REVIEW ARTICLE

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Autoimmune Encephalitis – Recent Guidelines for Diagnosis and Management

ABSTRACT

Autoimmune neurology is a rapidly advancing field with the advent of neuronal auto antibodies panel. This diagnostic facility is accessible in our country too though cost remains a limiting factor in resource poor setting. We have made an attempt to review the available literature on 'Autoimmune encephalitis' to draw recent guidelines for diagnosis and management. This should help clinicians to suspect, diagnose early, and treat effectively the spectrum of 'Autoimmune encephalitis' in appropriate setting.

Key words: Autoimmune encephalitis, Limbic encephalitis, Anti-NMDAR encephalitis, NAA

INTRODUCTION

Autoimmune encephalitis (AE) is a group of acute to subacute onset, rapidly progressive, non-infectious, immune-mediated, inflammatory disorders affecting the cortical or deep gray matter.[1-4] There may be involvement of white matter, meninges, or spinal cord. An estimated prevalence rate for AE is 13.7/100,000, so possibly as common as infectious encephalitis.[5] "Autoimmune neurology" is coming up with the advent of newer antibodies and associated syndromes.[6] Identifying these disorders is rewarding in view of favorable response to immunotherapy compared to infectious encephalitis with limited therapeutic options. Clinicians need to suspect AE clinically first to plan investigations and early treatment.[1] Long-term management depends on antibody identified. Recent guidelines for diagnosis and management of AE are discussed here.

DIAGNOSIS

When to suspect?

A detailed history and examination is the first step. It is often acute or subacute onset, monophasic, with duration <3 months, preceded by viral prodrome.[1,7] Progressive course may be seen in some paraneoplastic syndromes. Patients with personal or family history of other autoimmune disorders are at increased risk of idiopathic AE while patients with known cancer, smokers, the elderly, or having rapid weight loss are prone to paraneoplastic AE.[8] Herpes simplex virus encephalitis, immune-modulating therapies (TNF-α inhibitors), and immune-checkpoint inhibitors (ICIs) may act as triggers.[1,9] Common clinical presentations include cognitive, encephalitic, psychiatric, epileptic, movement disorder, and autonomic. Table 1 shows AE classification based on anatomy, serology, and etiology.[10]

The immune reaction in AE results in multifocal brain inflammation, and occasionally, there is involvement of the meninges, spinal cord, and/or peripheral nervous system leading to polysyndromic manifestation – a clinical hallmark.[3,10] Except some antibodies having characteristic symptomatology as seen in NMDAR-antibody encephalitis and LGI1-antibody encephalitis, symptomatic overlap exists among various antibodies and AE types.[1,8] Symptoms depend on anatomical localization of inflammation as summarized in Table 2.

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How to investigate?

In most cases, the workup starts with brain imaging and CSF analysis.

Step 1: To confirm focal or multifocal brain abnormality
- i. Brain MRI
- ii. EEG
- iii. Brain FDG-PET.

Step 2: To confirm autoimmune inflammatory etiology
- i. CSF analysis
- ii. Blood tests
- iii. Brain biopsy.

Step 3: Screening for associated neoplasm
- i. CT chest, abdomen, and pelvis (contrast)/MRI (contrast)
- ii. Mammogram and breast MRI
- iii. Pelvic or testicular ultrasound or MRI
- iv. Whole-body FDG-PET scan.

Types of AE

1. Definite – requires autoantibody status
2. Possible – autoantibody status not needed
3. Probable – autoantibody status not needed.

Brain MRI

Presence of bilateral limbic encephalitis [Figure 1] confirms definite AE even when neuronal auto-antibodies (NAAs) are not detected provided viral panel in CSF is negative.[1] Criteria for definite autoimmune limbic encephalitis are shown in Table 3. Other MRI features can favor possible or probable AE along with positive NAAs.[1,2] Diffuse or patchy but not intense enhancement may be present.[3,11] Rarely, there may be meningeal enhancement, focal or extensive demyelination, and cortical diffusion restriction (often related to secondary seizures). Initial brain MRI may be normal and repeat MRI few days later may show changes. Specific MRI features include radial perivascular enhancement in autoimmune GFAP astrocytopathy and punctate brainstem/cerebellar enhancement in CLIPPERS.[12,13]

Electroencephalogram (EEG)

EEG helps in detecting subclinical status epilepticus, monitoring treatment response, and differentiating some diseases (CJD). AE is the leading etiology of NORSE including non-convulsive pattern too.[14] EEG can reveal underlying abnormality when MRI is normal.[1] EEG features include focal slowing/seizures, lateralized periodic discharges, and/or extreme delta brush seen in NMDAR-antibody encephalitis.[15] A normal EEG does not exclude AE.

