Mohamed *et al.*
*Egypt J Neurol Psychiatry Neurosurg (2023) 59:83*
https://doi.org/10.1186/s41983-023-00685-9

The Egyptian Journal of Neurology, Psychiatry and Neurosurgery

RESEARCH

Open Access

# Neuronal autoantibodies in a sample of Egyptian patients with drug-resistant epilepsy

Hadeer Mohamed[1*], Mahmoud Hemeda[1], Ahmed Gaber[1], Hany Zakieldine[1], Salwa Ibrahim Bakr[2], Abeer Shehab[2], Nesrine Mohamed[2], Hala A. Talkhan[2], Dina Elshennawy[2], Marwa Rushdy[2], Doaa M. Abdelaziz[2], Yara Masry[2], Ahmed Magdy Tohamy[2] and Mona Wahid El Din[1]

## Abstract

**Background** Epilepsy is one of the most common and chronic neurological diseases. About one-third of epilepsy patients do not achieve seizure freedom despite adequate therapy with antiseizure medications (ASMs) and develop drug-resistant epilepsy (DRE). Autoimmunity is increasingly being recognized as a cause of epilepsy in those patients. Some cases are associated with antibodies against several target antigens, including neuronal extracellular proteins as well as intracellular structures. In such patients, immunotherapy may be highly effective. This study aimed to investigate the presence of NMDA-R, AMPA1-R, AMPA2-R, CASPR2, LGI1, GABAB-R, and GAD65 autoantibodies in a sample of Egyptian patients with new-onset DRE; also, to assess the clinical, cerebrospinal fluid (CSF), electroencephalogram (EEG), and radiological characteristics of those patients. Twenty-five patients with recent onset DRE were recruited from the department of Neurology at Ain Shams University (ASU) hospitals. All patients underwent serum and CSF antibody testing using cell-based assay (CBA) at the Immunology unit of the Clinical pathology laboratory at ASU hospitals. This is beside routine CSF analysis, EEG and MRI brain with contrast.

**Results** Out of 25 patients with recent onset DRE, one (4%) patient tested positive to anti-NMDA-R antibodies and another one (4%) tested positive to anti-GAD 65 in both serum and CSF. Although the remaining 23 patients tested negative for the 7 autoantibodies, yet 92% of them achieved either seizure freedom or more than 50% reduction in the frequency of seizure and 84% had marked improvement in seizure-associated symptoms after receiving immunotherapy trial. Also, evidence of neuroinflammation was detected in the CSF and MRI brain of the majority of those patients.

**Conclusions** Autoimmunity should be considered as a possible etiology of new-onset DRE. It is essential to provide insight into the clinical phenotypes and other associated features of those patients, as there are probably numerous patients who are not positive for one of the available antibodies via clinical laboratory testing. In addition to early diagnosis, early treatment and empirical immunotherapy trial based on the clinical judgment is crucial and is likely to improve outcomes with near-complete seizure freedom.

**Keywords** Autoimmune epilepsy, Drug-resistant epilepsy, Autoantibodies, Immunotherapy, Antiseizure medications

*Correspondence:
Hadeer Mohamed
Hadeer_mohamed@med.asu.edu.eg
Full list of author information is available at the end of the article

## Background

Epilepsy is one of the most common and chronic neurological diseases, there were about 50 million people diagnosed with epilepsy worldwide in 2016. The Global Burden of Disease study classifies epilepsy as the second most burdensome neurological disease regarding the disability-adjusted life years, it resulted in 18.3 million years lost due to disability in 2019 and more than 125,000 deaths each year [1].

About one-third of epilepsy patients develop DRE. Those patients do not achieve seizure freedom despite medical therapy with adequate trials of two tolerated, appropriately chosen ASMs whether as monotherapy or in combination [2, 3]. Drug-resistant epilepsy further increases the disease burden, as it results in increased morbidity and lower quality of life than in patients with controlled epilepsy [4].

Different explanations for the pathophysiology of DRE have been proposed including medication tolerance, neuroinflammation and alterations in the integrity of the blood–brain barrier [3], also, there has been increasing evidence that immune mechanisms underlie the pathogenesis of some types of intractable epilepsy [5].

Autoantibodies have been identified as an underlying cause of unexplained drug-resistant epilepsy, and a link between autoimmunity and epilepsy has been suggested [6]. Besides the lowered seizure threshold caused by inflammation, a direct epileptogenic role has been approved for many of those autoantibodies, especially those targeting neuronal extracellular antigens [7].

