DOI: https://doi.org/10.53350/pjmhs20221612194

ORIGINAL ARTICLE

Various Phenotypes related with Epilepsy in Autoimmune Encephalitis

LAL CHAND DHINGRA[1], DEEPAK KUMAR[2], ZUHAIB AHMED SOOMRO[3], ABDUL GHAFOOR MAGSI[4], NAJAM-US-SAQIB ANSARI[5], ISHFAQUE AHMED SIMAIR[6]

[1]Associate Professor & HOD, [2,3,5]Assistant Professors of Neurology, [6]Consultant Neurosurgeon, Ghulam Muhammad Mahar Medical College, Sukkur

[4]Associate Professor, Department of Neurology, Chandka Medical College @ Shaheed Mohtarma Benazir Bhutto Medical University, Larkana

Correspondence to Dr. Deepak Kumar, E-mail: dr.deepakbadlani@gmail.com Cell: 0332-2732543

ABSTRACT

Aim: To observe and analyses the epileptic phenotypes in autoimmune encephalitis ranging from acute symptomatic-seizures to autoimmune related epilepsy.

Study design: Retrospective-observational cohort study

Place and duration of study: Ghulam Muhammad Mahar Medical College Sukkur and Shaheed Mohtarma Benazir Bhutto Medical University Larkana from 1st August 2020 to 30th September 2021.

Methodology: One hundred and twenty seven patients who were enrolled with a new onset of seizures in reference to autoimmune encephalitis. Clinical as well as through para-clinical tests, including electroencephalogram, cerebrospinal fluid/neuroimaging techniques including magnetic resonance index or fluorine-18-fluorodeoxyglucose positron-emission tomography/computed tomography was used for confirming the cases. Each patient underwent anti-nuronal antibody test and was grouped as positive or negative for the test and clinically compared.

Results: There were 66 (51.96%) females and 61 (48.04%) males with mean age was 54±5.5 years. There were 62.9% cases who were having anti-neuronal antibodies as positive while 37.1% had a negative result. Majority of the positive group had multiple type seizures whereas SE was more common in negative group cases. There were 111 (87.4%) cases were given immunotherapy. Within these 111 cases the immunotherapy was effective in 60% of the cases. There were 81% cases with psychological as well as cognitive disturbances with 43.75% having long term sequel. The most common phenotype for seizure was focal impaired awareness seizures followed by focal bilateral tonic clonic seizures.

Conclusion: Early onset of immunotherapy and recognition of seizures may avoid long term irreversible outcomes of sequela.

Key words: Epileptic phenotype, Autoimmune encephalitis, Acute symptomatic seizure, Autoimmune associated epilepsy

INTRODUCTION

Epilepsy is a common neurological problems affecting millions of people worldwide. Its symptoms can be controlled with antiepileptic treatment, despite of it, more than 30% of the epileptic patient's experience seizures throughout their lifetime.1 Autoimmune encephalitis is an auto-immune disorder in which body' own defence cell start attacking healthy brain cell leading to inflammation of brain. Autoimmune encephalitis is a serious condition in which acute symptomatic seizures are the secondary condition which is commonly associated with this condition. Epileptic seizures can also be secondary to autoimmune brain disorders[2]. Neural antibodies are mostly used as a detection strategy for autoimmune encephalitis. These antibodies mainly target cell surface receptors including ion channels and synaptic receptors[3-5].

Chances of autoimmune encephalitis are any folds higher in patients who had intracellular neuronal antibodies as compared to surface antibodies. Many studies have proved that, autoantibodies against surface antigens are directly involved in the development and progression of acute symptomatic seizures. A key diagnostic strategy is to obtain cerebrospinal fluid for the detection of neuronal antibody[6-8]. Various treatment strategies have been adopted to control seizures development. Good immunosuppressant is mostly considered primary treatment that not only minimizes the chances of seizures but also reduce the requirement of lifelong anti-seizure medications[9-11].

Present study was designed to evaluate the incidence of autoimmune encephalitis in consideration with epilepsy. Long term outcomes and consequences were also documented for better understanding and close look into the disease condition. Treatment at pathogenic level and early detection may reduce the long term and lifelong irreversible sequelae.

