

Factors related to possible autoimmune etiology in patients with drug-resistant epilepsy

Magdalena Kowalska, Ewa Nagańska, Urszula Fiszer

Department of Neurology and Epileptology
Centre of Postgraduate Medical Education*
Orłowski Hospital, Warsaw, Poland

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Correspondence

Magdalena Kowalska,
Department of Neurology and Epileptology,
Centre of Postgraduate Medical Education,
Orłowski Hospital, Warsaw, Poland
e-mail: magda.maria.kowalska@gmail.com
phone: +48 22 625 05 78

SUMMARY

Background. Between 14% and 20% of cases of drug-resistant epilepsy may be attributed to an impaired cellular or humoral immune response.

Aim. Our study aimed to assess disorders of the immune response of the humoral or cellular type and their impact on the course of the disease, factors suggesting the diagnosis of an autoimmune etiology. We wanted to analyse these factors, looking for correlations with a history of status epilepticus.

Materials and methods. This study prospectively analysed 30 patients who were diagnosed with drug-resistant epilepsy. The patients were divided into two groups: those who had previously experienced status epilepticus and those who had not. The study collected and analysed detailed information about the patient's medical history, routine blood laboratory tests, albumin and immunoglobulin (IgG) levels, neuropsychological evaluations, electroencephalography tests (EEG), general cerebrospinal fluid (CSF) examinations, tests for the presence of oligoclonal bands, IgG index determination, MRZ-reaction (MRZR), chitotriosidase activity, and the presence of anti-herpes type 1 (anti-HSV-1) antibodies and neural autoantibodies. Each patient underwent magnetic resonance imaging (MRI) of the head with intravenous contrast administration using the epileptic protocol.

Results. There was no statistically significant difference in age, gender, onset and disease duration up to the time of our study. None of the patients showed the presence of the tested antibodies against neuronal surface antigens and oligoclonal bands in the CSF.

Conclusion. Lack of antibodies against neuronal antigens does not necessarily rule out autoimmune epilepsy. The exact diagnostic criteria are still a subject of debate. A history of SE increases the risk of autoimmune epilepsy.

Key words: drug-resistant epilepsy • autoimmune epilepsy • neuronal autoantibodies

BACKGROUND

Epilepsy affects approximately 1% of the general population (Ong et al., 2014), of which in European countries, 20–30% of patients are diagnosed with drug-resistant epilepsy (Dalic and Cook, 2016). More and

more studies on drug-resistant epilepsy of immunological or inflammatory etiology have appeared in recent years. This was reflected by modifying the classification of epilepsy. The International League Against Epilepsy (ILAE) has recognised autoimmune epilepsy as a distinct entity (Scheffer et al., 2017). It is estimated that 14–20% of drug-resistant epilepsy is autoimmune (Husari and Dubey, 2019), and the presence of

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disturbances in the cellular and humoral immune response plays an important role (Feyissa et al., 2017). It was confirmed in animal models of temporal epilepsy and models of resected human brain tissue that the stimulation of the immune system and inflammatory processes are a consequence of the occurrence of epileptic seizures (Walker and Sills, 2012). Studies suggest that anywhere from 14% to 20% of cases of drug-resistant epilepsy are caused by autoimmune factors (Husari and Dubey, 2019). The immune system's cellular and humoral response has been found to play an important role in developing these cases (Feyissa et al., 2017). Research has confirmed that the occurrence of epileptic seizures can lead to the stimulation of the immune system and inflammatory processes, as demonstrated in animal models of temporal epilepsy and resected human brain tissue models (Walker and Sills, 2012).

