CLINICAL PROFILE AND OUTCOMES IN PATIENTS WITH AUTOIMMUNE ENCEPHALITIS

Dr AMOD R

DM NEUROLOGY THESIS

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SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND

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A THESIS SUBMITTED BY

Dr AMOD R

TO

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM

IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE AWARD OF

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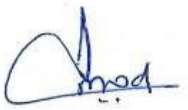
DECLARATION BY THE STUDENT

CERTIFICATE

I, Dr Amod . R., hereby certify that I had personally carried out the work depicted in the thesis titled "Clinical profile and outcomes in patients with autoimmune encephalitis".

No part of this thesis has been submitted for the award of any other degree or diploma prior to this date.

Date: 27.8.23



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The thesis titled "Clinical profile and outcomes in patients with autoimmune encephalitis" was carried out under my direct supervision. No part of the thesis was submitted for the award of any degree or diploma prior to this date.

*Clearance was obtained from the Institutional Ethics Committee for carrying out the study.

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APPROVAL OF THE THESIS

The thesis entitled

CLINICAL PROFILE AND OUTCOMES IN PATIENTS WITH AUTOIMMUNE ENCEPHALITIS

Submitted by

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LIST OF ABBREVIATIONS

S No	Abbreviation	Full Form
1	AIE/AE	Autoimmune encephalitis
2	mRS	Modified Rankin Scale
3	MMSE	Mini Mental State Examination
4	MRI	Magnetic resonance imaging
5	ASL	Arterial spin labelling
6	EEG	Electroencephalography
7	CSF	Cerebrospinalfluid
8	FBDS	Faciobrachial dystonic seizures
9	ADEM	Acute disseminated encephomyelitis
10	NMDA	N methyl D aspartate
11	LGI1	Leucine rich glioma inactivated
12	CASPR2	Contactin associated protein like 2
13	PLEX	Plasma exchange
14	IVMP	Intravenous methylprednisolone
15	IVIG	Intravenous immunoglobulin
16	HSV	Herpes simplex virus
17	CNS	Central Nervous system
18	IL	Interleukin
19	VGKC	Voltage gated potassium channel
20	VGCC	Voltage gated calcium channel
21	WNV	Westnile virus
22	VZV	Varicella zoster

23	MSA	Multisystem atrophy
24	SCA	Spinocerebellar ataxia
25	CPM	Central pontine myelinolysis
26	PET	Positron emission tomography
27	CJD	Creutzfeldt Jakob disease
28	GAD 65	Glutamic acid decarboxylase 65
29	NMO	Neuromyelitis optica
30	MOG	Myelin oligodendrocyte glycoprotein
31	PANS	Pediatric acute onset neuropsychiatric syndrome

SYNOPSIS

Objectives

This study aimed to investigate the epidemiological characteristics, clinical manifestations, investigations, short term and long-term outcomes of patients with autoimmune encephalitis (AE) in the southern India(single tertiary care centre experience).

Methods

From January 2014 to December 2021, 222 potential AE patients' data were analysed of which both seropositive and seronegative AIE, non-paraneoplastic cases, and a total of 55- NMDA, 19-LGI1 15 -CASPR2 and 116-Seronegative AIE who met the diagnostic criteria were included in the study. We retrospectively reviewed clinical features, auxiliary examinations, details of treatments, and outcomes of AE, and identified factors predicting good and poor prognosis. Modified Rankin Scale scores were used to evaluate neurological function, and scores of 0-2 indicates good outcome and 3–6 indicates a poor-prognosis. Both short (3months) and long-term (1 year) prognosis were assessed.

Results

Patients with four main subtypes of AE were enrolled in the study, as follows: anti-NMDAR (55), anti-LGI1 (19), anti-CASPR2 (15), seronegative (116). Among 222 patients, 40% were male and 60% were female. The mean age at disease onset was 31.5 ± 20.3yrs. The most common

clinical manifestations of AE were seizures (95%) and behavioural issues (92%). A total of 65.5% patients had abnormal brain magnetic resonance imaging results. Electroencephalographic findings were abnormal in 86% patients but CSF study was abnormal only in 13%. 100% and 25% patients were treated with first- and second-line immunotherapies, respectively. All surviving patients were followed-up for at least 1 year. Good clinical outcomes were achieved in 80%,90%,93% at discharge,3months and 1year respectively. Further 16% patients relapsed and 1.8% died. Abnormal MRI, EEG at presentation to have a poorer prognosis and initiation of first line and second line treatment have good prognosis both at short term and long term.

Conclusions

AE is a treatable disease, and most patients have a good prognosis. There are differences in the clinical manifestations of patients with different AE subtypes. Early treatment initiation is the key to success and predicts the favourable outcome.

INTRODUCTION

Encephalitis is defined as brain inflammation of any cause. There is high mortality associated with any cause of encephalitis(Thakur et al., 2013) ranging from 8-18.5%.Encephalitis can be enumerous causes but underlying autoimmunity is the cause then we call it as autoimmune encephalitis. Autoimmune encephalitis comprise spectrum of illness with acute to subacute presentation with cognitive issues, behavioural symptoms, seizures along with severe brain parenchymal inflammation.

It can be broadly classified into antibodies against cell surface antigen and against intracellular antigen. It's crucial to distinguish between these two things since antibodies that attack cell surfaces can lead to neuronal dysfunction that can be reversed

The disease spectrum is getting wider after the discovery of NMDA encephalitis in 2007 by Dalmau etal(Sansing et al., 2007). Studies have revealed that AE has a negative impact on a person's quality of life and places a significant financial burden on individuals as well as society (Cohen et al., 2019). Although early management is crucial for improving these patients' prognoses, AE is challenging to detect due to its complicated clinical presentations (Vollmer and McCarthy, 2016). Changes in antibody titre are closely connected to the clinical course of AE and are essential for the identification of neuronal autoantibodies ((Gresa-Arribas et al., 2014)). Neuronal autoantibodies assist clinicians recognise AE subgroups and spot people with unusual clinical symptoms. Consequently, an important step in the diagnosis of AE is the detection of antibodies(Graus et al., 2016).

US National prion disease pathology surveillance centre has shown that 7% of the patients diagnosed as prion disease had AE on autopsy. Studies shown that 35% patients treated as

neurodegenerative dementia had autoimmune encephalitis which later detected in tertiary centres after extensive evaluation.

There have not been many epidemiological studies of AE to date, and there are no data from extensive epidemiological studies at this time from India. As a result, it is still unknown what the condition's epidemiological characteristics are. In India the commonly identified autoimmune encephalitis subtypes includes anti-NMDA receptor (NMDAR), anti-gamma-aminobutyric acid-B receptor (GABABR), anti-leucine-rich glioma-inactivated 1 (LGI1) antibody, anti-contactin-associated protein-like 2 (CASPR2) antibody, anti-amino-3-hydroxy-5-methyl-4-isoxazolepropionic. According to the diagnostic criteria for AE, the epidemiological characteristics of 222 individuals with AE both antibody positivite and negative were examined in this investigation. The findings will increase clinicians' grasp of the epidemiological traits of AE,treatment lacuna and outcomes with factors affecting the outcomes and speed up the diagnostic process.

REVIEW OF LITERATURE

Encephalitis is an inflammatory process affecting brain parenchyma due to different aetiologies including infections, immune, toxic causes leading on to encephalopathy. Acute encephalitis syndrome is defined as sudden onset of fever and a change in mental status in form of disorientation, confusion or coma with or without new onset of seizures irrespective of any age group.

Immune mediated encephalitis is caused by varied systemic autoimmune disorders or postinfectious immune process (ADEM) or antibodies specific to antigens located in the brain (autoimmune encephalitis). Autoimmune encephalitis is group of disorders causing inflammatory immune encephalitis secondary to antibodies against cell surface antigens (receptors, ion channels, synaptic proteins, supporting proteins) or intracellular antigens. Some patients present with autoimmune encephalitis symptoms without any antibodies detected which is considered as seronegative (yet to identify new antibodies). Autoimmune neurology is growing by the advent of rapidly advanced antibody detection. But there are so many knowledge gaps and unanswered queries in the clinical spectrum, acute and long-term managements. The heterogeneity in presentation and findings makes it more difficult to characterise the disease entity(Graus et al., 2016).

Incidence

10.5 per 100,000 AES cases was reported for children and 2.2 per 100,000 for adults. A minimum incidence rate of 6.34 per 100,000 was reported for all ages from a tropical setting. The estimated incidence of encephalitis in high-income countries is about 5–10 per 100 000 inhabitants per year(Jmor et al., 2008).

History

History of this illness dated back in 1938 when a patient with ovarian cancer presented with cerebellar degeneration which was reported by Brouwer and Biemond. But they can't postulated the etiological reason and later Russell described a autoantibody triggered brain injury by certain malignancy and later Corsellis and colleagues conducted an autopsy of patient with neuropsychiatric symptoms and lung cancer found limbic inflammation without metastasis(Graus et al., 2016). Many paraneoplastic neurological syndromes were found out from 1980 to 2000 which includes anti Yo, Ma-2, Tr, amphiphysin and anti Hu.

In 2001 Ligouri etal and Buckley etal separately described limbic encephalitis with VGKC responding to plasma exchange(Brilot et al., 2009). First case of NMDA encephalitis was described by Dalmau et al in 2005 and later he published 12 cases of neurobehavioral symptoms with memory impairment and seizures with NMDA positivity(Dalmau et al., 2011). Initially it was thought of paraneoplastic as its association with ovarian teratoma and later a series of autoantibodies against cell surface and synaptic protein presenting with varied neurological presentation without any cancer association were found out. These were later called as Autoimmune encephalitis. These autoantibodies include NMDA, VGKC including LGI1 and CASPR-2, AMPA, GABA A and B etc. In 2011 Najjar et al put forward the seronegative autoimmune encephalitis group without any identifiable autoantibodies(Najjar et al., 2018).

In 2015 Armangue et al described the autoimmune neurological illness triggered by herpes simplex (HSV) encephalitis which was almost in 12-27% patients. In 2016 several papers were published regarding cancer immune therapy with check point inhibitors precipitating autoimmune and paraneoplastic encephalitis(Armangue et al., 2018).

Pathogenesis

Overall basis of autoimmune encephalitis is immune mediated destruction of CNS by inflammatory immune response that can be either triggered due to underlying malignancy or of unknown reasons. The immune mechanisms in autoimmune encephalitis is of 2 types.

First one is an autoantibody against cell surface /synaptic antigens including receptors, ion channels, supporting proteins. These antibodies will lead on to synaptic dysfunction through cross linking and receptors will get internalised as in NMDA encephalitis or by preventing neurotransmitter attachment to its receptors (Anti GABA-A and B) or bind to ion channels leads to its disruption (anti LGI1 and CASPR-2).After binding these causes surrounding inflammation and neuronal apoptosis. But if the disease is detected early the extend on injury can be reduced and can prevent the long term sequala's second mechanism is T cell mediated neuronal injury in paraneoplastic AIE. The antibodies are directed against intracellular antigens are considered to be a marker which are not directly involved in the mechanism of neuronal injury. The T cell mediated cytotoxicity to neurons make this disorder limited response to treatment and worse outcome because of the accelerated neuronal injury(Armangue et al., 2018; Vollmer and McCarthy, 2016).

How the circulating antibodies gain access to the CNS is largely unknown as the CNS is protected by blood brain barrier and blood CSF barrier. Postulated mechanism involves through G lymphatics that exist around the arterioles and parenchymal extracellular spaces where the privileged neuronal antigens are exposed and trigger inflammation. Other mechanisms involve inflammation induce damage on blood brain and blood csf barrier that exposures the brain antigens to peripheral immune cells. Some viral infection like HSV can trigger a autoimmune encephalitis may be due to above proposed mechanism of inflammation induced exposure of brain antigens. Some proinflammatory cytokines responsible for the above mechanism are

IL6,IL-10,CXCL-13.The above told mechanism are provoked as per brain biopsy and autopsy studies. Exact mechanism is still not known(Sansing et al., 2007).

Clinical features and classification

Usual clinical presentation of autoimmune encephalitis is subacute that is duration of less than 3months but anti VGKC associated disorder can present chronic. The clinical presentation varies based on the area of CNS involved. Immune reactions appear to be diffuse and multifocal with additional meninges, spinal cord and peripheral nervous system involvement. A recurrent illness points towards a surface antigen type as intracellular antigen associated disease are usually chronic. This type of recurrent disorder needs to be differentiated from other relapsing disorders like MS. Proceeding fever or upper respiratory/diarrheal illness may be present in few. Mostly HSV can trigger an NMDA encephalitis.

Current proposed classification of autoimmune encephalitis is based on the anatomical site of involvement, type of antibody and the underlying aetiology. Detailed classification and corresponding antibodies in each presentation are illustrated in tables down.

Clinical spectrum

Clinical features of each autoimmune subtypes vary based on the presence of underlying malignancy or not and which antibody is present. Most of the clinical presentation is characterised by acute to subacute onset rapidly progressive neurological syndrome with neuro-behavioural, seizures, cognitive and abnormal movements.

The issue in long-term is the persistence of neuro behavioural and seizure sequele in case of delayed initiation of treatment and delayed identification. These disorders may mimic an underlying infectious, metabolic or demyelinating or neurodegenerative diseases.

Several studies showed that almost 100% patients present with neuropsychiatric issues mainly anxiety, mania, hallucinations, and psychosis. The usual dictum is the lack of response of these

symptoms to conventional antipsychotic medications and even some tried ECT without any benefits. Rarely the patient present with schizophrenia like presentation(Zandi et al., 2011).

Antipsychotics frequently fail to work as intended and are more likely to cause serious adverse effects such neuroleptic malignant syndrome

Other commonly presenting symptoms is of seizures which manifest as clinical seizures or electrographic seizures. New onset refractory status epilepticus in a young adult or children is mostly due to underlying autoimmune encephalitis. The best antiseizure medications for these immune seizures are not antiepileptics but immunotherapy. Some autoimmune subtypes have distinctive seizure subtypes and seizure semiology/ EEG finding. Faciobrachial dystonic seizures which are short lasting (1-3 seconds) posturing and jerking of face and upper limb is a common manifestation for LGI1 encephalitis. Sometimes EEG may show specific signs as in NMDA encephalitis showing delta brush. Both focal and generalised seizures can be seen any subtypes.

Next presentation which are commonly seen is of different movement disorders including chorea, myoclonus, parkinsonism, orofacial and limb dyskinesia, tremors or myokymia and peripheral nerve hyperexcitability states(Honnorat and Joubert, 2018). Some of the presentations are classical for each subtype of movement disorders. Some are myokymia and neuromyotonia in anti CAPR-2 encephalitis(Vincent and Irani, 2010),orofacial and limb dyskinesia in anti NMDA encephalitis(Dalmau et al., 2011), rigidity and myoclonus in anti GlyR encephalitis(Hutchinson et al., 2008), anti GABA and anti Ri encephalitis(Escudero et al., 1993)

Next is the cognitive impairment is mostly seen in NMDA, LGI1 and GAD associated encephalitis. Most deficits are in the memory domain usually short term memory impairment(Cohen et al., 2019; Hansen, 2019). Other domains include language, attention, praxis, executive functions. Most cognitive dysfunction is seen in limbic encephalitis subtypes(Long and Day, 2018). Some may go into akinetic mute state and even catatonia.

Cognitive sequele is a most common long term morbidity associated in immune mediated encephalitis(Nicolle and Moses, 2018).Early immunotherapy is a key to prevent this impairment.

Another important symptom is the sleep disturbances(Graus et al., 2016).Almost 70-80% patients had sleep disturbances as per the study published. Commonly affected is of the hypersomnolence in anti ma encephalitis(Kawamura et al., 2005). REM behavioural disorder in Anti VGKC encephalitis(Iranzo et al., 2006),periodic limb movements and stridor in anti IgLON5 disease(Gaig et al., 2017).

There are some red flags to be considered for autoimmune encephalitis

1. New behavioural symptoms which are not responding to conventional antipsychotics
2. Rapidly progressive multidomain cognitive affliction with predominant memory impairment
3. New seizures which are drug refractory or new onset refractory status epileptics
4. Movement disorder presentations like chorea, dystonia or perioral dyskinesia
5. New onset of autonomic dysfunction
6. Relapse of seizures and behavioural symptoms following a viral encephalitis usually HSV
7. Symptoms and clinical examination are similar to a viral encephalitis but workup is negative for the same
8. Absence of family history
9. Presence of malignancy elsewhere or malignancy follow the symptom onset within 4yrs
10. Investigations showing CSF abnormality with raised lymphocytes and proteins, EEG showing delta brush or electrographic seizures or focal or generalised slowing and MRI showing typical patterns of involvement

Case definitions for autoimmune encephalitis

International Encephalitis Consortium in 2013 put forward a case definition for encephalitis of infectious or immune aetiology and is shown below(Venkatesan and Benavides, 2015).

Major Criterion (required): Patients with altered mental status in the form of decreased or altered level of consciousness or lethargy or behavioural issues) which lasts >24hrs without any alternate cause

Minor Criteria:

- Fever ≥38° C within the 72 h before or after presentation
- Focal or generalized seizures
- New focal neurological deficits
- Abnormal CSF in the form of WBC >5/mm3
- Brain parenchymal imaging abnormality which is suggestive of encephalitis
- EEG abnormality – may focal or generalized

2 required for possible encephalitis; ≥3 required for probable or confirmed encephalitis

Later in 2016 Grauss etal put forward criteria for autoimmune encephalitis(Graus et al., 2016). Diagnosis can be made when all three of the following criteria have been met:

1. Subacute onset (rapid progression of less than 3 months) of working memory deficits (short-term memory loss), altered mental status, or psychiatric symptoms

2. At least one of the following:

• New focal CNS findings

• Seizures not explained by a previously known seizure disorder

• CSF pleocytosis (white blood cell count of more than 5 cells per mm^3)

• MRI features suggestive of encephalitis

3. Reasonable exclusion of alternative causes

Diagnostic criteria for definite autoimmune limbic encephalitis

Diagnosis can be made when all four* of the following criteria have been met:

1. Subacute onset (rapid progression of less than 3 months) of working memory deficits, seizures, or psychiatric symptoms suggesting involvement of the limbic system
2. Bilateral brain abnormalities on T2-weighted fluid-attenuated inversion recovery MRI highly restricted to the medial temporal lobes†
3. At least one of the following:
    - CSF pleocytosis (white blood cell count of more than five cells per mm^3)
    - EEG with epileptic or slow-wave activity involving the temporal lobes
4. Reasonable exclusion of alternative causes

For autoantibody-negative but probable autoimmune encephalitis diagnosis can be made when all four of the following criteria have been met:

1. Rapid progression (less than 3 months) of working memory deficits (short-term memory loss), altered mental status, or psychiatric symptoms

2. Exclusion of well-defined syndromes of autoimmune encephalitis (eg, typical limbic encephalitis, Bickerstaff 's brainstem encephalitis, acute disseminated encephalomyelitis)

3. Absence of well characterised autoantibodies in serum and CSF, and at least two of the following criteria:

• MRI abnormalities suggestive of autoimmune encephalitis

• CSF pleocytosis, CSF-specific oligoclonal bands or elevated CSF IgG index, or both

• Brain biopsy showing inflammatory infiltrates and excluding other disorders (eg, tumour)

4. Reasonable exclusion of alternative causes

Diagnostic criteria for anti-NMDA receptor encephalitis

For Probable anti-NMDA receptor encephalitis diagnosis can be made when all three of the following criteria have been met:

1 Rapid onset (less than 3 months) of at least four of the six following major groups of symptoms:

• Abnormal (psychiatric) behaviour or cognitive dysfunction

• Speech dysfunction (pressured speech, verbal reduction, mutism)

• Seizures

• Movement disorder, dyskinesias, or rigidity/abnormal postures

• Decreased level of consciousness

• Autonomic dysfunction or central hypoventilation

2 At least one of the following laboratory study results:

• Abnormal EEG (focal or diffuse slow or disorganised activity, epileptic activity, or extreme delta brush)

• CSF with pleocytosis or oligoclonal bands

3 Reasonable exclusions of other disorders

- Diagnosis can also be made in the presence of three of the above groups of symptoms accompanied by a systemic teratoma

Definite anti-NMDA receptor encephalitis

Diagnosis can be made in the presence of one or more of the six major groups of symptoms and IgG anti-GluN1 antibodies, after reasonable exclusion of other disorders

Classification of autoimmune encephalitis

There are 3 ways of classification of immune mediated encephalitis. First is the anatomical classification based on the location of brain parenchymal involvement. Second is the type of

antibody and whether it is against cell surface or intracellular antigen. Third is the presence of underlying aetiology like malignancy or post infectious or idiopathic.

