Neurological Sciences (2022) 43:5029–5037
https://doi.org/10.1007/s10072-022-06044-5

ORIGINAL ARTICLE

Do the neurologists recognize autoimmune epilepsy well enough? What is the effect of the pandemic on this matter?

Ebru Nur Vanli Yavuz[1] · Ebru Altındağ[2] · Erdem Tüzün[3] · Betül Baykan[4]

Received: 19 December 2021 / Accepted: 30 March 2022 / Published online: 5 April 2022

Abstract

Introduction The concept of "autoimmune epilepsy" (AE) has been emphasized more frequently through the recent increase in recognition of various autoantibodies specific to neuronal proteins.

Aims To evaluate the attitudes of neurologists in regard to AE, to review the differential diagnosis, treatment options, and to reveal the effect of COVID-19 on this matter.

Methods A detailed questionnaire prepared for AE was sent to neurologists via social media and WhatsApp after the approval of the Ethics Committee. The responses of 245 respondents working in different settings were analyzed, and the group with 15 years or less experience in neurology was statistically compared to the group with more than 15 years of experience.

Results Awareness and knowledge levels on AE seemed high in all groups, while 11% had never thought about AE during the differential diagnosis in real life. Before starting treatment, 20% thought that the autoantibody result should definitely support it, and 77.6% reported that they did not recognize AE well. Participants stated that satisfactory guidelines for diagnosis and treatment (88.2%) and widespread laboratory support (83.7%) were lacking. Neurologists with less experience and those working outside of training hospitals get more often consultation from an experienced clinician while diagnosing and conduct more detailed investigations at the diagnosis stage ($p = 0.0025$, $p = 0.0001$).

Conclusion This first survey study conducted in a large group of neurologists on the attitudes for the concept of AE suggested that postgraduate education, and diagnostic and treatment guidelines should be organized and antibody screening tests need to be better disseminated.

Keywords Autoimmune epilepsy · Anti-neuronal antibodies · Neurologist · Awareness · COVID-19

Introduction

Although epilepsies are caused by many different etiologies such as structural, metabolic, genetic, and infective causes, the etiology is not yet elucidated in a large patient group [1].

In recent years, the concept of "autoimmune epilepsy (AE)" has become increasingly recognized in etiology, along with the presence of anti-neuronal antibodies in many patients presenting with encephalopathy and/or seizures. In addition, the decrease in the frequency and severity of seizures with immunosuppressive treatments in some patients increased the interest in this concept of "AE" [2]. For this reason, AE is now included as a separate entity in the last classification of the International League Against Epilepsy (ILAE) [1]. The definition of AE mostly depends on the presence of various types of associated neuronal autoantibodies, and the current knowledge of the associated clinical phenotypes gradually developed over the years. The clinical spectrum is regarded as being only epilepsy or accompanied by typical limbic encephalitis (LE) features like encephalopathy, behavioral, cognitive impairments, and also movement disorders. Accurate diagnosis and treatment of AE can significantly improve clinical outcomes, as affected patients often

✉ Ebru Nur Vanli Yavuz
ebruvanli@gmail.com

[1] Department of Neurology, Faculty of Medicine, Demiroğlu Bilim University, Büyükdere Caddesi No: 120, 34394 Şişli/Istanbul, Turkey

[2] Department of Neurology, Istanbul Florence Nightingale Hospital, Istanbul, Turkey

[3] Department of Neuroscience, Aziz Sancar Research Institute of Experimental Medicine, Istanbul University, Istanbul, Turkey

[4] Department of Neurology, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey

have treatment-resistant seizures that improve only with immunotherapy. Although the triggering event of autoimmunity is generally unknown, underlying cancer that causes a paraneoplastic immune response can be detected in some patients. In addition, the concept of immune-mediated epileptogenesis may lead to other treatment trials targeting the main cause of seizure formation, and new treatment options can be offered to these patients [2, 3].

The described different autoantibodies detected in the sera of the patients with AE arise mainly against neuronal membrane proteins such as ion channel or receptor proteins, which also have the potential to be pathogenic [4, 5]. Neuronal surface antibodies have also been reported in other cases with complaints such as psychosis, nystagmus, and palatal tremor in addition to epilepsy [6, 7]. Diagnosis is confirmed by demonstration of antibodies in serum and/or cerebrospinal fluid (CSF). Besides neuronal autoantibodies targeting extracellular synaptic and cell membrane proteins, those targeting intracellular antigens like GAD have also been associated with AEs. Neuronal surface antibodies are apparently not specific to a particular neurological syndrome; low titers should be evaluated carefully and together with clinical findings [8]. Anti-N-methyl-D-aspartate (NMDA) receptor antibody, one of these antibodies, was first described in 2007 in young female patients with ovarian teratoma-associated encephalitis. Thus, malignancy screening of patients with these antibodies is of crucial importance [9].

When autoantibody screening tests are not available or antibody tests yield negative results, clinicians may seek for different predictive findings in patients' EEG, CSF, cranial MRI, or PET examinations, as listed elsewhere [10]. These particular findings suggest that AE can be a reasonable diagnostic option. Furthermore, in these high-risk individuals, positive response to a trial of immunotherapy further supports the AE diagnosis [10]. A clinically significant response to immunotherapy may favor the administration of long-term immunosuppressive therapy, as well. Treatment recommendations are largely based on observational reports and the clinical experience of major neuroimmunology centers, as there are no randomized controlled studies. As a result of all these developments, in epilepsy cases that are thought to associate with autoimmune mechanisms, defining the clinical phenotypes will be very beneficial in the diagnosis and treatment of subgroups with seizures that may respond to immunosuppression [2, 3].

