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Original Research Article

CLINICAL PROFILE OF AUTOIMMUNE ENCEPHALITIS

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Abstract

Background: Auto immune encephalitis with antibodies to neuronal cell surface/synaptic antigens is a recently described group of neuropsychiatric disorders in which the antibodies react with extracellular epitopes of the corresponding target antigen. They affect individuals of all ages, while some syndromes preferentially affect young adults and children. The immunological trigger of autoimmune encephalitis is varied and yet to be established. In some patients the presence of a systemic tumor that expresses the target neuronal/synaptic proteins appears to be important. **Materials and Methods:** A longitudinal study conducted at Department of Neurology, Kasturba Medical College, Dr.B.R. Ambedkar Circle, Mangalore, Manipal Academy of Higher Education, Karnataka. After taking written and informed consent about the enrollment in the study and maintaining adequate privacy and confidentiality, all patients with clinical picture of Autoimmune encephalitis will be subjected to detailed history taking, general and systemic examination. A questionnaire will be provided to the patients to know about their past history, family history and list of medications. Based on clinical examination diagnosis of AIE is considered and routine hematological and biochemical investigations, serum and CSF autoimmune panel, EEG and MRI are done confirming the diagnosis. **Result:** The data were tabulated and analysed using Microsoft excel and IBM SPSS version 25 software. The continuous and categorical variables have been represented as means and percentages respectively. Total 30 patients of AIE were screened for neurological manifestations. 17 out of 30 cases had serological autoimmune positivity. The Mean Age distribution among the cases was 29.63 years with children accounting to 36.7 % and adults 56.5% and elders 6.7%. There were 18 (60%) males and 12 (40%) females out of 30 total cases. Analysis for presenting symptom reveal refractory seizures in 76.7%, movement disorders in 60%, Psychiatry disturbances in 13.2%, cognitive behavioural changes in 13.3%, fever in 10%, echolalia in 3.3%. Among Movement disorders myoclonus being noted in 6 of them and limb dyskinesis noted in 4, faciobrachial dystonia in 3, orofacial dyskinesis in 2 and chorea, limb dystonia and neuromyotonia was noted in each of the patients. Association with hypothyroid was seen with 2 cases (6.6%). Medulloblastoma (post-surgery) and treated case of prostatic carcinoma were each noted in single patient. One of the patient was pregnant in our study. 24 of the patients didn't have any other associations. **Conclusion:** Recognition of rapidly emerging autoimmune encephalitis is pivotal for a prompt treatment with subsequent favourable outcomes. Evaluation should often begin with a detailed history taking and physical examination for an understanding of the specific causes. Auxiliary investigations- MRI and EEG may further support a diagnosis of encephalitis. Treatment should depend on the pathophysiology of the disorder- whether T-cell-mediated or antibody mediated, apart from the clinical situation of the patient. Patients with relapse should receive appropriate follow-up care. Further studies on the effect of type and duration of treatment on outcome are recommended.

INTRODUCTION

Auto immune encephalitis with antibodies to neuronal cell surface/synaptic antigens is a recently described group of neuropsychiatric disorders in which the antibodies react with extracellular epitopes of the corresponding target antigen. They affect individuals of all ages, while some syndromes preferentially affect young adults and children.[1]

The immunological trigger of autoimmune encephalitis is varied and yet to be established. In some patients the presence of a systemic tumor that expresses the target neuronal/synaptic proteins appears to be important.[2]

The clinical features include complex neuropsychiatric symptoms like memory loss, changes in behavior or cognition, psychosis, seizures and movement disorders. At presentation one or a few of these symptoms may predominate and can mislead the diagnosis. So, Autoimmune encephalitis should be included in the differential diagnosis of any patient, especially if young, with a rapidly progressive encephalopathy of unclear origin.[3]

Disease can have a relapsing course and therefore the diagnosis of these disorders should be considered in patients with a past history of encephalitis or relapsing encephalopathy.

The diagnosis of autoimmune encephalitis is confirmed by the presence of specific neuronal cell surface/synaptic antibodies in serum and CSF.

Supporting findings such as inflammatory signs in cerebrospinal fluid (CSF) or the presence of oligoclonal bands can be useful. Abnormalities on MRI fluid-attenuated inversion recovery (FLAIR) sequences are more commonly seen in some syndromes.