Anatomical classification

1. Limbic
2. Cortical/subcortical
3. Striatal
4. Diencephalic
5. Brainstem
6. Cerebellar
7. Encephalomyelitis
8. Meningoencephalitis
9. Combined

Serological classification

1. Antibodies to intracellular antigens (classical onconeural antibodies)
2. Antibodies to surface antigens and other antigens with high clinical relevance (eg: NMDAR, AMPAR, LGI1, CASPR2, GABAR A/B, DPPX, glycine receptor, AQP4, MOG, GFAP).
3. Antibodies to surface antigens with low clinical relevance (eg: VGKC, VGCC)
4. Seronegative autoimmune encephalitis.

Aetiological classification

1. Idiopathic
2. Paraneoplastic
3. Postinfectious

4. Iatrogenic (eg: in the setting of immune check point inhibitors or other immune-modulating agents)

Table 1: AIE subtypes

Anatomical classification	Clinical syndromes	Antibody associated
Limbic encephalitis	Cognitive presentation Psychiatric presentation Epileptic presentation	Hu,CRMP5,Ma2,NMDAR,AMPAR,CASPR2,LGI1,GAD65, GABA BR,DPPX,mGluR5,AK5,Neurexin-3a
Corical/subcortical	Cognitive presentation Seizure presentation	PCA-2,NMDAR,GABA A/B, DPPX,MOG
Striatal encephalitis	Movement disorders	CRMP5,DR2,NMDAR,LGI1,PD10A
Diencephalic encephalitis	Autonomic Sleep disorder	Ma1-2,IgLON5, DPPX,AQP4
Brain stem encephalitis	Cognitive, movement disorder,craniobulbar	Ri,Ma 1-2,KLH11,igLON5,DPPX,AQP4,MOG,GQ1b
Cerebellitis, cerebellar degeneration	Ataxia	Hu,Ri,Yo,Tr,CASPR2,KLH11,NIF,mGLUR1, GAD 65,VGCC
Meningoencephalitis	Cognitive,seizure,meningeal	Seronegative, GFAP
Encephalomyelitis	PERM and SPS,Spinal ,opticospinal	GAD65,Amphyphysin,glycine,PCR2,GABA-A/B,DPPX,CRMP5,AQP4,MOG

Workup for Autoimmune encephalitis

Once the immune mediated encephalitis is suspected common differential diagnosis including infectious, inflammatory and infiltrative mimics should be ruled out by adequate investigations.

Common differential diagnosis

Table 2 : Common differential diagnosis for AIE

Anatomical classification	Differential diagnosis
Limbic encephalitis	HSV, VZV, HHV6
Cortical/subcortical encephalitis	ADEM, AHL, Tumefactive demyelination, Marburg variant, PML, CJD, Lupus cerebritis, Behcets, Sarcoidosis, syphilis, lymphoma, anoxic injury, seizure related
Striatal encephalitis	CJD, WNV, Toxic encephalopathy, anoxic injury, hyperglycemic injury, uremic
Diencephalic encephalitis	Neurosarcoidosis, Behcets, Wernicke, whipple
Brainstem encephalitis	Rhombencephalitis(listeria), viral, clippers, sarcoidosis, behcets, lymphoma, PML, CPM, Whipple
Cerebellitis or degeneration	Viral or post viral, celiac disease, miller fisher syndrome, vitamin E def, MSA-c, SCA
Meningoencephalitis	TB, Sarcoidosis, Behcets, bacterial or viral infection, leptomeningeal carcinomatosis, GPA, iGG4 disease
Encephalomyelitis and or optico-spinal syndrome	ADEM, WNV

Investigations maybe done in 3 steps. First step of investigations is to prove focal and multifocal inflammation by doing MRI, PET brain or EEG. Second step to prove parenchymal inflammation by doing CSF, characterise the type and antibody subtypes by doing antibody testing CSF and serum. After proving the immune mediated encephalitis relevant investigations should be done to rule-out closed differentials as given above. If the immune mediated cannot be proven or doubt exist in the diagnosis, brain biopsy should be planned. Final investigations to look for any paraneoplastic association by doing CT chest and abdomen, USS abdomen, USS testes, PET scan, MRI abdomen and pelvis, USS breast/mammogram and tumour markers.

First and foremost, investigation is the MRI brain with contrast to look for the parenchymal and extra parenchymal involvements. It includes T2/FLAIR hyperintensities involving limbic structures, basal ganglia, cortical/subcortical system, brainstem. Additional contrast enhancement may point towards active inflammation.MR perfusion during active inflammation will show increased perfusion with diffusion restriction.

Different antibody involves different brain regions(Ball et al., 2022).

Imaging in Limbic encephalitis

Table 3 : Imaging features of AIE

Limbic system	Extra limbic	Basal ganglia	Cerebellum	Brainstem	Spinal cord
Anti Hu Anti VGKC Anti GAD65 Anti GABA B	Anti NMDA Anti VGCC Anti GABA - A Anti GluR3	Anti CV2 Anti D2 Anti NMDA	Anti Yo Anti GluR1 Anti Hu Anti GAD65 Anti VGCC	Anti Ma Anti Ri Anti Hu Anti Yo	Anti GlyR Anti Hu Anti GAD65 Anti CV2

Anti LGI1 Anti VGCC					

Main involvement is of the limbic structure mainly medial temporal lobes. Usually bilateral involvement with T2/FLAIR hyperintensity with contrast enhancement without any diffusion restriction or blooming is the catch. In addition, there will be insular and cingulate involvement. Initially there may be cortical swelling but later goes into atrophy. Initial perfusion scans will show increased perfusion but later there will be hypoperfusion. Similarly, FDG-PET may initially show increased uptake and latter hypometabolism as gliosis sets in. Common examples for this type of involvement includes Anti Hu, VGKC, GAD 65, GABA B, AMPA, LGI1, VGCC etc. Closest differential is of the viral encephalitis mainly HSV which will demonstrate restricted diffusion along with blooming in gradient scans. Basal ganglia involvement is most common in AIE than HSV encephalitis. Other closest mimicker is the temporal mass lesion like glioma but serial scans will decide the differentiation as there will be enlarging lesion on serial scans in a glioma.

Extra-limbic cortical autoimmune encephalitis

It includes multifocal cortical lesions with contrast enhancement and associated meningeal involvement occasionally. But lack of restricted diffusion and blooming is an important feature to differentiate from other aetiologies. Serial images shows progressive atrophy and sometimes cortical laminar necrosis. These types of MRI are usually seen in anti-NMDAr, anti-VGCC, anti-GABA-A and anti-GluR3.Most common differential diagnosis includes HSV, low-grade gliomas, and metabolic disorders. HSV encephalitis mainly involves temporal and frontal cortex and in metabolic aetiology like hyperammonaemia and hyperglycaemia along with cortical lesions there may be basal ganglia involvement as well.

Striatal autoimmune encephalitis

Imaging features in this subtype includes bilateral basal ganglia involvement without any diffusion restriction. Common examples of these subtypes include anti-CV2/CRMP5, anti-D2. Anti-NMDA. Other closest mimickers include CJD, Hyperglycaemia, carbon monoxide poisoning, deep vein thrombosis etc.

Autoimmune cerebellitis

Usually, the immune mediated cerebellitis can have normal MRI especially in paraneoplastic cerebellar degeneration (PCD) which may only shows cerebellar atrophy on follow-up. Most common antibodies involved are anti-Yo, mGluR1, Anti-Hu, GAD65, and anti-VGCC. Common differentials to be kept in mind is of antiepileptic medication use, toxins or heredodegenerative causes. Only help is with aid of good clinical history to differentiate the same.

Autoimmune brainstem encephalitis

Common imaging finding is of T2/FLAIR hyperintensity within the brainstem, with or without cerebellar involvement which may lead on to atrophy later. Common antibodies involved are Anti-Ma, Ri, Hu, Yo. Most common differentials that needs to be considered are of infections like listeria, lymes, tuberculosis etc, inflammatory disorders like Behçet's and neurosarcodosis.

Autoimmune myelitis

MRI may selective tract involvement or diffuse LETM like lesions with patchy contrast enhancement. Sometimes MRI may be normal also. Most common antibodies associated are anti GlyR, Anti-Hu, anti-GAD65, and anti-CV2 AEs. Common differentials are of neuroinfectious like TB, syphilis, lymes, brucella, inflammatory disorders like sarcoidosis, Bechet’s, demyelinating disorders like NMO, MOG, infiltrative aetiology like lymphoma.

ELECTROENCEPHALOGRAM

AE is a major etiological consideration in newly developed refractory or super refractory status epileptics which may be convulsive or non-conclusive.

EEG abnormalities in a suspected autoimmune encephalitis includes focal or multifocal slowing, lateralised periodic discharges, extreme delta brush (NMDA), subclinical electrographic seizures. EEG helps in detecting AIE in which MRI are normal. EEG may be sometimes normal as in faciobrachial dystonic seizures (LGI1). EEG also helps in differentiating from other close mimics like CJD (periodic discharges), metabolic encephalopathy (diffuse slowing). When MRI is negative which would support encephalitis over metabolic encephalopathy.

PET BRAIN

Utility is limited as most of the pattern are not specific for any subtypes of autoimmune encephalitis but bilateral temporal hypermetabolism is indicative of limbic encephalitis either seropositive or seronegative. Bilateral parietooccipital hypometabolism is seen in NMDA encephalitis. During active phase of autoimmune encephalitis increased uptake can be seen and during inactive stage hypometabolism can be seen. In the clinical context of seizures PET may be misleading. So current use in AIE is no widely considered.

CSF STUDY

CSF is done as a second step to prove the parenchymal involvement's is mandatory in all AIE cases except for contraindications for the procedure like brain herniation, coagulopathy etc. CSF cell counts, protein, glucose, IgG index and oligoclonal band should be done. Common CSF findings seen in classical AIE are mild to moderate pleocytosis mainly lymphocytes(20–200 cells),raised protein, normal sugar in almost 70-80% cases and elevated IgG index/positive intrathecal oligoclonal bands. Similar clinical picture may be seen other inflammatory disorders like neurosarcoidosis. Antibody testing may be done in CSF as well. But some antibodies are

sensitive in CSF than serum includes anti NMDA and GFAP and serum is more sensitive for paraneoplastic antibodies, LGI1, CASPR2 and NMO. Some cases CSF may be normal which range from 10-30% cases.1 If the clinical picture is highly suggestive of an immune mediated encephalitis normal CSF is not against the diagnosis. Other infectious aetiologies should be considered if there is pleomorphic leucocytosis, very high lymphocyte counts, very high proteins, abnormal low CSF sugars. CSF infectious panel including antibodies and PCR should be tested mainly for HSV, Varicella, CMV, listeria, tuberculosis, brucellosis, fungal aetiologies. Malignant cytology should be done to rule out lymphomas and carcinomatous meningitis.

SEROLOGICAL EVALUATION

Serological antibody should be done to confirm the diagnosis. As already discussed, some antibodies are most sensitive in serum and some in CSF. Some labs incorporate all the antibody into AIE panels and paraneoplastic panels. Serum is most sensitive for anti VGKC antibodies. Blood test should be done to rule out the closest differentials including antithyroid antibodies, toxicology analysis, ammonia, inflammatory markers, ANA, ANCA, APLA profile, infectious markers, RTQULC for CJD. when appropriate.1 Hyponatraemia is important diagnostic marker for LGI-1 antibody encephalitis.19 Blood test should be done prior to immunotherapy to avoid false negatives.

BRAIN BIOPSY

Most patients never require brain biopsy as the clinical radiological parameters helps in finding out the subtypes. In rare situations like inappropriate clinical setting or abnormal radiological findings a biopsy may be needed. Usual histopathological finding includes inflammatory infiltrates including T and or B cells in the perivascular and parenchymal regions with surrounding fibrosis.

SCREENING FOR ASSOCIATED MALIGNANCY

Paraneoplastic and autoimmune encephalitis clinically may appear similar and may be impossible to differentiated subtypes in the absence of classical antibodies. Some rare presentations are there only for paraneoplastic encephalitis including PERM. So, for all patients presenting as immune mediated encephalitis should be screened for malignancy. presentation(Titulaer et al., 2011). The most common malignancy with AE is small cell lung cancer, thymic neoplasm, testicular teratoma/seminoma, lymphoma, breast cancer, ovarian teratoma, neuroblastoma etc. In some the clinical presentation itself may be classical of paraneoplastic encephalitis like encephalomyelitis. As we all know for paraneoplastic encephalitis there of 95% association with cancer but for cell surface antibody mediated encephalitis the frequency of cancer varies according to the antibody subtypes. In NMDA receptor encephalitis is associated with ovarian teratoma and the frequency of malignancy varies with age and sex. In AMPA thymoma and small cell carcinoma is seen in almost 65% patients. GABAB associated limbic encephalitis is associated with small cell carcinoma lungs in almost 50%. 5% of GABA A patients has thymoma. mGLUR 5 encephalitis has association with Hodgkin's lymphoma in almost 70% patients. Others include Anti LGI1 limbic encephalitis with 5-10% in thymoma and 20-50% 0f CASPR2, DPPX in less than 10% with lymphoma. There is tumour association for dopamine 2 receptor encephalitis

CT chest with abdomen and pelvis contrast enhanced is a better initial investigation to delineate the mass but the contrast enhancement may be subtle in early stages and may miss the mass. Some malignancy including breast and testicular mass are missed most often. MRI may be better in pelvic masses and pregnancy. Other investigations includes PET scan, mammogram, ultrasound to find out masses elsewhere(Mandel-Brehm et al., 2019).

TREATMENT OF AUTOIMMUNE ENCEPHALITIS

Early initiation of treatment is crucial for the early recovery and to prevent catastrophic complications and morbidity. There are different lines of management in autoimmune encephalitis. Head-to-head comparison study for the efficacy and tolerability of first line immunotherapy is not yet available. The best first line agent to be started is pulse steroids which appears to be effective across the antibody subtypes. Sometimes first may be given in combination such as pulse steroids with IVIG or PLEX or sometimes all together as in NMDA encephalitis, NORSE, severe dysautonomia. LGI1 antibody usually responds excellent to steroid therapy. But paraneoplastic encephalitis poor responds to these first line agents and are better responsive to tumour therapy or 2ndline agents like cyclophosphamide.

IVIG may be used as a first line agents in case of poor response to steroids or PLEX. Also, in situations where steroids are contraindicated as in severe uncontrolled blood sugars or underlying infections. IVIG is not suited for prothrombotic states and severe hyponatremia. Usual dose suggested is 2gm/kg for 2-5 days.

PLEX is an alternative first line agents in whom both the IVIG and steroids are contraindicated. PLEX has the fastest onset of action for a given first line therapy. It is most effective in severe immune encephalitis. PLEX is contraindicated in those with underlying infections, not cooperative for central line insertion and procedure, those having coagulopathy.

Combined immunotherapy may be required in selected situation as already discussed above.

Regarding the second line immunotherapy available there are 2 options either of rituximab or cyclophosphamide. Both are immunomodulators but rituximab is a primary anti B cell agent and cyclophosphamide is active against both B and T cells. Considering the efficacy of a given agent rituximab is used frequently over and above cyclophosphamide in view of better safety profile and lesser long-term side-effects. When to start the second line agent is a next concern, most starts after 2-4 weeks of first line agent failure either lack of adequate response in clinical or

radiologically. But the good response is not defined anywhere. Current guidelines states to starts a second line agent if first line agent fails. But for NMDA it is better to start both second line and first line agent together. Rituximab is widely used as first agent in non-neoplastic encephalitis but if paraneoplastic encephalitis is considered it better to start cyclophosphamide as paraneoplastic is more of Tcell mediated. How long a immunotherapy is continued is not yet defined.

PROGNOSIS

Usually, immune mediated encephalitis which are treated early has the best prognosis with mild behavioural and seizure sequele. But for paraneoplastic encephalitis the treatment response is poor. In subtypes of AIE patients VGKC has excellent response to immunotherapy. Patient should be serially followed up for further years for later development of neoplasms especially in paraneoplastic ones and seronegative cases as neoplasm after 4yrs has been described.

Anti NMDA Encephalitis

Anti-*N*-methyl-D -aspartate (NMDA) receptor encephalitis was first enumerated by Dalmau etal in 2007 after studying 12 patients with predominant new onset neuropsychiatric symptoms and seizures(Anderson and Barber, 2008).

Anti NMDA encephalitis is a female predominant disease with age of onset in adolescent to young adults. It is the most common subtype of AIE affecting cell surface antigen. Even though it is not a paraneoplastic encephalitis, there is 0-5% association with ovarian teratoma in children younger than 12yrs and up to 58% in women older than 18yrs.The typical clinical presentation is of neurobehavioral symptoms with psychosis, delusions, hallucinations, aggression and even catatonic state. There may be loss of consciousness, speech dysfunction, dyskinesia, memory

impairment. There may be profound autonomic dysfunction. There may be abnormal limb or perioral dyskinesias which may be profound during the disease course. Seizures is another common presentation. Usual ones are temporal like hypo motor events. There will be cognitive involvement with predominate memory impairment, executive dysfunction. Other rare presentations include cerebellar ataxia and hemiparesis. The definite criteria put forward by graus etal in 2016 is used to diagnose the disease which is delineated above(Graus et al., 2016). Typical laboratory tests are frequently non-specific. The disease can be identified by indirect immunofluorescence assays that identify anti-NMDAR IgG antibodies in the serum and CSF. Because of the greater antibody titres in the CSF, diagnosis may occasionally be made following CSF testing and concurrently negative blood results. Low-grade hypercellularity and oligoclonal bands can also be present in CSF.CSF abnormality is seen in almost 70% patients.

MRI are usually normal or non-specific white matter HI involving cortex and subcortical areas.

EEG usually shows non specific changes but characteristic finding is the delta brush which shows intermixed beta in delta waves and seen in 5% patients.

As NMDA is associated with ovarian teratoma in young female, these patients should be screened for the same with adequate investigations including MRI abdomen and PET scan other than USS abdomen. Only tumour removal leads to sustained remission in such patients.

Early treatment initiation is crucial to prevent long-term morbidity and mortality. Aggressive immunotherapy is the treatment of choice. Along with pulse steroids patients should be initiated on IVIG or PLEX or together. After the first line treatment patients should be continued on a second line agent either anti CD20 agents like Rituximab or alkylating agents like cyclophosphamide. If patient is refractory to above treatment, they can be initiated on alemtuzumab(humanized monoclonal antibody against CD52), intrathecal methotrexate,

bortezomib(proteasome inhibitor) or tocilizumab(a monoclonal antibody against interleukin-6 receptor).

Prognosis of this patients are excellent if treated aggressively and early. Death ranges up to 5% in most studies. Most long term sequala is of mild memory and executive dysfunction. Relapse rates comes up to 10% in most case series. The need for an ICU stays, therapy delays longer than four weeks, no improvement after four weeks of treatment, aberrant brain MRI results, and white blood cell counts larger than 20 cells/microL are some independent indicators of worse outcomes. A functional score can be created by assigning one point to each of these factors. Poor functional status one year from the commencement of the disease is related with a higher score, however this should not be used to direct therapy or establish the final prognosis because one-third of patients with poor functional status at one year may improve at two years

CASPR 2 associated immune encephalitis

Contactin associated protein2 (CASPR2) comes under the neuroxin family as cell adhesion molecule. Its is seen along the axon at the synaptic terminal and juxta paranodal portion of node of Ranvier. These are mainly found in the neurons of basal ganglia, motor areas, limbic system, temporal lobes and in peripheral nervous system. It forms the part of VGKC complex which is important for the clustering of K channels in the juxtaparanode.

CASPR2 antibodies are presented with varied presentations which includes varied central and peripheral presentations

Central presentations are episodic ataxia, epilepsy, psychiatric symptoms, encephalitis.

Peripheral presentations are neuropathic pain, Issac syndrome.