In addition, it is highlighted that the diagnosis of AE and many other neurological diseases can be delayed or even ignored due to the increased popularity and awareness of COVID-19 encephalopathy in the last 2 years of the pandemic [11–13].

The aim of this study was to evaluate the current diagnosis and treatment approaches of the neurologists in Turkey for AE, which requires early diagnosis of malignancies and correct and prompt initiation of immunosuppression in addition to administration of antiepileptic drugs. We also aimed to reveal the effect of COVID-19 on diagnosing AE.

Methods

In June 2021, a detailed questionnaire (Supplementary Table) aimed at investigating the views and orientations of the neurologists in the determined areas regarding AE was designed by the authors. First, a pilot study was conducted with a small group of neurologists and questions considered necessary for revision were corrected. The last form of the questionnaire included a total of 28 questions. The questionnaire consisted of six sections: profiles of the participants, diagnosis, examination, treatment, follow-up of AE, and further suggestions for AE. Except for a total of 5 yes/no questions and a total of 2 demographic numeric data (age and experience time as a year), all questions were designed as multiple choice. The invitation to participate in the survey was sent to all neurologists, from residents to expert neurologists at every level, working in Turkey between May 25 and July 11, 2021, via social media. They were asked to participate in this questionnaire about AE after giving informed consent via the internet. Each participant could complete the questionnaire only once. Participation in the survey was without any charge.

Given that the aim was to evaluate the level of knowledge of neurologists about AE, the neurologists were asked to choose the answer most appropriate for them. There was no time limit when completing the questionnaire. Participants were given the right to choose to answer or not answer some questions, except for compulsory ones, like age, clinical duty, and professional experience. As the literature on AE is growing in the last 15 years, participants with 0–15 years of professional experience were named group I, and those with 16 or more years of professional experience were considered group II.

The responses of the groups with different experience durations and working in different settings were compared statistically to evaluate the differences of the approach to AE. The SPSS version 26 package program was used for data analysis. Descriptive analyses were performed and percentage values were given for categorical variables. The chi-square test was used for comparisons between two independent categorical variables. Statistical significance was accepted as $p < 0.05$.

Results

A total of 245 neurologists participated in the survey. The average age of the participants was 41.74 ± 10.24 (minimum–maximum 25–71) years. The average duration of

professional experience of the participants was 16.01 ± 10.01 (minimum–maximum 0–42) years. As for the distribution of duties in the clinic, specialists constituted the largest group with 119 (48.5%) people. Of the remaining participants, 79 (32.2%) were lecturers, 40 (16.3%) were residents, and 7 (3%) were retired physicians. Training and research hospitals (37.1%) and university hospitals (37.1) were the main institutions.

A total of 218 (88.9%) neurologists had considered AE at least once during daily practice. The distribution of the number of patients considered by neurologists to have AE when diagnosing during real life is shown in Fig. 1. It was observed that those who did not make this diagnosis before were not only the new beginners to professional life but also participants with 1–38 years of professional experience working in different institutions. Among the suggestive clinical findings for autoimmune epilepsy, the most reminded ones are presentation with memory impairment, seizures with confusion (175/265), and coexistence of psychosis and seizure (164/265). The antibody screening tests were not available in the institutions of 198/245 (80.81%) neurologists. These neurologists referred the patient or shipped the patient's samples to another center. When autoimmune epilepsy was strongly suspected, only 49/245 neurologists chose to wait for the autoantibody results to support the diagnosis before commencing the treatment. Most of the participants (64.5%) reported difficulty in reaching the antibody screening tests. Ninety percent of the neurologists stated that CSF examination should be performed in every patient for AE diagnosis and 49% were aware that CSF examination may yield normal findings in autoimmune epilepsy cases. During the pandemic, 45.7% of neurologists stated that they might have ignored the diagnosis of AE and have wrongfully attributed AE symptoms to COVID-19 encephalopathy.

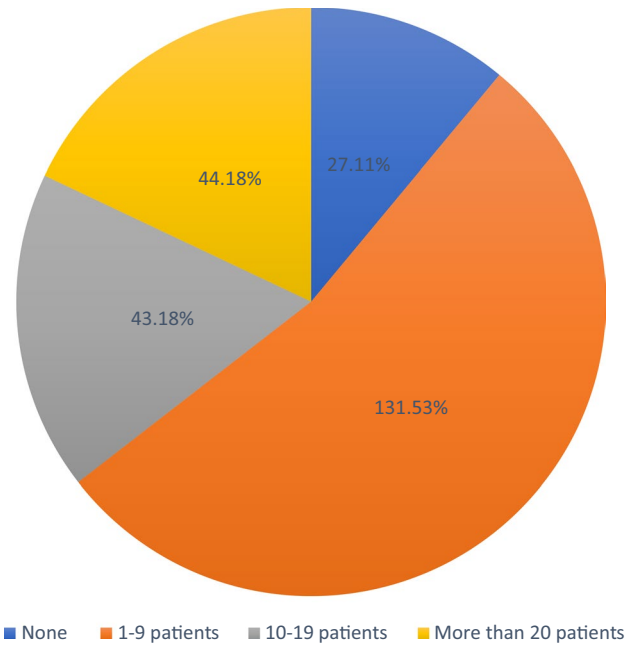

Fig. 1 The total number of patients evaluated in the differential diagnosis as AE during real life

In cases that immunotherapy was considered, pulse methylprednisolone (89.8%) was used most frequently in the first-line treatment; IVIG (87.3%) was used in non-steroid-responsive patients, and seizure control was used as the main response parameter. 27.3% of the participants reported that they were unaware of the prognosis of the patients with chronic epilepsy and autoantibodies. Only 55 out of the 245 participants were confident that they could recognize AE well enough.

