7. CASPR2

Frequent focal seizures, very rare generalized seizure, neuropathic pain, neuromyotonia, hyperhidrosis, Weight loss, severe insomnia, hallucinations.

6.8. GABAaR

- Status epilepticus, cortical and subcortical FLAIR signal abnormalities, association with thymoma.
- Seizure response to immunotherapy.

6.9. GABAbR

Acute limbic encephalitis, rapid progressive dementia, 50% association with small cell lung cancer.

6.10. AMPAR

Manifested with acute confusion, seizures, amnesia, psychiatric symptoms, association with small cell lung cancer, cancer breast, ovary and thymus.

7. Management

CSF usually showed lymphocytic pleocytosis.

- First line immunotherapy includes methyl prednisolone, plasmapheresis and intravenous immunoglobulin is the least effective.
- Second line therapy includes Rituximab, Cyclophosphamide, Mycophenolate, and Azathioprine.
- Third line includes Tocilizumab and Bortezomib.

8. Conclusion

Autoimmune encephalitis is a common disease characterised by highly distinctive features like Seizures, movement disorders, neuropsychiatric symptoms, dysautonomia, and underlying malignancies, and neuronal sell surface autoantibodies, it is a disease not to miss as early diagnosis and initiation of immunotherapy prevent fatality and neurological disability.

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