Combined peripheral and central presentation is morvan syndrome.

Morvans syndrome is an autoimmune disorder characterised by autonomic with mixed central and peripheral presentation. Main presentation is of peripheral nerve hyperexcitability syndrome

also called neuromyotonia leading to cramps, fasciculations, myokymia, stiffness. There will be associated encephalopathy, insomnia, dysautonomia (hyperhidrosis, cardiovascular instability), neuropathic pain. Weight loss, itching and skin lesions are due to autonomic dysfunction.

Most commonly seen in elderly males at age of 50s (19-80yrs). Usually this antibody may be present idiopathic or with underlying malignancy (usually thymoma-30%).Second presentation is of peripheral nerve hyperexcitability without CNS manifestations called Issac syndrome. It may be of insidious onset and long duration with muscle hypertrophy, persistent muscle activity in sleep, clinical hyperexcitability inform of fasciculations or myokymia. Additionally, there may be positive trousseau and Chvostek sign.

Focal seizures of mainly temporal semiology are seen.

Investigations will show abnormal CSF in only 40% and may range upto60%. MRI may be normal in 50% and if associated limbic encephalitis there can be mesial temporal HI seen. EEG may show non-specific slowing or occasional IEDs in those with seizures. For definite testing demonstration of antibody in either CSF or serum is required. Different studies showed that cell-based assays are better and serum has more sensitivity and specificity than CSF. Treatment of this type of encephalitis did not differ from the standard treatment of autoimmune encephalitis. First line treatment for both central and peripheral presentation is of corticosteroids. If patients are not responding immunotherapy may be hiked to plasma exchange or IVIG. The usual response to this immunotherapy is excellent and for continuation therapy either oral or parenteral agents are used. Oral agents include azathioprine, mycophenolate mofetil and parenteral agents includes anti CD20 drugs like rituximab and if refractory even cyclophosphamide can be used.

Prognosis

Usual response of the disease is immunotherapy is excellent. The relapse rates range from 5-10%. Rapid tapering of steroids or immunotherapy and late initiation of treatment is associated

with more relapses. Relapses are seen even at 7yrs after the initial presentation. So how long to continue the treatment is not standardised.

LGI1 encephalitis

It's a subtype of encephalitis comes under the anti VGKC group. LGI1 is a glycoprotein released by the presynaptic membrane which interact with ADAM metallopeptidase which affect the normal functioning of signal transmission and potassium channel functioning.

These antibodies will affect the signal transmission and lead on to clinical manifestations like epilepsy, cognitive dysfunction, hyponatremia, dysphrenia, autonomic manifestations and peripheral nerve hyperexcitability syndromes. Most seen in mid to late adults in 40-50yrs. It is a male predominant disorder. Epilepsy is the common presentation which includes partial seizures, myoclonus and generalised tonic clonic seizures. The characteristic seizure subtype is the FBDS(faciobrachial dystonic seizures) which is a short lived dystonic posturing of arm and leg with face last <3s without or without LOC. Its happens in almost 20-100 times per day. Occurs in 20-40% of LGI1 antibody positive cases. These patients usually have and contralateral basal ganglia lesion. These seizures subtypes occurs on excitement, sudden loud noise or in stress.

Second commonest presentation is the cognitive disturbance usually memory impairment. Usually affect the recent memory. Other cognitive domains including executive visuospatial, language, praxis is well preserved in most.

Hyponatremia is seen in 60% of the patients. Mechanism of because of the antibody affliction to hypothalamus or renal system. Personality and behavioural changes are seen in majority that range from mild anxiety, impulse behaviour to frank psychosis, visual hallucinations and coma. Peripheral nerve manifestations like neuromyotonia and hyperexcitability are less commonly seen in LGI1 encephalitis. Movement disorders are seen rarely in this antibody groups. Cerebellar ataxia in almost 8% patients were noted in western studies. Parkinsonism and limb

dystonia's are noted. Neuropathic pains are seen less commonly in LGI1 as compared to CASPR2.Rare manifestations include autonomic dysfunction, sleep disturbances.

Investigations includes brain imaging and EEG.

EEG may be normal or sometimes show temporal or nonspecific slowing. Frontocentral slowing is a feature of FBDS during the event. Brain MRI may be normal in 50% and others may show FLAIR/T2 HI in the medial temporal regions and after long-term it may leave behind an atrophy. In patients with FBDS there may be basal ganglia HI seen. Antibody testing is found to be sensitive in both serum and CSF and even better in serum. Double negative VGKC without LGI1 or CASPR2 is not taken as a significant result. Tumour workup should be done extensively as the most common association is with thymoma.

Close differentials to be kept in mind while evaluating is the viral encephalitis, other immune mediated encephalitis, Hashimoto's encephalopathy, CJD etc.

Regarding treatment of the entity steroid is considered as the first line and almost 70-80% will respond. If there is inadequate response other first line agents like immunoglobulin, plasma exchanges may be used. After the acute therapy patient is maintained on oral agents or anti CD20 agents. Even cases relapsed after 7yrs so how long to continue the immunotherapy is still a question.

Prognosis

Almost 90% patient improved with a single or combination immunotherapy. Relapses is seen in almost 10-15% patients

Seronegative Autoimmune encephalitis

Seronegative AIE is an immune mediated encephalitis with negative antibody and without any tumour association. Actual prevalence of this entity is unknown.

This entity is widely misdiagnosed leading to unnecessary immunotherapy and patient harm. First algorithmic approach in any case of autoimmune encephalitis is when to suspect this disorder. In 2016 grauss etal put forward a criteria about when to suspect autoimmune encephalitis(Graus et al., 2016). If a patient has subacute onset (<3months) history of memory deficits with altered mentation and psychiatric symptoms with one or more of the 2nd items like focal CNS deficits, seizures, abnormal CSF or abnormal MRI with reasonable exclusion other alternative aetiologies. These criteria are met patient may be evaluated for distinct subtype of immune encephalitis by clinical, radiological and CSF parameters including antibody subtypes. The exclusion should include CNS infections mainly HSV, syphilis, metabolic encephalopathy, drug toxicity, functional neurogenic disorders, CJD, mitochondrial disorders, neurodegenerative disorders, inborn errors of metabolisms etc. The list is huge but minimum inflammatory, infectious, infiltrative, metabolic disorders needs to be excluded.

The main consideration in this subgroup is the lack of definite points to confirm the diagnosis. As in successive years there can be chance of later development of malignancy then it becomes the paraneoplastic encephalitis. Newer techniques will detect newer antibodies and then it becomes the seropositive ones.

After evaluation if the antibody status remains negative, they can be divided into 2 subtypes. First subset comprises the established clinical and radiological syndromes including limbic encephalitis, Bickerstaff encephalitis, ADEM which are seronegative. Second subset is the more challenging one to diagnose and there is a criteria for the second group. That criteria is enumerated in above session. So, in order to reduce the misdiagnosis Dalmau etal published refinements in the diagnostic process of seronegative AIE.

First step is to select the patient according to the clinical criteria for suspicious AIE with fulfilment of all 3 requirements and crucial one is the exclusion of alternate aetiology by

extensive evaluations and then apply the clinical criteria and further antibody testing to look for seropositive AIE.

Second step is to apply the criteria for seronegative AIE and ruling out other close mimics like GABA -A, igLON5, NORSE, PANS, PANDAS etc.

Third step is regarding the neural antibody testing which suggests to test both CSF and Serum for autoantibodies and in CSF check with cell based and brain-based assays.

Regarding treatment there is no guidelines published till now but expert opinion is to follow the treatment for seropositive autoimmune encephalitis. As first line start the patient on steroids if severe symptoms can be escalated to plasma exchange or IVIG.As second line either oral agents like Azathioprine, MMF or methotrexate and if severe rituximab or cyclophosphamide.

If patient did not respond to treatment in 3-4 months with adequate immunotherapy it is ideal to think an alternate aetiology other than trying or hiking alternate immunotherapy.

Prognosis

Usually, seronegative autoimmune encephalitis is well after an early immunotherapy with less documented relapses than an sero positive ones. Mortality is also less when compared to Sero-positive ones. Repeat titres are not done usually and there is no consensus regarding the same.

OBJECTIVES OF THE STUDY

Primary Objectives

- Prevalence of Autoimmune encephalitis and it subtypes in patients presenting with encephalitis in this tertiary referral centre

- Factors predicting good and bad outcome at short term and long-term

Secondary Objectives

- Seropositive/ Seronegative AIE- clinical profile, imaging, EEG and outcome differences

MATERIALS AND METHODS

Study design

- Hospital based retrospective observational study

Study population

Data were collected from patients admitted in the tertiary care centre in the southern Kerala, Sree Chitra Thirunal centre Trivandrum which is referral centre of many hospital in and out Kerala. From January 2015 to February 2022, 222 patients with AE were diagnosed with antibody positivity and antibody negative. The patients' demographic details, medical records, laboratory results and prognoses were reviewed from electronic medical records.

Inclusion criteria

According to the AE diagnostic criteria by grauss etal were used to select the patients, the following four criteria were used, along with positivity for neuron surface antibodies: (1) subacute onset (rapid progression over <3 months); working memory deficits, epilepsy, or psychiatric symptoms related to the limbic system; (2) bilateral brain abnormalities highly restricted to the medial temporal lobe on T2-weighted fluid-attenuation inversion recovery MRI; (3) at least one of the following: 1) an increase in the number of cerebrospinal fluid (CSF) cells (white blood cell count exceeding 5/mm^3) 2) EEG indicating epilepsy or slow-wave activity in the medial temporal lobe; and (4) reasonable exclusion of other diseases. For antibody negative cases following criteria was used.

All age groups are included

Adequate follow-up period of 1yr

Exclusion criteria

The exclusion criteria for the study were as follows: (1) Incomplete clinical data from the period of hospitalization; (2) Central nervous system infection caused by specific intracranial pathogens; (3) Thyroid disease, a recent history of thyroid hormone replacement, or a lack of test results on thyroid function and antibodies; (4) Immunosuppressed state (including long-term immunosuppressive therapy due to chemotherapy, organ transplantation, or cancer) (5) Paraneoplastic encephalitis,inflammatory,demyelinating disorders of CNS were excluded (6) Loss to follow-up.

This study was approved by the ethics committees. All patients or their families were informed of the study and gave signed consent to allow the use of their medical records for the study.

Antibody detection methods

CSF and serum of the patients were assessed in the same laboratory in the hospital, which began to detect AE-related antibodies from 2015. Six types of antibodies were detected: anti-NMDAR antibody, anti-$GABA_BR$ antibody, anti-LGI1 antibody, anti-CASPR2 antibody, anti-AMPA1 receptor antibody, and anti-AMPA2 receptor antibody using a Serum and CSF AIE panel. The laboratory used indirect immunofluorescence (IIF) assays for antibody detection. A cell-based assay (CBA) with high specificity and sensitivity was used to analyse the CSF and serum of each patient. Indirect immunofluorescence (IIF) autoimmune panel consisted of anti-NMDAr, anti-AMPAr-1 and 2, anti-CASPR2, anti-LGI-1, anti-GABAr-A and B and DPPX (EUROIMMUN®). The IIF paraneoplastic (PNS) panels and immunoblot anti-neuronal IgG profile comprised of anti-Hu (ANNA-1), anti-Ri (ANNA-2), anti-Yo (PCA-1), PCA-2, anti-Tr, anti-MAG, anti-myelin, anti-GAD, anti-CV2, anti-PNMA2, anti-ampiphysin, anti-neuroendothelium, anti-GFAP, anti-synaptophysin and AGNA/anti-SOX1 (EUROIMMUN®)

which were used to exclude other AIE due to intracellular antigens. After collection, the sample was diluted 10-fold and incubated for 30 min at room temperature on slides containing either specific antigen-expressing HEK cells or tissues that naturally expressed these antigens (e.g., cerebellum, pancreas, intestine and nerve cell). They were then incubated in secondary antibody conjugated with fit-C fluorescence and observed under an inverted fluorescence microscope. As for the immunoblot assay (EUROLINE®), specimen was diluted accordingly (1:101 for anti-neuronal) put on the test strip and incubated for 30–120 min. After a wash, the strip was incubated with conjugated enzyme and substrate before being evaluated by EUROLineScan®. The IIF assay for aquaporin-4 (AQP4) antibody, anti-thyroid peroxidase and anti-thyroglobulin was also conducted in some cases based on clinical suspicion. The initial dilution titres of CSF and serum were 1:1 and 1:10, respectively. Serum antibody titres were considered weakly positive at 1:10, positive at 1:32 to 1:100, and strongly positive at 1:320. The titres of CSF antibodies were considered weakly positive at 1:1, positive at 1:3.2 to 1:10, and strongly positive at 1:32 or above.

Data collection procedures

The demographic data, clinical characteristics, blood parameters, EEG findings, MRI findings, treatment strategy, responses and outcomes are studied. Data was taken from the electronic medical records. Outcomes at 3months (short term) and 1year (long term) was taken. mRS and MMSE was used to assess the outcomes. mRS 0-2 is considered as good outcome and mRS 3-6 as bad outcome. MMSE <24 was considered as bad outcome and MMSE 24 and more as good outcome. Data were collected yearly till last follow-up.

Score	Description
0	No symptoms
1	No significant disability. Able to carry out all usual activities, despite some symptoms
2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities
3	Moderate disability. Requires some help, but able to walk unassisted
4	Moderately severe disability. Unable to attend to own bodily needs without assistance, or unable to walk unassisted
5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent
6	Dead

Figure 1 : mRS scale used for assessing outcomes

Mini-Mental State Examination (MMSE)

Patient's Name:_____ Date:_____

Instructions: Ask the questions in the order listed.
Score one point for each correct response within each question or activity.

Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day of the week? Month?"
5		"Where are we now: State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible. Number of trials: _____
5		"I would like you to count backward from 100 by sevens." (93, 86, 79,72, 65, …) Stop after five answers. Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 
30		**TOTAL**

Figure 2 : MMSE to look at outcome of patients

Statistical analysis

The classification variables are described as percentages, and the characteristics of each subgroup are represented by the median. The chi-squared test or Fisher's exact test was used to compare differences among the subsets of classification variables. A Spearman correlation analysis was used to analyse correlations among classified variables. SPSS 20 software was utilized to analyse and sort the data, with $P < 0.05$ indicating a significant difference.

RESULTS

This study conducted with 222 patients with autoimmune encephalitis showed a age predilection towards an adult population with mean age of the population being 31.5 yrs ± 20.3yrs(fig 3) and female predominant(fig 4).

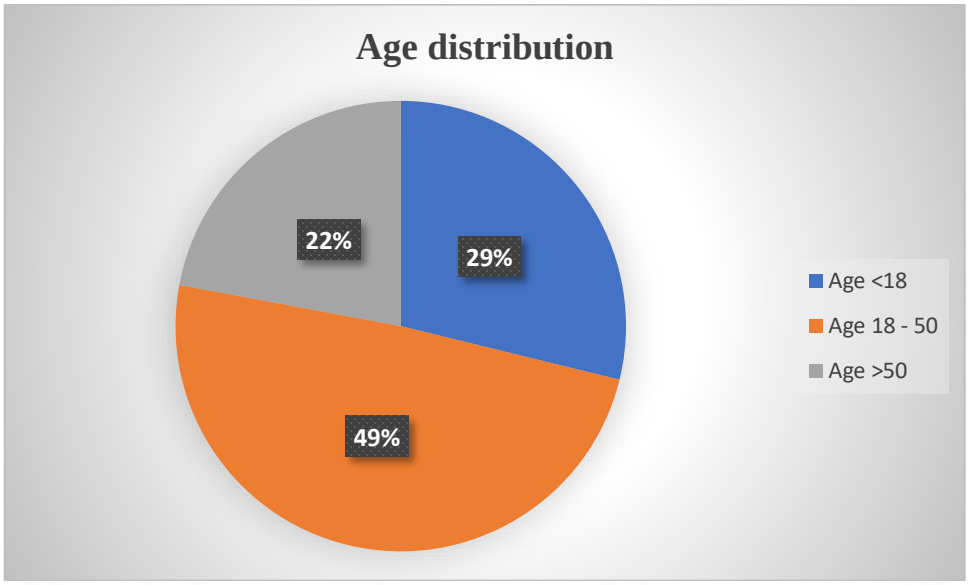

Figure 3 : Age distribution

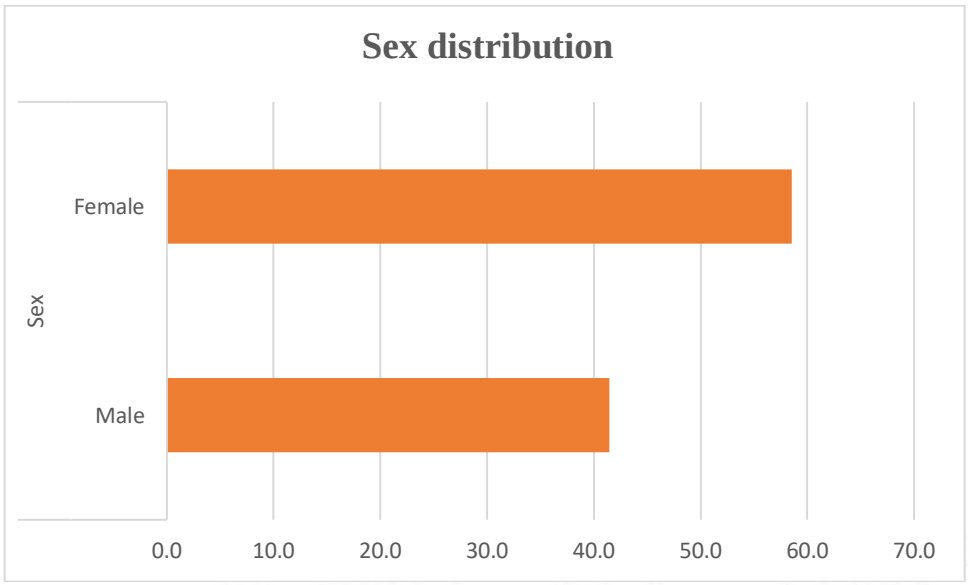

Figure 4 : Sex distribution showed mild female predominance

Regarding the clinical characteristics and symptomatology (fig 5)of the patients assessed, the initial premonitory symptom was present in 20% of patients only and commonly seen presentation was fever. After the premonitory symptom patients initial presenting symptoms commonly seen were seizures(60%) followed by behavioural issues(30%) and rarely cognitive decline, mainly memory impairments (3%) and frank psychosis(2.3%).After the initial symptoms when assessing the cumulative symptoms during the disease course, seizures (95%) was the most common with extratemporal(45%) being the most common subtype followed by temporal(21%).Convulsive status was seen in 6.8% and super refractory seizures were seen in almost 5% (fig 6).Second most common symptom were behavioural(92%) mainly agitation in 86% followed by psychosis in 33%.2.7% patients were in coma. Most common movement disorder(50%) seen were perioral/limb dyskinesia(30%) followed by dystonia(12%) and chorea(12%)(fig 7).Cognitive issues were seen in 49.5% and most were memory complaints(60%).Autonomic involvement was seen in 38%.Cerebellar and focal deficits were rare(5%).