Studies suggest that anywhere from 14% to 20% of cases of drug-resistant epilepsy are caused by autoimmune factors (Husari and Dubey, 2019). The immune system's cellular and humoral response has been found to play an important role in developing these cases (Feyissa et al., 2017). Research has confirmed that the occurrence of epileptic seizures can lead to the stimulation of the immune system and inflammatory processes, as demonstrated in animal models of temporal epilepsy and resected human brain tissue models (Walker and Sills, 2012). However, autoantibodies have been found in cases of newly diagnosed epilepsy, which confirms that they may be a causative factor (Vicent, 2012). In cases of autoimmune epilepsy, the most frequently reported antibodies are those directed against neural surface proteins such as the N-methyl-D-aspartate receptor (NMDAR), leucine-rich glioma inactivated 1 (LGI1), and contactin-associated protein-2 (CASPR2) – the latter two being elements of the voltage-gated potassium channel (VGKC) complex, the 2-amino-3-propanoic acid receptor (AMPA), the γ -aminobutyric acid B receptor (GABABR), or against intracellular proteins such as glutamic acid decarboxylase (GAD). Failure to identify the presence of neuronal autoantibodies does not exclude the diagnosis of epilepsy of this etiology. Observations show no difference in prevalence or incidence between autoimmune and infectious agents in inflammatory lesions of the central nervous system, and more than 50% of patients do not have specific autoantibodies (Dubey et al., 2018).

Based on the patient's medical history and clinical presentation, certain factors suggest a higher likeli-

hood of an inflammatory or immunological cause for their condition. These factors may include frequent seizures, seizures with varying symptoms occurring in the same person, drug resistance, a positive family or personal history of autoimmune diseases, or a history of neoplastic diseases. Along with seizures, other symptoms like cognitive problems, behavioral changes, and autonomic dysfunction may also be present (de Bruijn et al., 2021).

Early and proper diagnosis of autoimmune epilepsy is essential because affected patients have seizures that are resistant to common antiepileptic therapy. Effective treatment following the pathophysiological process requires an immunomodulating treatment (Toledano et al., 2014). Interestingly, some cases of autoimmune epilepsy show spontaneous remission, but some may relapse after many years in the presence of triggers (Jang et al., 2020).

The researchers emphasise that the selection of antiepileptic drugs in patients with drug-resistant epilepsy of inflammatory and immune causes should not be accidental. Research shows that some antiepileptic drugs may influence the cellular response, others the humoral one. For example, valproate and carbamazepine have been shown to increase the serum levels of IL-1b, IL-2, IL-4, IL-6, IL-17, and tumor necrosis factor- α (TNFa) production (Feyissa et al., 2017). Recent reports attempt to link the antiepileptic effect of drugs used in autoimmune epilepsy with their mechanism of action and pharmacokinetic profile (Feyissa et al., 2017).

There are still no clear-cut criteria for the diagnosis of autoimmune epilepsy, and additional tests that could be a screening or the first stage of diagnosis, preceding the hard-to-reach, expensive tests, for example, detection of antibodies against neuronal surface antigens. That is why newer and newer scales are being developed to help select patients with cryptogenic epilepsy who should have a detailed diagnosis of autoimmune epilepsy. One of the first such scales to assess the likelihood of autoimmune epilepsy was an antibody prevalence in epilepsy and encephalopathy (APE) (Dubey et al., 2017), then modification APE2 (Dubey et al., 2019). Another attempt to define risk factors for autoimmune epilepsy based on the prospectively collected data of patients with focal epilepsy of unknown etiology is antibodies contributing to focal epilepsy signs and symptoms (ACES Score) (de Bruijn et al., 2021) and antibodies in drug-resistant temporal lobe epilepsy (ARTE score).

Autoimmune epilepsy often manifests as new-onset refractory status epilepticus (NORSE) (Jang et al., 2020). Autoimmune etiologies are more common than paraneoplastic or infection (Jang et al., 2020). Moreover, a chronic and untreated autoimmune process can cause recurrent focal SE (Sculier et al., 2019). Our initial hypothesis following the literature was that drug-resistant epilepsy and a history of SE are a hallmark of autoimmune seizures (Cabezudo-Garcia, 2018). Some researchers associate the presence of recurrent, focal states of epilepsy with a chronic and untreated autoimmune process (Cabezudo-Garcia et al., 2021).

AIM

Our study aimed to evaluate any immune response disorders, either humoral or cellular, in the cerebrospinal fluid. We also looked into the blood-cerebrospinal fluid barrier function and any factors that suggest an autoimmune cause. Additionally, we aimed to investigate if there was a correlation between a history of status epilepticus (SE) and the likelihood of autoimmune epilepsy in patients with refractory cryptogenic epilepsy.