MATERIALS AND METHODS

This retrospective-observational cohort study was conducted at Ghulam Muhammad Mahar Medical College Sukkur and Shaheed Mohtarma Benazir Bhutto Medical University Larkana from 1st August 2020 to 30th September 2021. After IRB permission 127 patients were enrolled in this study depending upon the inclusion criteria. The sample size was generated through WHO calculator for sample size which referred to 80% power of test and 95% CI with 5% margin of error. The inclusion criteria consisted of an age between 5-75 years with a new onset of seizures in reference to autoimmune encephalitis. The autoimmune encephalitis was confirmed through clinical and biochemical assessments such as distorted consciousness and attention, hallucinations occurrence or being delusional, altered-circadian rhythm, as well as through para-clinical tests, determined through EEG, CSF study/ neuroimaging techniques including MRI or through the Fluorine-18-fluorodeoxyglucose positron-emission tomography/ computed tomography (18F-FDG PET/CT). Seizures classification was done through International League-Against Epilepsy 2017 operational-classification regarding type of seizure. Those patients who were suffering from epileptic seizures without the clinical diagnosis of autoimmune involvement were not included in this study. Each patient underwent anti-nuronal antibody test. The tests included, all antibody test including onco-neural antibody against NSA, GAD antibody. As well as anti-neuronal antibodies against Tr, Hu, Yo, Ma, amphyphysin, CV2 or CRMP5, SOX-1 as well as Zic4. N-methyl-D-aspartate receptor (NMDAR), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), γ-aminobutyric acid receptor (GABABR), and dipeptidyl-peptidase-like protein-6 (DPPX) were also performed. Depending upon the anti-neuronal antibody tests findings the patients were divided into two groups as +ve group and –ve group. A complete clinical and preclinical assessment were conducted in both groups and compared. Phenotype determination related to autoimmune encephalitis was observed. Radiological assessments including brain CT scanning was performed routine wise. Depending upon radiological and EEG assessment results patient's clinical history was generated. Patients were prescribed immunotherapy and the results were followed up. A complete psychiatric assessment was performed in follow up of the patients and outcomes of immunotherapy were documented. A detailed documentation of epileptic medication and all other clinical as well as demographic variables was carried out through application of a well-structured proforma. Data was analyzed by using SPSS-26.0 where Chi square test was performed. P value <0.05 was taken significant for the test.

Received on 23-07-2022
Accepted on 12-11-2022

RESULTS

There were 66 (51.96%) females and 61 (48.03%) males with mean age were 54±5.5 years. There were 62.9% cases that were having anti-neuronal antibodies as positive while 37.1% had a negative result. Majority of the +ve Group had multiple type seizures whereas SE was more common in –ve group cases (Table 1).

There were 111(87.4%) cases were given immunotherapy, within these 111 cases the immunotherapy was effective in 60% of the cases while early immunotherapy was given in 55% of cases. There were 84% those cases from the 111 patients who were only given first line immunotherapy while 46% were also given second line immunotherapy (Fig. 1).

The independent-predictors for the development of seizures included difficulty in treatment of seizure especially at the onset with a p value as 0.04. Moreover, anti-seizure medications which persisted interictal-epileptic as well as inefficient response to immunotherapy were some of the major factor for development of seizures. There were 81% cases with psychological as well as cognitive disturbances with 43.75% having long term sequel (Fig. 2). The most common phenotype for seizure was FIAS followed by BTCS at onset as well as at follow-ups (Table 2).

The MRI scan of patients showed various results as presence of autoimmune encephalitis was observed as a result of NMDAR antibodies in a patient with FLAIR sequences with bilateral-amygdala and involvement of left hippocampus hyper-insensitivities and increase in the volume of both structures. The early EEG confirmed the same. After the resolution of autoimmune encephalitis persistence in hyper-intensity was observed with hippocampal atrophy development. bipolar montage observed presenting IED over left fronto-temporal region (Fig. 3).

Table 1: Anti-neuronal antibodies presence and clinical characteristics

Variables	Anti-neuronal antibodies				P value
	+ve Group (n=80)		-ve Group (n=47)		
	No.	%	No.	%	
Type of Antibody					
Anti-GAD	15	18.8	--	--	--
Anti-NMDAR	50	62.5	--	--	--
Anti-LGI1 or VGKC	12	15.0	--	--	--
Paraneoplastic (anti-Yo)	3	3.75	--	--	--
Type of Seizures					
Multiple	72	90	18	38.29	0.0015
Prevalent temporal involvement	75	93.7	10	21.2	0.0002
SE	35	43.7	46	97.8	0.049