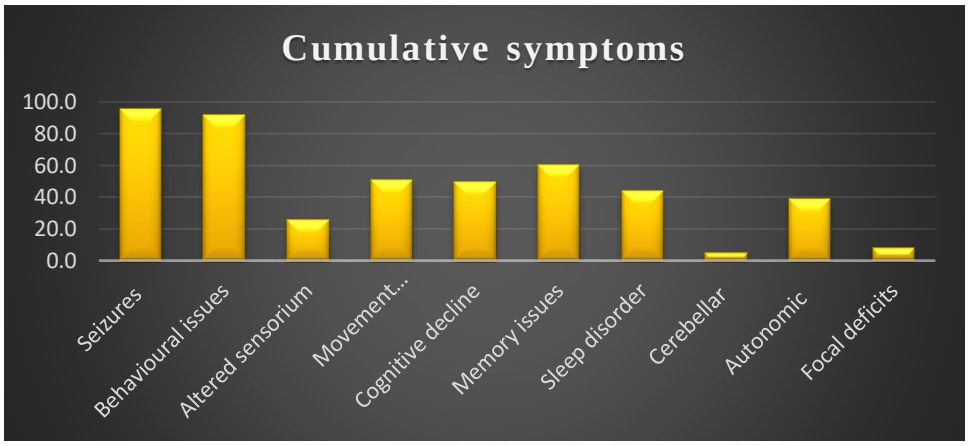

Figure 5 : Cumulative symptoms of patients

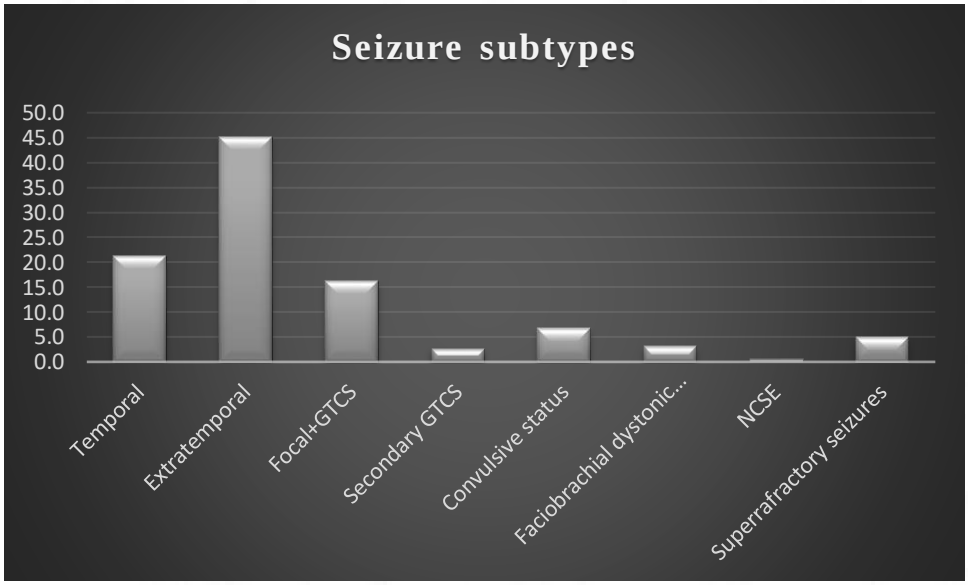

Figure 6 : Seizure subtypes in patients

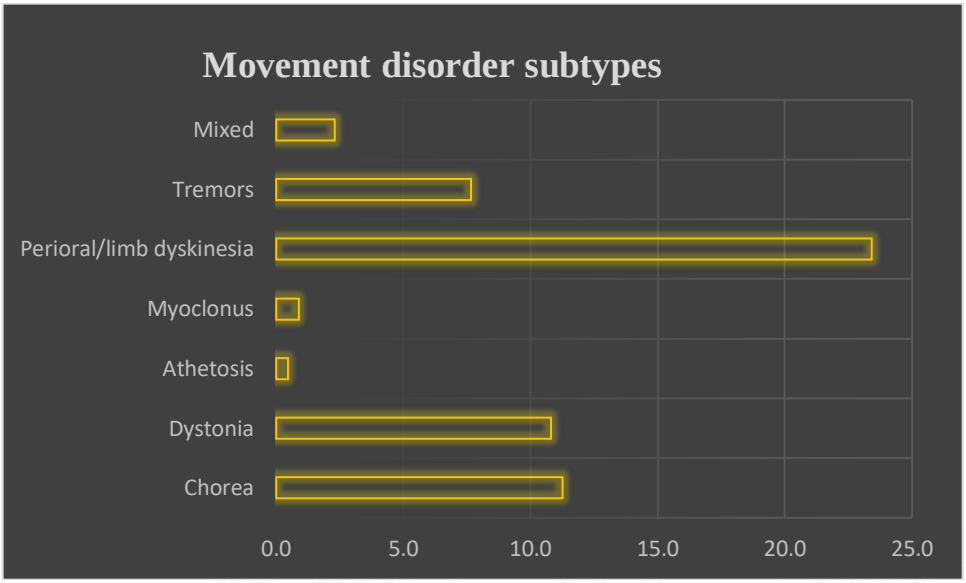

Figure 7 : Various movement disorder presentation in the study group

Most patients were mis-diagnosed (85%) as viral meningoencephalitis (56.3%) followed by psychiatric illness (18.9%)(fig 8).

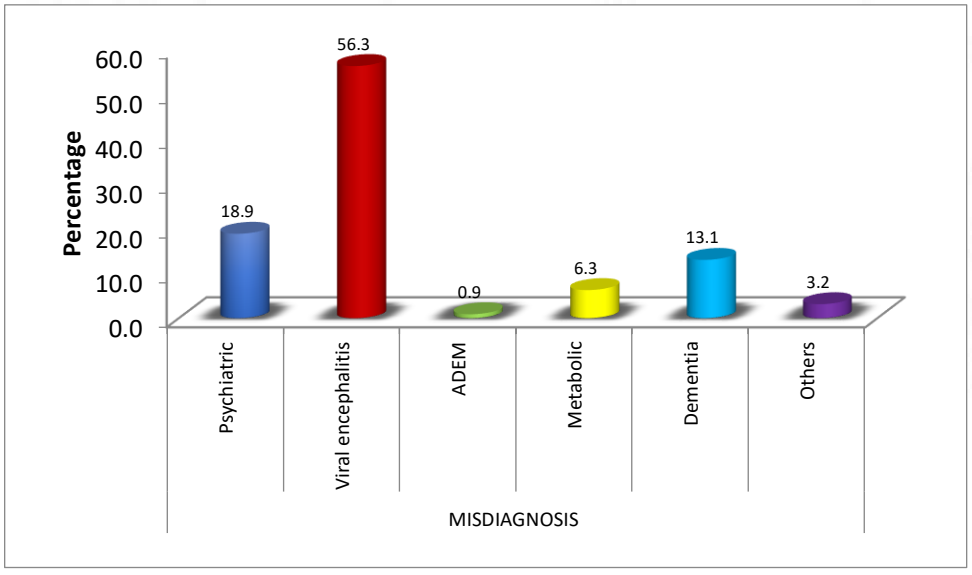

Figure 8 : Misdiagnosis of patients

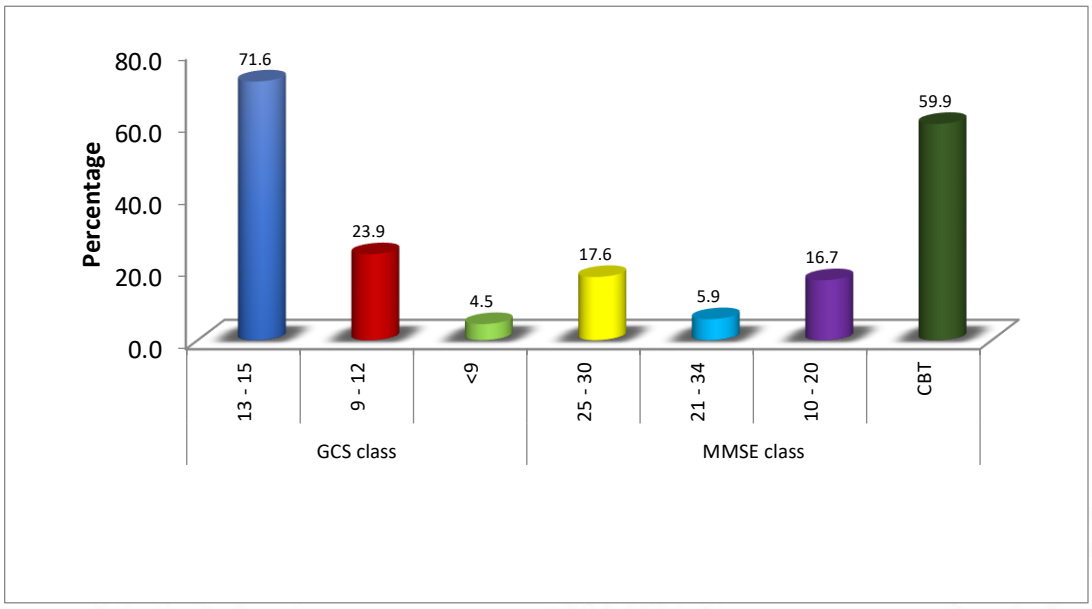

Figure 9 : GCS and MMSE at admission

At presentation most patients had an GCS of 13-15(72%) and MMSE were non testable in majority(60%)(fig 9).

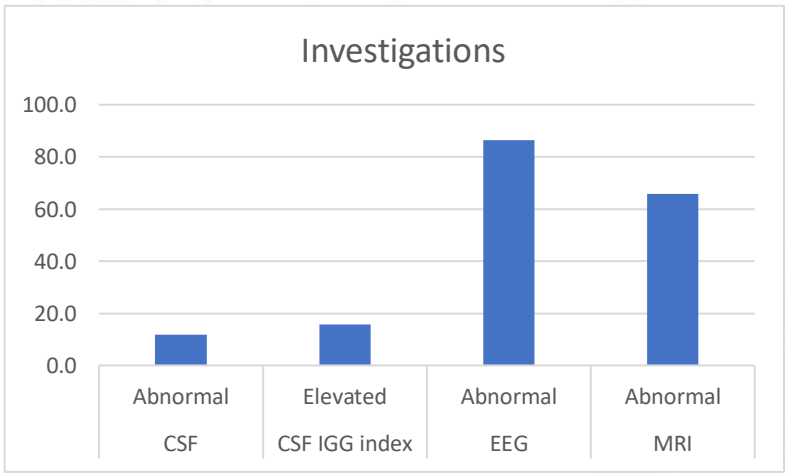

Figure 10 : Investigations of the study group

In investigations (fig 10) CSF was abnormal in 11.7% patients with most common abnormality is lymphocytic pleocytosis (TC<20cells/mm3) followed by mildly elevated protein(50-60mg/dl). CSF IgG index was elevated in 13% patients. All patients underwent antibody testing in both CSF and serum. CSF and S NMDA was positive in 24.8%, LGI1 in 8.6% and CASPR2 in 6.8% patients (fig 11).60% patients were seronegative. MRI was abnormal in 65.5% patients and most common abnormality was FLAIR HI in medial temporal lobes (60%) followed by basal ganglia and parietooccipital (25%) areas. ASL abnormality were seen in 15 % but contrast and diffusion were normal in all. EEG abnormality was seen in 86% patients with common finding of nonspecific electrophysiological dysfunction (80%). Delta brush pattern were seen in 2% patients.

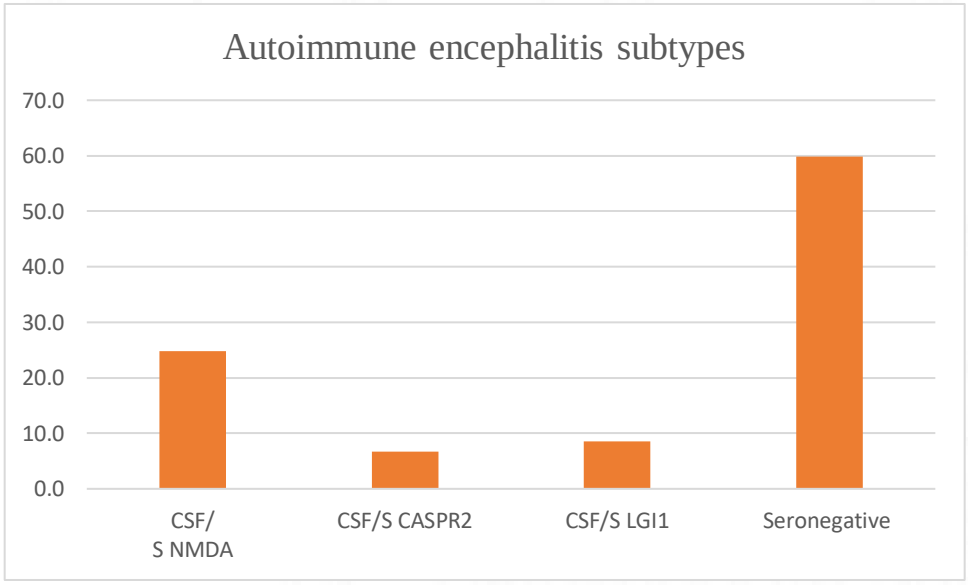

Figure 11 : Different subtypes of AIE in the study group

Treatment of AIE patients

All patients received first line treatment and mostly used agent is IVMP(43%) followed by IVIG+IVMP(34%)(table 4).There was a delay of > 3week between symptom onset and treatment initiation in 36% patients.27.5% patients required ventilatory support and 33% patients required prolonged ICU stay(>1month).Second line was administered in 25% patients and commonly used agent is rituximab(19%) followed by cyclophosphamide(5.9%).Most patient requiring second line agent was initiated with 20days of first line therapy without much delay(table 4).

Table 4 : Percentage distribution of the sample according to treatment of AIE patients

Treatment		Count	Percent
First line therapy	IVMP	96	43.2
	PLEX+/IVMP	23	10.4
	IVIG+/IVMP	76	34.2
	PLEX+IVIG	26	11.7
Delay in first line	<24 hrs	1	0.5
	24 hrs - 3 weeks	140	63.1
	>3 Weeks	80	36.0
Ventilatory support	Yes	61	27.5
No of days in ICU	<1 Month	38	17.1
	>1 Month	73	32.9
Second line therapy	Cyclophosphamide	13	5.9
	Rituximab	43	19.4
Delay between end of first and second line initiation	<10 days	25	11.3
	10 - 20 days	166	74.8
	>21 days	29	13.1

Outcomes

Regarding follow-up of autoimmune encephalitis patients(table 5), they are assessed at 3months and 1yr for the short-term and long-term treatment outcomes. Almost 88% patients were available for follow-up at 3months and 75% were available for follow-up at 1yr.

Table 5 : Percentage distribution of the sample according to follow up of AIE patients

Follow up		Count	Percent
Follow up at three months	Yes	196	88.3
	No	26	11.7
Follow up at one year	Yes	168	75.7
	No	54	24.3
Last follow up	>2yrs	117	52.7

At discharge almost 80% patients had favorable outcome(mRS<3) and at 3months- 90% patients and at 1yr – 93% had favorable outcome(fig 12).

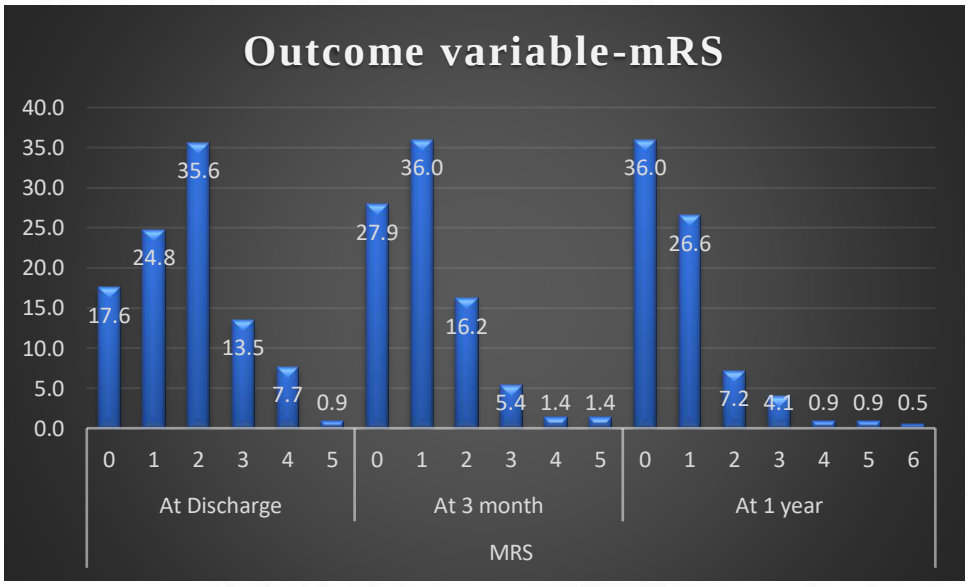

Figure 12 : Outcomes- mRS at discharge,3month and 1year

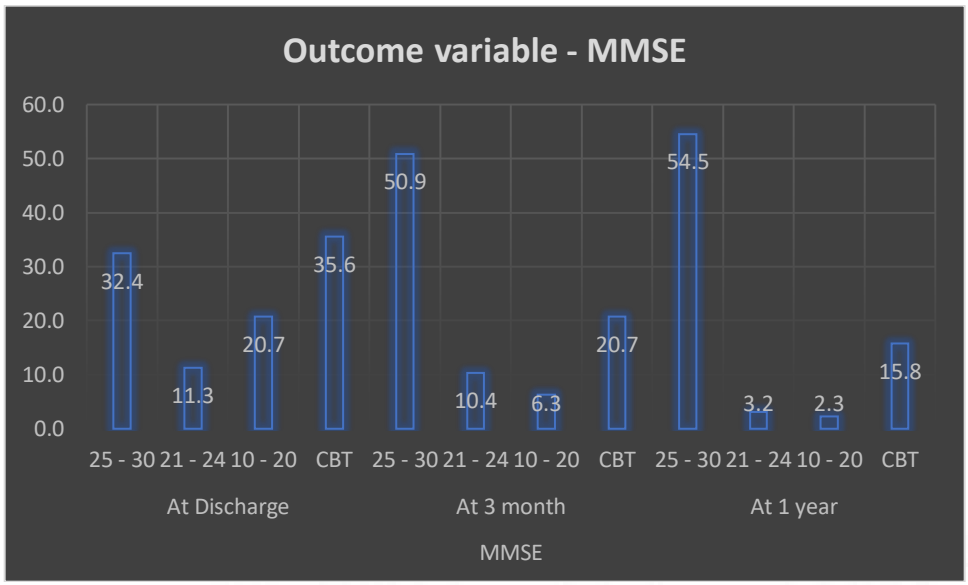

Figure 13 : Outcome – MMSE at discharge, 3month and 1year.

When comparing MMSE at discharge almost 32% have good outcome (MMSE>24) and 50.9% at 3months and 54.5% at 1yr had good cognitive outcomes(fig 13).

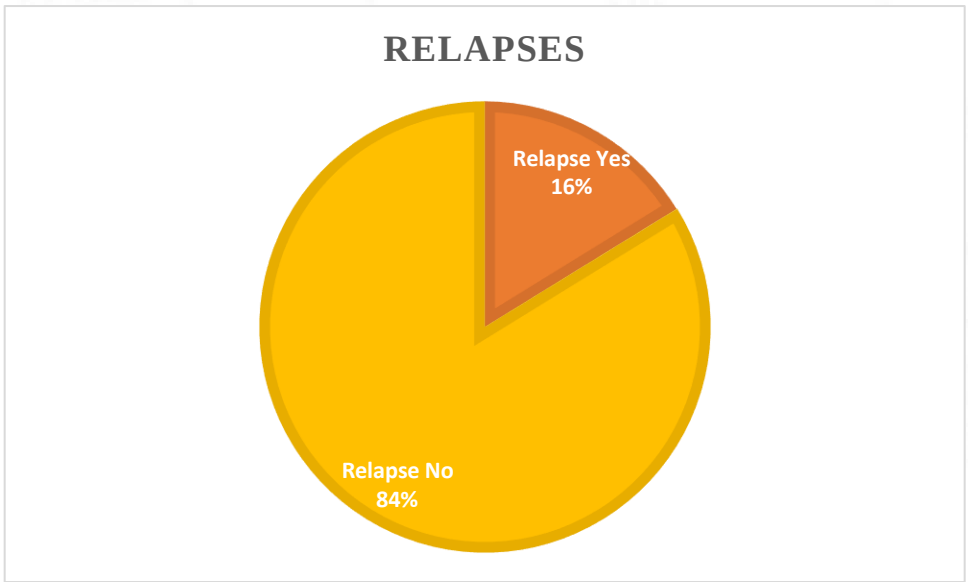

Figure 14 : Relapse rates

Relapses were seen in 16% patients (fig 14)and all were treated with first line therapy followed by maintenance steroids (50%) or second line agents use(30%).