Positron emission tomography (PET)

Brain FDG-PET has greater sensitivity and can show abnormalities earlier than MRI.[16] Commonly, limbic encephalitis shows bitemporal hypermetabolism and NMDAR-antibody encephalitis shows bilateral parietooccipital hypometabolism. Cortical metabolism can change due to seizures, antiepileptic drugs, immunosuppressants, and anesthetic agents. The lack of specificity, availability, and high cost are limitations of FDG-PET.

Cerebrospinal fluid analysis

This is the second most important test after brain MRI unless contraindicated. If timely brain MRI is not possible, clinicians should proceed with LP after CT head so as not to delay immunotherapy. CSF shows lymphocytic pleocytosis (20–200 cells) and elevated protein. IgG index and/or IgG synthesis rate may be increased and oligoclonal bands can be present (unmatched in the serum) in some cases.[1,17] A normal CSF does not rule out AE.

NAAs panels testing

It is recommended to include both CSF and serum for NAAs testing because CSF detection is more sensitive for NMDAR and GFAP antibodies while serum is more sensitive for onconeuronal, LGI1, and AQP4 antibodies.[1] Many of the antibodies can have overlapping syndromes and a patient can have more than 1 antibody.[18] Neuronal surface antibodies are detected preferably by cell-based assay while antibodies against intracellular antigens require indirect tissue immunofluorescence, immunohistochemistry, and confirmation by Western blot.[8] Treatment decisions should rely more on clinical assessment than on antibody titers because antibodies often remain detectable after clinical recovery.[19]

Blood tests

Several blood tests are often needed to exclude other competing etiologies. Hyponatremia is common in LGI-1 antibody encephalitis.[20] Blood samples should be drawn before IV Ig or plasmapheresis to avoid false-positive or false-negative results.

Brain biopsy

A brain biopsy is rarely required for atypical or mass-like lesions.[1] There are non-specific pathological changes comprising of T-cell and/or B-cell perivascular and parenchymal infiltrates along with secondary gliosis.[21]

Screening for an associated neoplasm

The most commonly associated malignancies are from lung, breast, thymus, testis, and ovary.[18] The suspicion of associated neoplasm is high in advanced age, smokers, having rapid weight loss, and NMDAR-antibody encephalitis. Apart from cancer screening initially and at relapse, antibodies against intracellular antigens have stronger cancer association demanding screening every 6–12 months for 4 years.

MANAGEMENT

Acute treatment

One can start with empiric intravenous acyclovir and antibiotics with ICU admission if indicated.

Acute immunotherapy

Immunotherapy should be started when AE is highly suspected and infection is excluded in CSF as early immunotherapy results in better outcomes.[1,22] It is hazardous to delay immunotherapy until confirmation by positive antibody.

High-dose corticosteroids

Empiric intravenous methylprednisolone 1 g per day for 3–7 days is recommended to achieve initial immunosuppression.[1] It is also preferred in demyelinating pattern on MRI (AE overlap with demyelinating syndromes),[23] CLIPPERS or autoimmune GFAP astrocytopathy,[12,13] FBDS suggestive of LGI1-antibody encephalitis,[20] and accelerated paraneoplastic AE in the

Table 1: Classification proposed based on anatomy, serology, and etiology[10]

Anatomical	Serological – based on antibodies to	Etiological
1. Limbic	1. Intracellular antigens – classical onconeuronal antibodies	1. Idiopathic
2. Cortical/subcortical	2. Surface antigens with high clinical relevance – NMDAR, AMPAR, LGI1 CASPR2, GABAR A/B, DPPX, glycine receptor, AQP4, MOG, GFAP	2. Postinfectious
3. Striatal	3. Surface antigens with low clinical relevance – VGKC, VGCC	3. Paraneoplastic
4. Diencephalic	4. Seronegative AE	4. Iatrogenic – immune-checkpoint inhibitors or other immune-modulating agents
5. Brainstem		
6. Cerebellar		
7. Meningoencephalitis		
8. Encephalomyelitis		
9. Peripheral		
10. Mixed		

setting of ICI treatment. Corticosteroids should be delayed if primary CNS lymphoma and sarcoidosis are suspected.