Table 2: Distribution of various seizure types (n=127)

Variables	No.	%
Seizure types		
BTCS	26	20.47
FAS	18	14.1
FIAS	75	59.0
FBDS	7	5.5
Aphasic seizure	1	0.78
Seizure types in follow up		
BTCS	40	31.5
FAS	25	19.6
FIAS	45	35.43
FBDS	17	13.3

Fig. 1: Immunotherapy deliverance and efficiency

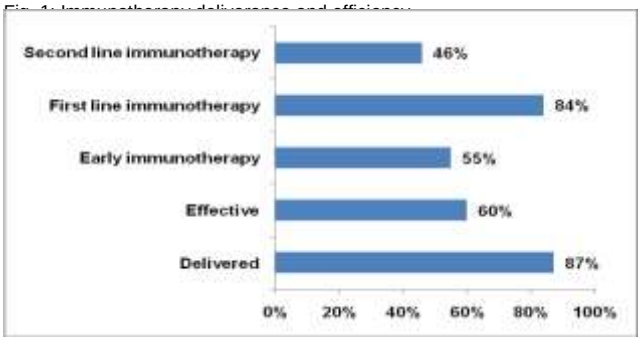


Fig. 2: Prevalence of psychological disturbances and long term effects

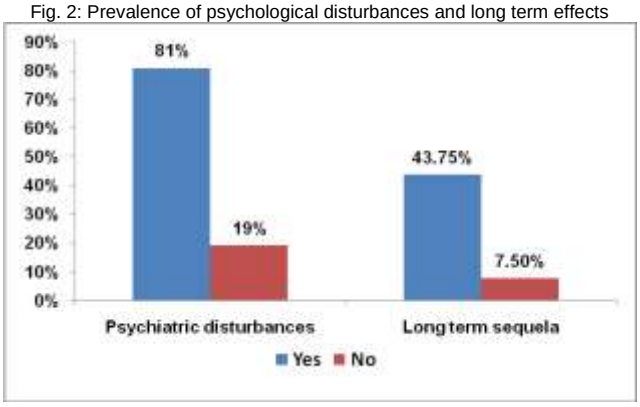
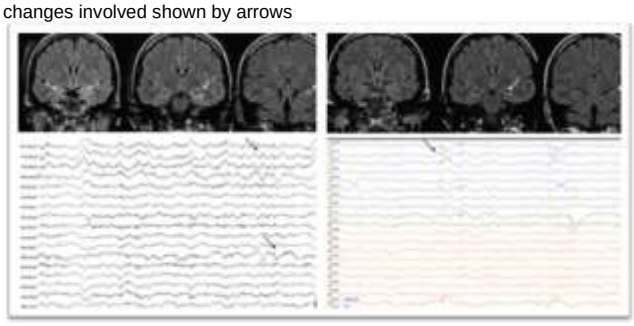


Fig. 3: Autoimmune encephalitis presentation through MRI and EEG and changes involved shown by arrows



DISCUSSION

There are various studies which has reported the development of the autoimmune encephalitis in patients. The risk of development of epileptic seizures has been reported as 42.11% in cases of autoimmune encephalitis. This chance of epileptic seizure is highest within the first 12 months as reported in the literature[12,13]. A study by Shen et al[14] in 2020 reported the risk to be higher as 72.73% within the first year. The present study has reported all such cases of epileptic seizures up to the development of autoimmune related epilepsy in the patient.

The major risk in development of epilepsy is hippocampal-atrophy at follow-up as similar has been observed in various researches as well as present study[14,15]. This risk of development is further added on in cases where immunotherapy has not been introduced at early stages. Therefore, causing a delay increases the risk of epilepsy development[16,17].

There are studies which have also identified specified types of antibodies which were more associated with the development of epileptic seizures. In our study the major type of antibodies found was anti-NMDAR and anti-GAD. Anti-GAD has been related with the formation of epileptic seizures in various reports[17].

The causes of epilepsy are worst observed in elderly population. The current research also reported majority of the cases to be in above 50 years of their age. Stroke being the major reason of epilepsy in this population with a reported incidence as 2-20% with hemorrhagic stroke been the most prevalent reason[18-21].

CONCLUSION

Early onset of immunotherapy and recognition of seizures may avoid long term irreversible outcomes of sequela. The severity of seizures as observed at onset are the main factor need to be managed for preventing chronic epilepsy in patients.