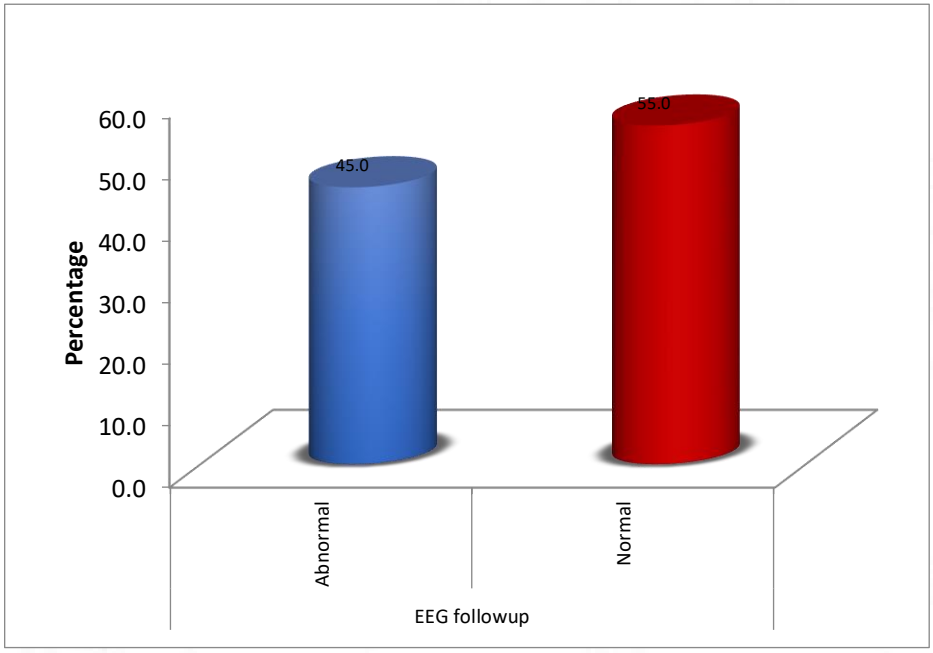

Figure 15 : EEG follow-up of patients

EEG at follow-up(fig 15) remained abnormal in 45% which signifies the sequale of the disorder on long-term prognosis.

Factors favouring outcomes

Table 6 : Association of MRS at discharge with selected variables

		Good(173)		Bad(49)		χ^2	p
		Count	Percent	Count	Percent		
Age	<18	46	71.9	18	28.1	1.94	0.379

	18 - 50	88	80.7	21	19.3		
	>50	39	79.6	10	20.4		
Sex	Male	70	76.1	22	23.9	0.31	0.578
	Female	103	79.2	27	20.8		
First symptom	Seizures	100	74.1	35	25.9	3.97	0.137
	Behavioural issues	52	81.3	12	18.8		
	Others	21	91.3	2	8.7		
Behavioural issues	Agitation	151	78.6	41	21.4	0.6	0.742
	Nil	12	70.6	5	29.4		
	Others	10	76.9	3	23.1		
Movement disorder	Yes	144	79.1	38	20.9	0.84	0.361
	No	29	72.5	11	27.5		
Autonomic dysfunction	Yes	64	74.4	22	25.6	1.01	0.316
	No	109	80.1	27	19.9		
GCS class	13 - 15	141	88.7	18	11.3	37.65	p<0.01
	<13	32	50.8	31	49.2		
MMSE class	25 - 30	38	97.4	1	2.6	10.47**	0.001
	<25	135	73.8	48	26.2		
First line therapy	IVMP	86	89.6	10	10.4	21.58	p<0.01
	PLEX+/IVMP	15	65.2	8	34.8		
	IVIG+/IVMP	58	76.3	18	23.7		
	PLEX+IVIG	13	50.0	13	50.0		
Delay in first line	<3 Weeks	109	77.3	32	22.7	0.06	0.804
	>3 Weeks	63	78.8	17	21.3		
Second line therapy	Cyclophosphamide	12	92.3	1	7.7	7.86*	0.020
	Rituximab	27	62.8	16	37.2		
CSF/S NMDA	Yes	42	76.4	13	23.6	0.1	0.747
	No	131	78.4	36	21.6		
S CASPR2	Yes	12	80.0	3	20.0	0.04	0.841
	No	161	77.8	46	22.2		
S LGI1	Yes	16	84.2	3	15.8	0.48	0.490
	No	157	77.3	46	22.7		
EEG	Normal	27	96.4	1	3.6	6.26*	0.012
	Abnormal	145	75.5	47	24.5		
MRI_brain	Normal	67	88.2	9	11.8	7.03**	0.008
	Abnormal	106	72.6	40	27.4		

**: - Significant at 0.01 level, *: - Significant at 0.05 level

When assessing the factors affecting outcome at discharge(mRS) it was found that GCS class 13-15, MMSE 25-30, normal MRI, normal EEG, initiation of first line and second-line agent irrespective of the agent used were associated with good outcome(table 6).

Abnormal EEG, abnormal MRI, MMSE<25, GCS<13 were factors associated with bad outcomes(table 6). When looking into multivariate analysis it was found that GCS class >13, MMSE>25 at admission, normal MRI were independently associated with good outcome at discharge(table 7).

Table 7 : Independent predictors of mRS at discharge

		B	S.E.	p	Odds (95% CI)
First symptom (Seizures®)	Behavioural issues	-0.05	0.46	0.912	0.95 (0.38 - 2.35)
	Others	0.86	0.85	0.314	2.36 (0.44 - 12.6)
GCS class (<13®)	13 - 15	1.33	0.43	0.002	3.78 (1.62 - 8.84)
MMSE class (<25®)	25 - 30	1.72	1.09	0.113	5.58 (0.67 - 46.81)
First line therapy (PLEX+IVIG®)	IVMP	0.91	0.70	0.193	2.48 (0.63 - 9.77)
	PLEX+/IVMP	0.10	0.71	0.884	1.11 (0.28 - 4.46)
	IVIG+/IVMP	0.73	0.61	0.229	2.07 (0.63 - 6.79)
Second line therapy (Others®)	Cyclophosphamide	1.41	1.17	0.228	4.08 (0.42 - 40.11)
	Rituximab	-0.09	0.51	0.855	0.91 (0.34 - 2.46)
EEG(Abnormal®)	Normal	1.46	1.07	0.172	4.32 (0.53 - 35.2)
MRI brain (Abnormal®)	Normal	1.08	0.45	0.017	2.95 (1.22 - 7.17)

Table 8 : Association of MRS at 3 month with selected variables

		Good(178)		Bad(18)		χ^2	p
		Count	Percent	Count	Percent		
Age	<18	47	85.5	8	14.5	3.06	0.217
	18 - 50	93	93.9	6	6.1		
	>50	38	90.5	4	9.5		
Sex	Male	70	89.7	8	10.3	0.18	0.672
	Female	108	91.5	10	8.5		
First symptom	Seizures	106	90.6	11	9.4	0.59	0.744
	Behavioural issues	52	89.7	6	10.3		

	Others	20	95.2	1	4.8		
Behavioural issues	Agitation	154	90.6	16	9.4	1.66	0.436
	Nil	12	85.7	2	14.3		
	Others	12	100.0	0	0.0		
Movement disorder	Yes	150	90.4	16	9.6	0.27	0.604
	No	28	93.3	2	6.7		
Autonomic dysfunction	Yes	72	90.0	8	10.0	0.11	0.742
	No	106	91.4	10	8.6		
GCS class	13 - 15	140	94.0	9	6.0	7.36**	0.007
	<13	38	80.9	9	19.1		
MMSE class	25 - 30	35	97.2	1	2.8	2.17	0.141
	<25	143	89.4	17	10.6		
First line therapy	IVMP	81	95.3	4	4.7	23.67	p<0.01
	PLEX+/IVMP	18	81.8	4	18.2		
	IVIG+/IVMP	62	96.9	2	3.1		
	PLEX+IVIG	16	66.7	8	33.3		
Delay in first line	<3 Weeks	116	92.1	10	7.9	0.71	0.399
	>3 Weeks	61	88.4	8	11.6		
Second line therapy	Cyclophosphamide	11	91.7	1	8.3	10.01**	0.007
	Rituximab	32	78.0	9	22.0		
CSF/S NMDA	Yes	47	88.7	6	11.3	0.4	0.528
	No	131	91.6	12	8.4		
S CASPR2	Yes	12	92.3	1	7.7	0.04	0.847
	No	166	90.7	17	9.3		
S LGI1	Yes	16	100.0	0	0.0	1.76	0.184
	No	162	90.0	18	10.0		
EEG	Normal	25	96.2	1	3.8	0.91	0.341
	Abnormal	152	90.5	16	9.5		
MRI	Normal	68	95.8	3	4.2	3.28	0.070
	Abnormal	110	88.0	15	12.0		

When looking for outcome variables mRS at 3months(table 8) GCS class 13-15, normal MRI brain, first-line (any agent) and second line (any agent) treatment were associated with favourable outcome whereas GCS <13 was associated with bad outcome. In multivariate analysis(table 9) only first-line treatment with IVIG and IVMP had independently associated with favourable outcome.

Table 9 : Independent predictors for MRS at 3months

		B	S.E.	p	Odds (95% CI)
GCS class(<13®)	13 - 15	0.32	0.66	0.627	1.38 (0.38 - 5.08)
MMSE class(<25®)	25 - 30	0.94	1.15	0.414	2.55 (0.27 - 24.18)
First line therapy(PLEX+IVIG®)	IVMP	1.76	0.93	0.057	5.83 (0.95 - 35.98)
	PLEX+/IVMP	0.81	0.81	0.316	2.24 (0.46 - 10.86)
	IVIG+/IVMP	2.53	0.95	0.008	12.5 (1.93 - 80.9)
Second line therapy(Others®)	Cyclophosphamide	0.32	1.17	0.787	1.37 (0.14 - 13.73)
	Rituximab	-0.48	0.68	0.483	0.62 (0.16 - 2.37)
MRI_brain(Normal®)	Abnormal	1.33	0.71	0.059	3.8 (0.95 - 15.13)

Table 10 : Association of MRS at 1 year with selected variables

		Good(155)		Bad(14)		χ^2	p
		Count	Percent	Count	Percent		
Age	<18	42	85.7	7	14.3	3.76	0.153
	18 - 50	81	95.3	4	4.7		
	>50	32	91.4	3	8.6		
Sex	Male	62	91.2	6	8.8	0.04	0.835
	Female	93	92.1	8	7.9		
First symptom	Seizures	95	92.2	8	7.8	0.61	0.738
	Behavioural issues	42	89.4	5	10.6		
	Others	18	94.7	1	5.3		
Behavioural issues	Agitation	134	91.8	12	8.2	1.77	0.413
	Nil	11	84.6	2	15.4		
	Others	10	100.0	0	0.0		
Movement disorder	Yes	132	91.7	12	8.3	0	0.955
	No	23	92.0	2	8.0		
Autonomic dysfunction	Yes	63	92.6	5	7.4	0.13	0.719
	No	92	91.1	9	8.9		
GCS class	13 - 15	122	93.8	8	6.2	3.36	0.067
	<13	33	84.6	6	15.4		
MMSE class	25 - 30	30	96.8	1	3.2	1.28	0.258
	<25	125	90.6	13	9.4		
First line therapy	IVMP	74	93.7	5	6.3	12.47**	0.006
	PLEX+/IVMP	14	87.5	2	12.5		
	IVIG+/IVMP	55	96.5	2	3.5		
	PLEX+IVIG	12	70.6	5	29.4		
Delay in first line	<3 Weeks	101	93.5	7	6.5	1.28	0.258
	>3 Weeks	54	88.5	7	11.5		
Second line therapy	Cyclophosphamide	7	87.5	1	12.5	7.01*	0.030
	Rituximab	24	80.0	6	20.0		
CSF/S NMDA	Yes	42	91.3	4	8.7	0.01	0.905
	No	113	91.9	10	8.1		

S CASPR2	Yes	9	90.0	1	10.0	0.04	0.839
	No	146	91.8	13	8.2		
S LGI1	Yes	14	100.0	0	0.0	1.38	0.240
	No	141	91.0	14	9.0		
EEG	Normal	23	95.8	1	4.2	0.64	0.425
	Abnormal	131	91.0	13	9.0		
MRI_brain	Normal	61	96.8	2	3.2	3.45	0.063
	Abnormal	94	88.7	12	11.3		

At 1yr only first-line and second line treatment was associated with favourable outcome(mRS <3) irrespective of the agent used(table 10). Multivariate showed a significance for IVIG + IVMP independently at 1yr (table 11).

Table 11: Independent predictors for MRS at 1yr

		B	S.E.	p	Odds (95% CI)
GCS class(<13®)	13 - 15	0.26	0.76	0.735	1.29 (0.29 - 5.69)
Firstline therapy(PLEX+IVIG®)	IVMP	1.34	1.06	0.205	3.81 (0.48 - 30.31)
	PLEX+/IVMP	0.94	1.08	0.383	2.55 (0.31 - 21.03)
	IVIG+/IVMP	2.08	1.05	0.047	8.04 (1.03 - 62.66)
Second line therapy(Others®)	Cyclophosphamide	-0.58	1.21	0.632	0.56 (0.05 - 5.98)
	Rituximab	-0.90	0.82	0.270	0.4 (0.08 - 2.02)
MRI_brain(Abnormal®)	Normal	1.57	0.83	0.058	4.8 (0.95 - 24.31)

Table 12 : Association of MMSE at 3 month with selected variables

		Good(113)		Bad(83)		χ^2	p
		Count	Percent	Count	Percent		
Age	<18	15	27.3	40	72.7	30.32	p<0.01
	18 - 50	72	72.7	27	27.3		
	>50	26	61.9	16	38.1		
Sex	Male	47	60.3	31	39.7	0.36	0.549
	Female	66	55.9	52	44.1		
First symptom	Seizures	64	54.7	53	45.3	2.13	0.345
	Behavioural issues	38	65.5	20	34.5		
	Others	11	52.4	10	47.6		

Behavioural issues	Agitation	97	57.1	73	42.9	4.52	0.104
	Nil	6	42.9	8	57.1		
	Others	10	83.3	2	16.7		
Movement disorder	Yes	97	58.4	69	41.6	0.27	0.603
	No	16	53.3	14	46.7		
Autonomic dysfunction	Yes	44	55.0	36	45.0	0.39	0.532
	No	69	59.5	47	40.5		
GCS class	13 - 15	98	65.8	51	34.2	16.78	p<0.01
	<13	15	31.9	32	68.1		
MMSE class At admission	25 - 30	36	100.0	0	0.0	32.39	p<0.01
	<25	77	48.1	83	51.9		
First line therapy	IVMP	58	68.2	27	31.8	14.5**	0.002
	PLEX+/IVMP	12	54.5	10	45.5		
	IVIG+/IVMP	36	56.3	28	43.8		
	PLEX+IVIG	6	25.0	18	75.0		
Delay in first line	<3 Weeks	79	62.7	47	37.3	4.03*	0.045
	>3 Weeks	33	47.8	36	52.2		
Second line therapy	Cyclophosphamide	8	66.7	4	33.3	2.74	0.254
	Rituximab	19	46.3	22	53.7		
CSF/S NMDA	Yes	26	49.1	27	50.9	2.2	0.138
	No	87	60.8	56	39.2		
S CASPR2	Yes	9	69.2	4	30.8	0.76	0.382
	No	104	56.8	79	43.2		
S LGI1	Yes	11	68.8	5	31.3	0.88	0.349
	No	102	56.7	78	43.3		
EEG	Normal	22	84.6	4	15.4	8.89**	0.003
	Abnormal	90	53.6	78	46.4		
MRI_brain	Normal	38	53.5	33	46.5	0.78	0.378
	Abnormal	75	60.0	50	40.0		

Factors for good outcome according to MMSE at 3months(table 12) were age >18yrs, MMSE at admission >25,GCS at admission >13,first line initiation irrespective of agents used, first-line treatment initiation within 3 weeks and normal EEG at admission

Factors for bad outcome according to MMSE at 3months were age <18yrs, GCS less than 13 at admission, MMSE at admission <25, first-line treatment delay of >3 weeks, abnormal EEG at admission.

In multivariate analysis (table 13) age more than 18yrs and normal EEG at admission was independently associated with better outcome.

Table 13: Independent predictors for MMSE at 3months

		B	S.E.	p	Odds (95% CI)
Age(<18®)	18 - 50	1.98	0.49	0.000	7.24 (2.77 - 18.93)
	>50	1.66	0.65	0.011	5.25 (1.47 - 18.79)
Behavioural issues(Agitation®)	Nil	-0.63	1.21	0.599	0.53 (0.05 - 5.63)
	Others	1.62	1.02	0.112	5.07 (0.69 - 37.45)
GCS class(<13®)	13 - 15	0.63	0.48	0.190	1.88 (0.73 - 4.84)
MMSE class(<25®)	25 - 30	8.96	16.10	0.578	7805.2 (0 - 0)
First line therapy(PLEX+IVIG®)	IVMP	0.72	0.72	0.318	2.05 (0.5 - 8.39)
	PLEX+/IVMP	1.00	0.79	0.208	2.71 (0.57 - 12.78)
	IVIG+/IVMP	1.13	0.65	0.084	3.1 (0.86 - 11.17)
Delay in first line(>3 Weeks®)	<3 Weeks	0.23	0.39	0.557	1.26 (0.59 - 2.7)
CSF/S NMDA(No®)	Yes	0.26	0.46	0.580	1.29 (0.52 - 3.21)
EEG(Abnormal®)	Normal	1.31	0.64	0.041	3.7 (1.06 - 12.97)

Table 14: Association of MMSE at 1 year with selected variables

		Good(121)		Bad(47)		χ^2	p
		Count	Percent	Count	Percent		
Age	<18	17	34.7	32	65.3	47.88	p<0.01
	18 - 50	73	86.9	11	13.1		
	>50	31	88.6	4	11.4		
Sex	Male	51	75.0	17	25.0	0.5	0.479
	Female	70	70.0	30	30.0		
First symptom	Seizures	66	64.1	37	35.9	8.66*	0.013
	Behavioural issues	38	82.6	8	17.4		
	Others	17	89.5	2	10.5		
Behavioural issues	Agitation	106	73.1	39	26.9	2.53	0.282
	Nil	7	53.8	6	46.2		
	Others	8	80.0	2	20.0		
Movement disorder	Yes	107	74.8	36	25.2	3.74	0.053
	No	14	56.0	11	44.0		
Autonomic dysfunction	Yes	46	67.6	22	32.4	1.09	0.297
	No	75	75.0	25	25.0		
GCS class	13 - 15	99	76.7	30	23.3	6.15*	0.013
	<13	22	56.4	17	43.6		
MMSE class	25 - 30	31	100.0	0	0.0	14.77	p<0.01
	<25	90	65.7	47	34.3		
First line therapy	IVMP	65	82.3	14	17.7	9.49*	0.023
	PLEX+/IVMP	11	68.8	5	31.3		

	IVIG+/IVMP	37	64.9	20	35.1		
	PLEX+IVIG	8	50.0	8	50.0		
Delay in first line	<3 Weeks	82	75.9	26	24.1	2.29	0.131
	>3 Weeks	39	65.0	21	35.0		
Second line therapy	Cyclophosphamide	5	62.5	3	37.5	1.18	0.555
	Rituximab	19	65.5	10	34.5		
CSF/S NMDA	Yes	32	71.1	13	28.9	0.03	0.873
	No	89	72.4	34	27.6		
S CASPR2	Yes	9	90.0	1	10.0	1.71	0.192
	No	112	70.9	46	29.1		
S LGI1	Yes	13	92.9	1	7.1	3.29	0.070
	No	108	70.1	46	29.9		
EEG	Normal	23	95.8	1	4.2	7.97**	0.005
	Abnormal	97	67.8	46	32.2		
MRI_brain	Normal	46	73.0	17	27.0	0.05	0.824
	Abnormal	75	71.4	30	28.6		

Factors for good outcome according to MMSE at 1year (table 14) were age >18yrs, MMSE at admission >25, GCS at admission >13,first line initiation irrespective of agents used, normal EEG at admission

Factors for bad outcome according to MMSE at 1year were age <18yrs, GCS less than 13 at admission, MMSE at admission <25, abnormal EEG at admission.