Intravenous Ig (IVIg)

IVIg in a dose of 2 g/kg over 2–5 days with ease of availability and administration is a good choice for rapid immunomodulation when corticosteroids are contraindicated or clinical picture is indicative of antibody-mediated disease.[22] IVIg should be used cautiously in paraneoplastic AE, heavy smokers, and the elderly due to increased thromboembolic risk. Paraneoplastic AE is likely to be cell mediated so IVIg is less effective. Hyponatremia may worsen with the use of IVIg.[24]

Plasma exchange (PLEX)

PLEX (5–10 sessions every other day) is effective for acute immunomodulation when corticosteroids are contraindicated or ineffective. PLEX may be more beneficial in the presence of central demyelination or coexisting NMOSD. It provides much rapid immunomodulation in severe or fulminant situations. It is devoid of thromboembolic risk and psychiatric side effects. Major limitations include enhanced bleeding risk, volume shifts, and central line placement with its associated risks. It is less suitable for agitated patients.

Table 2: Anatomical-clinical presentations of AE[10]

Anatomical classification antibodies	Clinical presentation	Associated antibodies
1. Limbic encephalitis	Cognitive/ psychiatric/ epileptic	Hu, CRMP5/CV2, Ma2, NMDAR, AMPAR, LGI1, CASPR2, GAD65 GABABR, DPPX, mGluR5, AK5, Neurexin-3α
2. Cortical/subcortical encephalitis	Cognitive/ seizure	PCA-2 (MAP1b), NMDAR, GABA A/B R, DPPX, MOG
3. Striatal encephalitis	Movement disorder	CRMP5/CV2, DR2, NMDAR, LGI1, PD10A
4. Diencephalic encephalitis	Autonomic/ sleep disorder	Ma 1–2, IgLON5, DPPX, AQP4
5. Brainstem encephalitis	Cognitive/ movement disorder/ craniobulbar	Ri, Ma 1–2, KLHL11, IgLON5, DPPX, AQP4, MOG, GQ1b
6. Cerebellitis or cerebellar degeneration	Ataxic	Hu, Ri, Yo, Tr, CASPR2, KLHL11, NIF, mGluR1, GAD65, VGCC
7. Meningoencephalitis	Cognitive/ seizure/ meningeal	GFAP or seronegative AE
8. Encephalomyelitis	Movement disorder including PERM and SPS/spinal/ opticospinal	GAD65, amphyphysin, glycine PCA-2 (MAP1B), GABA A/B R, DPPX, CRMP5/CV2, AQP4, MOG
Possible associated peripheral syndromes		
1. Neuropathy/ neuronopathy	Ataxic/ sensorimotor	Hu, PCA-2 (MAP1B), CRMP5, amphyphysin, CASPR2, CASPR1, CONTACTIN1, NIF155
2. Autonomic neuropathy/ ganglionopathy	Autonomic	Hu, CRMP5, anti-ganglionic AChR
3. Neuromuscular junction dysfunction	Myasthenic	VGCC, AchR
4. Myopathy	Motor	Striational

Combined first-line therapies

Combined first-line therapies may be used from the beginning in severe cases including NMDAR-antibody encephalitis, NORSE, and severe dysautonomia. However, usually, IVIg and/or PLEX are added in sequence after corticosteroids when response to first therapy is not satisfactory.

