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A Comprehensive Review of Autoimmune Encephalitis: From Clinical Syndromes to Management Strategies

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ABSTRACT:
BACKGROUND--Encephalitic syndromes are common medical emergency. The importance of early diagnosis and appropriate treatment is of paramount importance. Autoimmune encephalitis are being increasingly recognized as these are potentially reversible and due to non-infectious causes.
SUMMARY--Autoimmune encephalitis is characterised by subacute onset encephalopathy, seizures, memory disturbance, and neuro–psychiatric symptoms. It is often associated with a variety of other neurological symptoms, and its differential diagnosis is wide, leading to challenges in its recognition. One of the initial antibodies described were those against the voltage gated potassium channel (VGKC), which causes limbic encephalitis (LE). Later antibodies against N–methyl D–aspartate receptors (NMDAR) were found associated with ovarian teratoma, with a prominent neuropsychiatric onset.NMDAR induced LE is now known to occur mainly in a non–paraneoplastic setting. Antibodies have also been described against other glutamate receptors (AMPAR1, AMPAR2 etc) and against GABA b receptors.
KEY MESSAGE--Advances in autoimmune encephalitis research in the past 10 years have led to the identification of new syndromes and biomarkers that have transformed the diagnostic approach to these disorders. Ancillary testing with MRI and EEG may be helpful for excluding other causes, managing seizures, and, rarely, for identifying characteristic findings. Appropriate autoantibody testing can confirm specific diagnoses, although this is often done in parallel with exclusion of infectious and other causes.
KEY WORDS—Encephalitis, VGKC antibody, Anti NMDA receptor,

I. INTRODUCTION

Autoimmune encephalitis causes subacute deficits of memory and cognition, often followed by suppressed level of consciousness or coma. A careful history and examination may show early clues to autoimmune causes. Autoimmune encephalitis may be divided into several groups of diseases: a) Those with pathogenic antibodies to cell surface proteins, b) Those with antibodies to intracellular synaptic proteins, c) T-cell diseases associated with antibodies to intracellular antigens, and d) Those associated with other autoimmune disorders. Many forms of autoimmune encephalitis are paraneoplastic; hence tumor screening is necessary for proper management. Due to a broad differential diagnosis, the recognition of AIE is frequently difficult and delayed. The aim of this article was to facilitate recognition of the clinical features and to simplify the diagnostic approach, with the ultimate objective of rapid immunotherapy administration and good prognosis if is expected if treated. The process of caring for these patients requires patience and repeated evaluations (Autoimmune encephalitis may relapse) to determine the proper degree of immune therapy needed at any given time.

CLASSIFICATION OF COMMON ANTIGENS

1)Antibodies to cell membrane surface antigens – VGKC-complex (LGI1, CASPR2, contactin-2) and the NMDA, AMPA, GABAB and Glycine receptors

2) Antibodies to intracellular antigens (inside the neu¬ron) – Hu, Ma2, CV2, Antiphiphysin, glutamic acid de¬carboxylase (GAD)