When group I ($n = 121$) and group II ($n = 124$) were compared, no statistical difference was observed in terms of referral to another center and waiting for the support of positive antibody results before treatment. When suggestive clinical findings for autoimmune epilepsy in groups compared seizure with pre-infection, febrile illness– and viral illness–like pictures were statistically significant in group 2 ($p = 0.034$). Due to the increased awareness and newly recognized antibodies, the concept of autoimmune epilepsy has become more known in the last 15 years; therefore, 15 years of experience was chosen as a cutoff. The comparison of the approaches of the neurologists regarding the diagnostic findings and treatment options of AE is shown in Table 1. Furthermore, Table 2 shows comparison between neurologists working in institutions providing specialty education and other institutions. Comparisons of attitudes towards clinical findings and EEG, MRI, PET, and CSF findings of AE according to the answers of group I and group II are shown in Fig. 2.

On the other hand, 217/245 neurologists stated that there should be guidelines for diagnosis and treatment, and 205/245 neurologists stated that laboratory support should be provided in all institutions and should allow widespread autoantibody screening.

Discussion

We evaluated the approach of the Turkish neurologists to the diagnosis, examination, treatment, and follow-up processes of AE and compared the responses of neurologist groups with longer (16 or more years) and shorter (1–15 years) experience levels. The results suggest that less experienced neurologists had a higher rate of screening for LGI1 and mGluR5 antibodies, a higher screening rate even for non-specific findings on MRI and normal findings on PET, more frequent counseling rate when diagnosing AE, and a higher rate of the use of thorax and abdomen CT, whereas the experienced group had a higher rate of screening for AE

Table 1 Comparative approaches of neurologists regarding the diagnostic findings and treatment options of autoimmune epilepsy

	Group I with experience ≤ 15 years $n = 121(\%)$	Group II with experience > 15 years $n = 124$ (%)	Statistical significance
Screened antibodies			
GAD	100	93	NS
VGKC-complex	89	93	NS
LGI1	95	75	*0.02¥*
CASPR2	80	78	NS
NMDAR	114	110	NS
AMPAR	81	72	NS
GABAAR	67	63	NS
GABABR	61	55	NS
MGluR5	49	34	*0.031¥*
IgLON5	22	21	NS
DPPX	18	15	NS
Glycine receptor	35	29	NS
Paraneoplastic	95	84	NS
Supplementary diagnostic tests for AE			
EEG	102 (84.29)	110 (88.70)	NS
Cranial MRI	112 (92.56)	114 (91.93)	NS
PET	52 (42.97)	61 (49.19)	NS
CSF	112 (92.56)	124 (100)	NS
CSF examination should be performed in every patient for AE diagnosis	106 (87.60)	115 (92.74)	NS
Rate of taking consultation/opinion from experienced colleagues during the AE diagnosis (rates over 50%)	88 (72.72)	65 (52.41)	*0.0025¥*
Primary diagnosis in a patient presenting with fever, acute confusion and seizure during the pandemic			
AE	91 (75.20)	104 (83.87)	NS
COVID-19-associated encephalopathy	30 (24.80)	20 (16.12)	NS
Ignoring the diagnosis of AE in the pandemic	57 (47.10)	55 (44.35)	NS
Examinations for the differential diagnosis between AE and COVID-19-associated encephalopathy*			
PCR test	96 (79.33)	106 (85.48)	NS
Autoantibodies	80 (66.15)	90 (72.58)	NS
Thorax CT	86 (71.07)	91 (73.38)	NS
MRI	77 (63.63)	90 (72.58)	NS
EEG	70 (57.85)	84 (67.74)	NS
First-line therapy in AE			
Antiepileptic drugs	95 (78.51)	86 (69.35)	NS
Pulse steroid	110 (90.90)	111 (89.51)	NS
Oral high-dose corticosteroid	9 (7.43)	13 (10.48)	NS
Follow-up marker for treatment response in AE			
Seizure remission	118 (97.52)	117 (94.35)	NS
EEG	98 (80.99)	115 (92.74)	NS
MRI	64 (52.89)	59 (47.58)	NS
CSF	17 (14.04)	26 (20.96)	NS
Autoantibody tests	17 (14.04)	30 (24.19)	NS
Second treatment choice in patients unresponsive to first-line therapy			
IVIG	102 (84.29)	112 (90.32)	NS
Plasmapheresis	83 (68.59)	75 (60.48)	NS
Rituximab	30 (24.79)	35 (28.22)	NS
Malignancy screening tools in encephalopathic processes with epilepsy or seizure suggestive of autoimmune etiology			
Tumor markers	107 (88.47)	86 (69.35)	NS
Paraneoplastic autoantibodies	106 (87.60)	106 (85.48)	NS
PET scan	72 (59.50)	80 (64.51)	NS
Autoimmune antibodies	57 (47.10)	58 (46.77)	NS
Screening for common cancers	81 (66.94)	83 (66.93)	NS
Thorax and abdomen CT	104 (85.95)	90 (72.58)	*0.01¥*
I don't scan	1 (0.08)	4 (3.22)	NS

NS, not significant; *n*, number; *GAD*, glutamic acid dehydrogenase; *VGKC*, voltage-dependent potassium channel; *LGI1*, leucine-rich glioma-inactivated 1; *CASPR2*, contactin-associated protein-like 2; *NMDA*, N-methyl-D-aspartate receptor; *AMPA*, alpha-amino-3-hydroxy-5-methyl-4-isoxazolpropionic acid receptor; *GABAA*, gamma-aminobutyric acid-A; *GABAB*, gamma-aminobutyric acid-B; *mGluR5*, metabotropic glutamate receptor 5; *DPPX*, dipeptidyl-peptidase-like protein 6; *EEG*, electroencephalography; *MRI*, magnetic resonance imaging; *PET*, positron emission tomography; *CSF*, cerebrospinal fluid; *AE*, autoimmune epilepsy; *PCR*, polymerase chain reaction; *CT*, computed tomography; *IVIG*, intravenous immunoglobulin.