Autoimmune epilepsy (AE) has been associated with autoantibodies that target both *intracellular proteins* as glutamic acid decarboxylase (GAD65) and onconeural antigens, and *cell surface antigens* as N-methyl-D-aspartate receptor (NMDAR), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), gamma-aminobutyric acid B1 subunit (GABA-B), voltage-gated potassium channel complex (VGKC) including leucine-rich glioma-inactivated 1 (Lgi1) and contactin-associated protein-like 2 (Caspr2) [8, 9].

The International League Against Epilepsy (ILAE) currently classifies AE as a distinct entity in their epilepsy classification, it's an epilepsy that results from an immune disorder in which seizures are a core symptom of the disorder [10]. Intractable seizures in AE patients may occur as one of a number of other autoimmune encephalitis features as behavioral changes, cognitive impairments, and movement disorders, which if found would help early diagnosis. However, in some patients, seizures are the main symptoms and other features of encephalitis are not existing, which can cause delay in diagnosis.

Valuable clinical clues of AE diagnosis include acute or subacute onset of an unusually high seizure frequency, multiple seizures per day, intraindividual seizure variability or multifocality, shorter seizure duration, ASMs resistance [11]. Pilomotor autonomic seizures often occur (especially when there are Abs to LGI1, Hu, and Ma). Also, facial brachial dystonic seizures (FBDS) are common seizure type in LGI1 AE [12]. A previous study observed that new-onset refractory status epilepticus (NORSE) occurred in almost half of the patients (47%) with autoimmune etiologies (37%, with positive antibodies, 19% non-paraneoplastic and 18% paraneoplastic). These results indicate that it is possible to consider NORSE as potentially AE that requires early immunotherapy [13, 14].

Although one of the features of this type of epilepsy is that it is usually resistant to ASMs, it generally responds better to targeted immunotherapies in combination with ASMs. Therefore, it is crucial to make early diagnosis, for initiation of immunotherapy which can decelerate or even reverse the epileptogenic process in those patients and leads to a better outcome [15].

The present study aimed to investigate the presence of 7 different autoantibodies (NMDA-R, AMPA1-R, AMPA2-R, GABAB-R, CASPR2, LGI1 and GAD65) in a sample of Egyptian patients with new-onset DRE; also, to assess the clinical, CSF, EEG, and radiological characteristics of those patients.

## Methods

### Study design and participants

This is an observational, cohort study that included a sample of 25 drug-resistant epilepsy patients recruited from the Department of Neurology at ASU hospitals. All patients were diagnosed with DRE based on the ILAE consensus [16] and all were newly diagnosed (within 12 months of onset). Patients were excluded from the study if there was evidence of other causes which could have precipitated the seizures such as the presence of brain structural lesions or metabolic abnormalities. Also, patients with false refractoriness (e.g., non-compliance–ASMs not appropriately chosen–low dose ASMs–drugs that can lower the seizures threshold) were excluded.

All patients were subjected to full clinical assessment and detailed history taking regarding age, family and past history including history of autoimmune diseases and neoplasia, history of present illness including, seizure semiology and frequency, seizure-associated symptoms, latency from onset to start of treatment, received ASMs and immunosuppressive therapies and outcome 3 months after completion of immunotherapy trial.

All patients underwent serum and CSF antibody testing, samples were sent to the Immunology unit at the Clinical pathology laboratory of ASU hospitals and tested for (anti-NMDA-R–anti-AMPA1-R–anti-AMPA2-R–

Anti-CASPR2–anti-LGI1–anti-GABAB-R–anti-GAD 65) antibodies using indirect immunofluorescence cell-based assay CBA. This is beside routine CSF analysis, EEG and MRI brain with contrast.

### Statistical analysis

For adequate assessment and evaluation of outcome, Data were collected, coded and entered to the Statistical Package for Social Science (SPSS) version 23 for analysis. Descriptive analysis of the qualitative data was calculated using the frequency and percentage statistics which count the number of times that each variable occurs and were expressed as number (*n*) and percentage (%), while the quantitative data were presented using the mean and standard deviation.

## Results

### Demographic data and medical history

The mean age of patients was 31.200 ± 17.229 years. Fifteen (60%) patients were males, while 10 (40%) patients were females. Three (12%) patients had history of autoimmune disorders (one patient was diagnosed with Behcet's disease, another was diagnosed as autoimmune thyroiditis and the third had rheumatoid arthritis). One (4%) patient discovered to be Hodgkin lymphoma at follow-up, 2 months after being diagnosed anti-GAD 65 positive. None of the patients had family history of epilepsy, 1 (4%) patient had family history of psoriatic arthritis in mother, and 1 (4%) patient had family history of breast cancer in mother.