These pathogenetic effects are reversible and although the process of recovery can be prolonged, patients with these syndromes often have full or substantial recovery after immunotherapy.

The other type of autoimmune encephalitis is paraneoplastic encephalitis in which the antibodies target intracellular proteins such as Hu or CRMP5. In these disorders T-cell mechanisms appear to play a predominant role in mediating the neuronal dysfunction that is often irreversible.[4]

The incidence of autoimmune encephalitis has been rising globally from 0.4/100,000 person-year (1995–2005) to 1.2/100,000 person-year (2006–2015). Additionally, with several novel neuronal antibodies discovered recently such as LGI1, CASPR2, GABA-A/Br, anti-dopamine2 receptor, antiDPPX, anti-IgLON5 and neurexin-3α, it is plausible that the diagnosis of autoimmune encephalitis will continue to rise. It represents a significant burden to patients, families, and society.[5]

Aims and Objectives

1. To evaluate the clinical profile in cases of autoimmune encephalitis
2. To observe serum and CSF autoantibody panel
3. To describe MRI and EEG pattern of these patients
4. To monitor clinical outcome, following treatment for a period of 4 weeks

MATERIALS AND METHODS

Study Setting: Department of Neurology, Kasturba Medical College, Dr.B.R.Ambedkar Circle, Mangalore, Manipal Academy Of Higher Education, Karnataka.

Study Design: Longitudinal Study.

Study Duration: The study was conducted from July 2020 to July 2021 (12 months).

Study Participants and Selection Criteria: Patients with presenting features of autoimmune encephalitis.

Inclusion criteria

Patients with rapidly progressive mental status changes, speech deficits, movement disorders over 1-6 weeks or new onset seizure activity.

Plus at least two of the following criteria

Autoimmune antibodies in serum or CSF which have been associated with autoimmune encephalitis.

CSF findings consistent with inflammation.

Brain MRI showing characteristics suggesting inflammation (FLAIR or T2 hyper intensities, contrast enhancement)

New onset seizure or mental status changes responding to immunotherapy.

Exclusion criteria

Children below 2 years of age

Persons with encephalitis due to an infective, metabolic, structural, stroke, genetic, demyelinating causes were excluded.

Study Duration: From the date of approval to February, 2022.

Sample Size: Time Bound Study; all the cases observed will be included in the study. (Approximately 30 cases.

Sampling Method: Convenient Sampling Technique

Tool for Data Collection: Pre Structured Questionnaire and Examination Investigation Proform

Data Collection Methodology: After taking written and informed consent about the enrollment in the study and maintaining adequate privacy and confidentiality, all patients with clinical picture of Autoimmune encephalitis will be subjected to detailed history taking, general and systemic examination. A questionnaire will be provided to the patients to know about their past history, family history and list of medications. Based on clinical examination diagnosis of AIE is considered and routine hematological and biochemical investigations, serum and CSF autoimmune panel, EEG and MRI are done confirming the diagnosis.

Test Procedure (Where Applicable): Blood Investigations: Routine investigations and serum autoimmune antibody tests

Autoimmune tests include: Anti-Hu, Ri, Yo, CV2, Recoverin, Titin, GAD, Zic4, amphiphysin, SOX1,

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Tr, PNMA 1&2 GABAB, NMDA, AMPA1 & 2, CASPR2,LGI-1
Csf analysis for routine tests, autoimmune and paraneoplastic panel
Electrophysiological: EEG
Neuroimaging: MRI
Outcome Variables: Percentage of various neuropsychiatric manifestations of autoimmune encephalitis
Biological Materials Required: Blood for routine investigations and autoantibody tests, CSF for analysis and autoantibody panel
Data Analysis: All data will be entered in Microsoft excel and analysed using appropriate statistical software – SPSS v 25.0 armonk

Ethical Considerations: The study will commence after getting necessary approval from institutional Scientific and Ethical Committee. The participant will not be exposed to any potential risk in this study.
Budget Estimation: Rs. 2,10,000.

RESULTS

Analysis summary
The data were tabulated and analysed using Microsoft excel and IBM SPSS version 25 software. The continuous and categorical variables have been represented as means and percentages respectively.

Table 1: Descriptive data for continuous variables.