*Thirty-eight had no experience with this issue. It was calculated from the answers of 207 people.

¥Pearson's chi-square.

Table 2 Comparative approaches of neurologists according to working in centers giving neurology training, regarding the diagnostic findings and treatment options of autoimmune epilepsy

	Group I Working in a center giving neurology training $n=183$(%)	Group II Working in other centers or individually $n=62$ (%)	Statistical significance
Use of supplementary diagnostic tests for AE			
EEG	158 (86.33)	54 (87.09)	NS
Cranial MRI	169 (92.34)	57 (91.93)	NS
PET	82 (44.80)	11 (50.00)	NS
CSF	169 (92.34)	59 (95.16)	NS
CSF examination should be performed in every patient for AE diagnosis	169 (92.34)	52 (83.87)	NS
Rate of taking counseling from an experienced colleague during the AE diagnosis (over 50%)	104 (56.83)	60 (96.77)	*0.0001†*
Primary diagnosis in a patient presenting with fever, acute confusion and seizure during the pandemic			
AE	142 (77.60)	53 (85.48)	NS
COVID-19-associated encephalopathy	41 (22.40)	9 (14.52)	NS
Ignoring the diagnosis of AE in the pandemic	82 (44.80)	30 (48.38)	NS
Examinations for the differential diagnosis between AE and COVID19-associated encephalopathy*			
PCR test	158 (96.93)	44 (100.00)	NS
Autoantibodies	136 (83.43)	34 (77.27)	NS
Thorax CT	141 (86.50)	36 (81.81)	NS
MRI	129 (79.14)	38 (86.36)	NS
EEG	121 (74.23)	33 (75.00)	NS
First-line therapy in AE			
Antiepileptic drugs	130 (71.03)	51 (82.25)	NS
Pulse steroid	167 (91.25)	54 (87.09)	NS
Oral high-dose corticosteroid	14 (7.65)	8 (12.90)	NS
Follow-up marker for treatment response in AE			
Seizure remission	179 (97.81)	56 (90.32)	0.019¥
EEG	156 (85.24)	57 (53.22)	NS
MRI	90 (49.18)	33 (47.58)	NS
CSF	28 (15.30)	15 (24.19)	NS
Autoantibody tests	29 (15.84)	18 (29.03)	NS
Second treatment choice in patients unresponsive to first-line therapy			
IVIG	161 (99.38)	53 (85.48)	NS
Plasmapheresis	118 (64.48)	40 (64.51)	NS
Rituximab	46 (25.13)	19 (30.64)	NS
Malignancy screening tools in encephalopathic processes with epilepsy or seizure suggestive of autoimmune etiology			
Tumor markers	147 (80.32)	46 (74.19)	NS
Paraneoplastic autoantibodies	162 (88.52)	50 (80.64)	NS
PET scan	116 (63.38)	36 (58.06)	NS
Autoimmune antibodies	91 (49.72)	24 (38.70)	NS
Screening for common cancers	129 (70.49)	35 (56.45)	NS
Thorax and abdomen CT	155 (84.69)	39 (62.90)	*0.01¥*
Not scanning for malignancy	2 (1.09)	3 (4.83)	NS

NS, not significant; *n*, number; *EEG*, electroencephalography; *MRI*, magnetic resonance imaging; *PET*, positron emission tomography; *CSF*, cerebrospinal fluid; *AE*, autoimmune epilepsy; *PCR*, polymerase chain reaction; *CT*, computed tomography; *IVIG*, intravenous immunoglobulin.

*Thirty-eight had no experience with this issue. It was calculated from the answers of 207 people.

¥Pearson's chi-square.

†Fisher's exact test.

in patients with seizures with febrile illness– and viral illness–like pictures.

Fortunately, we observed that awareness and knowledge levels of AE were high in both groups. The reason for the high level of knowledge is that many studies have been carried out from different groups in our country about AE [14–19]. In addition, it is noteworthy that the AE subject was given a separate place in congresses and webinars before and during the pandemic, and the subject attracted a lot of attention from the participants. However, it was clearly stated that

