Irish Journal of Medical Science (1971 -) (2018) 187:1057–1063
https://doi.org/10.1007/s11845-018-1777-2

ORIGINAL ARTICLE

Neurological autoantibodies in drug-resistant epilepsy of unknown cause

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Received: 16 January 2018 / Accepted: 24 February 2018 / Published online: 9 March 2018

Abstract

Background Autoimmune epilepsy is a rarely diagnosed condition. Recognition of the underlying autoimmune condition is important, as these patients can be resistant to antiepileptic drugs.

Aims To determine the autoimmune and oncological antibodies in adult drug-resistant epilepsy of unknown cause and identify the clinical, radiological, and EEG findings associated with these antibodies according to data in the literature.

Methods Eighty-two patients with drug-resistant epilepsy of unknown cause were prospectively identified. Clinical features were recorded. The levels of anti-voltage-gated potassium channel complex (anti-VGKCc), anti-thyroid peroxidase (anti-TPO), anti-nuclear antibody (ANA), anti-glutamic acid decarboxylase (anti-GAD), anti-phospholipid IgG and IgM, anti-cardiolipin IgG and IgM, and onconeural antibodies were determined.

Results Serum antibody positivity suggesting the potential role of autoimmunity in the aetiology was present in 17 patients with resistant epilepsy (22.0%). Multiple antibodies were found in two patients (2.6%). One of these patients (1.3%) had anti-VGKCc and ANA, whereas another (1.3%) had anti-VGKCc and anti-TPO. A single antibody was present in 15 patients (19.5%). Of the 77 patients finally included in the study, 4 had anti-TPO (5.2%), 1 had anti-GAD (1.3%), 4 had anti-VGKCc (5.2%) 8 had ANA (10.3%), and 2 had onconeural antibodies (2.6%) (1 patient had anti-Yo and 1 had anti-MA2/TA). The other antibodies investigated were not detected. EEG abnormality (focal), focal seizure incidence, and frequent seizures were more common in antibody-positive patients.

Conclusion Autoimmune factors may be aetiologically relevant in patients with drug-resistant epilepsy of unknown cause, especially if focal seizures are present together with focal EEG abnormality and frequent seizures.

Keywords Autoimmune epilepsy · Drug-resistant epilepsy · Epilepsy · Neuronal autoantibodies

Introduction

Epilepsy is among the most common neurological disorders, affecting approximately 1–3% of the general population. Drug resistance remains a serious problem in the treatment of epilepsy, with approximately 30% of epilepsy patients classified as resistant to antiepileptic drugs [1]. Resistant epilepsy is a condition in which a sustained lack of seizures cannot be ensured despite administration of two antiepileptic drugs (monotherapy or combined) appropriate for the seizure type that can be tolerated at the appropriate doses and for the appropriate duration [2]. Another definition is the complete or partial absence of a drug response (i.e., a failure to prevent seizures), leading to significant neuropsychiatric and social disorder, decreased quality of life, and increased morbidity and risk of sudden death [3].

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Whereas structural, metabolic, and genetic factors are commonly identified as contributors to the aetiology of epilepsy, the underlying causes of this condition remain undetermined in the majority of cases (30–60%) [4]. Recent studies assume autoimmune processes to be a potential aetiological factor in epilepsy of unknown cause [5]. Several neurological autoantibodies related to epilepsy and limbic encephalitis/encephalopathy have been identified [6]. Although most of these serum antibodies operate against neuronal cell-surface antigens, including synaptic neurotransmitter receptors, ion channels, or related proteins, another group of antibodies target intraneuronal or cytoplasmic antigens [7].