Second-line agents

If there is no meaningful clinical/radiological response to first-line therapy after 2–4 weeks, second-line agents such as rituximab or cyclophosphamide can be added for better outcome.[22] Rituximab is less toxic than

cyclophosphamide although it may not be as effective for cell-mediated inflammation. Rituximab is given 375 mg/m2 weekly for 4 weeks or two doses of 1000 mg 2 weeks apart. Cyclophosphamide is given 600–1000 mg/m^2. Cases not showing rapid response to conventional second-line agents may benefit from proteasome inhibitors that block plasma cell generation (bortezomib), interleukin (IL)-6 inhibition (tocilizumab), or low dose IL-2.[25-27] Clinical trials of ocrelizumab (a humanized anti-CD20 monoclonal antibody) are underway. A second-line agent in acute setting also serves as a bridging therapy to prevent early relapses on abrupt discontinuation of immunosuppression.[28]

Symptomatic and supportive therapy

Although various symptoms may improve with acute immunotherapy, symptomatic treatment may be required. Physical and neuropsychological rehabilitation is equally important.

MANAGEMENT OF ASSOCIATED NEOPLASM

Tumor resection provides highest benefit in cases with onconeuronal antibodies since neurological symptoms tend to be immunotherapy resistant in many of them.[29] In inoperable tumors, debulking surgery, radiotherapy, or chemotherapy may prove beneficial.[30] The recent cancer-directed immune-checkpoint inhibitors add to the management of paraneoplastic AE, however, there is an associated risk of new paraneoplastic reactions or deterioration of pre-existing paraneoplastic AE as the immune response is not checked against tumor (and neuronal) antigens although it responds to steroids.[9]

Characteristics of some commonly encountered types of AE, their tumor associations and other features are presented in Table 5.[31]

Table 3: Criteria for definite autoimmune limbic encephalitis

1. Clinical – subacute onset (rapid progression<3 months) working memory deficits, seizures, or psychiatric symptoms
2. MRI (PET) – bilateral brain abnormalities on T2-weighted FLAIR MRI highly restricted to the medial temporal lobes (18F-FDG-PET can be used)
3. CSF cells>5 WBC per mm3 OR electroencephalogram-temporal lobes epileptic or slow-wave activity
4. Reasonable exclusion of alternative causes

All four of the above required. If one of the first three criteria is not met, detection of antibodies is necessary.[1]

Table 4: Criteria for anti-NMDA receptor encephalitis

Probable anti-NMDA receptor encephalitis[1]
1. Rapid onset (<3 months) of at least four of the following six
• Abnormal behavior or cognitive dysfunction
• Speech dysfunction
• Seizures
• Movement disorder, dyskinesias, or rigidity/abnormal postures
• Decreased consciousness
• Autonomic dysfunction or central hypoventilation
2. Abnormal EEG (focal or diffuse slow or disorganized activity, epileptic activity, or extreme delta brush) OR CSF with pleocytosis/oligoclonal bands
3. Reasonable exclusion of other disorders

All three of the above criteria required. Diagnosis can also be made in three of the above symptoms with systemic teratoma. Definite anti-NMDA receptor encephalitis. One or more of the six major groups of symptoms and IgG anti-GluN1 antibodies in CSF

BRIDGING IMMUNOTHERAPY

Abrupt discontinuation of acute immunotherapy should be avoided to prevent early recurrence.[23,28,33] A common bridging strategy is to use oral prednisone 1–2 mg/kg/day for weeks to months overlapping with long-term immunotherapy if indicated, followed by gradual taper. Alternatively, periodic IV MPS or IVIg may be given as maintenance therapy.[8] Rituximab used for acute attack may serve as a bridging therapy along with corticosteroid overlap initially.[23,28,32] A short bridging therapy may be advisable for patients with antibodies against intracellular antigens.[28,33,34]

LONG-TERM MANAGEMENT

Long-term management of AE is one of the most understudied aspects and here comes the importance of "Autoimmune Neurology Fellowships."