### Clinical data

Seizures refractory to ASMs were the first presenting symptoms in 19 (76%) patients, majority of patients (76%) had focal seizure, with high frequency (daily in 56%, status epilepticus (SE) in 16% and refractory status epilepticus (RSE) in 8%). Details of clinical characteristics are displayed in Table 1.

### Electroencephalography and radiological data

EEG showed abnormalities in 88% of the patients that was focal epileptiform activity with/without 2nd generalization in near half of the patients (48%), and MRI brain with contrast showed evidence of neuroinflammation in 72% of the patients, as summarized in Table 2**.**

### Laboratory data

Patients underwent serum and CSF antibody testing for 7 neuronal autoantibodies (anti-NMDA-R–anti-AMPA1-R–anti-AMPA2-R–anti-CASPR2–anti-LGI1–anti-GABAB-R–anti-GAD 65). One (4%) patient tested positive to anti-NMDA antibodies and another one (4%) tested positive to anti-GAD 65 in both serum and CSF.

**Table 1** Clinical characteristics of the studied patients

| | *N* | % |
|---|---|---|
| First presenting symptom | | |
| Refractory seizures | 19 | 76.00 |
| Psychiatric changes | 5 | 20.00 |
| Cognitive dysfunction | 3 | 12.00 |
| Movement disorder | 2 | 8.00 |
| Seizure associations | | |
| None | 7 | 28.00 |
| Psychiatric | 12 | 48.00 |
| Cognitive | 8 | 32.00 |
| Movement disorder (tremor, dystonia) | 5 | 20.00 |
| Dysautonomia | 2 | 8.00 |
| Seizure type | | |
| Focal motor onset | 5 | 20.00 |
| Focal non-motor onset (autonomic) | 1 | 4.00 |
| Focal with impaired awareness | 3 | 12.00 |
| Focal to bilateral tonic clonic | 11 | 44.00 |
| Generalized (tonic clonic/myoclonic) | 6 | 24.00 |
| Frequency | | |
| Daily | 14 | 56.00 |
| Weekly | 5 | 20.00 |
| Status epilepticus (SE) | 4 | 16.00 |
| Refractory status epilepticus (RSE) | 2 | 8.00 |

**Table 2** Electroencephalography and radiological data of the studied patients

| | *N* | % |
|---|---|---|
| Electroencephalogram (EEG) | | |
| Normal | 3 | 12.00 |
| Focal/generalized slowing | 6 | 24.00 |
| Focal epileptiform activity with/without 2nd generalization | 12 | 48.00 |
| Generalized epileptiform activity | 4 | 16.00 |
| Periodic lateralized epileptiform discharge (PLEDs) | 2 | 8.00 |
| Diffuse dysrhythmia | 1 | 4.00 |
| Extreme delta brush | 2 | 8.00 |
| Magnetic resonance imaging (MRI) | | |
| Normal | 7 | 28.00 |
| T2/FLAIR hyperintense lesions in medial temporal/bitemporal | 9 | 36.00 |
| T2/FLAIR hyperintense cortical and/or subcortical lesions involving two or more brain regions | 6 | 24.00 |
| Non-specific T2/FLAIR hyperintensities | 3 | 12.00 |

Routine CSF analysis was normal in 8 (32%) patients, while 14 (56%) patients had elevated proteins, 4 (16%) patients had positive oligoclonal bands, 3 (12%) patients had increased IgG index and 2 (8%) patients had elevated lymphocytes (Fig. 1).