According to one study, the anti-cardiolipin IgG (ACL IgG) level, which was higher in epileptic patients with new seizures than in patients without seizures or controls, has been associated with persistent resistant seizures [8]. The anti-cardiolipin IgM (ACL IgM) level was reported to be elevated in patients with focal seizures, although this relationship was not highly specific to this phenotype [9]. Higher anti-nuclear antibody (ANA) levels were found in adults with newly diagnosed resistant focal epilepsy compared to in those with generalised epilepsy [10]. Another study identified anti-thyroid peroxidase (anti-TPO) in 13.4%, anti-glutamic acid decarboxylase (anti-GAD) in 12.5%, and anti-voltage-gated potassium channel complex (anti-VGKCc) in 10.7% of patients with epilepsy of unknown aetiology [11]. Paraneoplastic epilepsy should be suspected in cases of adult-onset resistant epilepsy even when no cancer has been detected [12]. Epilepsy and seizures are also more common in patients with anti-phospholipid syndrome (APS) than in the general population [13].

This study was performed to determine the autoimmune and onconeural antibody frequencies in drug-resistant epilepsy of unknown cause and to compare the associated clinical, radiological, and EEG findings to those in the literature.

Methods

Participants

In total, 1926 patients presenting to the Inonu University Medical Faculty's Neurology Department Epilepsy Outpatient Unit in the 12 months between July 2016 and July 2017 were evaluated, and 82 patients with drug-resistant epilepsy of unknown cause were prospectively included in this study (patients who could not sustain a seizure-free state despite administration of two antiepileptic drugs, administered as monotherapy or combined therapy, that were appropriate for the seizure type and that could be tolerated at the proper dose and duration). The patients were over 18 years old. None of the patients included in the study had any neurological signs or neurological diseases other than epilepsy. Patients with focal and diffuse atrophy, nonspecific white matter lesions and idiopathic mesial temporal sclerosis (MTS) were not excluded. The seizures and syndromes were diagnosed according to the International League Against Epilepsy (ILAE) Commission on Classification and Terminology 2017 [14].

The exclusion criteria were as follows:

1. Structural brain lesions (ischaemia, tumour, head trauma, vascular malformation, abscess, congenital malformation, heterotypic conditions).
2. Metabolic abnormalities (severe hypoglycaemia or hyperglycaemia, severe renal or hepatic deficiency, malignant hypertension, alcoholism).
3. Proven or suspected chromosomal anomalies and genetic syndromes.
4. Any malignancy.

Clinical evaluation

All patients underwent detailed neurological examinations. Data on age at seizure onset, epilepsy duration, family history, brain magnetic resonance (MRI) findings, electroencephalography (EEG) findings, seizure type, seizure frequency, additional diseases, number of antiepileptics used, aura presence, neuropsychiatric changes (agitation, emotional lability, aggressiveness), and autonomic dysfunction (persistent atrial tachycardia or bradycardia, orthostatic hypotension, hyperhidrosis, ventricular tachycardia or cardiac asystole, persistent labile blood pressure) were recorded. All MRI studies were performed on a 1.5 T scanner with T1, T2 and fluid-attenuated inversion recovery (FLAIR) sequences in the coronal, sagittal, and axial planes.

This study was approved by the Institutional Ethics Committee. Informed consent was obtained from all participants before blood samples were drawn.

Autoantibody test

We recommended that all patients meeting the inclusion criteria undergo an autoantibody test. The plasma obtained from the patients was frozen at − 80 °C, and the anti-VGKCc complex, anti-TPO, ANA, anti-GAD, anti-phospholipid (aPL) IgG and IgM, ACL IgG, and IgM and onconeural antibody levels were determined. The methods used were Anti-TPO chemiluminescent microparticle immunoassay (CMIA) (Architect, Wiesbaden. Germany), Anti-GAD immunoradiometric assay (IRMA) (Beckman Coulter, Fullerton, CA, USA), ANA Indirect immunofluorescence (IFA) (Immco, Buffalo, NY, USA), aPL IgG and IgM enzyme-linked immunosorbent assay (ELISA) (Inova, Wellington, FL, USA), onconeural antibodies Western

blotting (immunoblot) (Euroimmun, Lubeck, Germany), ACL IgG and IgM enzymatic immunoassay (EIA) (Inova) and anti-VGKCc radioimmunoassay (RIA) (Inova).