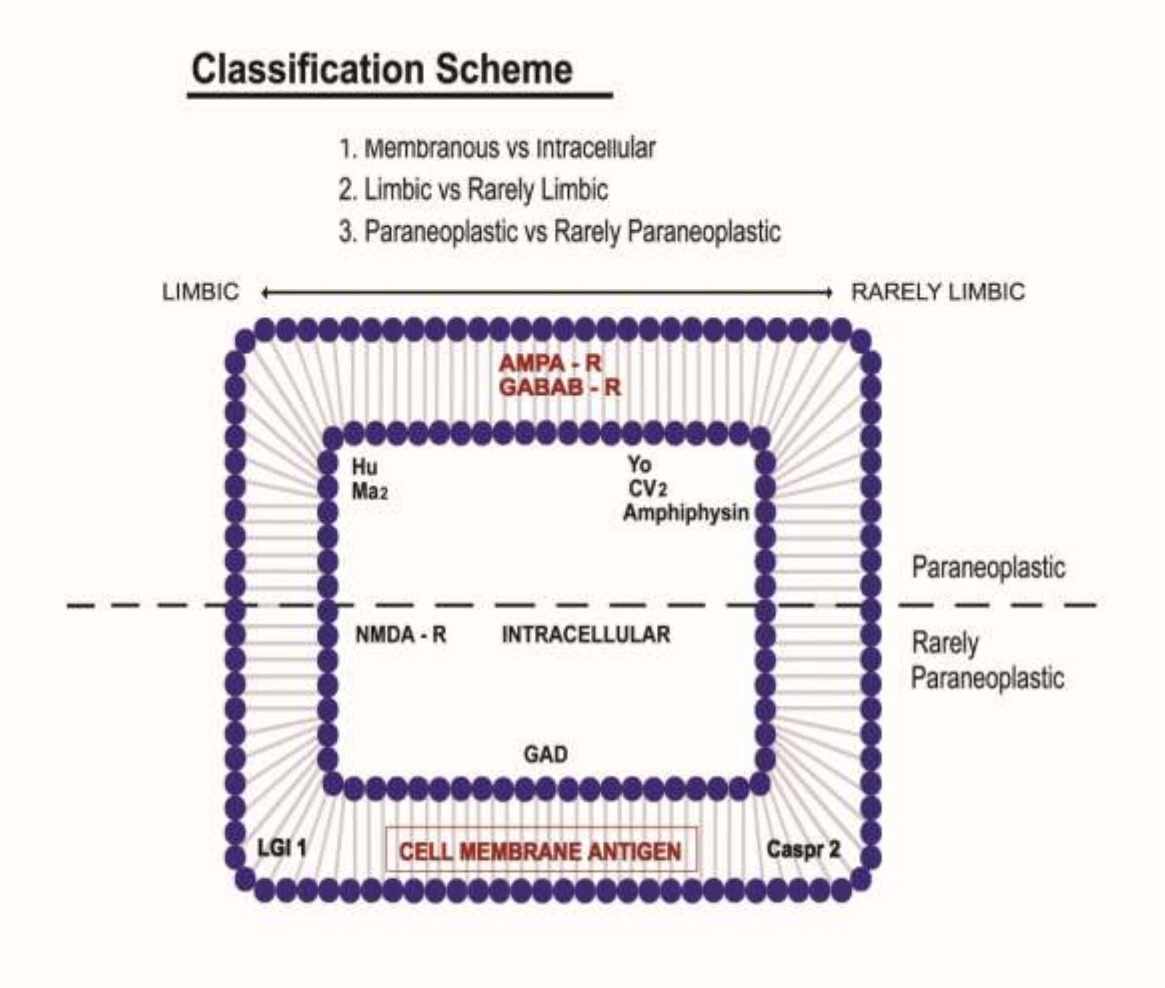

FIGURE 1: FIGURE DEPICTING THE LOCATION OF ANTIGENS

RECOGNIZING THE SYNDROMES OF AUTOIMMUNE ENCEPHALITIS

Important clinical clues to suspect autoimmune encephalitis are subacute onset, fluctuating course, mood and behaviour changes, cognitive dysfunction, seizures, dyskinesiae and tremors.

Clinical finding	Associated autoantibody disorders
PSYCHOSIS	NMDAR, AMPAR, GABA-B-R
DYSTONIA,CHOREA	NMDAR, anti-streptococcal antibody, D2R
HYPERKPLEXIA	GlyR
STATUS EPILEPTICUS	Most characteristic of GABA-B-R and GABA-A-R but NMDAR is much more common
NEW ONSET TYPE 1 DM	GAD65
FACIOBRACHIAL DYSTONIC SEIZURE	LGI 1
NEUROMYOTONIA,MUSCLE SPASM,FASCICULATION	Caspr2
STIFF PERSON SYNDROME(SPS) AND/OR EXAGGERATED STARTLE	GAD65, GlyR, Amphiphysin (with GAD65 being most common in stiff person/stiff limb and GlyR in PERM, and Amphiphysin in women with breast cancer)

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CNS (MYOCLONUS, STARTLE, DELIRIUM) AND GASTROINTESTINAL HYPER-EXCITABILITY)	DPPX
CRANIAL NEUROPATHY	Ma2, Hu, Miller-fisher, Bickerstaff (but also infections like sarcoidosis, Lyme, TB)
ENCEPHALOMYELITIS, RIGIDITY& MYOCLONUS	GlyR
CEREBELLITIS	GAD65, PCA-1 (Yo), ANNA-1 (Hu), mGluR1, VGCC