MATERIAL AND METHODS

The local Bioethics Committee at the Centre of Postgraduate Medical Education in Warsaw approved the study protocol, and written and informed consent was obtained from each patient. This was a prospective analysis of 30 patients with an accurate diagnosis of drug-resistant epilepsy according to the ILAE criteria and unknown etiology. This group was chronologically selected from 86 patients with a diagnosis of epilepsy hospitalised at the Department of Neurology and Epileptology in Warsaw from the period 2018 to 2019. The group of 86 patients included patients with any diagnosis of epilepsy, not necessarily drug-resistant, according to the ILAE criteria (Fisher et al., 2014). Each patient had a contrast-enhanced head MRI in the past. The use of the epilepsy protocol was not a prerequisite. The study included patients with no correlation between changes in neuroimaging and the occurrence of epileptic seizures. Patients with contraindications to conduct CSF collection and head magnetic resonance imaging (MRI) were excluded from the analysis. The exclusion criteria were also changes in the brain MRI indicating the structural etiology of epilepsy or data from the history and clinical picture indicating the genetic or metabolic etiology of epilepsy. We divided the patients included in the study into two groups - those

with a history of status epilepticus and those without such an interview. We investigated whether individuals who have a history of status epilepticus are at a higher risk of developing autoimmune epilepsy and whether there are any significant differences between the groups formed by this division. Furthermore, we evaluated the entire patient cohort using the APE2 scale.

Informed consent signatures were required to perform the lumbar puncture technique and participate in the study. There was carried out in the study group a detailed history of the course of epilepsy, including more detailed information on status epilepticus, routine blood laboratory tests supplemented with the determination of albumin and immunoglobulin (IgG) levels, neuropsychological evaluation, electroencephalography test (EEG), general cerebrospinal fluid (CSF) examination, and examination for the presence of oligoclonal bands, determination of the IgG index, MRZ-reaction (MRZR), chitotriosidase activity and the presence of anti-herpes type 1 (anti-HSV-1) antibodies, antibodies against surface antigens: LGI1, CASPR2, NMDAR, AMPAR1/2, GABAB. Moreover, each patient underwent a head MRI with intravenous contrast administration with the protocol extended with the T1 D3 sequence and FLAIR thin scan.

The collected data underwent statistical processing. Numeric variables were summarised as mean and standard deviation, while categorical variables were presented as numbers and percentages. Multivariate analysis of variance and the χ^2 test were performed to determine the significance of differences between study groups. Pearson's linear correlation analysis was used to assess the relationship between variables, while Kendall's tau B correlation and the Wilcoxon Signed Rank Test were used for non-parametric variables. The level of statistical significance was set at $p < 0.05$ for all analyses.

RESULTS

History of SE, which potentially indicates a higher risk of drug-resistant seizures, was used as the criterion for the primary division of the studied group of patients. We analysed whether there were any patients in this group where status epilepticus could be caused by non-compliance with the recommendations, e.g. irregular intake of anticonvulsants. We found no such case. Of the 14 patients, 3 had more than one status epilepticus (2 patients – 2 status epilepticus, one patient – 3 status epilepticus). In the case of 2 patients, it was the first symptom of the disease.

Table 1. Demographic and clinical parameters of patients

Patients n = 30	SE n = 14	None SE n = 16
Age in years	23–50 (34.21 ± 8.89)	22–65 (35.25 ± 11.42)
Female	6 (42.9%)	9 (56.3%)
New-onset seizures age	0.25–19 (6.71 ± 5.18)	8–37 (15.19 ± 7.42)
Duration of the disease in years	16–46 (27.43 ± 7.89)	2–36 (20.06 ± 8.80)
Neuropsychiatric changes	4 (30.8%)	6 (37.5%)
Sleep seizures	12 (87.5%)	6 (37.5%)
Protein CSF Level > 50 mg/dl	7 (50%)	3 (18.8%)
CSF pleocytosis	4 (28.6%)	4 (25.0)
EEG findings		
theta waves (> 5% EEG recording)	9 (64.3%)	3 (18.8%)
epileptiform discharges	1 (7.1%)	9 (56.3%)
MRI changes in the hippocampus	1 (7.1%)	3 (18.8%)
APE 2 score ≥ 4	7 (50%)	5 (31.3%)