Statistical analysis

Statistical analyses were performed using SPSS 15 (SPSS Inc., Chicago, IL, USA). Comparisons were performed using independent samples *t* tests and Fisher's exact tests when the data were distributed homogenously; the Mann–Whitney *U* test was used for quantitative data, and the chi-square test was used for heterogeneously distributed qualitative data. In all analyses, $P < 0.05$ indicated statistical significance.

Results

Clinical and demographic findings

In total, 82 adult patients with drug-resistant epilepsy of unknown cause were seen within the year from 1 July 2016 to 1 July 2017. Five patients (6.1%) were later excluded (an intracranial tumour was found in three, and non-epileptic psychogenic seizures were found in two). The remaining 77 patients consisted of 29 females (37.7%) and 48 males (62.3%). The mean age (± standard deviation) was 33.6 ± 11.3 years in the total population, 34.7 ± 12.1 years among males, and 31.8 ± 9.8 years among females (difference not significant). The mean duration after epilepsy diagnosis was 18.9 ± 10.9 years in the total population, 21.0 ± 10.7 years among males, and 15.5 ± 10.6 years among females.

Autoantibody findings and clinical relationships

Serum antibody (Ab) positivity suggesting a potential role of autoimmunity in the aetiology was present in 17 patients with resistant epilepsy (22.0%). Multiple antibodies were found in two patients (2.6%), one of whom (1.3% of all patients) had anti-VGKCc and ANA, whereas the other (1.3%) had anti-VGKCc and anti-TPO. A single antibody was present in 15 patients (19.5%). Of the 77 patients included in the study, 4 had anti-TPO (case 1, 252.8 IU/L; case 2, 9.9 IU/L; case 3, 125.7 IU/L; case 4, 13.8 IU/L) (normal value < 5.61 IU/L) (5.2%), 1 had anti-GAD (1.8 U/ml) (normal value 0–1 U/ml) (1.3%), 4 had anti-VGKCc (case 1, 231 pmol/L; case 2, 271 pmol/L; case 3, 201 pmol/L; case 4, 95 pmol/L) (normal value < 85 pmol/L) (5.2%), 8 had ANA (+) (±) (10.3%), and 2 had onconeural antibodies (+) (±) (2.6%) (1 patient had anti-Yo and the other had anti-MA2/TA). None of the other antibodies investigated was detected (aPL IgG and IgM, ACL IgG and M) (Fig. 1).

There was no statistically significant difference between the antibody-positive (Ab^+) and antibody-negative (Ab^-) groups in terms of age, duration since onset of epilepsy, aura, MRI abnormality, neuropsychiatric disorder, autonomic dysfunction, presence of frequent seizures, and multiple drug use. However, several striking differences were observed. The incidence of aura was higher in Ab^+ patients, although the difference was not statistically significant (29.4 vs. 10%, respectively; $p = .058$). Neuropsychiatric disorders were more common in Ab^+ patients than in Ab^- patients (35.3 vs. 16.7%, respectively; $p = .095$). No pathology was found in any patient on the neurological examination performed during the ictal or interictal period. The brain MRI of Ab^+ patients revealed MTS (anti-$VGKCc^+$) in one patient and nonspecific gliotic foci in three patients (ANA^+ in two, anti-TPO^+ in one). The results of the brain MRI were normal in 13 patients. The MRI of Ab^- patients revealed MTS in 4 patients, nonspecific gliotic foci in 14 patients, and normal findings in 42 patients. None of the patients had a personal or family history of inflammatory or autoimmune disease (e.g., type 1 diabetes mellitus, systemic lupus erythematosus, pernicious anaemia, Hashimoto thyroiditis, or psoriasis) or malignancy that could explain the neuronal autoantibody positivity. The patients had no findings