Table 1. Clinical clues in the recognition of types of autoimmune Encephalitis

AMPAR = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; Caspr2 = Contactin-associated protein relates 2; CV2/CRMP5 = Crossveinless-2/collapsing response mediated protein 5, $GABA_BR$ = Gamma-aminobutyric acid receptor LGI1: leucine-rich glioma inactivated 1; GAD: glutamic acid decarboxylase, GlyR—glycine receptor,mGluR1/5--. glutamate receptor, metabotropic, PCA—purkinje cell antibody, VGCC—voltage gated calcium channel, PERM--progressive encephalomyelitis, rigidity,and myoclonus, DPPX--Dipeptidyl-peptidase-like Protein-6, D2R—dopamine receptor

Psychiatric manifestations

• Although this presentation is well known for anti-NMDAR encephalitis,[1] anti-AMPAR and anti-GABA-B-R both may have prominent early psychiatric manifestations [2] Certain features should raise the suspicion of autoimmune encephalitis, particularly in a first psychotic episode—

a) Recent flu-like syndrome
b) Rapid onset of psychosis and/or catatonia
c) Seizures/neurological dysfunction
d) Signs of autonomic dysfunction
e) Refractory hyponatremia
f) No past psychiatric illness
g) Known history of malignancy, especially if small cell lung cancer, teratoma or thymus cancer
h) Worsening of symptoms after antipsychotic therapy
i) Long history of smoking
j) Personal/family history of auto-immune disease

Abnormal movements

- These include anti-NMDAR encephalitis, where movement symptoms may occur early in the disease course, especially in children, who generally have more motor symptoms and fewer psychiatric symptoms than adults.[3]
- GlyR autoimmunity may present with stiff person syndrome (SPS) or progressive encephalomyelitis with rigidity and myoclonus (PERM).[4]
- A striking feature of PERM with GlyR antibodies is a pathologically exaggerated startle response, resembling hereditary hyperekplexia, a genetic disease caused by GlyR mutations.[5]
- GAD65 is more associated with classical SPS while GlyR antibodies may be seen more with symptoms of hyperekplexia and myoclonus, which are prominent in PERM.
- Sydenham chorea or anti streptococcal antibody chorea is a well-recognized autoimmune movement disorder thought to be triggered by streptococcal infections and should be considered in children with this presentation.[6]

Seizures

- Faciobrachial dystonic seizures (FBDS) are brief seizures consisting of rapid jerks of the face and/or ipsilateral arm and shoulder.[9]FBDS are characteristic of LGI1 autoimmunity.
- In anti-NMDAR encephalitis seizures may occur at any stage of the illness.
- Autoantibodies to two important inhibitory receptors in the brain, GABA-B and GABA-A receptors (at high titer) convey a high risk of severe seizures and intractable status epilepticus.[7],[8]
- GAD65 antibodies may present with epilepsy, perhaps also with memory impairment

Cerebellitis.

- Presentation of a subacute cerebellar syndrome portends a good probability a specific autoimmune etiology and also a significant risk of tumors. Paraneoplastic cerebellar degeneration is associated with conventional onconeuronal autoantibodies such as Yo.

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Peripheral nerve hyperexcitability

Isaacs syndrome (muscle spasms, cramps and fasciculations) [10],[11] and Morvan syndrome i.e. Morvan's fibrilllary chorea (peripheral nerve hyper-excitability with encephalitis and severe insomnia). Some cases of Isaacs syndrome are associated with autoantibodies to Caspr2 or other, often undefined, members of the voltage-gated potassium channel (VGKC) complex.[12],[13]

EXCLUSION OF OTHER AUTOIMMUNE DISORDERS

In addition to the antibody-mediated and paraneoplastic forms of encephalitis, there are other autoimmune diseases that may present with encephalitis.