In multivariate analysis(table 15) age more than 18yrs was independently associated with better outcome

Table 15 : Independent predictors for MMSE at 1yr

		B	S.E.	p	Odds (95% CI)
Age(<18®)	18 - 50	2.38	0.55	0.000	10.83 (3.68 - 31.85)
	>50	1.95	0.83	0.018	7.02 (1.39 - 35.51)
First symptom(Seizures®)	Behavioural issues	0.28	0.59	0.636	1.32 (0.41 - 4.24)
	Others	1.40	0.92	0.126	4.06 (0.67 - 24.43)
Movement disorder(No®)	Yes	1.74	0.78	0.025	5.67 (1.24 - 25.95)
GCS class(<13®)	13 - 15	0.11	0.61	0.861	1.11 (0.34 - 3.67)
MMSE class(<25®)	25 - 30	10.25	26.32	0.697	28259.59 (0 - 0)
	IVMP	0.15	0.87	0.866	1.16 (0.21 - 6.31)

First line therapy(PLEX+IVIG®)	PLEX+/IVMP	0.05	0.97	0.962	1.05 (0.16 - 7.03)
	IVIG+/IVMP	0.20	0.76	0.794	1.22 (0.28 - 5.37)
Delay in first line(<3 Weeks®)	>3 Weeks	0.13	0.48	0.785	1.14 (0.45 - 2.9)
S LGI1(No®)	Yes	0.86	1.22	0.480	2.36 (0.22 - 25.54)
EEG(Abnormal®)	Normal	2.03	1.16	0.080	7.62 (0.78 - 74.02)

Table 16 : Association of relapse with selected variables

		Relapse				χ^2	p
		Yes(36)		No(186)			
		Count	Percent	Count	Percent		
Age	<18	13	20.3	51	79.7	3.25	0.197
	18 - 50	19	17.4	90	82.6		
	>50	4	8.2	45	91.8		
Sex	Male	9	9.8	83	90.2	4.79*	0.029
	Female	27	20.8	103	79.2		
First symptom	Seizures	26	19.3	109	80.7	3.52	0.172
	Behavioural issues	9	14.1	55	85.9		
	Others	1	4.3	22	95.7		
Behavioural issues	Agitation	32	16.7	160	83.3	0.75	0.687
	Nil	3	17.6	14	82.4		
	Others	1	7.7	12	92.3		
Movement disorder	Yes	29	15.9	153	84.1	0.06	0.808
	No	7	17.5	33	82.5		
Autonomic dysfunction	Yes	15	17.4	71	82.6	0.16	0.694
	No	21	15.4	115	84.6		
GCS class	13 - 15	25	15.7	134	84.3	0.1	0.752
	<13	11	17.5	52	82.5		
MMSE class	25 - 30	6	15.4	33	84.6	0.02	0.877
	<25	30	16.4	153	83.6		
First line therapy	IVMP	6	6.3	90	93.8	12.17**	0.007
	PLEX+/IVMP	6	26.1	17	73.9		
	IVIG+/IVMP	18	23.7	58	76.3		
	PLEX+IVIG	5	19.2	21	80.8		
Delay in first line	<3 Weeks	26	18.4	115	81.6	1.98	0.159
	>3 Weeks	9	11.3	71	88.8		
Second line therapy	Cyclophosphamide	0	0.0	13	100.0	2.73	0.255
	Rituximab	8	18.6	35	81.4		
CSF/S NMDA	Yes	17	30.9	38	69.1	11.62	p<0.01
	No	19	11.4	148	88.6		
S CASPR2	Yes	2	13.3	13	86.7	0.1	0.754
	No	34	16.4	173	83.6		
S LGI1	Yes	3	15.8	16	84.2	0	0.958

	No	33	16.3	170	83.7		
EEG	Normal	6	21.4	22	78.6	0.73	0.393
	Abnormal	29	15.1	163	84.9		
MRI_brain	Normal	13	17.1	63	82.9	0.07	0.795
	Abnormal	23	15.8	123	84.2		

Factors for relapse(table 16) were female sex, positive CSF/S NMDA status at admission. But none of this factors were independently predicting the relapse risk(table 17).

Table 17 : Multivariate analysis for independent predictors of relapse

		B	S.E.	p	Odds (95% CI)
Sex(Male®)	Female	0.64	0.46	0.171	1.89 (0.76 - 4.7)
First line therapy(PLEX+IVIG®)	IVMP	-0.85	0.69	0.218	0.43 (0.11 - 1.65)
	PLEX+/IVMP	0.59	0.71	0.407	1.8 (0.45 - 7.29)
	IVIG+/IVMP	0.39	0.58	0.501	1.48 (0.47 - 4.63)
CSF/S NMDA(No®)	Yes	0.77	0.43	0.073	2.16 (0.93 - 5.02)

Table 18 : Different subtypes of AIE comparisons

	NMDA ENCEPHALITIS(n--55)	ANTI CASPR2 ENCEPHALITIS(n-15)	ANTI LGI1 ENCEPHALITIS(n-19)	SERONEGATIVE ENCEPHALITIS(n-116)
Mean age	20.2±8.5(4-47yrs)	46±20.9(16-82yrs)	57.2 ±14.3 (25-77yrs)	31.9 ± 20.5 (2-79yrs)
Age group				
<18yrs	23(41.8)	1(6.7%)	0	32(27.6%)
18-50yrs	32(58.2)	6(40%)	6(31.6%)	57(49.1%)
>50yrs	0	8(53.3%)	13(68.4%)	27(23%)

Sex(F:M)	48:7	8:7	5:14	1:1
Premonitory symptom	61.8% - Fever	60%- Fever	42% - fever	43% - Fever
First symptom	Seizures(56%) >Behavioural(38.2%)	Seizure(60%)>behavioural(26.7%)	Seizures(52%) >Behavioural issues(26.3%)	Seizures(69%)>behavioural(33%)
Cumulative symptoms	Behavioural(100%) > Seizures(96.4%)	Behavioural(93%)> hyperexcitability(88%)>seizures(60%)	Seizures(95%) >behavioural(93%)	Seizures(93%)>behavioural(89%)
Seizures	Temporal(41.8%)> extratemporal(38.2%) Refractory status-8%	Extratemporal(60%)	Extratemporal(42%) Faciobrachial dystonic seizures-21%	Extratemporal(53%) >temporal(18%) Refractory status - 8%
Movement disorder	98.2%(Perioral/limb dyskinesia-81.8%)	90% (Peripheral hyperexcitability(88%)>tremor(70%)	60%(dystonia-60%,peripheral hyperexcitability-30%)	70%(tremors,myoclonus)
Cognitive dysfunction	58%(Memory dysfunction-54.5%)	66.7%(memory dysfunction-86%)	68%(memory - 94%)	45%(memory - 50%)
Autonomic dysfunction	49%	40%	15.8%	33%
Misdiagnosis	Viral encephalitis(70.9%)>Psychiatric(27%)	Viral encephalitis(46%) >psychiatric(33%)	Dementia(52%) >viral encephalitis(26%)	Viral encephalitis(49%)>psychiatric(20%)

Abnormal CSF	16.4%	6.7%	5.3%	10%
Abnormal eeg	92.7%	80%	84%	83%
Abnormal MRI	45.5%	80%	68%	68%
Tumor screening	5.5%(Teratoma)	Normal	Normal	Normal
1st Line treatment	IVIG+IVMP(50.9%)>PLEX+IVIG(21.8%)	IVMP(60%)>IVIG+IVMP(20%)	IVMP(68%)>IVIG+IVMP(15.8%)	IVMP(55%)>IVIG+IVMP(28%)
Delay in firstline <3 weeks >3 weeks	64% 36%	66.7% 33.3%	78.9% 21.1%	60% 40%
2ndline treatment	Rituximab(36%) > cyclophosphamide(1.2%)	Cyclophosphamide(13.3%)=rituximab(13.3%)	Cyclophosphamide(5.3%) = rituximab(5.3%)	Rituximab(13.8%)> cyclophosphamide(8.6%)
mRS at discharge <3	82%	80%	85%	86%
mRS <3 at	88.6%	92.3%	100%	93%

3months				
mRS <3 at 1yr	91%	90%	100%	93%
Death	1 (2.2%)	1(6.7%)	0	3 (2.6%)
Relapse	29%	13.3%	15.8%	7.8%
Follow up abnormal EEG at 1yr	35%	50%	33%	30%

NMDA encephalitis

Total 55 patients with NMDA positive encephalitis were present in out cohort.

Mean age of the study population was 20.2±8.5 yrs with age group ranges from 4-47yrs.Most patients were in 18-50yrs group (58%) followed by 42% in age less than 18yrs.No patients were aged more than 50yrs. Female were mostly affected with type of encephalitis (87%). No prior comorbidities were detected in 98% patients.

Clinical features

Almost 62% patients had fever as premonitory symptom. Most common initial presentation was seizure(56%) followed by behavioural issues(38%.Rarely patient can present in frank psychosis(1.8%) or with movement disorders(3.6%).

When assessing the cumulative symptoms. Seizures (96%) were of temporal subtype (42%) followed by extratemporal (38%). Refractory status were seen in 8% patients. Most common

behavioural issue (100%) were of agitation(96%) followed by psychosis(56%).Regarding movement disorders were seen in 98% and most were perioral/limb dyskinesia. Chorea(5%), dystonia(7%) are rare manifestations.

Cognitive dysfunction were seen in 58% and mostly affected domain is of memory (54%).Autonomic dysfunction was seen in 49%.Rarely focal neurological deficits like hemiparesis, monoparesis, aphasia were seen in around 3% patients.

At presentation most had GCS of 13-15(65%).3% patients were in coma. MMSE was difficult to test and was impossible in 76% patients. Most patients were misdiagnosed and frequently misdiagnosed as viral encephalitis(71%) followed by psychiatric illness(27%).

Investigations

CSF study was found to be abnormal in only 16.4% patients and frequent abnormality were either lymphocytic pleocytosis (TC usually less than 20) and mildly raised protein(45-60mg/dl). CSF IgG index was elevated in all abnormal CSF results. CSF and S NMDA was positive in all patients. MRI was abnormal in 45.5% patients and most common abnormality was FLAIR HI in parietooccipital (30%) followed by basal ganglia (25%) and both in 20% patients . ASL abnormality were seen in 7% but contrast and diffusion were normal in all. EEG abnormality was seen in 93% patients with common finding of nonspecific electrophysiological dysfunction(80%).Delta brush pattern were seen in 15% patients.

All patients underwent Tumor screening (CT chest and abdomen contrast in 45%, PET scan in 40% and USS abdomen, pelvis-100%, tumor markers -100%) and showed teratoma in 5.5% patients.

Treatment

All patients received first-line treatment and mostly administered agent were IVIG with IVMP(51%) followed by PLEX + IVIG (22%).36% patients received first-line treatment after 3 weeks of symptoms onset.24% patients needed ventilatory support and 10% patients required prolonged ICU stay(>1month).2 patients expired of total 55(3.6%) because of multiple systemic complications including sepsis, organ failure.37% patient received second-line therapy of which 36% received rituximab and only 1 patient received cyclophosphamide. Second line agent was initiated within 3 weeks of first-line in most.

Outcome

At time of discharge 82% patients had mRS <3. MMSE at time of discharge was not testable for 45% patients. At 3month and 1yr follow-up, mRS improved to 88% and 91% respectively. Relapse were seen in 29% patients and all relapsed patients were treated with IVIG or PLEX followed by rituximab. Most symptoms at relapse were seizure(58%) followed by behavioural issues(32%).EEG remained abnormal in 35% patients on follow-up.

There were 12 patients with age less than 12 yrs in our study group of NMDA positive patients. When compared to adult group seizures were mostly extratemporal(50%) than temporal(33%),more refractory status epilepticus(10% vs 8%),less psychosis than adults(40% vs 56%), less autonomic symptoms(33% vs 49%), less CSF abnormality (16 vs 8%, less MRI abnormality(33% vs 45%), less tumour(0 vs 5.5%), more delay in first-line treatment (50% vs 36%),less second line treatment requirement (25% vs 37%) less ventilatory(12% vs 24%),more chance of death(8% vs 3.6%), less relapse (20 vs 29%).Outcomes remained equal among both the groups.

Variable associated with short term and longterm outcomes were assessed.

Table 19 : Association of variables for short term outcome(mRS at 3months)-NMDA

		Bad (10)		Good(40		p
		Count	Percent	Count	Percent	
Age	<18	5	25	15	75	0.379
Sex	Male	2	17	10	83	0.578
	Female	8	17	30	83	
First symptom	Seizures	5	18.5	22	81.5	0.137
	Behavioural issues	5	21	18	79	
Behavioural issues	Yes	9	20	38	80	0.742
	No	1	33	2	67	
Movement disorder	Yes	8	18	35	82	0.361
	No	2	28	5	72	
Autonomic dysfunction	Yes	5	20	20	80	0.316
	No	5	20	20	80	
GCS class	13 - 15	2	4	44	96	p<0.01
	<13	8	57	6	43	
MMSE class	25 - 30	2	4	44	96	0.001
	<25	8	57	6	43	
First line therapy	Yes	10	100	40	100	p<0.01
	No	0	0	0	0	
Delay in first line	<3 Weeks	8	18	36	82	0.804
	>3 Weeks	2	33	4	67	
Second line therapy	Cyclophosphamide	1	25	3	75	0.020
	Rituximab	2	20	8	80	
EEG	Normal	1	6	15	94	0.012
	Abnormal	9	26	25	74	
MRI_brain	Normal	3	12	22	88	0.008
	Abnormal	7	28	18	72	

**: - Significant at 0.01 level, *: - Significant at 0.05 level

Factors favouring good prognosis at 3months (short term outcomes,table 19) are MMSE >25, GCS>13,first line and second- line treatment irrespective of the agent used, normal EEG and MRI at presentation.

Factors favouring bad prognosis at 3months includes MMSE<25, GCS<13, abnormal EEG and MRI at presentation.

Table 20 : Association of variables for long term outcome(mRS at 1year)-NMDA

	Bad (5)		Good(42)		p
	Count	Percent	Count	Percent	

Age	<18	2	11	16	89	0.279
Sex	Male	1	17	5	83	0.58
	Female	4	9	37	91	
First symptom	Seizures	3	12	22	88	0.17
	Behavioural issues	2	9	20	91	
Behavioural issues	Yes	5	11	40	89	0.42
	No	0	0	2	100	
Movement disorder	Yes	4	12	32	88	0.61
	No	1	9	10	91	
Autonomic dysfunction	Yes	3	13	22	87	0.16
	No	2	9	20	91	
GCS class	13 - 15	2	5	35	95	p<0.01
	<13	3	30	7	70	
MMSE class	25 - 30	1	2	38	98	0.001
	<25	4	50	4	50	
First line therapy	Yes	5	100	42	100	p<0.01
	No	0	0	0	0	
Delay in first line	<3 Weeks	4	10	36	90	0.704
	>3 Weeks	1	14	6	86	
Second line therapy	Cyclophosphamide	1	25	3	75	0.010
	Rituximab	2	20	8	80	
EEG	Normal	1	6	15	94	0.02
	Abnormal	4	26	27	74	
MRI_brain	Normal	2	8	22	92	0.004
	Abnormal	3	13	20	87	

Factors favouring good prognosis at 1 year (long term outcomes, table 20) are MMSE >25, GCS>13, first line and second-line treatment irrespective of the agent used,normal EEG and MRI at presentation.

Factors favouring bad prognosis at 1year includes MMSE<25, GCS<13, abnormal EEG and MRI at presentation.

Lgi1 encephalitis

19 patients in this antibody subtype were included in this study.

The mean age of the patients included were 57.2±14.3 with age ranges from 25-77yrs.Most patients were aged >50yrs (68%). No patients in age <18yrs were found. This antibody type is

commonly seen in males (73%). Medical comorbidities were found in 80% patients, most were diabetic(33%).

Clinical features

Premonitory symptoms were found in 40% patients and most were fever. First symptom at disease onset were seizures (53%) followed by behavioural issues(26%).In the cumulative symptoms seizures were most common symptoms(95%) mostly extratemporal(42%).the characteristic seizure subtypes of LGI1- FBDS were seen in 21%.No one had refractory status. Second commonest symptom was behavioural issues that was seen in 93%. Most patient had agitation(93%) but frank psychosis was seen only in 10%.60% had movement disorders including dystonia in 60% and peripheral hyperexcitability in 30%.Cognitive disturbance was seen in 68% and most affected is the memory domain(94%).Autonomic dysfunction was seen in 15% patients only. Most had GCS of >13 at presentation(84%) but MMSE was not testable in majority(90%).Most were misdiagnosed as dementia(52%) followed by viral encephalitis(26%).

Investigations

CSF was abnormal only in 5.3% and mostly lymphocytic pleocytosis (TC<20) and mildly raised protein(50-60mg/dl). Both CSF and serum LGI1 antibodies were positive in 70% and only serum positivity in 30% patients. MRI brain was abnormal in 68% and most common abnormality is the symmetrical T2/FLAIR HI in the mesial temporal lobes(90%).ASL abnormality were seen in 30% mostly hypoperfusion. No diffusion restriction or contrast enhancement or meningeal enhancement were seen. EEG was abnormal in 84% patients and mostly nonspecific electrophysiological dysfunction(60%) followed by temporal slowing(40%).All patients

underwent tumour screening(CT chest and abdomen-100%,PET scan-30%,USS abdomen and pelvis-100%,tumor markers-100%) and was negative in all.

Treatment

All patients were treated with first-line agent and the most commonly used agent is IVMP(68%) followed by IVIG+IVMP(15.8%).Most patients(79%) were treated within 3 weeks of symptom onset.16% needed ventilatory support and 26% required prolonged ICU stay.2nd line treatment was given for 10% patients and used both cyclophosphamide and rituximab equally.

Outcomes

No patient expired in this antibody subtype. mRS at discharge was 85% with excellent outcome with immunotherapy. At 3months and 1yr almost 100% patients had excellent outcome(mRS<3). Relapse were seen in 15.8% patients. Most patients had seizures (33%) followed by psychosis (33%) as relapse symptoms. All relapse were treated with acute therapy followed by oral immunomodulators. EEG remained abnormal in 33% patients.

Caspr2 encephalitis

15 patients in this antibody subtype were included in this study.

The mean age of the patients included were 46 ± 20.9 yrs with age ranges from 16-82yrs.Most patients were aged >50yrs (53%). This antibody type is commonly seen in females (53%). Medical comorbidities were found in 60% patients, most were diabetic(30%).

Clinical features

Premonitory symptoms were found in 60% patients and most were fever. First symptom at disease onset were seizures (60%) followed by behavioural issues(26.7%).In the cumulative symptoms behavioural issues that was seen in 93%.Most patient had agitation(93%) but frank psychosis was more prevalent 66%.Second commonest symptom was peripheral nerve hyperexcitability(88%) followed by seizures(60%) mostly extratemporal(60%).No one had refractory status.50% had movement disorders including dystonia and myoclonus in 70%.Cognitive disturbance was seen in 68% and most affected is the memory domain(86%).Autonomic dysfunction was seen in 40% patie nts. Most had GCS of >13 at presentation(86%) but MMSE was not testable in majority(90%).Most were misdiagnosed viral encephalitis(46%) followed by psychiatric 33%.

Investigations

CSF was abnormal only in 6.7% and mostly lymphocytic pleocytosis (TC<20) and mildly raised protein(50-60mg/dl).Both CSF and serum CASPR2 antibodies were positive in 60% and only serum positivity in 40% patients. MRI brain was abnormal in 80% and most common abnormality is the symmetrical T2/FLAIR HI in the mesial temporal lobes (80%).ASL abnormality were seen in 20% mostly hypoperfusion. No diffusion restriction or contrast enhancement or meningeal enhancement were seen. EEG was abnormal in 80% patients and mostly nonspecific electrophysiological dysfunction(70%) followed by temporal slowing(30%).All patients underwent tumour screening(CT chest and abdomen-100%,PET scan-30%,USS abdomen and pelvis-100%,tumor markers-100%) and was negative in all.

Treatment

All patients were treated with firstline agent and the most commonly used agent is IVMP(60%) followed by IVIG+IVMP(20%).Most patients(67%) were treated within 3 weeks of symptom onset.20% needed ventilatory support and 27% required prolonged ICU stay.2nd line treatment was given for 26% patients and used both cyclophosphamide and rituximab equally.