The long-term management of AE is highly influenced by the presence of NAAs.[1] More recent NAAs panels emphasize the importance of clinical correlation rather than etiology. Clinically relevant neuronal surface antibodies have higher chance of recurrence while antibodies against intracellular antigens have lower recurrence which is progressive but remits with the treatment of cancer.[1,8] Relapse rates and the value of long-term immunosuppression are the key areas for future research. Although azathioprine (AZT) and mycophenolate

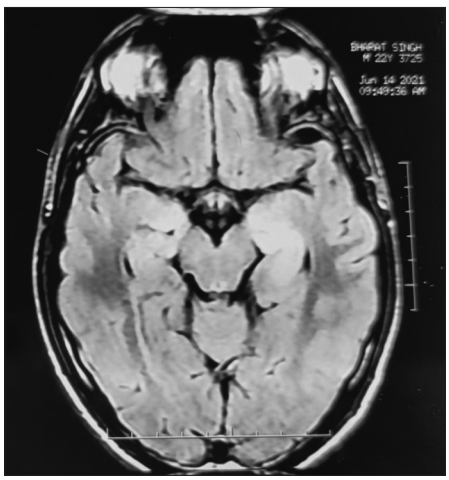

Figure 1: MRI brain T2 FLAIR showing bilateral medial temporal lobe hyperintensity

mofetil (MMF) have been used, rituximab acts faster and less carcinogenic when used for 3 or more years.[28,33] Rituximab can be used as acute, bridging, and long-term immunosuppressant. Rituximab is preferred for antibodies against neuronal surface antigens (humoral autoimmunity) and AZT/MMF is preferred for antibodies against intracellular antigens and for seronegative AE (cellular autoimmunity). Other B-cell therapies (humanized anti-CD20 and anti-CD19 monoclonal antibodies) may be worth exploring in future research. The value of non-cell depleting immunotherapies (complement or cytokine inhibitors) and interleukein-6 is yet to be fully explored

FUTURE RESEARCH

Future research is required to drive improvements in diagnosis and management though heterogeneity creates major