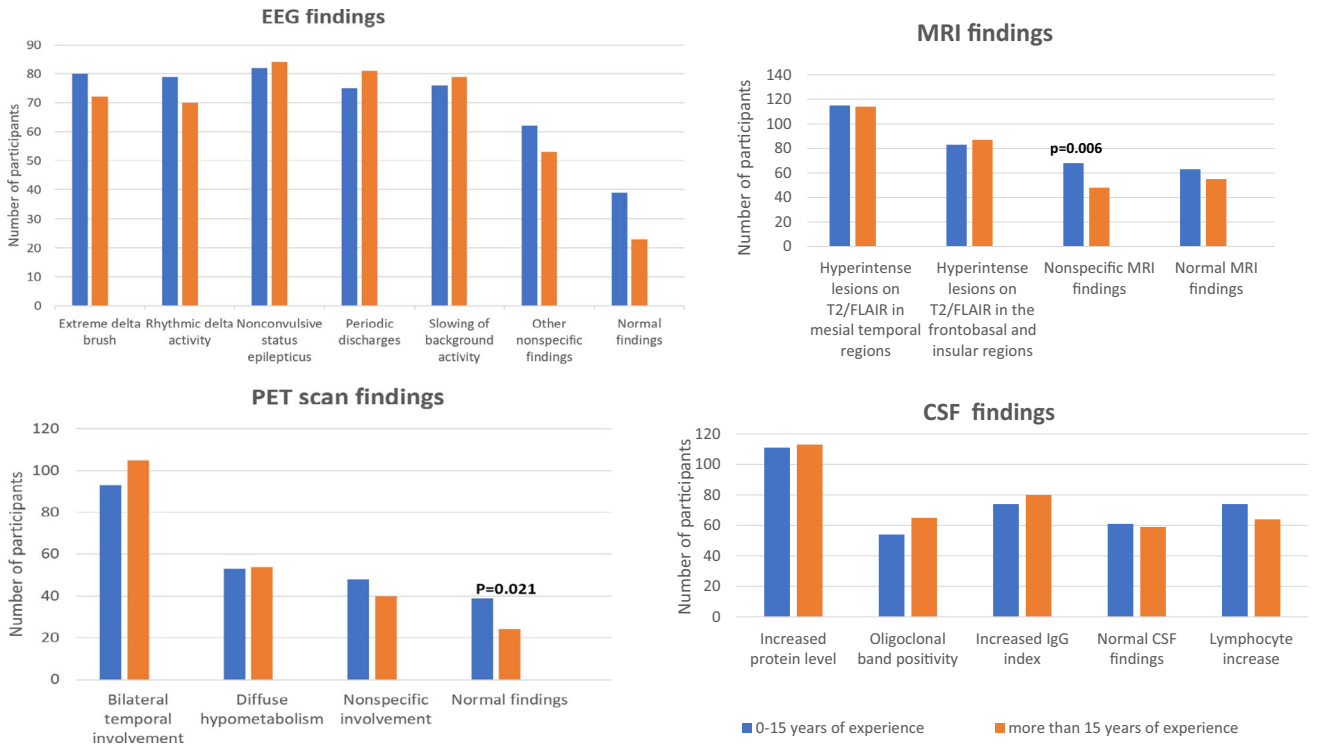

Fig. 2 Comparison of suggestive EEG, MRI, PET, and CSF findings for autoimmune epilepsy in groups with different experience levels

they had more education expectations regarding this issue. Neurologists mostly stated that guidelines for diagnosis and treatment of AE (88.2%) and widespread laboratory support (83.7%) were lacking. For this reason, neurologists with less experience get more consultation from an experienced clinician while diagnosing AE and conduct more detailed investigations at the diagnosis stage.

When the literature was reviewed, no survey study could be found on the recognition of the concept of AE by neurologists. Considering the development of the subject in the last 15 years, there may be a difference between new neurologists and experienced ones, and in our study, no significant difference was observed in their main approaches. A recent case-based survey study was conducted with a large number of participants from all over the world and the diagnosis and treatment approaches for only 2 case examples with neuropsychiatric disease suggestive of AE and temporal-type seizures along with cognitive impairment were presented to the participants. It came out that neuroimmunologists applied immunotherapy more effectively [20]. In another survey study in which adult neurologists, pediatric neurologists, and pediatric rheumatologists had participated, first-line therapy, the transition time to second-line therapy, and second-line therapy preferences were reviewed for NMDA receptor encephalitis. Although the treatment approaches were similar, slight differences were observed according to participants' specialties [21]. We assessed a more detailed approach to AE in terms of diagnosis, differential diagnosis, treatment, and suggestions for better recognition of the matter with multiple-choice questions.

Experienced neurologists are better acquainted with conditions like febrile infection-related epilepsy syndrome (FIRES), and their experience has led them to consider autoimmune therapy more often and rapidly. It was underlined that fever in FIRES started 24 h before the onset of symptoms in children. It is known that if untreated, it turns into new-onset refractory status epilepticus (NORSE) and progresses with a worse prognosis [22]. Neuronal autoantibodies are detected in 32% of patients who present with status epilepticus and a suspected autoimmune etiology. Clinical symptoms like headache and memory problems before the onset can be considered a precursor for antibody-positive patients [23]. It is also important to note that FIRES could also be seen in adults and may be misdiagnosed as "limbic encephalitis" without any evidence of paraneoplastic etiology [24]. It is necessary to raise awareness on this issue and to carry out further studies. Differential diagnosis of status epilepticus triggered by COVID-19 or autoimmune processes in a patient who applied with status epilepticus during the pandemic period is important because the treatment approaches are different [25]. It was widely appreciated that AE might be ignored during the pandemic in our study, and there was no statistical difference between the more and less experienced groups.

LGI1 was the leading antibody screened in both groups (78.5% and 60.5%, respectively). The voltage-gated potassium channel (VGKC) complex consists of leucine-rich glioma-inactivated 1 (LGI1), contactin-associated protein-like-2 (CASPR2), and contactin-2. LGI1 constitutes 70% of the complex [26]. Some patients with high titers of LGI1 antibodies may develop dystonic seizures of the face and arms (faciobrachial dystonic seizures) before temporal lobe seizures or other typical LE symptoms. These seizures, which are numerous during the day, are in the form of very short-term attacks in the form of simultaneous wrinkling of the face and dystonia in the ipsilateral arm. During follow-up, LE develops accompanied by amnesia, typical mesial TLE, and sometimes generalized tonic–clonic seizures [27]. In a previous study with a large cohort, the total ratio of various neuronal autoantibodies was 22.5%. However, LGI1 antibody was not detected in any patient, whereas CASPR2 was frequently observed [14]. The mGluR5 antibody, cited as one of the rarely screened antibodies, was better known to young neurologist participants. It can be seen clinically in a wide range of neuroimmunological diseases including patients with ataxia and Ophelia syndrome, and it accompanies Hodgkin lymphoma [10].

Regarding neuroimaging correlates of AE, it is clearly known that a high rate of signal increase can be observed characteristically in the mesial temporal lobes on cranial MRI in limbic encephalitis and seizures in which autoantibodies are detected [28]. In addition to these regions, it has been reported that there may be abnormal signals in the cortex, cerebellum, brainstem, and basal ganglia [27, 29]. In addition, Ekizoğlu et al. showed that patients with autoantibodies may have nonspecific MRI findings such as white matter lesions on MRI [15]. In our study, neurologists with less experience are aware of these nonspecific cranial MRI findings, which were defined in recent years.