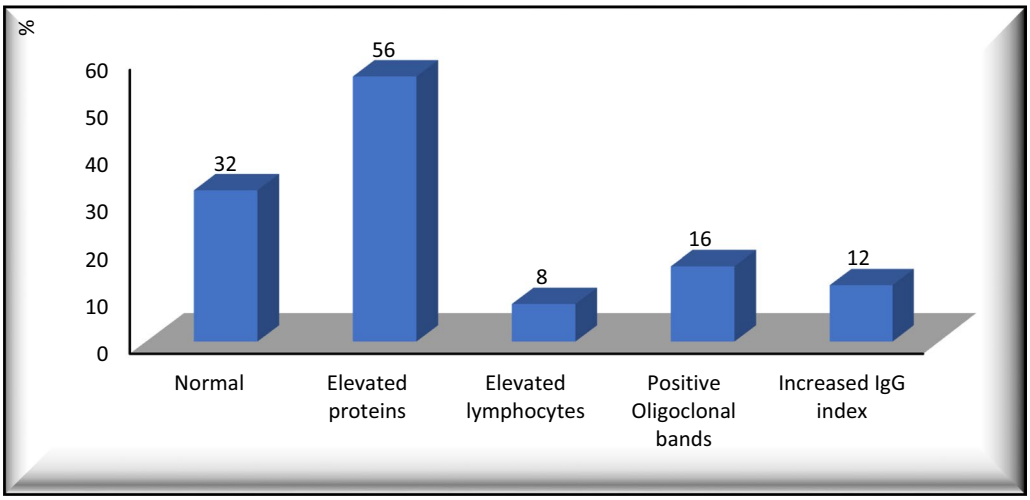


**Fig. 1** CSF data of the studied patients

### Antiseizure medications, immunotherapy and outcome

In the current study, all patients received ASMs and 88% of the patients received immunotherapy trial with first-line therapy. Regarding seizure outcome, 14 (56%) patients achieved seizure freedom, 9 (36%) patients had more than 50% reduction in seizure frequency and 2 (8%) patients showed no improvement after a mean of $19.82 \pm 6.14$ days from start of immunotherapy. Also, 84% of the patients showed marked improvement of the cognitive and psychiatric symptoms, as shown in Table 3.

**Table 3** Antiseizure medications, immunotherapy and outcome of the studied patients

| | *N* | % |
|---|---|---|
| Antiseizure medications (ASMs) | | |
| Carbamazepine | 16 | 64.00 |
| Phenytoin | 14 | 56.00 |
| Valproate | 12 | 48.00 |
| Levetiracetam | 8 | 32.00 |
| Lacosamide | 7 | 28.00 |
| Oxcarbazepine | 6 | 24.00 |
| Zonisamide | 5 | 20.00 |
| Eslicarbazepine | 4 | 16.00 |
| Topiramate | 4 | 16.00 |
| Clonazepam | 4 | 16.00 |
| Lamotrigine | 3 | 12.00 |
| Immunomodulatory treatment | | |
| (Intravenous methylprednisolone) IVMP | 20 | 80.00 |
| (Intravenous immunoglobulin g) IVIg | 5 | 20.00 |
| Plasma exchange (PLEX) | 6 | 24.00 |
| Oral prednisolone | 2 | 8.00 |
| None | 3 | 12.00 |
| Seizure outcome | | |
| Seizure freedom | 14 | 56.00 |
| 50% reduction in seizure frequency | 9 | 36.00 |
| No improvement | 2 | 8.00 |
| Seizure-associations outcome | | |
| None | 21 | 84.00 |
| Residual cognitive affection | 3 | 12.00 |
| Residual personality changes | 1 | 4.00 |

## Discussion

Autoimmune epilepsy should be considered among the possible etiologies of patients presenting with unusually high seizure frequency, variability of seizures semiology, resistance to ASMs, presence of an autoimmune disease in the person or his/her family, history of cancer or viral prodroma, demonstration of CNS inflammation in investigations.

Neuronal autoantibodies are important diagnostic markers of AE that is helpful to confirm the diagnosis. Moreover, early detection of antibodies would help early start of targeted immunotherapy in patients who are likely to show favorable response to it. However, diagnosing AE is delayed due to several causes, including factors related to the availability, sensitivity, and specificity of antibody testing, especially with variability in the used techniques and the new antibodies being rapidly discovered. Also, the non-specific findings of MRI, EEG, and CSF, and the challenging differential diagnoses [17].

The present study included 25 patients with new-onset DRE who were subjected to CBA of both serum and CSF to detect 7 different autoantibodies. All patients were tested negative except 2 patients, one tested positive to anti-NMDA-R antibodies and the other was positive to anti-GAD 65 antibodies, representing 8% of the studied sample. This is consistent with findings of a study by McGinty and his colleagues, where only 10.5% of patients

with new-onset DRE had positive serum autoantibodies to either known or novel surface antigens [18].

Similarly, in a study by Elisak and his colleagues who investigated the neuronal antibodies and clinical features in patients with chronic temporal lobe epilepsy. Neuronal antibodies (3 GAD, 2 CASPR-2) were detected in only 5% of serum and 2.5% of CSF of 165 patients [19]. This also has an agreement with the findings of Lee and Lee in 2016 who collected more than 2500 samples over 3 years to create the Korea Autoimmune Synaptic and Paraneoplastic Encephalitis registry, and they found that the rate of positive antibodies testing was only 8.6% [20].