Variable	N	Minimum	Maximum	Mean	Std. Deviation
Age	30	2	70	29.63	22.698
P	30	16	76	43.83	13.170
CC	28	1	22	8.86	6.422

Table 2: Distribution of age across the sample

Age (in years)	Number	Percentage
Children (2-12)	11	36.7
Adults (13-60)	17	56.6
Elderly (>60)	2	6.7

Table 3: Distribution of gender across the sample

Gender	Number	Percentage
Female	12	40.0
Male	18	60.0

Table 4: Distribution of sample based on symptoms at presentation

Symptoms	Number	Percentage
Refractory seizures	23	76.7
Echolalia	1	3.3
Ataxia	2	6.7
Psychiatric disturbances	4	13.3
Cognitive disturbances	4	13.3
Fever	3	10.0

Table 5: Distribution of sample based on movement disorders

Movement disorders	Number	Percentage
Orofacial dyskinesias	2	6.7
Limb dyskinesias	4	13.3
Chorea	1	3.3
Limb dystonia	1	3.3
Faciobrachial dystonia	3	10.0
Myoclonus	6	20.0
Neuromyotonia	1	3.3

Table 6: Other associations within the sample patients

Other associations	Number	Percentage
Hypothyroid	2	6.6
Medulloblastoma (post-surgery)	1	3.3
Nil	24	80.0
Past h/o AIE	1	3.3
Pregnant	1	3.3
Treated prostatic carcinoma	1	3.3

Table 7: Autoimmune profile within the sample

Autoimmune profile	Number	Percentage
Anti AMPAr Antibody	1	3.3
Anti GABAA receptor antibody	2	6.7
Anti GABAB receptor antibody	1	3.3
Anti LGI	2	6.6

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Anti mGluR 5	1	3.3
Anti mGluR1	1	3.3
Anti NMDA receptor antibody	7	23.3
Anti NMDAr, Anti mGluR5	1	3.3
CASPR 2	1	3.3
Negative	13	43.3

Table 8: Paraneoplastic profile within the sample

Paraneoplastic profile	Number	Percentage
Anti TPO	2	6.6
Anti TPO, AntiGAD 65	1	3.3
Negative	14	46.7
Not done	13	43.3

Table 9: MRI findings

MRI findings	Number	Percentage
B/L basal ganglia and Medial temporal lobe hyperintensities	1	3.3
Diffuse hyperintensities in white matter	1	3.3
Flair hyperintensities bilateral cerebellar	1	3.3
Flair hyperintensity of b/l deep gray nuclei	1	3.3
Meningeal enhancement noted	1	3.3
Multi focal hyperintensities in basal ganglia and thalamus	1	3.3
Multifocal cortical hyperintensities in bilateral frontal and temporal	1	3.3
Normal	11	36.6
Bilateral medial temporal flair hyperintensiries	12	40.0

Table 10: EEG findings

EEG findings	Number	Percentage
Diffuse slowing	15	50.0
Extreme Delta brush pattern	8	26.6
Neuromyotonia	1	3.3
Normal	2	6.7
PLEDS and delta brush pattern noted	1	3.3
PLEDS noted	3	10.0

Table 11: Immediate treatment given

Immediate treatment	Number	Percentage
IvIg	11	36.7
IvIg, MPS	4	13.3
MPS	7	23.3
PLEX	8	26.7

Table 12: Response to treatment (immediate)

Immediate response to treatment	Number	Percentage
Improved	23	76.6
Lip smacking persisted	1	3.3
No response	4	13.3
Psychiatric features persisted	1	3.3
Lower limb dyskinesias persisted	1	3.3

Table 13: Maintenance treatment given

Treatment	Number	Percentage
Azathioprine	8	26.7
Prednisone	8	26.7
Rituximab	9	30.0
Rituximab and Prednisone	1	3.3

Table 14: Symptoms at follow-up at 4 weeks

Follow-up at 4 weeks	Number	Percentage
Expired	4	13.3
Improved Seizures with Occasional dyskinesias	1	3.3
Lip smacking	1	3.3
Symptom free	23	76.6
Seizures improved mild ataxia gait	1	3.3

Table 15: CSF with lymphocyte predominance

Lymphocyte predominance	Number	Percentage
No	18	60.0
yes	12	40.0

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Table 16: Clinical presenting symptoms for each autoimmune profile