Outcomes

One patient expired in this antibody subtype and was due to multiorgan failure and sepsis. mRS at discharge was 80% with excellent outcome with immunotherapy. At 3months and 1yr almost 90% patients had excellent outcome(mRS<3). Relapse were seen in 13% patients.Most patients had seizures(33%) followed by psychosis(30%) as relapse symptoms. All relapse were treated with acute therapy followed by oral immunomodulators. EEG remained abnormal in 50% patients.

Seronegative autoimmune encephalitis

116 patients in this antibody subtype were included in this study.

The mean age of the patients included were 31.9 ± 20.5 yrs with age ranges from 2-79yrs.Most patients were aged 18- 50yrs (49.1%). This antibody type is equally distributed among males and females. Medical comorbidities were less frequent(35%).

Clinical features

Premonitory symptoms were found in 43% patients and most were fever. First symptom at disease onset were seizures (69%) followed by behavioural issues(33%).In the cumulative symptoms seizures was seen in 93% mostly extratemporal(53%).8% had refractory status. Behavioural issues were seen in 89%. Most patient had agitation(85%) but frank psychosis in 23%.60% had movement disorders including tremor and myoclonus in 70%.Cognitive disturbance was seen in 45% and most affected is the memory domain(50%).Autonomic dysfunction was seen in 33% patients. Most had GCS of >13 at presentation(80%) but MMSE was not testable in majority(80%).Most were misdiagnosed viral encephalitis(49%) followed by psychiatric 20%.

Investigations

CSF was abnormal only in 10% and mostly lymphocytic pleocytosis (TC<20) and mildly raised protein(50-60mg/dl).Both CSF and serum antibodies were negative in all. MRI brain was abnormal in 68% and most common abnormality is the symmetrical T2/FLAIR HI in the mesial temporal lobes (70%). ASL abnormality were seen in 50% mostly hypoperfusion. No diffusion restriction or contrast enhancement or meningeal enhancement were seen. EEG was abnormal in 83% patients and mostly nonspecific electrophysiological dysfunction(90%) followed by temporal and frontal slowing(10%).All patients underwent tumour screening(CT chest and abdomen-100%,PET scan-40%,USS abdomen and pelvis-100%,tumor markers-100%) and was negative in all.

Treatment

All patients were treated with first-line agent and the most commonly used agent is IVMP(55%) followed by IVIG+IVMP(28%).Most patients(60%) were treated within 3 weeks of symptom

onset.22% needed ventilatory support and 26% required prolonged ICU stay.2nd line treatment was given for 22% patients and used rituximab(13.8%) more than cyclophosphamide(8.6%).

Outcomes

Three patient expired in this antibody subtype and was due to multiorgan failure and sepsis. mRS at discharge was 86% with excellent outcome with immunotherapy. At 3months and 1yr almost 93% patients had excellent outcome(mRS<3). Relapse were seen in 7.8% patients. Most patients had seizures(35%) followed by behavioural issues(20%) as relapse symptoms. All relapse were treated with acute therapy followed by oral immunomodulators and 10% needed rituximab. EEG remained abnormal in 30% patients.

DISCUSSION

The prevalence of AE has been rising in recent years. The pathophysiology and aetiology of AE are yet unknown(Giordano et al., 2020). Given that AE is a dangerous but curable condition, the capacity to conduct a prompt and accurate evaluation of disease is crucial for selecting the right treatment and enhancing AE clinical results(Cafalli et al., 2020). In this research, retrospectively examining clinical traits, therapies, and clinical results of 222 AE patients from southern state of India. In addition, we preliminary assessed variables can have a negative impact on the patient prognosis.

Demographic data

In this study of 222 patients with autoimmune encephalitis(55 with NMDA,19 with LGI1,15 with CASPR2,116 with seronegative encephalitis patients) were included. The distribution of antibody subtypes is similar to other studies that the commonest autoimmune encephalitis is NMDA followed by LGI1which is similar to other studies(Saraya et al., 2019; Wang et al., 2016a).This showed age predilection towards an adult population with mean age of being 31.5 yrs ± 20.3yrs.There were equal proportion of patients under 18yrs and older than 50yrs(Samanta and Lui, 2023).There was mild female predominance(60%).Study conducted by Shan etal in China showed a similar affection of adult population but with a male predominance,58%(Qiao et al., 2021a). Another western studies also showed a male predominance(Endres et al., 2020).Study from southern India of 31 autoimmune patients which is the largest study available from India, showed a male predominance because of the more VGKC patients in the study patients and a mean age of 43yrs(Ramesh et al., 2023).

Clinical features

Premonitory symptoms was seen in 20% patients with fever as the predominant symptoms similar to other studies conducted in China and India of which none where positive for HSV antibodies or PCR(Qiao et al., 2021a; Ramesh et al., 2023).The previous studies showed HSV

encephalitis prior to the initiation of NMDA encephalitis exposing the brain antigens to immune attack(Gelfand, 2018; Venkatesan and Benavides, 2015; Wang et al., 2016a).In Chinese study there was 20% positive HSV antibodies in the NMDA group with prior infection(Armangue et al., 2018; Qiao et al., 2021a) but this matter was not looked in the Indian studies.

Initial symptoms were seizures followed by behavioural issues in our study. Other studies also showed similar finding except for predominant memory impairment also as clinical presentation(Qiao et al., 2021a).

Cumulative symptom showed seizures mainly extratemporal in most and convulsive status in 7% and super-refractory status in 5%. Second commonest symptoms were behavioural mainly agitation and psychosis. Similar trend was shown in other studies also(Qiao et al., 2021a; Ramesh et al., 2023).

Movement disorders were seen in 50% and most were perioral and limb dyskinesia which may be due to the predominant NMDA subtype in our study population. Dash etal showed similar pattern of perioral and limb dyskinesias prominence(Dash et al., 2019).

Cognitive issues in almost 50% and most were having memory problems similar to other studies(Corallo et al., 2018; Hébert et al., 2018).Cerebellar focal deficits were rare as in other studies(Dash et al., 2019; Titulaer et al., 2013).Autonomic disturbance was not in forefront as similar to other studies(Ramesh et al., 2023).

Misdiagnosis

Most were misdiagnosed as viral meningoencephalitis followed by psychiatric illness similar to that shown by Chandra etal(Chandra et al., 2018)

At presentation GCS were less than 13 in 30% and MMSE were non testable in majority. Even 3% presented in coma.

Investigations

CSF was abnormal only in 11% with most abnormality included lymphocytic pleocytosis (less than 20cells/mm3) and mildly raised protein in the range of 50-60mg/dl.This finding was against most of the studies as CSF abnormality were seen in almost 70%(Qiao et al., 2021a; Ramesh et al., 2023). This disparity may be due to referral bias as most of the patients were treated with immunotherapy elsewhere and only some patients underwent CSF during the early course of the disease. All patients underwent the antibody analysis in both CSF and serum.60% patients were seronegative. These seronegative cases needs utmost importance as they are frequently misdiagnosed and maltreated. Early identification and treatment affects the long-term outcomes of such patients.(Graus et al., 2016)

MRI was abnormal in 65% patients and most common abnormality was FLAIR hyperintensities in medial temporal followed by basal ganglia and parietooccipital areas. Contrast, ASL, diffusion were non contributary. Other studies showed abnormal MRI in almost 77% with similar abnormalities in temporal followed by frontal areas(Ramesh et al., 2023).Diffusion restriction and contrast enhancement were seen in few which may help to differentiate between infectious and inflammatory encephalitis.

EEG was abnormal in 86% with nonspecific dysfunction in 80%. Only 2% had delta brush pattern. EEG may not help in characterising the subtypes of autoimmune encephalitis and there are very few EEG finding specific for the antibody subtype that are less sensitive (delta brush pattern).It may be used to differentiate from other differential diagnosis. Normal EEG in a patient with suspected AIE warns the treating neurologist to look for alternate aetiology(Qiao et al., 2021a; Ramesh et al., 2023; Roberto et al., 2020).

None of the patients in our group showed any malignancy even after extensive evaluation which is similar to results from previous Indian and western studies. Except 5% of NMDA patient had teratoma which is much less when compared to western and Indian data(Chandra et al., 2018; Titulaer et al., 2013).

Treatment

The best medicine to control seizures in autoimmune encephalitis is not ASMs but immunotherapy.(Jia et al., 2018; Qiao et al., 2021b; Samanta and Lui, 2023; Saraya et al., 2019).All patients were treated with first-line and most commonly used agent was IVMP followed by IVMP with IVIG. Most series used the same approach to manage autoimmune encephalitis to initiated the treatment with steroid pulse therapy.(Qiao et al., 2021b; Titulaer et al., 2013)Most patients were treated within 3weeks and 36% patients treated >3 weeks indicating a significant delay in initiation of treatment. Several studies shown that early treatment initiation is associated with better short term and long term prognosis(Chandra et al., 2018; Titulaer et al., 2013)

Almost 30% required prolonged ICU stay and ventilatory support. Second line treatment was given for 25% and commonly used rituximab(Titulaer et al., 2013).

Outcomes

Almost 90% patients had favourable outcome at short term and long term indicating a better treatment response to immunotherapy in Indian population(Chandra et al., 2018; Datta et al., 2021; Kamble et al., 2015).Cognitive outcome was also better at long-term(Corallo et al., 2018). Relapses were seen in 16% patients almost similar to other studies and it ranged from 12-33%(Chandra et al., 2018; Irani et al., 2010; Raja et al., 2021)

Factors predicting outcomes

Factors associated with poor outcome were poor GCS, poor MMSE at admission, abnormal MRI, abnormal EEG for short term and on long term no variables were found to be significant. Other studies showed female sex and high titres of antibody with poor prognosis(Gu et al., 2019).

Factors favouring good outcomes were normal MRI, normal EEG, initiation of immunotherapy for both long and short term. Other studies also showed similar findings(Raja et al., 2021).

Mo et al. revealed that age, disturbance of consciousness, and ≥ 50% slow waves on EEG were independent risk factors of a poor AE prognosis (Mo et al., 2020). Proportion of abnormal brain MRI signals in the poor-prognosis group was significantly higher than that of the good-prognosis group, which was consistent with prior studies(Deng et al., 2019; Qiao et al., 2021a, 2021b). Findings of Qiu et al. suggested that low serum albumin, consciousness disorders, epileptic seizures, central hypoventilation, and pulmonary infection complications were associated with a poor AE prognosis (Qiu et al., 2019).

Factors predicting a relapse were female sex, positive NMDA status. Other studies showed patients who received second-line immunotherapy during the initial episode of encephalitis had fewer relapses and good functional outcome(Raja et al., 2021)

Till now no clinical scale are validated to use in clinical practise to assess the severity of autoimmune encephalitis. In 2019 Lim etal put-forward a scale to assess the prognosis of AIE called Clinical Assessment Scale in Autoimmune Encephalitis (CASE)(Lim et al., 2019).Further studies are required to validate the same.

Table 21 : Previous Indian studies

1	Cyril and colleagues (Cyril et al.,	Trivandrum	14	14 NMDA

	2015), 2009–2013			
2	Kamble and colleagues (Kamble et al., 2015), 2011–2015	Bangalore	16	10 NMDA, 4 anti-TPO, 2 Lgi1
3	Sudan and colleagues (Sudan et al., 2016), 2011–2014	Kochi	13	13 NMDA
4	Dash and colleagues (Dash et al., 2019)2013–2016	Delhi	41	24 NMDA, 12 LGi1; 5 GAD
5	Kannoth and colleagues (Kannoth et al.,	Kochi	54	34 Lgi1; 13 CASPR2; 7 Both

	2018), 2013–2016			
6	Chandra and colleagues (Chandra et al., 2018), 2013–2018	Bangalore	29	29 NMDA
7	Shivaraman and colleagues (Shivaram et al., 2021), 2014–2020	Bangalore	16	16 CASPR2
8	Raja and colleagues (Raja et al., 2021), 2018–2020	Bangalore	28	28 NMDA
9	Datta and colleagues (Datta et al., 2021)	Kolkata	25	25 NMDA

	2018–2020			

Subgroup analysis

When comparing between the subgroups as in previous studies most common AIE was seronegative followed by NMDA,LGI1 but GABABR antibodies were not prevalent in our population as in western studies(Cyril et al., 2015). Most common clinical presentation was seizures, behavioural symptoms, cognitive issues across the subtypes like prior studies(Datta et al., 2021; Deng et al., 2019; Raja et al., 2021; Titulaer et al., 2013). Autonomic symptoms and perioral dyskinesia were commonest in NMDA encephalitis whereas the facio-brachial dystonic seizures the signature of LGI1 was seen in 30%(Van Sonderen et al., 2016).Majority were misdiagnosed as a psychiatric illness or viral encephalitis which still points to lack of awareness of the entity(Chandra et al., 2018). MRI and EEG were abnormal in almost 80% studied as similar to other studies but CSF abnormality was seen only in 10-15% patients which were abnormal in 60-70% patients in other studies in all subtypes(Datta et al., 2021; Raja et al., 2021; Shivaram et al., 2021; Titulaer et al., 2013; Van Sonderen et al., 2016). This disparity may be due to referral bias and delay in CSF procedure. Response to first line immunotherapy were seen in almost 70% patients and 10-20% needed second line treatment and was mostly in NMDA encephalitis (31%)(Kamble et al., 2015; Qiu et al., 2019; Titulaer et al., 2013; Van Sonderen et al., 2016).100% response was seen with immunotherapy in LGI1(Van Sonderen et al.,

2016).Relapses were seen in almost 10% studied with least in seronegative group. At 3month and 1 year follow-up almost 90% recovered to baseline with mild cognitive, few seizures and behavioural issues in 20% most in NMDA(Titulaer et al., 2013).

NMDA encephalitis

Anti-NMDAR encephalitis is the most frequent cause of autoimmune encephalitis, and studies in the past have shown that early identification and treatment reduce the risk of morbidity and fatality(Samanta and Lui, 2023; Titulaer et al., 2013). We tried to study the clinical characteristics, results of ancillary exams, and therapeutic outcomes in 55 Indian patients with anti-NMDAR encephalitis.

More seen in younger patients with mean age of 20yrs, female predominant. Similar studies from India and western population showed a similar age preponderance and female sex predominance(Chandra et al., 2018; Titulaer et al., 2013).

Most common symptoms were behavioural followed by seizures which are of temporal semiology in majority. Most patients had perioral and limb dyskinesia on examination with more memory dysfunction. Predominant autonomic dysfunction than other subtypes. When compared to other studies there was more seizure predominance and autonomic dysfunction(Chandra et al., 2018; Wang et al., 2016b; Zhang et al., 2017).

More abnormal CSF than other antibody subtypes but only less than 20% were abnormal. EEG was abnormal in 93%, mostly non-specific dysfunction. MRI was abnormal in 45% less frequent than other antibody subtypes and the trend was similar to other studies except for the CSF. This disparity may be due to referral bias and early initiation of immunotherapy prior to CSF procedure(Chandra et al., 2018; Titulaer et al., 2013; Wang et al., 2016b; Zhang et al., 2017).

Only 5% had teratoma which was less than reported from other studies(Titulaer et al., 2013). However, as previously demonstrated by Dalmau et al.(Dalmau et al., 2011) this may be

attributable to the younger age of the patients in our cohort. An earlier study from South India by Chandra SR et al.(Chandra et al., 2018) also revealed a comparatively low rate of tumours, suggesting that ethnicity may be another contributing factor.

Table 22 : Comparison of epidemiological, clinical features and investigations amongst different studies

Epidemiological and clinical features	Wang, 2015(Wang et al., 2016b) (n = 51)	Zhang L, 2016(Zhang et al., 2017)(n = 432)	Chandra SR, 2018(Chandra et al., 2018) (n = 29)	Present study (n = 55)
Male (%)	37	32	10.3	15
Female (%)	63	68	89.7	85
Median/Mean age of onset (Range, in years)	21.6 (9-39)	22.0 (0.6-84)	17 (3-31)	20 (4-47)
Dysautonomia (%)	28	3	Not reported	49
Abnormal behaviour (%)	90	65	100.0	100
Dyskinesias/abnormal movement (%)	57	3	10.3	98
Seizures (%)	84	28	72.4	96
Abnormal MRI (Percentage)	33	40	40	45

Abnormal EEG (Percentage)	90	86	85	93
Abnormal CSF (Percentage)	79	63	58	16.4

Firstline treatment administration was equal but there was difference in second-line initiation with more patient requiring such treatment when compared other antibody positive and negative subtypes. Almost 90% patients had favourable response both at long term and short term. Relapse was more in NMDA subtypes(29%) than other AIE sub-types. There was a similar response to treatment in other studies with similar relapse rates which points the importance of early initiation to prevent the long-term morbidity and mortality.(Chandra et al., 2018; Titulaer et al., 2013; Zhang et al., 2017)

Factors predicting good outcome were MMSE >25, GCS >13 at admission, initiation of immunotherapy, normal MRI and EEG at admission both in long term and short term. Factors predicting bad outcome were abnormal MRI and EEG at admission in long-term but not in short term. Other studies showed paediatric age with good outcome(Datta et al., 2021).

LGI1 encephalitis

Out of 19 patients most were aged around 50yrs with male predominance which is similar to other studies(Li et al., 2018; Raja et al., 2021; Van Sonderen et al., 2016; Wang et al., 2016a). Most common symptoms were seizures which are of extratemporal semiology followed by behavioural issues in majority because of the predominant limbic encephalitis presentation. The characteristic seizure type FBDS were seen in 20% which is the hallmark finding of LGI1 encephalitis which is seen up to 30% patients in other studies(Li et al., 2018). Peripheral nerve

hyperexcitability was seen in 30% which is less florid than CASPR2(Van Sonderen et al., 2016).There are less autonomic dysfunction than other subtypes. Least abnormal CSF than other antibody subtypes but only less than 5% were abnormal which is less than found in other studies may be due to the referral bias(Li et al., 2018). EEG was abnormal in 84 % mostly non-specific dysfunction but there was no characteristic EEG finding in FBDS(Lai et al., 2010; Li et al., 2018; Van Sonderen et al., 2016).

MRI was abnormal in 68 % less frequent than other antibody subtypes and the common abnormality was mesial temporal hyperintensity similar to other studies(Li et al., 2018).Firstline treatment administration was equal but there was difference in second line initiation with more patient requiring such treatment than other antibody subtypes and 16% relapsed. The relapse rates were less when compared to other studies may be due to early identification and aggressive immunotherapy at onset helps(Li et al., 2018). There was excellent response to immunotherapy both short-term and long-term tumour association were found similar to other Indian studies(Cyril et al., 2015; Ramesh et al., 2023).

Anti caspr2 antibody

Out of 15 patients most were adult patients with mean age 46yrs , almost equal predominance which is against other studies which showed a male predominance(Shivaram et al., 2021).

Most well-known presentation of CASPR2 is neuromyotonia and morvan syndrome(Vincent and Irani, 2010).Some patients can present even as limbic encephalitis alone but additional peripheral nerve hyperexcitability features clinches the diagnosis(Kannoth et al., 2018).

In our study the common symptoms were behavioural issues mainly agitation with frank psychosis followed by peripheral nerve hyperexcitability in majority(88%).Seizures were there in 66%.Less autonomic dysfunction than other subtypes seen only in 40%.This was similar

finding seen in other studies with predominant motor manifestations(neuromyotonia)(Shivaram et al., 2021).

There are case reports behind siddha use, chronic mercury exposure or heavy metal toxicity behind the CASPR2 encephalitis but none of our patients were exposed to these(Grisold and Mamoli, 1984; Li et al., 2014; Panagariya et al., 2006).

Least abnormal CSF than other antibody sub- types, only in 6.7%. Other studies also showed almost 65% normal CSF study but this disparity may be due to referral bias. EEG was abnormal in 80 % and mostly non- specific dysfunction which will not aid in diagnosis. MRI was abnormal in 80 % mostly mesial temporal HI.MRI abnormality in other studies was almost 30% which may be due to more predominant limbic encephalitis presentation in our data(Vincent and Irani, 2010).

Firstline treatment administration in all with excellent response in most at short term and long term which is similar in all data indicating a better prognosis in these subtypes of AIE(Kannoth et al., 2018).

13% relapsed in this sub-types which are much less than NMDA groups.

Seronegative autoimmune encephalitis

116 patients were there in this group. To identify seronegative is a difficult task as there may be low titers of antibody in serum or CSF that may be missed but Graus etal 2016 case definition is used correctly identify these patients(Graus et al., 2016; Lee et al., 2022; Pradhan et al., 2019).