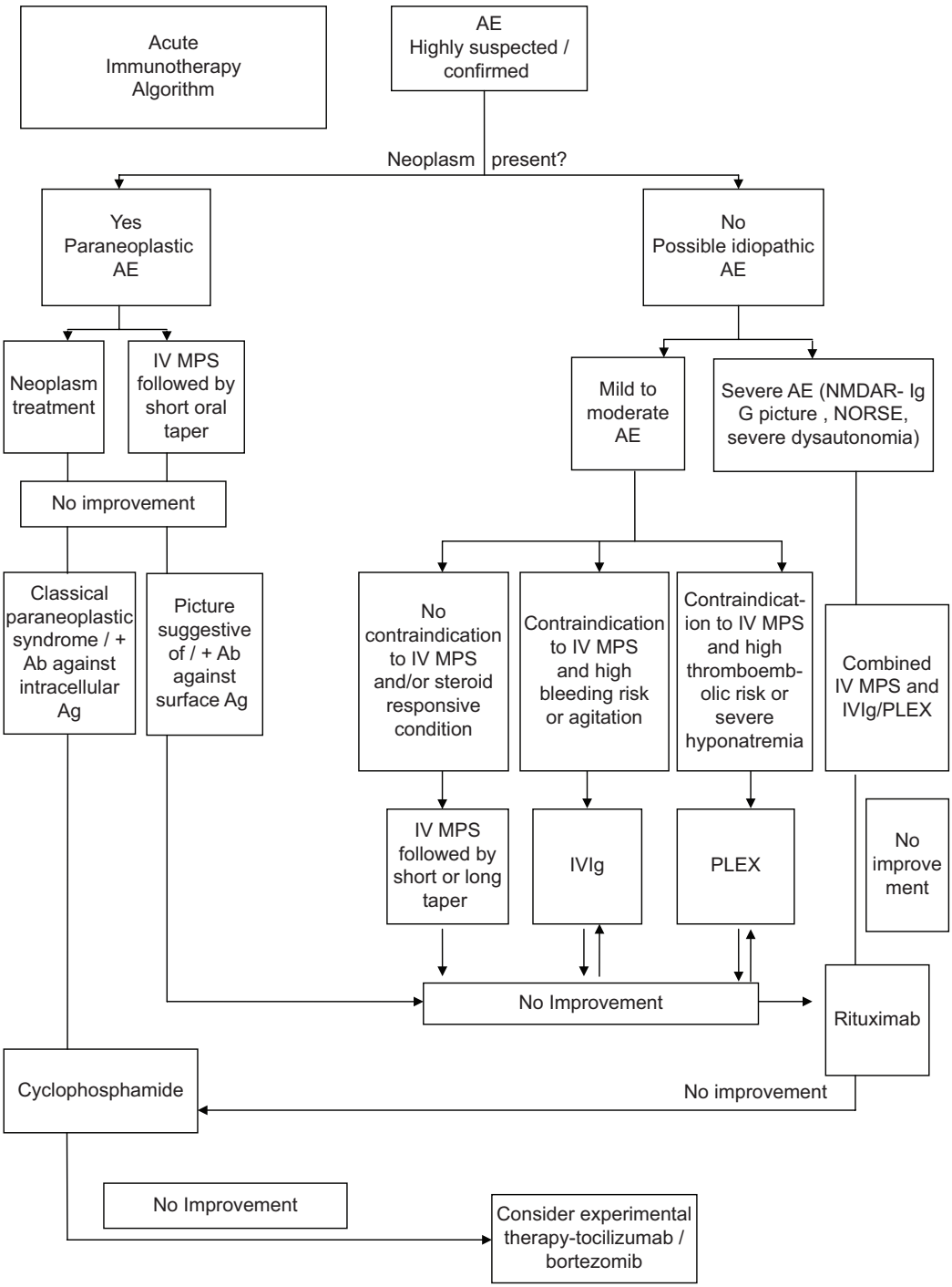

Table 5: Characteristic features of some commonly encountered types of AE

	Anti-NMDAR encephalitis	Anti-LGI l- encephalitis	Anti-CASPR2-associated encephalitis	Anti-GABABR-encephalitis	Anti-AMPAR-Ab encephalitis
Age and sex	Children and young women F: M: 4:1	Older men, median age 60 years	Adult males	Median age 62 years	Middle-aged women
Antibody target	NMDAR (mainly GluN1 in CSF)	VGKC-complex-associated LGI1 A	VGKC-complex associated CASPR2	GABABR1	GluRl/2
Tumor association	Ovarian (or other) teratomas in≤50%	Tumors are very rare.	Thymoma principally, small-cell lung cancer.	Thymoma, lung	Thymoma, lung, breast
Response to immunotherapy	Responds well to early immunotherapies and early tumor removal but non-paraneoplastic cases can be chronic and relapsing	Usually, monophasic, continuous immunosuppression not required	Can respond to treatment or recover spontaneously but prognosis subject to tumor presence	Treatment responsive	Treatment responsive but relapses common
Other characteristics	EEG – extreme delta brush	60% develop hyponatremia	EMG – myokymia	Frequent coexisting autoimmune diseases	

Modified from Khadilkar *et al.*[32]

obstacles for large-scale trials. Children and elderly >65 years pose greater challenges. Relapse rates, value of long-term immunosuppression, and neuropsychological rehabilitation are key areas for research.

LEARNING POINTS

1. Strong clinical suspicion supported by MRI/EEG/CSF analysis should prompt quick immunotherapy for better outcome with fine tuning on NAAs results
2. Initial normal MRI, EEG, and CSF do not exclude AE. Bilateral limbic encephalitis on MRI confirms definite AE in appropriate setting (negative CSF viral studies) without NAAs
3. Extreme delta brush pattern in EEG is characteristic of anti-NMDAR encephalitis
4. Brain FDG-PET is more sensitive than MRI but lacks specificity
5. A common general approach for initial treatment needs to be framed despite differing therapeutic responses in antibody-mediated versus cell-mediated AE
6. There is a significant syndromic overlap between antibodies and more than 1 antibody can coexist in same patient. NAAs testing should preferably be done in both serum and CSF. Treatment decisions should rely more on clinical judgment rather than antibody titer
7. Rituximab is increasingly being recognized as first-line therapy
8. Role of "Autoimmune Neurology" is immensely rising with the advancement in NAAs panels and newer therapies.

CONCLUSION

The spectrum of 'Autoimmune encephalitis' is becoming broad with rapid advances in diagnostic facilities and therapeutic options. Initial clinical presentation supported by neuroimaging, EEG, and CSF analysis should prompt to start immunotherapy for rewarding outcome. The cost and auto antibody test results should not delay the early decision making. Long term management requires expertise in 'Autoimmune neurology' which is progressing to be established as a sub-specialty.

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