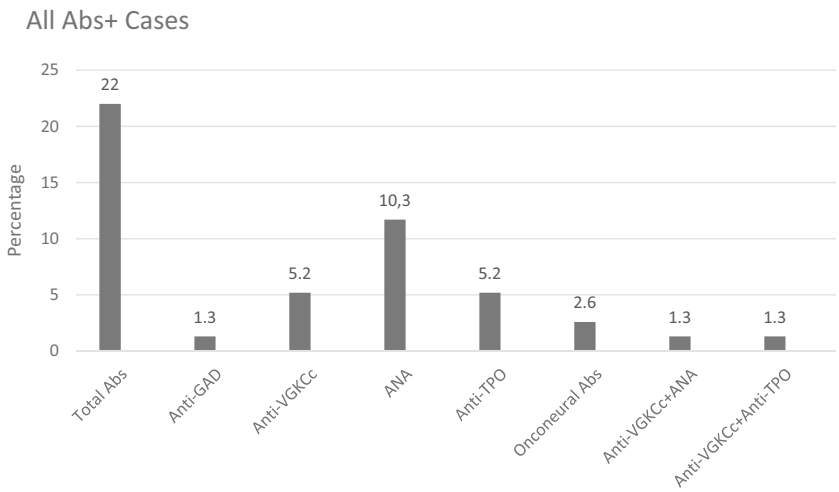

Fig. 1 Autoantibody distribution in patients with drug-resistant epilepsy of unknown cause

indicative of systemic infection during the evaluation period. All patients were using two or more antiepileptics in various combinations.

Frequent seizures (one or more per month) were more common in Ab^+ patients than in Ab^- patients (13 of 17 [76.5%] vs. 28 of 60 [46.7%], respectively; $p = .002$). Whereas Ab positivity was more common in female patients with resistant epilepsy of unknown cause, Ab negativity was higher in male patients (10 of 17 [58.8%] vs. 41 of 60 [68.3%], respectively; $p = .004$). EEG abnormalities were common in Ab^+ patients and rare in Ab^- patients (16/17 [94%] vs. 39/60 [65%], respectively; $p = .001$). Focal EEG abnormalities were more common in Ab^+ patients than in Ab^- patients (13 of 17 [76%] vs. 15 of 60 [25%], respectively; $p = .004$). Generalised EEG abnormalities were less common in Ab^+ patients than in Ab^- patients (2 of 17 [11.8%] vs. 14 of 60 [23%], respectively; $p = .004$). Correspondingly, the incidence of focal seizures was higher in Ab^+ patients than in Ab^- patients (9 of 17 [52.9%] vs. 18 of 60 [30%], respectively; $p = .007$). The rate of ANA positivity was significantly higher in females than in males (7 of 29 [24.1%] vs. 1 of 48 [2.1%], respectively; $p = .002$). EEG abnormalities were present in all ANA-positive patients, and 77.7% of these consisted of focal epileptic abnormalities. The frequency of aura was higher in ANA-positive patients than in other Ab^+ and Ab^- patients (44.4, 12.5, 10.0%, respectively; $p = .022$). There was no family history of epilepsy in ANA-positive patients, whereas 25% of the other Ab^+ patients and 3.3% of Ab^- patients had such a family history (Table 1).

Discussion

Initial clinical studies regarding autoimmune epilepsy began with the presentation of three non-infectious encephalitis cases by Bickerstaff in 1950 [15]. Autoantibodies were later detected in limbic encephalitis and in patients with faciobrachial dystonic seizures [15]. Neuronal autoantibodies have recently been identified in focal epilepsy [5, 16–18].

Studies on autoimmune epilepsy have implicated autoimmune factors in the aetiology of 17.5% of epilepsy patients [19, 20]. Another study detected autoantibodies in 23.5% of unselected adult epilepsy patients [21]. The autoantibody rates, which suggest a possible role of autoimmunity, were reported to be 34.8% [11] among patients with epilepsy of unknown cause and 13.8% [15] among patients with drug-resistant focal seizures of unknown cause. Neuronal autoantibody rates of 10–20% were reported among patients with focal seizures of unknown cause, suggesting a possible immune aetiology [7, 22, 23]. Our study found autoantibodies at a rate of 22.0% in patients with drug-resistant epilepsy, which is similar to the autoantibody rates reported in the literature.