Those findings could be explained by that some cases of AE may not have any identifiable antibodies, that is to say are seronegative and this characterizes a disease category with novel, yet to be identified antibodies. This is supported by findings of earlier study by Lee and Lee where they discovered more than 10 patients with novel antibodies and suggested the presence of new neuronal autoantibodies not yet available in laboratory testing [20]. Other justifications include false-negative results caused by a low titer of antibody, presence of T-cell-dominant AE, or possibly those patients might have other autoantibodies that would be detectable if the scope of the present study had been expanded to involve a larger panel of neuronal autoantibodies. Also, the low number of patients is considered to be an important factor leading to this result.

The presence of antibody-negative AE was supported by the good response to immunotherapy trial in those patients, in the current study all but three patients received immunotherapy trial with first-line therapy, 92% of those patients became seizure free or had 50% reduction in seizure frequency after a mean of $19.82 \pm 6.14$ days from start of immunotherapy. Also, 84% of the patients showed marked improvement of the cognitive and psychiatric symptoms. This is consistent with the findings of Lee and colleagues study, who demonstrated that 44% of patients who were rituximab responders and showed functional improvement had autoimmune encephalitis without detectable autoantibodies and that the effect of rituximab was the same regardless of autoantibody status (patients with synaptic autoantibodies, paraneoplastic autoantibodies, and antibody-negative) [21].

Came in the same line another study conducted on patient who had antibody-negative intractable multifocal epilepsy, where EEG demonstrated almost continuous spiking from five different foci. After receiving IVMP and immunoglobulin, spiking terminated while still off ASMs and the patient remained free of seizure on immunotherapy [22].

The excellent immunotherapy outcomes independent of autoantibody positivity, suggests autoimmunity as the etiology or a responsible cause for ongoing epileptogenic process. So, diagnosis should not be dependent on antibody testing alone, a more structured approach and diagnostic criteria for concluding antibody-negative AE in clinical practice is strongly recommended. This is based on clinical history including seizure characteristics and semiology, cognitive and mood phenotypes, investigations and supportive diagnostic tests which include but should not be dependent on the antibody testing only, so that immunotherapy can be applied promptly to improve the prognosis.

Regarding the clinical data of the studied patients, the current study demonstrated that the first presenting symptom was seizures refractory to ASMs in 19 patients, representing 76% of the studied sample and that 7 (28%) patients had only refractory seizures without other features of encephalitis. This is consistent with a study by de Bruijn and colleagues who found that seizures were the main presenting symptoms in patients with anti-GABABR (76%), anti-LGI1 (61%), and anti-NMDAR (48%), and remained either the only or the most prominent clinical feature in 22% of anti-LGI1 and 9% of anti-NMDAR patients [23]. This also agrees with findings of a study conducted by McGinty and his colleagues on 2021, they recruited 219 patients with new-onset DRE, where 14/23 patients with detected neuronal autoantibodies had only refractory seizures without clinical diagnosis of encephalitis [18].

This is concordant with Quek et al. study who reported that one-third of AE patients recruited in their study presented only with seizures with no other features of limbic encephalitis. Although the remaining two-thirds had other neurologic symptoms as cognitive dysfunction and personality changes, high frequent daily seizures were their predominant concerns. These findings prompt considering an autoimmune etiology in patients with new-onset seizures, even when all the other features of autoimmune encephalitis are lacking [24].

Seizures in the current study were focal in the majority of patients (80%), with high frequency, as more than half of the patients had daily seizures, 16% had status epilepticus and 8% developed refractory status epilepticus and needed ICU transferal to start anesthesia. This is consistent with findings of a study by Quek and his colleagues in 2012, where focal seizures were the predominant clinical presentation in more than 80% of the autoimmune epilepsy patients and most patients (81%) received at presentation median of 3 ASMs, yet seizures were frequent and 81% of patients had daily seizures [24]. Findings of Lv and colleagues' study were in line with these results, as they found that 73% of AE patients had focal seizures, either simple or complex partial seizures, and 70% of patients had daily seizures [11].

The current study also found that 12 (48%) patients had psychiatric changes, 8 (32%) patients had cognitive dysfunction, 5 (20%) patients had movement disorders in the form of dystonic movements and tremor, and 2 (8%) patients had dysautonomia. This is concordant with findings of a study by Nass and his colleagues where AE patients had significantly higher rates of cognitive dysfunction such as impairment in memory and executive functions, when compared to other epilepsy patients ($p < 0.0001$) [25].

Another agreement came from findings of van Sonderen, et al. who demonstrated that no AE patients had only seizures without any other neurologic symptoms or signs all thorough examination. Patient either had "epileptic seizures plus" which involves patients with prominent seizures and only subtle neurological signs or "full blown limbic encephalitis" with predominant clinical features of limbic system involvement [26].