It is known that PET may have important clinical and prognostic findings in terms of LE in which neuronal autoantibodies are detected, especially showing hippocampal dysfunction [30]. In a previous study, we showed that there was a significant difference between the seropositive and seronegative groups in terms of coexistence of temporal lobe and extra-temporal lobe hypometabolism [14], suggesting more widespread involvement in the presence of neuronal autoantibodies. In many related publications, it has also been stated that PET findings are not limited to the mesial temporal lobes, and that PET findings are more important than EEG findings [31, 32]. These findings are important in terms of the possible different involvement patterns of different autoantibodies and should be investigated with larger cohorts. It was remarkable that young neurologists follow the topic and had better knowledge of newly defined antibodies and MRI and PET findings in diagnosis. Also, considering that this group had little experience in diagnosing autoimmune epilepsy, they needed taking consultation/opinion from experienced colleagues while diagnosing AE at a higher level. Both the development of the AE as a remarkable clinical topic in the last 15 years and the lack of algorithms on this subject may have increased the need for counseling, taking consultation/opinion from experienced colleagues while diagnosing AE of young neurologists.

Although malignancy screening tools in encephalopathy or seizures suggestive of autoimmune etiology were performed at a similar rate in both groups, it was noteworthy that thorax and abdominal CT were performed more frequently in the younger group. When antibodies with high cancer relevance are detected, the cancer assessment should be very comprehensive and repeated after some time. If the initial computed tomography is negative, the body's computed tomography-positron emission tomography (CT-PET) will increase the diagnosis rate of cancer by an additional 18% [33].

During the pandemic period, while the etiology is investigated, especially in patients presenting with fever, confusion, and seizure, PCR and thorax CT are primarily performed for diagnosis. Considering the MRI, CSF, and EEG findings, it was noteworthy that COVID-related encephalitis did not present with specific findings and was similar to autoimmune encephalitis in terms of clinical presentation. Immunosuppressive treatments are used in both disease groups because of immune mechanisms in the etiology [34, 35]. In addition, autoimmune epilepsies, which are rarely seen after severe SARS-CoV-2, show clinical diversity [11]. Although there was no statistical difference between group I and group II, the fact that AE was neglected at the rate of 45.7% in the whole group suggests that more attention should be drawn to the issue during the pandemic.

Thus, the awareness level of general neurologists should be increased with appropriate educations and guidelines.

IV methylprednisolone (IVMP) or intravenous immunoglobulin (IVIg) selected according to the comorbidities of the patients can be used as first-line therapy. In unresponsive patients, if autoimmune epilepsy is still suspected, another first-line agent may be tried; these patients are then reassessed after 4 to 6 weeks of treatment [3]. Patients who present with seizures then rapidly progress to status epilepticus, or have signs of autoimmune encephalitis syndrome should receive rapid plasma exchange and even second-line treatments such as rituximab or cyclophosphamide [36]. It has recently been suggested that rituximab treatment in the early period may be an effective treatment option in NMDA receptor, LGI1, and CASPR2-related autoimmune encephalitis [37]. This data indicate clearly that proper management styles of AE are rapidly evolving underlining the need for further attention in the correct diagnosis and management.

As a relatively newer anti-neuronal antibody, data on glycine receptor antibodies are scant. Seven of the 13 patients with long-term follow-up with glycine receptor antibodies were resistant to antiepileptic drugs. Only 2 of them used immunotherapy options and showed benefit. Among the

heterogeneous group, one patient diagnosed with epileptic encephalopathy showed spontaneous remission, while 3 patients with mesial TLE-HS also benefit from epilepsy surgery [19]. This information indicates that it is possible to perform epilepsy surgery in some patients with autoantibodies if preoperative examinations like MRI and ictal records and PET findings are compatible with each other. In patients with a benign course, anti-seizure drugs alone are sufficient to achieve seizure freedom [14, 19]. In recent years, it has been underlined that patients with seropositivity for extracellular antibodies have a good prognosis and can even withdraw their antiepileptic drugs after immune therapy [38, 39].

Our study is a survey study distributed via social media during the pandemic period and has the known limitations of surveys. Since the participants could not ask questions face to face, we tried to optimize the survey as clearly as possible and there were positive feedbacks. Attempts were made to reach out to all general neurologists who were also "not interested in epilepsy" but the participant number remained limited. As the literature on AE is growing in the last 15 years, the participants are divided into 2 groups. The number of participants in both groups was similar to make the comparisons.

Conclusion

In our country, the general awareness level of neurologists on AE is high and this seems true despite the pandemic. The fact that the younger neurologists and those working outside institutions giving neurology training take consultation/opinion from experienced colleagues while diagnosing AE more frequently may indicate that awareness has increased in recent years in parallel with accumulating research. Our findings suggest that postgraduate education, guidelines, and antibody screening tests need to be better disseminated.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10072-022-06044-5.

Declarations

Conflict of interest None.

Ethical approval None.