The frequencies of neuronal autoantibodies varied between studies. Anti-VGKCc is more common in nonparaneoplastic limbic encephalitis with seizures [24, 25]. Anti-VGKCc has been reported in 10.7% of patients with epilepsy of unknown cause [11] and in 7.4% of patients with drug-resistant focal epilepsy [15]. Anti-VGKCc (5.2%) was found in four patients in the present study. MTS was present in one of these anti-VGKCc-positive patients, whereas the MRI findings were normal in the other three.

Table 1 The comparison of antibody-positive and antibody-negative patients

Variables	Total ($n = 77$)	Antibody negative ($n = 60$)	Antibody positive ($n = 17$)	P value
Sex (F/M), n (%)	29/48 (37.7%/62.3%)	19/41 (31.7%/68.3%)	10/7 (58.8%/41.2%)	.004
Mean age, years	33.6 ± 11.3	32.5 ± 10.7	37.5 ± 12.8	.107
Duration of epilepsy, years	18.9 ± 10.9	17.9 ± 10.6	22.7 ± 11.6	.108
Epilepsy in family history, n (%)	4 (5.2%)	2 (3.3%)	2 (11.8%)	.210
Aura, n (%)	11 (14.3%)	6 (10%)	5 (29.4%)	.058
Additional disease, n (%)	6 (7.8%)	4 (6.7%)	2 (11.8%)	.397
Mesial temporal sclerosis, n (%)	5(6.5%)	4 (6.7%)	1 (5.8%)	.903
Nonspeciic gliotic foci, n (%)	13 (16.8%)	10 (16.7%)	3 (17.6%)	.903
EEG abnormality, n (%)	55 (71.4%)	39 (65.0%)	16 (94.1%)	.001
Focal EEG abnormality, n (%)	28 (36.3%)	15 (25.0%)	13 (76.4%)	.004
Generalised EEG abnormality, n (%)	16 (20.7%)	14 (23%)	2 (11.7%)	.004
Seizure (focal), n (%)	27 (35.1%)	18 (30.0%)	9 (52.9%)	.007
Neuropsychiatric changes, n (%)	16 (20.8%)	10 (16.7%)	6 (35.3%)	.095
Autonomic dysfunction, n (%)	4 (5.2%)	3 (5%)	1 (5.9%)	.640
Frequent seizure, n (%)	41 (53.2%)	28 (46.7%)	13 (76.5%)	.002
Multiple AED (> 2), n (%)	42 (54.5%)	31 (51.7%)	11 (64.7%)	.250

Anti-GAD has been reported in young-onset epilepsy patients with chronic drug resistance, focal EEG abnormalities, and normal MRI findings [26–28]. Other studies reported anti-GAD antibodies in 2% of patients with epilepsy [7, 16] and 2.7% of patients with drug-resistant epilepsy [8]. Serum anti-GAD positivity was reported in two non-convulsive status epilepticus patients, and the neuropsychiatric symptoms of both these patients were resolved after immunosuppressive and antiepileptic treatment [29]. Anti-GAD antibodies have also been reported in patients with limbic encephalitis [30]. We found only one case of anti-GAD antibody positivity (1.3%) in the present study. Focal epileptic abnormalities were present in the EEG, whereas the MRI was normal in our anti-GAD-positive patient.

Anti-thyroid antibodies have rarely been studied in epilepsy patients without encephalopathy. High anti-TPO levels were reported in only one study with paediatric epilepsy patients, whereas anti-thyroid antibodies were found in 7.8% of adult epilepsy patients in another study [21]. Anti-thyroid antibodies were found in 47.8% of adult-onset temporal lobe epilepsy patients of unknown cause, whereas this rate was only 4.3% in patients with known aetiology [31]. We found anti-TPO antibodies in 5.2% of our patients. One patient positive for anti-TPO antibodies had myoclonic seizures, two had secondary generalised tonic-clonic seizures, and one had generalised tonic-clonic seizures. The few patients with temporal lobe epilepsy in the present study may explain our lower anti-thyroid antibody rate compared to that in previous reports. High anti-thyroid antibody levels may actually be related to increased autoantibody production due to confusion in the regulatory mechanisms in the immune system associated with ageing [32].