- **Multiple sclerosis** (MS) is generally easier to distinguish from autoimmune encephalitis due to more focal symptoms and characteristic brain imaging findings.
- **Systemic lupus erythematosus**--Lupus may affect diverse areas of the nervous system, causing neuropathy, vasculitis, myelitis, venous sinus thrombosis, stroke, and other manifestations.[14] Neuropsychiatric lupus may manifest with seizures, psychosis, cognitive dysfunction, or neurovascular disease. These manifestations are common with severe disease affecting other organ systems such as the gastrointestinal, renal, and hematological systems. In one large series, one fourth of deaths from lupus were related to CNS involvement and 16% were due to CNS infection, suggesting vigilance for both autoimmune and infectious encephalitis is warranted for these patients.[15]
- **Vasculitis** affecting the CNS may rarely present with symptoms resembling encephalitis. When this is suspected, imaging of the cerebral vessels, search for other evidence of vasculitis (such as serologies for lupus and other rheumatologic diseases) may be useful.
- **Bickerstaff encephalitis** - constellation of signs and symptoms including acute ophthalmoplegia (symmetric and usually progressive fashion), ataxia (truncal and limb involvement), altered sensorium (secondary to activation of the brain-stem reticular activating system). Dysarthria and either hyperreflexia or hyporeflexia on examination
- **Miller Fisher syndrome** This disease may at first resemble the brain-stem syndrome associated with anti-Ri, but the loss of reflexes is an important clue suggesting Miller Fisher syndrome. Detection of the GQ1b antibody may be helpful in securing these diagnoses.[16]

EXCLUSION OF INFECTIOUS CAUSES

VIRAL INFECTION—

Most cases of infectious encephalitis are viral. In the USA, leading viral infections include are HSV (herpes simplex virus), VZV (varicella zoster virus), enterovirus, and West Nile virus (WNV).[17] HIV and Prion disease can also present encephalitis like features. Japanese encephalitis (JE) was once the leading cause of viral encephalitis in East Asia. A detailed review of encephalitis in immunocompromised patients highlighted HSV and VZV as leading causes, along with a host of rarer entities.[18] Infections have been transferred by the organ donor to an organ transplant recipient, including rabies, LCMV(lymphocytic choreomeningitis virus), Westnile, CMV(cytomegalovirus), and EBV(Epstein barr virus);[19]

Human herpesvirus 6 (HHV-6), and less often HHV-7, may cause encephalitis and their reactivation may be an important cause of encephalitis in transplant patients.[20],[21],[22]

BACTERIAL INFECTION

Listeria, atypical presentations of streptococcus, syphilis, Lyme disease, and tuberculosis.

FUNGAL INFECTION—

Cryptococcus or aspergillus are particularly likely in immunocompromised patients.

NEOPLASTIC—

Certain types of tumors, such as lymphomas, may weaken the immune system and increase the risk of paraneoplastic/autoimmune diseases.

SPECIFIC TYPES OF AUTOIMMUNE ENCEPHALITIS

Autoantibodies to cell surface antigens

NMDAR, VGKC-complex (it has been re¬cently recognized that VGKC antibodies are directed to particu¬lar components of the VGKC-complex, most commonly LGI1, CASPR2 and Contactin-2 [23],[13]), AMPAR, GABA(B)R, GABA(A)R, GlycineR, mGluR5, DPPX 9