Regarding the received medications, 22 (88%) patients received immunotherapy with ASMs, and 3 (12%) patients received ASMs only and those 3 patients did not receive immunotherapy due to his/her own decision and as they showed partial decrease in seizure frequency after adjustment of therapy with ASMs. It was noticed that the partial response in seizure frequency and semiology in those patients was achieved after receiving ASMs with sodium channel blocking properties. The response to ASMs was seen within 5–6 weeks of the initiation of ASMs. This is consistent with a study by Dubey and his colleagues, which included a sample of 34 patients with AE, just two patients were treated with only ASMs, resulting in a significant reduction of seizure frequency in both cases [27]. Similarly, in a previous cohort, two patients became seizure-free by receiving ASMs only [24].

Came in the same line findings of previous clinical series conducted to assess efficacy of ASMs in patients with AE, where 10–15% of patients responded to ASMs and did not require immunotherapy for seizure control [9, 15]. This is important to keep in mind that a response to ASMs alone does not provide exclusionary evidence against an autoimmune etiology.

Regarding types of ASMs, the most commonly used drugs were carbamazepine (64%), phenytoin (56%), valproate (48%), levetiracetam (32%), lacosamide (28%), Oxcarbazepine (24%) and zonisamide (20%), and to lesser extent clonazepam, topiramate, eslicarbazepine and lamotrigine. It was observed that levetiracetam was the most commonly used drug at initiation of ASMs, the reason is likely due to lack of drug–drug interactions and availability in intravenous forms in our institutes for patients presenting with status epilepticus and cluster seizures. Although, majority of patients did not show satisfactory response and needed to be combined with or shifted to other ASMs particularly those with sodium channel blocking properties, upon which patients' seizure frequency improved. Yet, 3/8 patients who received Levetiracetam improved and continued on it as a monotherapy at follow-up and after completion of immunotherapy trial.

This is consistent with findings of a study by Cabezudo-García and his colleagues who found that a higher number of patients responded to sodium channel blockers than to levetiracetam, out of the 15 responding patients, 11 (73%) received ASMs with sodium channel blocking propertied. They also found that two patients responded to levetiracetam [15].

In another study that aimed to assess the efficacy of ASMs in patients with AE, initiation of carbamazepine (18.8%), lacosamide (16.6%), phenytoin (12.5%), or oxcarbazepine (18.1%) resulted in seizure freedom, while none of the patients became seizure free with levetiracetam [9]. Moreover, in the von Podewils study, which investigated 66 patients with epileptic seizures and suspected AE, they found that the only seizure-free patient after receiving ASMs only, reached this situation after adding a sodium channel blocker (lacosamide) to levetiracetam [28].

This has an agreement with a study by de Bruijn and colleagues who compared the efficacy and safety of various ASMs in patients with autoimmune encephalitis predominantly presenting with refractory seizures. Findings from this cohort study tend to suggest that sodium channel blockers, particularly carbamazepine, might be superior to other medications and should be favored [23].

Similarly, in the Quek and colleagues study, one of the two patients who became seizure-free after receiving ASMs only, achieved that after changing from levetiracetam to a sodium channel blocker (lamotrigine) [24]. This postulates a possible anti-inflammatory mechanism as a cause of higher efficacy of sodium channel blockers seen in AE. Also, this could be due to the effectiveness of sodium channel blockers in focal onset epilepsy which is seen in 80% of patients in our study. On the other hand, levetiracetam seems not preferable in patients with autoimmune epilepsy as it can exaggerate the behavioral changes and induce irritability in those patients.

However, this would appear contrary to the previous reports on the efficacy of levetiracetam and the potential anti-inflammatory mechanism attributed to it that was previously described in the literature [29, 30]. Also, levetiracetam was effective in seizure control as monotherapy for the two patients responding to ASMs in the Dubey study [27].

This study is limited by the small sample size, the restricted range of autoantibody testing, referral bias

could be present because patients were enrolled from a specialized tertiary epilepsy center. Finally, angiotensin converting enzyme (ACE) and full collagen battery for detection of sarcoidosis and other systemic autoimmune disorders highly associated with AE were not assessed in all patients in the study. Therefore, further investigations are urged for validation of the current evidence.