References

1. Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, Hirsch E, Jain S, Mathern GW, Moshé SL, Nordli DR, Perucca E, Tomson T, Wiebe S, Zhang YH, Zuberi SM (2017) ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. Epilepsia 58(4):512–521. https://doi.org/10.1111/epi.13709
2. Quek AM, Britton JW, McKeon A, So E, Lennon VA, Shin C, Klein C, Watson RE Jr, Kotsenas AL, Lagerlund TD, Cascino GD, Worrell GA, Wirrell EC, Nickels KC, Aksamit AJ, Noe KH, Pittock SJ (2012) Autoimmune epilepsy: clinical characteristics and response to immunotherapy. Arch Neurol 69(5):582–593. https://doi.org/10.1001/archneurol.2011.2985
3. Toledano M, Britton JW, McKeon A, Shin C, Lennon VA, Quek AM, So E, Worrell GA, Cascino GD, Klein CJ, Lagerlund TD, Wirrell EC, Nickels KC, Pittock SJ (2014) Utility of an immunotherapy trial in evaluating patients with presumed autoimmune epilepsy. Neurology 82(18):1578–1586. https://doi.org/10.1212/WNL.0000000000000383
4. Dalmau J, Rosenfeld MR (2008) Paraneoplastic syndromes of the CNS. Lancet Neurol 7(4):327–340. https://doi.org/10.1016/S1474-4422(08)70060-7
5. Brenner T, Sills GJ, Hart Y, Howell S, Waters P, Brodie MJ, Vincent A, Lang B (2013) Prevalence of neurologic autoantibodies in cohorts of patients with new and established epilepsy. Epilepsia 54(6):1028–1035. https://doi.org/10.1111/epi.12127
6. Antonini G, Nemni R, Giubilei F, Gragnani F, Ceschin V, Morino S, Bucci E, Accornero N (2003) Autoantibodies to glutamic acid decarboxylase in downbeat nystagmus. J Neurol Neurosurg Psychiatry 74(7):998–999. https://doi.org/10.1136/jnnp.74.7.998
7. Zandi MS, Irani SR, Lang B, Waters P, Jones PB, McKenna P, Coles AJ, Vincent A, Lennox BR (2011) Disease-relevant autoantibodies in first episode schizophrenia. J Neurol 258(4):686–688. https://doi.org/10.1007/s00415-010-5788-9
8. Lancaster E, Dalmau J. Neuronal autoantigens--pathogenesis, associated disorders and antibody testing. Nat Rev Neurol. 2012; 19;8(7):380–90. https://doi.org/10.1038/nrneurol.2012.99.
9. Dalmau J, Tüzün E, Wu HY, Masjuan J, Rossi JE, Voloschin A, Baehring JM, Shimazaki H, Koide R, King D, Mason W, Sansing LH, Dichter MA, Rosenfeld MR, Lynch DR (2007) Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol 61(1):25–36. https://doi.org/10.1002/ana.21050
10. Toledano M, Pittock SJ (2015) Autoimmune epilepsy. Semin Neurol 35(3):245–258. https://doi.org/10.1055/s-0035-1552625
11. Valencia Sanchez C, Theel E, Binnicker M, Toledano M, McKeon A (2021) Autoimmune encephalitis after SARS-CoV-2 infection: case frequency, findings, and outcomes. Neurology 97(23):e2262–e2268. https://doi.org/10.1212/WNL.0000000000012931 (Epub 2021 Oct 11 PMID: 34635560)
12. Kuroda N (2021) Epilepsy and COVID-19: updated evidence and narrative review. Epilepsy Behav 116:107785. https://doi.org/10.1016/j.yebeh.2021.107785
13. Özdağ Acarli AN, Samanci B, Ekizoğlu E, et al. Coronavirus disease 2019 (COVID-19) from the point of view of neurologists: observation of neurological findings and symptoms during the combat against a pandemic. *Noro Psikiyatr Ars*. 2020;57(2):154–159. Published 2020 May 1. doi:https://doi.org/10.29399/npa.26148
14. Vanli-Yavuz EN, Erdag E, Tuzun E, Ekizoglu E, Baysal-Kirac L, Ulusoy C, Peach S, Gundogdu G, Sencer S, Sencer A, Kucukali CI, Bebek N, Gurses C, Gokyigit A, Baykan B (2016) Neuronal autoantibodies in mesial temporal lobe epilepsy with hippocampal sclerosis. J Neurol Neurosurg Psychiatry 87(7):684–692. https://doi.org/10.1136/jnnp-2016-313146
15. Ekizoglu E, Tuzun E, Woodhall M, Lang B, Jacobson L, Icoz S, Bebek N, Gurses C, Gokyigit A, Waters P, Vincent A, Baykan B (2014) Investigation of neuronal autoantibodies in two different focal epilepsy syndromes. Epilepsia 55(3):414–422. https://doi.org/10.1111/epi.12528
16. Gozubatik-Celik G, Ozkara C, Ulusoy C, Gunduz A, Delil S, Yeni N, Tuzun E (2017) Anti-neuronal autoantibodies in both drug responsive and resistant focal seizures with unknown cause. Epilepsy Res 135:131–136. https://doi.org/10.1016/j.eplepsyres.2017.06.008