Mean age of presentation 24.5yrs with equal gender which was similar other studies(Lee et al., 2022; Pradhan et al., 2019). Most common presentation were seizures followed by behavioral changes and is similar to other seropositive subtypes(Wang et al., 2016b). MRI abnormality was seen in 68%(mostly flair HI temporal) and EEG abnormality(mostly focal or generalized slowing)in 83% which is also similar to seropositive group(Raja et al., 2021; Titulaer et al.,

2013).CSF was abnormal only in 10% and is different from other studies because of the referral bias and early treatment initiation prior to CSF study as discussed earlier(Lee et al., 2022).Most common first line treatment administered was pulse steroids. Second line agent was required in 21% mostly rituximab. Death occurred in 2.6%.These treatment initiation with steroids and second line use were similar in other studies(Pradhan et al., 2019).Favourable outcome at 3months and 1year was in 86% and 88% respectively.7.8% patient had relapse mostly seizures. Treatment response to immunotherapy was similar in both seropositive and seronegative groups but relapse rates were less than seropositive groups. This was also proven in Pradhan etal study(Pradhan et al., 2019). But Lee etal showed a less response to immunotherapy and more relapses in seronegative groups which may be due to inclusion of ADEM in the study group(Lee et al., 2022). Normal MRI at presentation, early initiation of treatment was associated with favourable long term outcome as similar to seropositive group and those patients with abnormal MRI at presentation has worst outcome.

STRENGTH OF THE STUDY

- Largest study including all subtypes of immune mediated encephalitis from India.
- Both clinical characteristics, demographic details, treatment and prognostic factors were assessed which makes the further treatment decisions much easier.
- Adequate number of AIE patients.

LIMITATIONS

- Due to the limited sample size, construction of a prognostic evaluation model was not possible.
- Retrospective nature of the study which may allow for selection bias.
- Our study is limited by its small sample size.
- Lack of long-term follow-up.
- All the patients received first line immunotherapy, hence efficacy of first line and second line therapies could not be compared head-to-head.
- CSF study was not done on follow up so role of antibody in disease monitoring were not assessed.
- Titre of anti NMDAR antibodies was not assessed by our laboratory assays.
- A small sample size also made comparison of clinical parameters difficult amongst categories of patients (adult and paediatric in our case) difficult.
- Subsequent studies with larger sample size are desirable. Since the treatment was not randomized, no definite analysis could be done.

CONCLUSIONS

The diagnosis of AIE still remains a challenge with wide differentials at first medical attention so more education and awareness are required.

- A subacute presentation with cognitive decline, seizures and behavioural symptoms should raise suspicion of AIE which should be worked up with appropriate serological investigation.

- Seronegative AIE is still the commonest subtype followed by NMDA.
- Early diagnosis and initiation of immunotherapy is the key to favourable outcomes which excellent response to immunotherapy.

- Early initiation with steroids and IVIG or PLEX may be better than individual therapies in NMDA

- Relapse rates are less when compared to western studies may be due to adequate treatment with adequate maintenance therapy.

- Abnormal MRI, EEG, poor GCS and MMSE is associated with bad prognosis.
- Among the various subtypes of AIE anti VGKC has the excellent response to immunotherapy (100%).

- Further exploration of prognostic factors and validation of study findings may be accomplished in the future by conducting a prospective, large-scale, randomized, controlled trial.

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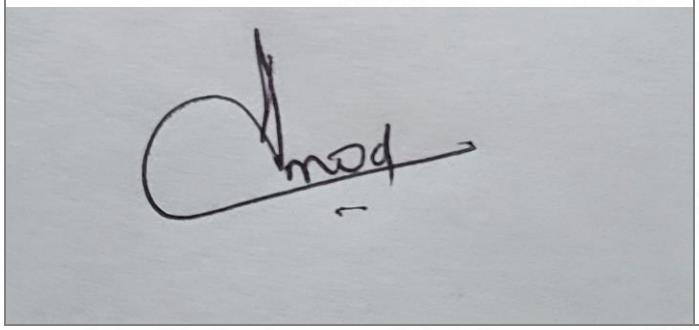
ANNEXURES

Format for CV of the Principal Investigators

Last Name – R	First Name - AMOD	Middle Name –
Date of Birth (dd/mm/yy) 30/10/1990		Sex MALE
Study Site AfLiliation (e.g. Principal Investigator, Co-Investigator, Coordinator) PRINCIPAL INVESTIGATOR AT SCTIMST		
Professional Mailing Address (Include Institution name)		Study Site Address (Include Institution name)
AMOD R DEPT. OF NEUROLOGY SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY THIRUVANANTHAPURAM, KERALA, INDIA -695011		DEPT. OF NEUROLOGY SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY THIRUVANANTHAPURAM, KERALA, INDIA -695011
Telephone (OfFice):		Mobile Number: 8547240067
Telephone (Residence):		Email- amodracl@gmail.com
Academic QualiLications (Most recent qualiLication List)		
Degree/CertiLicate	Year	Institution, Country
MD GENERAL MEDICINE	2020	GOVERNMENT MEDICAL COLLEGE,TRIVANDRUM
MBBS	2015	GOVERNMENT MEDICAL COLLEGE,TRIVANDRUM
Details of professional registration : (MCI/State Registration/Bar Council/DCI/etc including Registration Number and Year of Registration TRAVANCORE COCHIN MEDICAL COUNCIL REGISTRATION NUMBER- 55941, YEAR :2015		
Current and previous positions (most recent position List)		
Month and Year	Title	Institution/Company, Country
JAN 2021	SENIOR RESIDENT	SCTIMST THIRUVANANTHAPURAM, INDIA

Brief summary of relevant research experience: 1) MD THESIS : PROPORTION OF VITAMIN D DEFICIENCY IN RHEUMATOID ARTHRITIS AND ITS ASSOCIATION WITH DISEASE ACTIVITY	
Current project/s at hand:	
Signature: 	Date:28/8/23 Place: THIRUVANANTHAPURAM

Co-Principal
Investigator

Last Name: **Radhakrishnan**	First Name: **Dr Ashalatha**	Middle Name
Date of Birth (dd/mm/yy): 13/05/1970		Sex: Female
Study Site Affiliation (e.g. Principal Investigator, Co-Investigator, Coordinator) Principal Investigator		
Professional Mailing Address (Include Institution name)	Study Site Address (Include Institution name)	
Professor of Neurology, Department of Neurology, Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST), Medical College P.O, Thiruvananthapuram - 695011	SCTIMST, Medical College P.O, Thiruvananthapuram	
Telephone (Office): 91-471-2443520	Mobile Number: 9847416321	
Telephone (Residence):	Email:drashalatha@sctimst.ac.in	

Academic Qualifications (Most recent qualification first)

Degree/Certificate	Year	Institution, Country
Fellow of American Neurological Association (FANA) Fellow of Royal College of Physicians (Glasgow) MBA(Hospital Administration & HRD)	2017 -18	The Royal College of Physicians and Surgeons of Glasgow, Scotland
Training in Stereo EEG for utilization in surgical evaluation of refractory Epilepsy	2016	Montreal, Canada
Training in EEG co-registered MRI for application in refractory epilepsy	2012	Queen Square Hospital, University College, London
Fellowship in Epilepsy & Sleep Medicine	2007- 2008	Austin Health, Melbourne, Victoria, Melbourne University, Australia (under supervision of Prof. Samuel F Berkovic and Rob J Pearce, University of Melbourne)
M.D General Medicine	1999	Govt. Medical College, Alappuzha, University of Kerala
MBBS	1994	Govt. Medical College, Alappuzha, University of Kerala

Details of professional registration : (MCI/State Registration/Bar Council/DCI/etc including Registration Number and Year of Registration: TCMC-21956/1994

Current and previous positions (most recent position first)

Month and Year	Title	Institution/Company, Country
January 2016-continuing	Professor	SCTIMST, Trivandrum
2015-2017	Additional Professor	SCTIMST, Trivandrum
January 2009 - 2015	Associate Professor	SCTIMST, Trivandrum

June 2008 – December 2008	Consultant in Neurology(Sleep Project)	SCTIMST, Trivandrum
January 2007-May 2008	Fellowship Training in Epilepsy and Sleep Medicine	SCTIMST, Trivandrum
August 2006 – February 2007	Assistant Professor	SCTIMST, Trivandrum
June 2003 – July 2006	Ad Hoc Consultant in Neurology and Epilepsy Program	SCTIMST, Trivandrum

Brief summary of relevant research experience:

The applicant has been working as a faculty member in the Department of Neurology, Sree Chitra Tirunal Institute and Medical Sciences (an institute of national importance under the Department of Science and Technology, Govt. of India) since 2003 after completing the graduation in Neurology in the same institute. She is devoting 70% of her time in the R. Madhavan Nayar Center for Comprehensive Epilepsy Care which is the largest of its kind in the country with state of the art facilities catering to patients with epilepsy headed by Dr. Sanjeev Thomas, Professor of Neurology and a renowned epileptologist. During this period she has focused in the evaluation and management of medically refractory epilepsy and its surgical management by developing new neuroimaging techniques like functional MRI-coregistered EEG, diffusion tensor imaging and fiber tracking, voxel based morphometry etc related to epilepsy.

Functional MRI-EEG coregistration technique aids in the pre-surgical workup of epilepsy patients when other investigation tools fail to localize the area of epileptogenic focus. Dr Ashalatha along with her colleagues in Neuroradiology and Biomedical technology wing standardized the procedure of EEG- fMRI for the first time in the country which is now in the process of being utilized in the field of pre-surgical evaluation of refractory cases of epilepsy.

In conventional MRI negative epilepsy patients, she along with computer scientists has developed newer computational software for detection of subtle cortical dysplasia by a method called voxel based morphometry (VBM) which was presented for the first time from India in the International Conference on Epilepsy at Melbourne, Australia in October,2010. Newer sequences have been applied forthe clinical problem. These methods are now going to be utilized for the detection of such subtle lesions like focal cortical dysplasias which may aid the epileptologist to proceed with better treatment for epilepsy.
The applicant has also applied advanced neuroimaging protocols such as diffusion tensor imaging with fiber tracking of white matter tracts aiding in the mapping of white matter tracts in the pre-surgical evaluation of patients with epilepsy. This will aid the surgeon to plan out his surgery at or close to eloquent areas in order to avoid untoward complications like hemiparesis, speech difficulty etc which are the major hindrances in selection of candidates for brain surgery. This work is not being done in any other parts of the country and author won the Young Investigator award for this pioneering work at the 100th International Congress of Epilepsy at Budapest, Hungary in 2009.

Current project/s at hand:

1. Multimodal imaging in pre surgical evaluation of extra temporal lobe epilepsy-(PI)
2. Utility of 3D pseudo continuous ASL perfusion in pre- surgical evaluation of focal temporal and Extratemporal epilepsy -(Co- PI)
3. Prevalence of sleep disordered breathing (SDB) in children with attention deficit hyperactivity disorder (ADHD) and its response to treatment in school going children in Thiruvanathapuram district-(PI)
4. A genetic association for severe hyponatremia and central pontinemyelinolysis-(PI)
5. Genome-Wide Association and Blood Marker study in Narcolepsy and Hypersomania-(PI)
6. Association of Pulmonary arterial hypertension (PAH) and cardiac arrhythmias in patients of Obstructive sleep apnea (OSA) and possible therapeutic benefit with CPAP treatment-(PI)
7. Clinical profile and outcome in patients with autoimmune encephalitis-(PI)

8. Global audit of treatment of refractory Status Epilepticus-(PI) **9.** Development of intracranial electrodes for use in acute and chronic electrocorticography-(Co-PI) **10.** Indigenous Intracranial electrode manufacture (TRC) – (DST Funded) - (Co–PI) **11.** Model the effect of Mutations of HCN Channels in Neuronal Excitability and impact of GABABR on GIRK and HCN mutations using NEURON - (DBT Funded) – (Co-PI) **12.** Validation of memory fMRI paradigms and its utility in pre-surgical evaluation of patients with refractory TLE – (Co-PI) **13.** A resting state fMRI and task based fMRI study: Optimization, language lateralization, memory lateralization and connectivity in normal subjects versus patients with epilepsy - (DBT Funded) – (Co_PI)	
Signature: 	Date: 28/8/2023 Place: Thiruvananthapuram

PROFORMA

Sree Chitra Tirunal Institute for Medical Sciences and Technology
Thiruvananthapuram, Kerala-695011

AUTOIMMUNE ENCEPHALITIS: PROFILE, SUB TYPE ANALYSIS, CLINICAL OUTCOMES

1. Personal Data:

Age years

Sex 1. Male 2. Female

Demographics

2. Clinical Presentations (1- yes 2-No)

1.Fever

2.Headache

3.Cognitive decline

4. Behavioural issues

5. Speech problems

6. Focal neurological deficits

7.Seizures- a. Focal b. Focal impaired awareness c. Generalized d. Status

8.Ataxia

9.Memory issues

10.Movement disorder – a. Chorea b. Dystonia c. Myoclonus d. Dyskinesia e. Athetosis f. peripheral nerve hyperexcitability

11.Extrapyramidal- Parkinsonism

3. Clinical examination

1. GCS score

2.MMSE

3.Focal deficits

4.Lobe function – 1. Frontal 2. Temporal 3. Parietal 4. Occipital 5. Mixed

5.Brain stem

6.Pyramidal

7.Extrapyramidal

4.Investigations

1. Routine

Blood Routine with ESR

Renal function test

Liver Function test

Urine routine

2. Special Investigations

CRP

TFT

Vasculitis profile (ANA, ANCA, APLA, RF)

Viral Markers

Thyroid antibody profile

Tumour screening (CEA, CA19-9, CA125, AFP, BHCG)

CSF study (TC, DC, Sugar, Protein, Opening pressure)

HSV PCR

CSF IgG index

CSF and serum Autoimmune encephalitis panel

Onconeural antigen profile

3.Imaging

Ultrasound Abdomen

CT chest and Abdomen

MRI brain – 1. Areas involved 2. Contrast enhancement -yes/no 3. Diffusion restriction - yes/no 4. ASL- hypoperfusion/hyperperfusion

Whole body PET

4.EEG – a. Generalised or focal slowing b. IEDs c. NCSE d. electrographic seizures

5.Treatment and Follow up

First line therapy –1. IVIG 2. PLEX 3.IVMP+ IVIG 4.IVMP + PLEX 5. IVMP

Second line therapy – 1. Cyclophosphamide 2.Rituximab 3.Others

Symptom onset to initiation of treatment (in days)

Delay between 1st line and 2nd line treatment (in days)

Ventilatory support (yes/no)

Duration of ICU stay (in days)

Complications – 1. Sepsis 2.DVT 3. PTE 4.VAP 5. MODS 6.Others

mRS at discharge

Follow up at 3months and 1year (mRS)

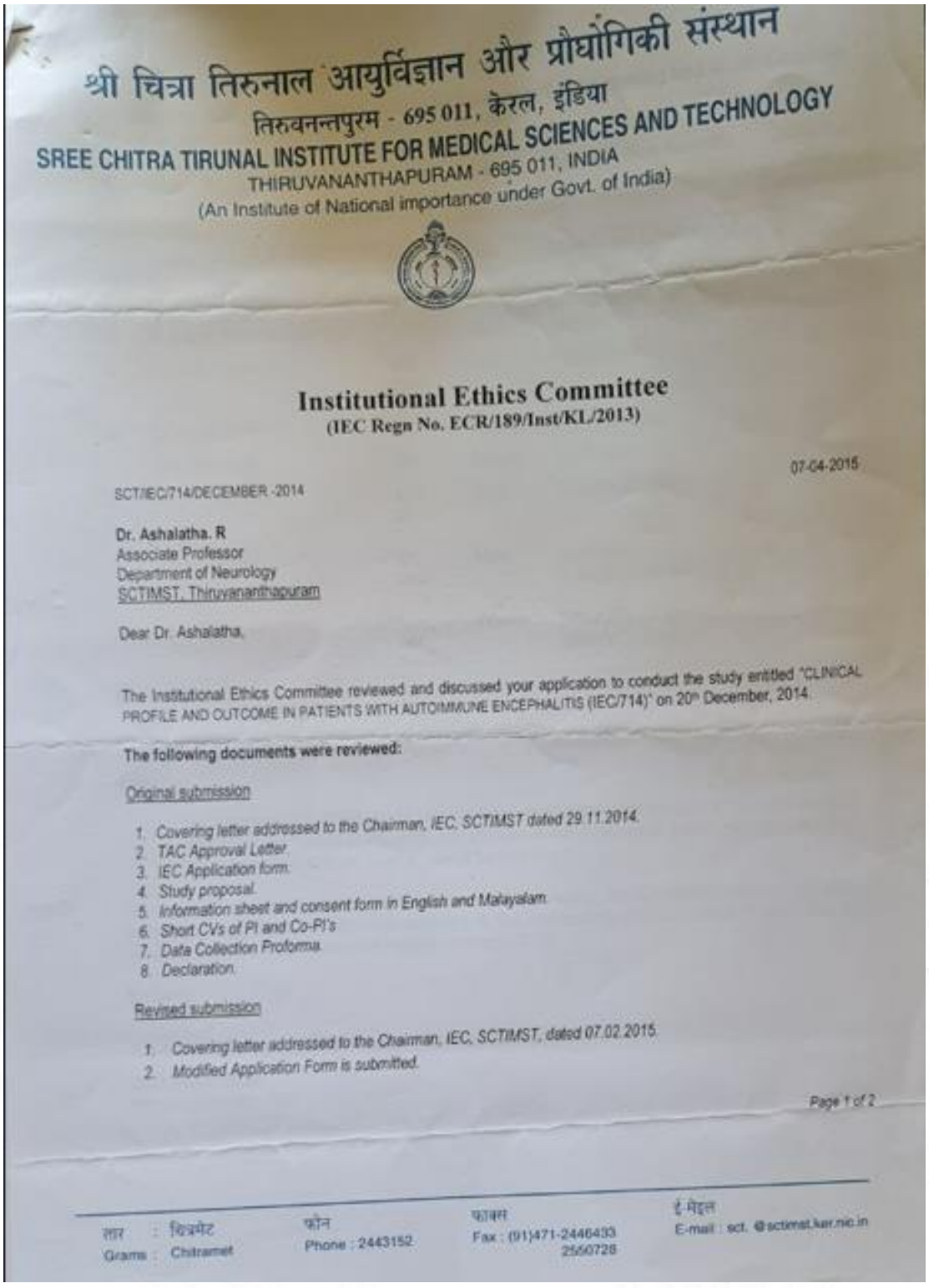
Follow up after 1year (mRS)

Events on follow up(seizures/headache/others)

Relapses (yes/no)

Characteristics of relapses

Treatment for relapses-1. IVIG 2. PLEX 3.IVMP+ IVIG 4.IVMP + PLEX 5. IVMP



श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान
तिरुवनन्तपुरम - 695 011, केरल, इंडिया
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY
THIRUVANANTHAPURAM - 695 011, INDIA
(An Institute of National importance under Govt. of India)

Institutional Ethics Committee
(IEC Regn No. ECR/189/Inst/KL/2013)

07-04-2015

SCT/IEC/714/DECEMBER -2014

Dr. Ashalatha. R
Associate Professor
Department of Neurology
SCTIMST, Thiruvananthapuram

Dear Dr. Ashalatha,

The Institutional Ethics Committee reviewed and discussed your application to conduct the study entitled "CLINICAL PROFILE AND OUTCOME IN PATIENTS WITH AUTOIMMUNE ENCEPHALITIS (IEC/714)" on 20th December, 2014.

The following documents were reviewed:

Original submission

1. *Covering letter addressed to the Chairman, IEC, SCTIMST dated 29.11.2014.*
2. *TAC Approval Letter.*
3. *IEC Application form.*
4. *Study proposal.*
5. *Information sheet and consent form in English and Malayalam.*
6. *Short CVs of PI and Co-PI's*
7. *Data Collection Proforma.*
8. *Declaration.*

Revised submission

1. *Covering letter addressed to the Chairman, IEC, SCTIMST, dated 07.02.2015.*
2. *Modified Application Form is submitted.*

Page 1 of 2

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by krishna mohan

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