Table 2: Neuronal surface autoantibody,clinicalfeature, and associated tumor

ANTIGEN	CLINICAL FEATURE	TUMOR
NMDA-R	• Starts with a psychotic stage (68-77% of patients[53]) and seizures (76% of patients[1]) followed by reduction in consciousness, autonomic instability (which includes fluctuation of blood pressure and temperature, tachycardia, bradycardia, cardiac pauses, and diaphoresis) and movement disorders, namely dyskinesias. • The oral-lingual-facial dyskinesias[1]are the most characteristic, but other abnormal movements, such as opisthotonic postures and a catatonic state [26], may also occur. • A curious feature is a dissociative response to stimuli: patients may resist eye opening, but show reduced or absent response to painful stimuli[27].	Young women with ovarian teratomas [25], of which 70% were benign.
LGI1	• Faciobrachial dystonic seizures (89% of patients[13])refractory to AED, precede the onset of cognitive symptoms by weeks in 40-71% of patients.[24] • Limbic encephalitis • Seizures including myoclonus • Rapidly progressive dementia • REM sleep behavioural disorder • 60% also develop hyponatremia	Thymoma(<10%)
CASPR2	• Peripheral nerve hyperexcitability or neuromyotonia (Isaacs' syndrome), neuropathy, allodynia [10,11] • Encephalopathy, hallucinations, seizures, autonomic i.e hypothermia [29] insomnia • Morvan's syndrome(high risk of an underlying tumour which is usually a thymoma)[30,13] • Coexisting immune-mediated disorders such as myasthenia gravis with anti-AChR(acetylcholine receptor), MUSK(muscle specific kinase) Ab.	Thymoma(38% case)
AMPAR	• Limbic encephalitis and atypical psychosis.	64% had an underlying tu-mour, and they are the most commonsmall cell lung cancer [31]followed by breast & thymoma
GABA(B)R	• Limbic encephalitis with prominent seizures [7]	Small cell lung cancer(SCLC)
GABA(A)R	• rapidly progressive encephalopathy • refractory seizures, status epilepticus, and/or epilepsiapartialis continua. • Seizures preceeded by change in behaviour or cognition	Small cell lung cancer
GlycineR	• Progressive encephalomyelitis with rigidity and myoclonus (PERM)[28], a rare condition showing limb and axial rigidity, muscle spasms, brainstem signs and hyperekplexia[32-34].	Thymoma

mGluR5	• Ophelia syndrome, • Memory impairment • Apart from limbic involvement, may show parietal and occipital cortex changes[35].	Hodgkin lymphoma
(DPPX)	• Rapidly progressive encephalopathy • Hyperekplexia • Cerebellar signs • Severe diarrhea and weight loss	Follicular B cell. lymphoma, chronic lymphocytic leukemiae(CLL)

Autoantibodies to intracellular synaptic proteins

Anti-GAD65 (glutamic acid decarboxylase 65kd) target the synaptic isoform of the enzyme necessary to synthesize GABA. GAD65 antibodies have diverse clinical associations, including type 1 diabetes, cerebellar ataxia, and SPS(stiff person syndrome).[36] In the paraneoplastic context (that is, when cancer is present), GAD65 antibodies associate with diverse syndromes including encephalitis, SPS and paraneoplastic cerebellar degeneration.[37]

Anti-Amphiphysin target an intracellular protein important for recycling synaptic vesicles.[38] The antibodies are very strongly associated with SPS in women with breast cancer.[39] The SPS more often affects the cervical region and responds to tumor therapy and/or immune therapy

Antibodies to intracellular antigens

Hu [anti neuronal nuclear antibody(ANNA-1)] – this type can involve any part of the ner¬vous system, including peripheral nerves, dorsal root ganglia, and spinal cord. A smoking history is often present as 75% of patients have small cell lung carcinoma (SCLC). [40]

Ma2 – the clinical clues are the presence of both hypo¬thalamic (daytime sleepiness, narcolepsy, cataplexy, hyper¬phagia, hormonal deficits) and brainstem dysfunction (par¬ticularly with supranuclear gaze palsy).[41] It occurs mostly in association with testicular germinal cell tumour in younger males, but in older individuals there may be an underlying non-small cell lung carcinoma or breast cancer.[42]

Anti-Ri (ANNA-2) associate with diverse syndromes including cerebellar degeneration and encephalitis. Most patients have lung or breast cancers.[43]

ANNA-3 have only rarely been described and the clinical features are multifocal and have a similar range as anti-Hu.[44]

Anti-Yo (PCA-1) are found in women with breast or ovarian cancers in more than 90% of cases.[45] Patients usually have paraneoplastic cerebellar degeneration.[46] There is some evidence that the antibodies may enter neurons, but other researchers think T-cell mechanisms are more likely.[47]

PCA-2 have only rarely been reported and may associate with encephalitis or cerebellar syndromes. [48]

Anti-CV2/CRMP-5-- have diverse associations including cognitive impairment, cerebellar syndromes, abnormal movements (chorea), and cranial neuropathies. Optic neuritis has also been reported.[49],[50],[51] There may be an under¬lying SCLC, malignant thymoma or other tumours.