SE – status epilepticus, CSF – cerebrospinal fluids, EEG – electroencephalography, MRI – magnetic resonance imaging, APE 2 – antibody prevalence in epilepsy and encephalopathy

Table 2. Characteristics of patients with SE history vs those without SE history

Student's t-test	SE	N	Average	Standard deviation	t	p-value
Age	.00	16	35.25	11.416	.274	.786
	1.00	14	34.21	8.894		
New-onset seizures	.00	16	15.1875	7.42266	3.575	.001
	1.00	14	6.7086	5.18461		
Duration of the disease	.00	16	20.06	8.797	-2.399	.023
	1.00	14	27.43	7.891		
Chitotriosidase in serum (mmol/ml/h)	.00	14	46.429	33.5896	.896	.379
	1.00	14	35.614	30.2185		
Chitotriosidase in CSF (mmol/ml/h)	.00	16	2.687500	1.8198443	2.240	.033
	1.00	14	1.440000	1.0807120		
APE 2 score	.00	16	3.00	1.155	-.768	.449
	1.00	14	3.36	1.393		

SE – status epilepticus, CSF – cerebrospinal fluids, APE 2 – antibody prevalence in epilepsy and encephalopathy

Regarding the type of status epilepticus, nine patients had focal onset to bilateral tonic-clonic, one patient focal motor to bilateral tonic; two patients had focal motor onset, two patients focal nonmotor onset, and one patient had focal onset myoclonic according to ILAE 2017 Seizure Type Classification Checklist (Fisher et al., 2017). One patient had status epilepticus during pregnancy after 35 years of illness.

Both subgroups describe demographic and clinical parameters. Detailed data are presented in Table 1. Characteristics of patients with SE history, and those without SE history with statistical data are also shown in Table 2.

There was no statistically significant difference in age between those groups (Student's t-test, $p = 0.786$)

or gender (χ^2 test, $p = 0.464$). There was a statistically significant difference in age at which the first seizure occurred (Student's t-test, $p = 0.001$) and in disease duration up to the time of our study (Student's t-test, $p = 0.023$). Moreover, a statistical difference was demonstrated in the level of chitotriosidase in the cerebrospinal fluid (Student's t-test, $p = 0.033$) and the presence of epileptic seizures during sleep (χ^2 test, $p = 0.007$), which were more frequent in the group with SE.

Focal onset impaired awareness seizures were present in 27 patients (90%, with temporal morphology in 10, 33%, frontal 11, 37%), and focal to bilateral tonic-clonic seizures in 25 (83%), myoclonic seizures: 4 (13, 3%). Polymorphic seizures were reported in 3 patients, and one patient had facial dyskinesia, which is a parame-

ter of the APE2 scale. Depending on the type of seizure, there was statistical significance in the frequency of seizures in sleep (χ^2 test, $p=0.012$), the level of lactic acid in the blood serum (χ^2 test, $p=0.023$), and the presence of neuropsychiatric changes (χ^2 test, $p=0.05$). For statistical purposes, we have created four frequency ranges for epileptic seizures: I – more than 1 per day, II – not every day but up to 6 per week, III not more than 1 per week, and IV not more than 1 per month. In 10 patients (36%), seizures occurred for more than 1 per day – in this group, the vast majority were patients with a history of SE (8 patients, 80%). There was no correlation found between the frequency of epileptic seizures and the amount of current and past antiepileptic drugs (Kendall Tau-b correlation, $p=0.251$ and $p=0.516$).

There was no statistically significant difference between the amount of anti-epileptic drugs used now and in the past and the presence of status epilepticus in the past (Mann-Whitney U, Pearson χ^2 test). On the other hand, after comparing the groups with the Wilcoxon rank test, the difference between the number of antiepileptic drugs in the past and at present was confirmed statistically (two-sided asymptomatic significance $p=0.001$).