Conflict of interest: Nil

REFERENCES

1. Epilepsy. World Health Organization website.www.who.int/newsroom/fact-sheets/detail/epilepsy. Accessed November 10, 2020.
2. Steriade C, Britton J, Dale RC, Gadoth A, Irani SR, Linnoila J, et al. Acute symptomatic seizures secondary to autoimmune encephalitis and autoimmune associated epilepsy: conceptual definitions. Epilepsia 2020; 61(7):1341-51.
3. Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Celluci T, et al. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol 2016;15(4):391-404.
4. Irani SR, Michell AW, Lang B, Pettingill P, Waters P, Johnson MR, et al. Faciobrachial dystonic seizures precede Lgi1 antibody limbic encephalitis. Ann Neurol 2011;69(5):892-900.
5. van Sonderen A, Schreurs MW, de Bruijn MA, Bouhrissi S, Nagtzaam MMP, Hulseenboom ESP, et al. The relevance of VGKC positivity in the absence of LGI1 and Caspr2 antibodies. Neurology 2016; 86(18):1692-9.
6. Dubey D, Singh J, Britton JW, Pittock S, Flanagan EP, lenon VA, et al. Predictive models in the diagnosis and treatment of autoimmune epilepsy. Epilepsia 2017; 58(7):1181-9.
7. Herdlevaer I, Kråkenes T, Schubert M, Vedeler CA. Localization of CDR2L and CDR2 in paraneoplastic cerebellar degeneration. Ann Clin Transl Neurol 2020;7(11):2231-42.
8. Quek AM, Britton JW, McKeon A, So E, Lennon VA, Shin C, et al. Autoimmune epilepsy: clinical characteristics and response to immunotherapy. Arch Neurol 2012;69(5):582-93.
9. Dubey D, Pittock SJ, McKeon A. Antibody prevalence in epilepsy and encephalopathy score: increased specificity and applicability. Epilepsia 2019;60(2):367-9.
10. Thompson J, Bi M, Murchison AG, Makuch M, Bien CG, Chu K, et al. The importance of early immunotherapy in patients with faciobrachial dystonic seizures. Brain 2018;141(2): 348-56.
11. Thompson J, Bi M, Murchison AG, Makuch M, Bien CG, Chu K, et al. The importance of early immunotherapy in patients with faciobrachial dystonic seizures. Brain 2018; *141*(2): 348-56.
12. Gifreu A, Falip M, Sala-Padró J, Mongay N, Morandeira F, Camins Á, et al. Risk of Developing Epilepsy after Autoimmune Encephalitis. Brain Sci 2021;11(9):1182.
13. Spatola M., Dalmau J. Seizures and risk of epilepsy in autoimmune and other inflammatory encephalitis. Curr Opin Neurol 2017;30:345-53.
14. Shen CH, Fang GL, Yang F, Cai MT, Zheng Y, Fang W, et al. Seizures and risk of epilepsy in anti-NMDAR, anti-LGI1, and anti-GABABR encephalitis. Ann Clin Transl Neurol 2020;7:1392-9.
15. Heine J, Prüb H, Scheel M, Brandt AU, Gold SM, Bartsch T, et al. Transdiagnostic hippocampal damage patterns in neuroimmunological disorders. Neuro Image Clin 2020;28:102515.
16. Dubey D, Singh J, Britton JW, Pittock SJ, Flanagan E, Lennon VA, et al. Predictive models in the diagnosis and treatment of autoimmune epilepsy. Epilepsia 2017;58:1181-9.
17. Dubey D, Farzal Z, Hays R, Brown LS, Vernino S. Evaluation of positive and negative predictors of seizure outcomes among patients with immune-mediated epilepsy: a meta-analysis. Ther Adv Neurol Disord 2016;9:369-77.
18. Vezzani A, Fujinami RS, White HS, Preux PM, Blümcke I, Sander J, et al. Infections, inflammation and epilepsy. Acta Neuropathol 2016;131:211-34.
19. Myint PK, Staufenberg EF, Sabanathan K. Post-stroke seizure and post-stroke epilepsy. Postgrad Med J 2006;82:568-72.
20. Lühdorf K, Jensen LK, Plesner AM. Etiology of seizures in the elderly. Epilepsia 1986;27:458-63.
21. Olsen TS. Post-stroke epilepsy. Curr Atheroscler Rep 2001;3:340-44.