Inconsistent results have been reported regarding ANA positivity in epilepsy patients. ANA positivity was reported to be more common in those with generalised seizures (11.4%) than in those with focal seizures (4.9%) in one study [21], but it was more common in adults who were newly diagnosed with localisation-related resistant epilepsy than in those with generalised epilepsy in another study [9]. The rate of ANA positivity was low in drug-resistant focal epilepsy according to one study [8], but it was high in patients with frequent seizures according to another [10]. ANA was positive in 10.3% of the patients in the present study. Three of our ANA-positive patients had generalised tonic-clonic seizures, one had absence seizures, and four had focal epileptic abnormalities. EEG abnormalities were present in all ANA-positive patients, and 77.7% showed focal epileptic abnormalities. Significant female predominance was observed in the ANA-positive patients (seven females, one male). None of the patients had a personal or family history of lupus or similar autoimmune diseases. Among the antiepileptics, phenytoin and carbamazepine may increase ANA production and lead to a lupus-like syndrome [33]. Other antiepileptics are not thought to be associated with elevated antibody levels [9, 10, 34, 35]. None of our ANA-positive patients was using phenytoin, and only one patient had a history of carbamazepine use.

Anti-cardiolipin has been associated with long epilepsy duration and poor seizure control in patients with focal epilepsy [10]. We did not detect ACL IgG or IgM in the present study. Similar to our results, another study showed no difference in ACL IGM between epilepsy patients and controls [8].

Anti-phospholipid antibodies are neuropathogenic in vitro and can potentially lead directly to seizures through their neurotoxic effects [36]. Epilepsy is more common in APS than in the general population [37]. We did not find aPL IgG or IgM in our patients.

Paraneoplastic epilepsy should be suspected in some specific clinical situations, such as adult-onset resistant seizures [12]. Paraneoplastic encephalitis was found in a previous series (anti-Hu, anti-amphiphysin, and anti-NMDA-R) [38]. Onconeural antibodies were found in two (2.6%) of our patients (anti-Yo in one patient, anti-MA2/TA in one patient). There was no history of malignancy and no signs of malignancy were found on screening for malignancy. Both of the patients had normal MRI, secondary generalised seizures, and focal EEG abnormalities. Additionally, neither of the patients had cerebellar syndrome, brainstem abnormalities, cognitive impairment, or polyneuropathy. Although the frequency of onconeural autoantibodies is not high in patients with resistant epilepsy, these autoantibodies should be considered in selected cases.

Female gender, frequent seizures, focal EEG abnormalities, focal seizures, aura, family history of epilepsy, and neuropsychiatric disorders were more common in the Ab^+ patients than in the Ab^- patients in the present study. The investigation and treatment of an underlying malignancy followed by intravenous corticosteroid (methylprednisolone) treatment, with cyclophosphamide or rituximab if there is no response are recommended for the management of autoimmune epilepsy [39]. Immunomodulatory treatment was not used in the present study.

Our study had several limitations, including the lack of a normal control group and the relatively small number of patients. The absence of anti-neuronal antibodies in normal healthy controls indicates that these antibodies are not present in the general healthy population [15]. However, as autoimmune and onconeural antibodies are often seen in patients with a personal and family history of autoimmune and paraneoplastic disease, those with these diseases were excluded from the study. None of our patients underwent epilepsy surgery.

In conclusion, various antibodies can have various levels of significance in drug-resistant epilepsy, and they may exert their effects via multiple pathophysiological and immunological mechanisms. Autoimmune factors may be aetiologically

relevant in patients with drug-resistant epilepsy of unknown cause. Understanding the role of autoimmunity in drug-resistant epilepsy of unknown cause requires further and larger multicentre studies with a larger variety of autoantibodies.

Funding This study was supported by the İnönü University Scientific Project Unit (Project no. 2016-64).

Compliance with ethical standards

Ethical approval This article does not include any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

Conflict of interest The authors declare that they have no conflict of interest.

Human and animal rights and informed consent All procedures in studies involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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