We tested for the presence of antibodies against measles virus (MV), rubella (RV), chicken pox (VZV), and herpes type 1 (HSV-1) in serum and CSF. In the blood serum, antibodies against one of the viruses mentioned above were found in 11 (36.7%) patients, against two in 7 (23.3%), and three in 2 (6.7%). We assessed whether there was a statistical correlation between the number of viruses against which the antibodies were detected and the history of the presence of SE. The statistical difference was significant for the likelihood ratio test ($p=0.042$). Moreover, two patients had an index calculated depending on the level of antibodies in the serum and CSF of more than 1.5 ($VZV=1.9$, $RV=2.08$).

None of the patients showed the presence of the tested antibodies against neuronal surface antigens. Based on the penetration rates for albumin and IgG (Q_{alb} and Q_{IgG}), disturbances in the blood-brain barrier function were diagnosed in 6 patients (20%).

In 4 (13.3%) patients, changes in the complex amygdalohippocampal were described on MRI with intravenous contrast, including one patient with a history of SE. Those abnormalities were atrophy, cystic lesion, and hyperintense signal in T2. The normal hippocampus was described in 8 (26.7%) patients with brain changes unrelated to seizures, e.g., pineal cyst single non-specific

ic hyperintense lesions in T2. The remaining patients had a perfectly normal picture of the brain on MRI.

DISCUSSION

Based on the literature, we estimated that up to 20% of our patients might have epilepsy of autoimmune origin (Husari & Dubey, 2019). We sought confirmation of this in our sample.

Considering a history of status epilepticus as one of the indicators that may suggest the presence of autoimmune epilepsy, we analysed our group of patients depending on the history of SE. However, none of our patients showed the presence of the tested antibodies against neuronal surface antigens. A recent publication demonstrated that the APE score lacked sensitivity for patients with a history of epilepsy lasting ≥ 12 months (de Bruijn et al., 2021). In our analysis, the mean (SD) duration of the disease in the SE group was 27.43 (± 7.89) years and without a history of SE 20.06 (± 8.80). Therefore, the long course of the disease in our patients could be one of the factors contributing to the absence of neural antibodies. Another reason may be the low number of patients included in the study. What's more, according to recent publications, we have two concepts (Steriade et al., 2020): “acute symptomatic seizures secondary to autoimmune encephalitis.” and “autoimmune-associated epilepsy”. In our study, we have patients with epilepsy of unknown etiology, and in this group, the prevalence of neuronal autoantibodies is low, opposite to the patients with autoimmune encephalitis (Yeshokumar, 2021).

Our statistical analysis indicates that there is a relation between a history of status epilepsy and drug resistance. Specifically, the majority of patients who experienced seizures more than once a day had a history of status epilepsy. However, we did not find any relationship between the amount of anti-epileptic drugs and the frequency of seizures in any of the groups.

Despite the previously described correct results of standard head MRI in 4 patients, we found changes in the amygdalohippocampal complex according to the epilepsy protocol during our study. After the end of the study, one patient has been qualified for deep brain stimulation of the anterior nucleus of the thalamus (ANT-DBS), the next patient is in the process of being qualified for this procedure, and another patient is in the process of being qualified for conventional epilepsy surgery. This demonstrates the importance of using an appropriate head MRI protocol in patients with drug-resistant epilepsy. An example of a protocol

that will hopefully be routinely used in the future is developed by The Neuroimaging Task Force Harmonized Neuroimaging of Epilepsy Structural Sequences (HARNESS-MRI) two-dimensional (2D) protocol at 3T (Bernasconi, 2019). It can potentially transform MRI-negative into MRI-positive (Bernasconi, 2019).

The low number of our patients with changes in the amygdalohippocampal complex may also be because temporal lobe hyperintensities are usually only present in the acute phase of the disease (Kelley et al., 2017).

One of the research hypotheses assumed a correlation between changes in the hippocampus in the head MRI and the presence of inflammatory and immune changes in the CSF. Only in the above four patients did we find changes in the hippocampus, and in this group, 2 had no changes in CSF; in one patient increased contraction of protein to 57.4 mg/dl with blood-brain barrier dysfunction, and in the last one, cytosis was 21 cells/ μ l and protein level up to 61 mg/dl with blood-brain barrier dysfunction.