## Conclusions

In summary, it is important to consider autoimmunity as a possible etiology of new-onset intractable epilepsy. Some AE patients have specific autoantibodies to cell surface or intracellular targets. However, it is common for antibody testing to return negative, in such case clinicians must make a diagnosis based on a combination of clinical features and other supportive investigations rather than solely on antibodies testing. When clinical, serological and radiological clues suggest an autoimmune etiology for intractable epilepsy, early initiation of immunotherapy is crucial as AE is a reversible condition with a rapid response to immunotherapy. Besides management, immunotherapy responsiveness plays a major role in the diagnosis of AE, especially in seronegative cases.

#### Abbreviations

| | |
|---|---|
| ACE | Angiotensin converting enzyme |
| AE | Autoimmune epilepsy |
| AMPA | α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid |
| ASMs | Antiseizure medications |
| ASU | Ain Shams University |
| CASPR | Contactin-associated protein 1 |
| CBA | Cell based assay |
| CNS | Central nervous system |
| CSF | Cerebrospinal fluid |
| DRE | Drug-resistant epilepsy |
| EEG | Electroencephalogram |
| FBDS | Faciobrachial dystonic seizure |
| GABAB | Gamma-aminobutyric acid B subunit |
| GAD | Glutamic acid decarboxylase |
| ILAE | International league against epilepsy |
| IVIg | Intravenous immune globulins g |
| IVMP | Intravenous methyl prednisolone |
| LGI | Leucine-rich glioma-inactivated 1 |
| MRI | Magnetic resonance imaging. |
| NMDA | N-Methyl-D-aspartate |
| NORSE | New-onset refractory status epilepticus |
| PLED | Periodic lateralized epileptiform discharges |
| PLEX | Plasma exchange |
| RSE | Refractory status epilepticus |
| SE | Status epilepticus |
| SPSS | Statistical Package for Social Science |
| VGKC | Voltage-gated potassium channel |

#### Acknowledgements

Not applicable.

#### Author contributions

All authors had made a substantial contribution to the design of work, data collection and interpretation, writing the manuscript, revising it, and approving the final version. HM made the main effort in patient data collection and drafting the manuscript. MH, AG, HZ and MW contributed mainly to research project execution and revision of the manuscript. SB, AS, NM, HT, DE, MR, DA, YM, and AM made major effort in analysis and interpretation of data. All authors read and approved the final manuscript.

#### Funding

The research was totally funded by the researchers.

#### Availability of data and materials

The dataset created and analyzed during the current study will be available from the corresponding author on the editor's request.

## Declarations

#### Ethics approval and consent to participate

The study conformed to the standards of the Ethical Review Committee, Ain Shams University (FMASU MD 274/2019). Before the study was inaugurated, a written informed consent was signed from study participants after adequately explaining the study aims and outcomes. The anonymity of the subjects was ensured, no identifying information were obtained, and the results were stored in a secure place with access only to the main author of the study.

#### Consent for publication

Not applicable.

#### Competing interests

The authors declare that they have no competing interests.

#### Author details

[1]Neurology Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt. [2]Clinical Pathology Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt.

Received: 13 February 2023 Accepted: 8 June 2023
Published online: 22 June 2023

#### References

1. GBD 2016 Epilepsy Collaborators. Global, regional and national burden of epilepsy, 1990–2016: a systematic analysis for the Global Burden of Disease Study. Lancet Neurol. 2019;18:357–75.
2. Higdon LM. Autoimmune epilepsy: more than just a paraneoplastic syndrome. Practical neurology; pp. 59–63; 2018
3. Campos-Bedolla P, Feria-Romero I, Orozco-Suárez S. Factors not considered in the study of drug-resistant epilepsy: drug-resistant epilepsy: assessment of neuroinflammation. Epilepsia Open. 2022;7(1):S68–80.
4. Strzelczyk A, Griebel C, Lux W, Rosenow F, Reese JP. The burden of severely drug-refractory epilepsy: a comparative longitudinal evaluation of mortality, morbidity, resource use, and cost using German Health Insurance Data. Front Neurol. 2017;8:712.
5. Bhatia S, Schmitt SE. Treating immune-related epilepsy. Curr Neurol Neurosci Rep. 2018;18(3):10. https://doi.org/10.1007/s11910-018-0821-y.
6. Geis C, Planagumà J, Carreño M, Graus F, Dalmau J. Autoimmune seizures and epilepsy. J Clin Invest. 2019;129(3):926–40.
7. Dalmau J, Geis C, Graus F. Autoantibodies to synaptic receptors and neuronal cell surface proteins in autoimmune diseases of the central nervous system. Physiol Rev. 2017;92:839–87.
8. Dubey D, Alqallaf A, Hays R, Freeman M, Chen K, et al. Neurological autoantibody prevalence in epilepsy of unknown etiology. JAMA Neurol. 2017;74(4):397–402.
9. Feyissa AM, Lopez Chiriboga AS, Britton JW. Antiepileptic drug therapy in patients with autoimmune epilepsy. Neurol Neuroimmunol Neuroinflamm. 2017;4(4): e353.
10. Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58(04):512–21.
11. Lv RJ, Ren HT, Guan HZ, Cui T, Shao XQ. Seizure semiology: an important clinical clue to the diagnosis of autoimmune epilepsy. Ann Clin Transl Neurol. 2018;5(2):208–15.