Autoimmune profile	Refractory seizures	echolalia	Ataxia	Psychiatric disturbances	Memory impairment	Fever	Altered sensorium
Anti AMPAr Antibody	1	0	0	0	1	0	1
	100.0%	0.0%	0.0%	0.0%	100.0%	0.0%	100.0%
Anti GABAA receptor antibody	2	0	0	0	0	0	2
	100.0%	0.0%	0.0%	0.0%	0.0%	0.0%	100.0%
Anti GABAB receptor antibody	1	0	0	0	0	0	0
	100.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Anti LGI	0	0	0	0	0	0	0
	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Anti mGluR 5	1	0	0	0	0	1	0
	100.0%	0.0%	0.0%	0.0%	0.0%	100.0%	0.0%
Anti mGluR1	1	0	1	0	0	0	0
	100.0%	0.0%	100.0%	0.0%	0.0%	0.0%	0.0%
Anti NMDA receptor antibody	6	0	0	1	0	2	3
	85.7%	0.0%	0.0%	14.3%	0.0%	28.6%	42.9%
Anti NMDAr, Anti mGluR5	1	0	0	0	0	0	0
	100.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
CASPR 2	0	0	0	0	0	0	0
	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
LGI 1 antibody	0	0	0	0	0	0	0
	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Negative	10	1	1	3	3	0	3
	76.9%	7.7%	7.7%	23.1%	23.1%	0.0%	23.1%

Table 17: movement disorders for each autoimmune profile

Autoimmune profile	Orofacial dyskinesia	Limb dyskinesia	Chorea	Limb dystonia	Faciobrachial dystonia	myoclonus	Neuromyotonia
Anti AMPAr Antibody	0	0	0	0	0	1	0
	0.0%	0.0%	0.0%	0.0%	0.0%	100.0%	0.0%
Anti GABAA	0	0	0	0	0	0	0
	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Anti GABAB	0	0	0	0	0	0	0
	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Anti LGI	0	0	0	0	1	1	0
	0.0%	0.0%	0.0%	0.0%	100.0%	100.0%	0.0%
Anti mGluR 5	0	1	0	0	0	0	0
	0.0%	100.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Anti mGluR1	0	0	0	0	0	0	0
	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Anti NMDA	0	1	1	0	1	2	0
	0.0%	14.3%	14.3%	0.0%	14.3%	28.6%	0.0%
Anti NMDAr, Anti mGluR5	1	1	0	0	0	0	0
	100.0%	100.0%	0.0%	0.0%	0.0%	0.0%	0.0%
CASPR 2	0	0	0	0	0	0	1
	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	100.0%
LGI 1 antibody	0	0	0	1	0	0	0
	0.0%	0.0%	0.0%	100.0%	0.0%	0.0%	0.0%
Negative	1	1	0	0	1	2	0
	7.7%	7.7%	0.0%	0.0%	7.7%	15.4%	0.0%

Table 18: presenting symptoms at follow up for each autoimmune profile

Autoimmune profile	Expired	Mild ataxic gait	Occasional dyskinesia	Occasional lip smacking	Symptom free
Anti AMPAr Antibody	1	0	0	0	0
	100.0%	0.0%	0.0%	0.0%	0.0%
Anti GABAA	0	0	0	0	2
	0.0%	0.0%	0.0%	0.0%	100.0%
Anti GABAB	0	0	0	0	1
	0.0%	0.0%	0.0%	0.0%	100.0%
Anti LGI	0	0	0	0	1
	0.0%	0.0%	0.0%	0.0%	100.0%
Anti mGluR 5	0	0	0	0	1
	0.0%	0.0%	0.0%	0.0%	100.0%
Anti mGluR1	0	1	0	0	0
	0.0%	100.0%	0.0%	0.0%	0.0%
Anti NMDA	0	0	1	0	6
	0.0%	0.0%	14.3%	0.0%	85.7%
Anti NMDAr, Anti mGluR5	0	0	0	1	0
	0.0%	0.0%	0.0%	100.0%	0.0%
CASPR 2	0	0	0	0	1

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	0.0%	0.0%	0.0%	0.0%	100.0%
LGI 1 antibody	0	0	0	0	1
	0.0%	0.0%	0.0%	0.0%	100.0%
Negative	3	0	0	0	10
	23.1%	0.0%	0.0%	0.0%	76.9%