In the study of the MRZR and the presence of HSV-1 antibodies, the index was positive in 2 patients. A positive index indicates the production of specific antibodies in the CNS and local infection. Studies show a high prevalence of positive MRZR in multiple sclerosis (MS), especially in patients with primary-progressive multiple sclerosis (PPM) and in patients with relapsing-remitting multiple sclerosis (RRMS) (Hottenrott et al., 2017). This fact suggests that it may be an indicator suggesting an autoimmune basis of epilepsy after excluding other diseases.

Chitotriosidase activity is a very sensitive marker of activated macrophages, which means it points to inflammation or immune activation, and for this reason, we chose this parameter for our study. For example, its level is elevated in MS in the type RRMS and secondary progressive multiple sclerosis (SPMS) (Verbeek et al., 2010). The results of the determination of chitotriosidase activity in serum and CSF did not indicate exceeding the upper limit of normal in serum (average value below 150 nmol/ml/h) and no significant increase in CSF (average value approx. 5.5 nmol/ml/h). Interestingly, two patients were suspected of chitotriosidase deficiency in CSF, and eight patients had very low serum results (<1 nmol/ml/h). However, the interpretation of these results requires further research.

We also monitored the patients for the coexistence of autoimmune diseases, which is also a factor supporting the presence of autoimmune epilepsy. Reduced thy-

roid stimulating hormone (TSH) levels were found in 3 people with normal free triiodothyronine (FT3) and free thyroxine (FT4) levels without the presence of anti-thyroid antibodies. One patient also had celiac disease and drug-induced thrombocytopenia. Based on the history and clinical picture, as well as basic laboratory tests of blood serum, no coexistence of autoimmune disease was suspected, and no patients were diagnosed with neoplastic disease, apart from a pituitary tumor.

Our study has certain limitations that need to be taken into consideration. Firstly, the number of patients included in our study was small. The pilot nature of our study was the main reason behind this. However, in the future, we aim to conduct a study on a larger group of individuals and analyse the results based on the duration of the disease. Secondly, due to the high cost of the study, we only tested for the presence of neuronal autoantibodies in CSF. However, the latest publications recommend that both serum and CSF should be tested for a more comprehensive analysis (Cabezudo-Garcia et al., 2021).

Moreover, in some studies, the detection of autoantibodies was much higher in serum than in CSF (12/14, 85.71% vs 4/14, 28.57%) (Cabezudo-Garcia et al., 2021). Other recommendations for determining autoantibodies are to perform panel testing of multiple autoantibodies rather than single antibody testing. Another point is to consult cases with the reference centres for further procedures in doubtful cases, such as weak positive result antibodies directed to surface antigens only in serum or if the results of additional tests are inconsistent with the clinical symptoms (Vogrig et al., 2019). The interpretation of positive results only in serum has to be careful. For example, the presence of the anti-NMDAR IgG subclass in CSF is required for the diagnosis of definitive anti-NMDAR encephalitis, which is why only positive results in serum can be considered to be unspecified (Grauset al., 2016).

It is important to note that we have not conducted tests for glycine receptor (GlyR) antibodies, which have been found to be one of the most common types of antibodies in autoimmune epilepsy, according to recent systematic reviews of studies (Cabezudo-Garcia et al., 2021). These antibodies have been linked to long-term epilepsy without any other neurological symptoms (Ekzoglu et al., 2019). However, the test for these antibodies is not widely available. Moreover, one of the limitations of our study was the inability to determine neuronal antibodies in a reference laboratory.

CONCLUSION

Determining antibodies against neuronal antigens remains a complex and cost-consuming test. Moreover, a negative result does not necessarily rule out the possibility of autoimmune epilepsy, which is indicated by the APE2 scale. Efforts are still underway to establish diagnostic criteria for autoimmune epilepsy and develop new scales to screen patients with drug-resistant epilepsy. The patient's history of status epilepticus is one of the factors that suggest autoimmune epilepsy diagnosis. We anticipate that the next step in managing drug-resistant epilepsy with an unknown cause will involve developing a new therapeutic strategy following the identification of autoimmune processes.

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DISCLOSURE

The authors report no conflict of interest.

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