12. Bien CG, Holkamp M. "Autoimmune epilepsy": encephalitis with autoantibodies for epileptologists. Epilepsy Curr. 2017;17:134–41.
13. Gaspard N, Foreman BP, Alvarez V, Cabrera-Kang C, Probasco JC, et al. New-onset refractory status epilepticus: etiology, clinical features, and outcome. Neurology. 2015;85:1604–13.
14. Jang Y, Kim DW, Yang KI, Byun JI, Seo JG, et al. Drug Committee of Korean Epilepsy Society. Clinical approach to autoimmune epilepsy. J Clin Neurol. 2020;16(4):519–29.
15. Cabezudo-García P, Mena-Vázquez N, Villagrán-García M, Serrano-Castro PJ. Efficacy of antiepileptic drugs in autoimmune epilepsy: a systematic review. Seizure. 2018;59:72–6.
16. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia. 2010;51(6):1069–77.
17. Ganesh A, Wesley SF. Practice current: when do you suspect autoimmune encephalitis and what is the role of antibody testing? Neurol Clin Pract. 2018;8(1):67–73.
18. McGinty RN, Handel A, Moloney T, Ramesh A, Fower A, et al. Clinical features which predict neuronal surface autoantibodies in new-onset focal epilepsy: implications for immunotherapies. J Neurol Neurosurg Psychiatry. 2021;92(3):291–4.
19. Elisak M, Krysl D, Hanzalova J, Volna K, Bien CG, et al. The prevalence of neural antibodies in temporal lobe epilepsy and the clinical characteristics of seropositive patients. Seizure. 2018;63:1–6.
20. Lee SK, Lee ST. The laboratory diagnosis of autoimmune encephalitis. J Epilepsy Res. 2016;6(2):45–50.
21. Lee WJ, Lee ST, Byun JI, Sunwoo JS, Kim TJ, et al. Rituximab treatment for autoimmune limbic encephalitis in an institutional cohort. Neurology. 2016;86(18):1683–91.
22. Gillinder L, Papacostas J, Dionisio S. Electroclinical insights into autoimmune epilepsy. J Neuroimmunol. 2019;330:44–7.
23. De Bruijn MAAM, van Sonderen A, van Coevorden-Hameete MH, Bastiaansen AEM, Schreurs MWJ, et al. Evaluation of seizure treatment in anti-LGI1, anti-NMDAR, and anti-GABABR encephalitis. Neurology. 2019;10:1212.
24. Quek AM, Britton JW, McKeon A, So E, Lennon VA, et al. Autoimmune epilepsy: clinical characteristics and response to immunotherapy. Arch Neurol. 2012;69(5):582–93.
25. Nass RD, Akgün K, Dague KO, Elger CE, Reichmann H, et al. CSF and serum biomarkers of cerebral damage in autoimmune epilepsy. Front Neurol. 2021;16(12):647428.
26. van Sonderen A, Thijs RD, Coenders EC, Jis-koot LC, Sanchez E, et al. Anti-LGI1 encephalitis: clinical syndrome and long-term follow-up. Neurology. 2016;87(14):1449–56.
27. Dubey D, Samudra N, Gupta P, Agostini M, Ding K, et al. Retrospective case series of the clinical features, management and outcomes of patients with autoimmune epilepsy. Seizure. 2015;29:143–7.
28. von Podewils F, Suesse M, Geithner J, Gaida B, Wang ZI, et al. Prevalence and outcome of late-onset seizures due to autoimmune etiology: a prospective observational population-based cohort study. Epilepsia. 2017;58(9):1542–50.
29. Stienen MN, Haghikia A, Dambach H, Thone J, Wiemann M, et al. Anti-inflammatory effects of the anticonvulsant drug levetiracetam on electrophysiological properties of astroglia are mediated via TGFbeta1 regulation. Br J Pharmacol. 2011;162(2):491–507.
30. Beghi E, Shorvon S. Antiepileptic drugs and the immune system. Epilepsia. 2011;52(3):40–4.

## Publisher's Note