Glial fibrillary acidic protein (GFAP) astrocytopathy is a newly proposed autoimmune neurologic syndrome characterized by meningitis, encephalitis, or myelitis associated with immunoglobulin G (IgG) antibodies to GFAP. Glial fibrillary acidic protein-specific IgG identifies a distinctive, corticosteroid-responsive, sometimes paraneoplastic autoimmune meningoencephalomyelitis. It has a lethal canine equivalent: necrotizing meningoencephalitis. Expression of GFAP has been reported in some of the tumor types identified in paraneoplastic cases. [52]

DIAGNOSIS

Zuliani et al. proposed further diagnostic criteria in suspected cases of an anti-surface associated AE. According to the authors, in patients displaying suggestive clinical fea¬tures, with acute or subacute onset (<12 weeks), evidence of CNS inflammation, and after excluding other causes of encephalopathy. [53]

As far as the diagnosis is concerned, the first step is to consider other treatable disorders, such as viral encephali¬tis and systemic autoimmune diseases .Seizures, movement disorders, language dysfunction, and psychiatric manifestations are commoner in AE when compared to viral encephalitis, while autonomic dysfunc¬tion is very suggestive of the former.[54] When suspect¬ing a paraneoplastic syndrome associated with anti-CV2/

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CRMP5, it is wise to exclude Huntington's and Wilson's disease, due to the coexistence of chorea or dystonia and psychiatric symptoms. Another common presentation can be acute dementia,[55]and other causes of rapidly progressive dementia should also be excluded.

Algorithm: Basic steps to investigate autoimmune encephalitis

AUTOIMMUNE ENCEPHALITIS SUSPECTED FROM HISTORY

↓

RULE OUT OTHER INFECTIVE, NON-INFECTIVE INFLAMMATORY, ENDOCRINOLOGIC, METABOLIC, IMMUNE MEDIATED DISEASE AND OTHER POTENTIALLY TREATABLE CAUSE

↓

EXCLUSION OF UNDERLYING NEOPLASM

↓

ANCILLARY INVESTIGATION INCLUDING MRI, CSF, EEG

↓

APPROPRIATE AUTOANTIBODY TESTING BASED ON CLINICAL CLUES

Secondly, the basic workup includes the following investigations:

(1) MRI –. Brain MRI in patients with NMDAR, AMPAR, LGI1, Caspr2, and GABA-B antibodies may be normal or show increased T2 signal, especially in the medial temporal lobes.[1],[6],[12] This pattern is like the findings seen in HSV encephalitis, where 95% of patients have abnormalities on MRI,[56] or other viral causes of encephalitis. Tuberculosis, Syphilis, or other infections may present similarly. Autoantibodies to DPPX or GABA-A may have fewer characteristic findings. [8],[57] Brain MRI therefore does not distinguish between infectious and autoimmune causes.

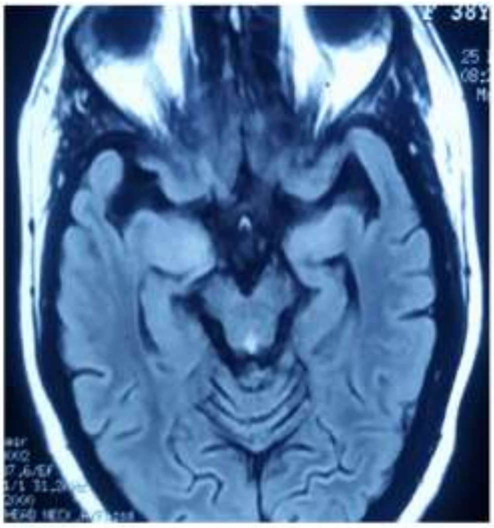

FIGURE 2: MRI BRAIN SUGGESTIVE OF FLAIR HYPERINTENSE SIGNAL IN BILATERAL MESIAL TEMPORAL LOBE(PRESENTED WITH ATAXIA & COGNITIVE DECLINE)

(2) CSF – CSF analysis often reveals lymphocytic pleocytosis, in¬creased protein concentration or presence of oligoclonal bands (OCB). [58],[59] In anti-NMDAR AE, over 80% of patients have an abnormal CSF at presentation; progres¬sion of findings is usually characterized by an early phase with lymphocytic pleocytosis, with or without elevated protein levels, followed by the decrease of white blood cells in CSF and the appearance of OCB. On the other hand, only half of the individuals with anti-VGKC AE show ab¬normal CSF screen and rarely present OCB. [60], [61]