DISCUSSION

Encephalitis refers to an inflammatory disorder of the brain resulting in altered mentalstatus, seizures, or focal neurologic deficits, and is usually accompanied by inflammatory signs in the cerebrospinal fluid with mostly normal to extensive abnormal magnetic resonance imaging (MRI) findings. Autoimmune encephalitis is caused by a misdirected immune response against the antigens within in the central nervous system. The presentation of associated AE syndromes varies with the antibody.[6]

Target antigens have diverse roles in neuronal function, including- synaptic transmission/ plasticity (AMPA, GABA, mGluR5, mGluR1, NMDA, dopamine, glycine receptors, LGI1), clustering of ion channels (Caspr2), and modulation of potassium channels and somato-dendritic signal integration (DPPX). The correlation of patients' symptoms with antibody titres (mostly CSF), and their reversibility have suggested a primary pathogenic role of the antibodies for several syndromes. For example, patients' antibodies to NMDA receptors cause a titre dependent, reversible decrease of synaptic and extra synaptic NMDA receptors which occurs through capping, crosslinking, and internalization.[7]

Anti-AMPA receptor antibodies affect function through similar mechanisms, causing a reversible decrease in synaptic AMPA receptors. GABAA receptor antibodies on the other hand, disrupt their signalling by reducing their density in synapses significantly, rather than at extra synaptic sites, thus suggesting an antibody-mediated relocation of receptors from synaptic to extra synaptic sites instead of a total removal of receptors.[8]

Due to this widely variable spectrum with clinical features mimicking other pathologic processes, autoimmune encephalitis often poses a diagnostic challenge. Antibody testing is not readily accessible, whose results can take several weeks; moreover, the mere absence of autoantibodies does not exclude the possibility of the disorder being immune mediated. Hence, a thorough knowledge of the clinical profile of various antibody types is crucial, for, a prompt and timely treatment impacts the outcome considerably.[9]

We evaluated the clinical profile of 30 AE patients, along with their serum autoantibody testing, MRI and EEG. AE is known to affect people of different age varying from 2-80 years. The age range of 2-70 years in our study matched with the existing literature, with a mean age of 29.6 years. A study by Kamble et al also found a similar mean age of 28.05 years for 16 patients with AE. Another study by Pandit et al, also found a mean age of 24 years in their sample of AE patients. The following is a summary of the age range found in different studies.

Some of the relevant risk factors for encephalitis as suggested by Lancaster et al include- lymphomatous/carcinomatous tumors and paraneoplastic syndrome-based tumors; relapse of initial encephalitis, secondary autoimmune causes, and opportunistic infections in patients with compromised immunity. In the current study, Medulloblastoma, a past history of AIE, and treated prostatic carcinoma were found in 3.3% of the patients each; whereas hypothyroid was found in 6.6%.[10]

CSF findings like leukocytic pleocytosis, increased protein, and glucose, might reveal an inflammatory origin for neurologic manifestations, suggestive of AE, thus helping in its diagnosis prior to the other test results. We measured the CSF protein levels, cell count, and glucose levels and found that the protein measure was well within the normal limits (43.83 mg/dl); CSF glucose/plasma glucose of <2/3 in 16.6%; and lymphocyte predominance was noted in 40%. In a study by Dubey et al, CSF was with normal protein and cell count in 36.7%, with a median CSF protein of 42.4 mg/dl- in line with our study. Kamble et al found that one patient with NMDA type had lymphocytic predominance, and normal protein and sugar; while three patients with other subtypes had mildly elevated protein with normal cell count and sugar. Saraya et al also found a normal CSF protein level of 26.5mg/dl.

The laboratory diagnosis of autoimmune encephalitis can be done through detection of auto Abs, EEG, MRI, functional neuroimaging, and a look-out for systemic tumors- all of which help in its differential diagnosis. The appropriate diagnostic approach that best suits a specific situation can be selected after weighing the advantages and drawbacks of each.

CONCLUSION

Recognition of rapidly emerging autoimmune encephalitis is pivotal for a prompt treatment with subsequent favourable outcomes. Evaluation should often begin with a detailed history taking and physical examination for an understanding of the specific causes. Auxiliary investigations- MRI and EEG may further support a diagnosis of encephalitis. Treatment should depend on the pathophysiology of the disorder- whether T-cell-mediated or antibody mediated, apart from the clinical situation of the patient. Patients with relapse should receive appropriate follow-up care. Further studies on the effect of type and duration of treatment on outcome are recommended.

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