(3) EEG – EEG is useful for excluding subclinical seizures, for prognosis, and sometimes for suggesting particular diagnoses. In patients with HSV encephalitis, EEG may predict prognosis in addition to helping exclude non-convulsive seizures; normal EEG correlates with good outcomes independent of other prognostic factors.[62] EEG abnormalities are almost universal, usually non¬specific, including diffuse or focal slowing, frontal or temporal intermittent rhythmic delta activity (FIRDA or TIRDA), or temporal epileptiform activity. [63],[64] In anti-NMDAR AE, a specific pattern, called "extreme del¬ta brush" (EDB) has been observed in 30% of patients in small series. This pattern has not been described in any other disorder, and these patients show more frequently a normal MRI, longer hospitalization, and worse prognosis, suggesting that it might be a marker of more severe disease. [65], [66] In the pediatric group, EEG findings also seem to have prognostic value: those patients who had more diffuse abnormalities without physiological background activity showed more severe neurological symptoms and a poorer outcome. [67]

(4) A comprehensive investigation to exclude an under¬lying neoplasm should be considered in all cases for several reasons. a) Treating the relevant tumor is thought to be helpful for treating the autoimmune disorder. b) Tumor therapy and immune therapy may need to be given simultaneously and in a coordinated fashion. c) Treatment with steroids, rituximab, or cyclophosphamide could complicate tumor diagnosis in the case of tumors like lymphoma.

(5) The final step is to detect the autoantibodies either in se¬rum or CSF. In almost all patients, serum shows higher con¬centrations of antibodies than CSF. Antibody testing to be guided by clinical clues in examination. [68].

BIOPSY

Brain biopsy generally is not used in the diagnosis of encephalitis for several reasons. Infections may be detected by PCR, culture, or other less invasive methods. In addition, the results of biopsy are generally not definitive for a particular autoimmune etiology. Overall, the clinical impact of biopsy done for suspected encephalitis is low, with only about 8% of cases having clear benefit. [69]

MANAGEMENT AND FOLLOW-UP

When autoimmune encephalitis is considered likely, treatment should be started promptly. If there is an identified neoplasm, its removal may be im¬portant for the neurological improvement. [70],[71],[25] However, in traditional paraneoplastic cases associated with intracellu¬lar antibodies, there is rarely a favourable response to this approach even with immunotherapies. On the other hand, those cases of AIE associated with membrane antibodies may have a good response to immune interventions, plus tumour removal when indicated, [72] IVIG, plasma exchange (PE), corticosteroids, cyclophosphamide, and rituximab have all been used with success. (TABLE 4)

In anti-NMDAR AE, the most used strategy is IV-IG 0.4 g/kg/day for 5 days, plus methylprednisolone 1 g/day for 5 days; Plasma exchange is postponed for treat¬ment failure cases. If no improvement occurs after 4 weeks of first therapy, second line drugs should be con¬sidered.[73] In anti-VGKC-complex AE, immunotherapy has been tried with intravenous methylprednisolone 1 gram or 30- 50 mg/kg for 5 days, or IV-IG 0.4 g/kg for 3-5 days, or 5 to 7 cycles of plasmapheresis (on alternate days). If patients respond to this treatment within 6 weeks, then a steroid ¬sparing agent can be initiated. If not, or in case of relaps¬ing disease, second line therapy should be promptly con¬sidered. [74] Second line therapies include rituximab (often 375 mg/m2 weekly for 4 weeks) or cyclophosphamide (750 mg/m2 IV monthly until improvement is noted), or both.

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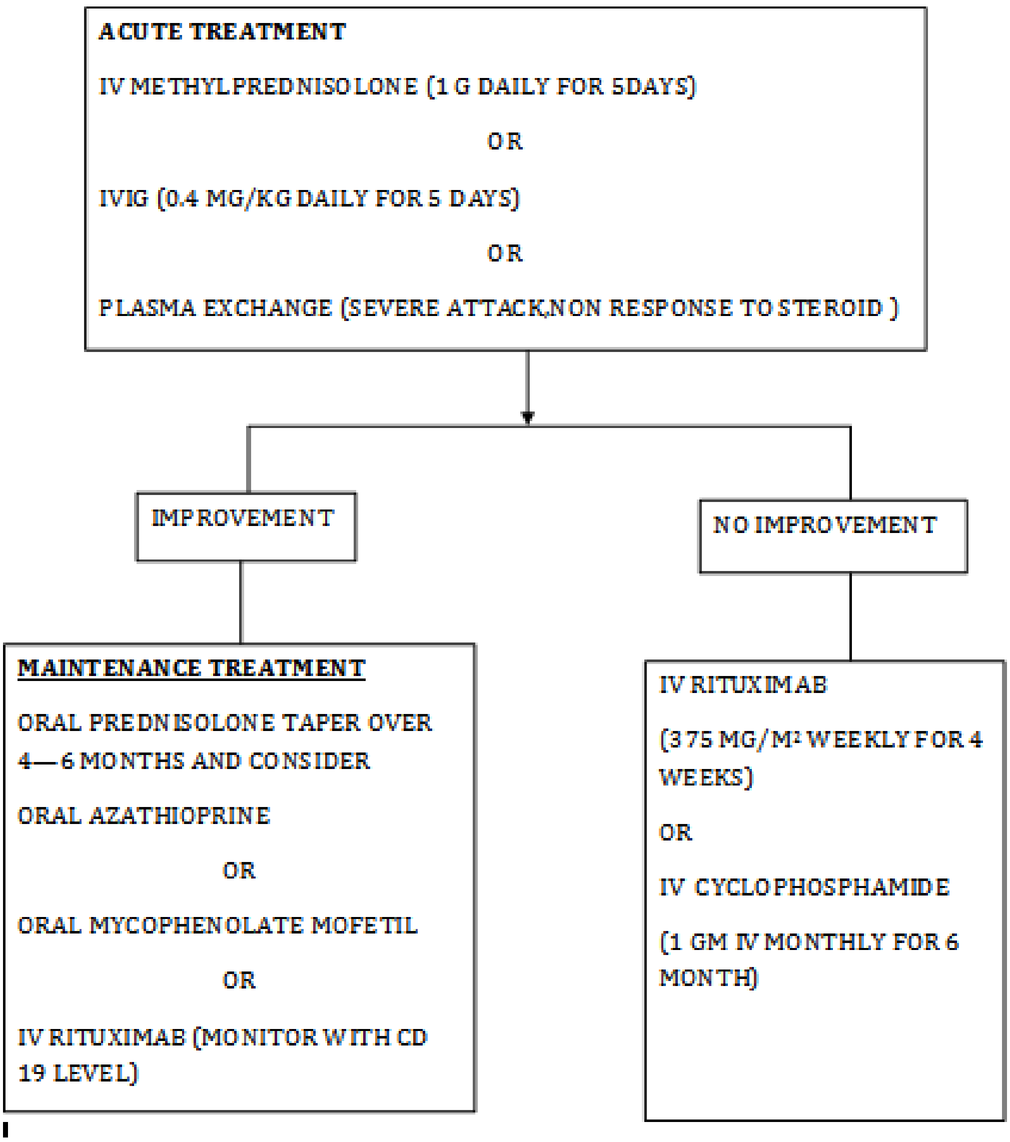
Algorithm 2: Treatment protocol for autoimmune encephalitis



II. CONCLUSIONS

The proper diagnosis and management of autoimmune encephalitis require an organized approach. Evaluation should begin with a detailed history and physical examination to detect clues to specific causes. A diverse range of infections should be considered, and appropriate testing should be done to exclude relevant pathogens. Ancillary testing with MRI, EEG, and lumbar puncture may further support a diagnosis of encephalitis and potentially suggest causes. Antibody screening may lead to the correct diagnosis and provides clues regarding prognosis and likely response to therapy. Further exploration is needed to accurately assess the clinical spectrum of autoimmune en¬cephalitis, the clinical course of its various subgroups, and to determine the most effective management strate¬gies during acute illness and thereafter.

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