17. Tezer FI, Firat A, Tuzun E, Unal I, Soylemezoglu F, Bilginer B, Kaymaz F, Oguz KK, Saygi S (2018) Immunopathology in drug resistant mesial temporal lobe epilepsy with different types of hippocampal sclerosis. Int J Neurosci 128(5):421–428. https://doi.org/10.1080/00207454.2017.1389928
18. Baysal-Kirac L, Tuzun E, Erdag E, Ulusoy C, Vanli-Yavuz EN, Ekizoglu E, Peach S, Sezgin M, Bebek N, Gurses C, Gokyigit A, Vincent A, Baykan B (2016) Neuronal autoantibodies in epilepsy patients with peri-ictal autonomic findings. J Neurol 263(3):455–466. https://doi.org/10.1007/s00415-015-8002-2
19. Ekizoglu E, Baykan B, Sezgin M, Erdag E, Gundogdu-Unverengil G, Vanlı-Yavuz EN, Tekturk P, Yılmaz E, Bebek N, Tuzun E (2019) Follow-up of patients with epilepsy harboring antiglycine receptor antibodies. Epilepsy Behav 92:103–107. https://doi.org/10.1016/j.yebeh.2018.09.034
20. Ganesh A, Bartolini L, Wesley SF (2020) Worldwide survey of neurologists on approach to autoimmune encephalitis. Neurol Clin Pract 10(2):140–148. https://doi.org/10.1212/CPJ.0000000000000701
21. Bartolini L, Muscal E (2017) Differences in treatment of anti-NMDA receptor encephalitis: results of a worldwide survey. J Neurol 264(4):647–653. https://doi.org/10.1007/s00415-017-8407-1
22. Sculier C, Barcia Aguilar C, Gaspard N, Gaínza-Lein M, Sánchez Fernández I, Amengual-Gual M, Anderson A, Arya R, Burrows BT, Brenton JN, Carpenter JL, Chapman KE, Clark J, Gaillard WD, Glauser TA, Goldstein JL, Goodkin HP, Gorman M, Lai YC, McDonough TL, Mikati MA, Nayak A, Peariso K, Riviello J, Rusie A, Sperberg K, Stredny CM, Tasker RC, Tchapyjnikov D, Vasquez A, Wainwright MS, Wilfong AA, Williams K, Loddenkemper T; pSERG. Clinical presentation of new onset refractory status epilepticus in children (the pSERG cohort). Epilepsia. 2021 Jul;62(7):1629–1642. https://doi.org/10.1111/epi.16950.
23. Suga H, Yanagida A, Kanazawa N, Ohara H, Kitagawa T, Hayashi M, Onozawa Y, Nagata N, Kaneko J, Kitamura E, Nishiyama K, Iizuka T (2021) Status epilepticus suspected autoimmune: neuronal surface antibodies and main clinical features. Epilepsia 62(11):2719–2731. https://doi.org/10.1111/epi.17055
24. Tektürk P, Baykan B, Tüzün E. Febrile infection related epilepsy syndrome (FIRES) in adults imitating limbic encephalitis. Journal of Neurological Sciences [Turkish] 32:(1) 43; 000–000, 2015.
25. Monti G, Giovannini G, Marudi A, Bedin R, Melegari A, Simone AM, Santangelo M, Pignatti A, Bertellini E, Trenti T, Meletti S (2020) Anti-NMDA receptor encephalitis presenting as new onset refractory status epilepticus in COVID-19. Seizure 81:18–20. https://doi.org/10.1016/j.seizure.2020.07.006
26. Vincent A, Bien CG, Irani SR, Waters P (2011) Autoantibodies associated with diseases of the CNS: new developments and future challenges. Lancet Neurol 10(8):759–772. https://doi.org/10.1016/S1474-4422(11)70096-5
27. Irani SR, Michell AW, Lang B, Pettingill P, Waters P, Johnson MR, Schott JM, Armstrong RJ, S Zagami A, Bleasel A, Somerville ER, Smith SM, Vincent A. Faciobrachial dystonic seizures precede Lgi1 antibody limbic encephalitis. Ann Neurol. 2011;69(5):892–900. https://doi.org/10.1002/ana.22307.
28. Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Cellucci T, Cortese I, Dale RC, Gelfand JM, Geschwind M, Glaser CA, Honnorat J, Höftberger R, Iizuka T, Irani SR, Lancaster E, Leypoldt F, Prüss H, Rae-Grant A, Reindl M, Rosenfeld MR, Rostásy K, Saiz A, Venkatesan A, Vincent A, Wandinger KP, Waters P, Dalmau J (2016) A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol 15(4):391–404. https://doi.org/10.1016/S1474-4422(15)00401-9
29. Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R (2011) Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol 10(1):63–74. https://doi.org/10.1016/S1474-4422(10)70253-2
30. Heine J, Prüss H, Bartsch T, Ploner CJ, Paul F, Finke C (2015) Imaging of autoimmune encephalitis–relevance for clinical practice and hippocampal function. Neuroscience 19(309):68–83. https://doi.org/10.1016/j.neuroscience.2015.05.037
31. Ances BM, Vitaliani R, Taylor RA, Liebeskind DS, Voloschin A, Houghton DJ, Galetta SL, Dichter M, Alavi A, Rosenfeld MR, Dalmau J (2005) Treatment-responsive limbic encephalitis identified by neuropil antibodies: MRI and PET correlates. Brain 128(Pt 8):1764–1777. https://doi.org/10.1093/brain/awh526
32. Wei YC, Tseng JR, Wu CL, Su FC, Weng WC, Hsu CC, Chang KH, Wu CF, Hsiao IT, Lin CP (2020) Different FDG-PET metabolic patterns of anti-AMPAR and anti-NMDAR encephalitis: case report and literature review. Brain Behav 10(3):e01540. https://doi.org/10.1002/brb3.1540
33. McKeon A, Apiwattanakul M, Lachance DH, Lennon VA, Mandrekar JN, Boeve BF, Mullan B, Mokri B, Britton JW, Drubach DA, Pittock SJ (2010) Positron emission tomography-computed tomography in paraneoplastic neurologic disorders: systematic analysis and review. Arch Neurol 67(3):322–329. https://doi.org/10.1001/archneurol.2009.336
34. Zhai P, Ding Y, Wu X, Long J, Zhong Y, Li Y (2020) The epidemiology, diagnosis and treatment of COVID-19. Int J Antimicrob Agents 55(5):105955. https://doi.org/10.1016/j.ijantimicag.2020.105955
35. Siow I, Lee KS, Zhang JJY, Saffari SE, Ng A (2021) Encephalitis as a neurological complication of COVID-19: a systematic review and meta-analysis of incidence, outcomes, and predictors. Eur J Neurol 28(10):3491–3502. https://doi.org/10.1111/ene.14913
36. Titulaer MJ, McCracken L, Gabilondo I, Armangué T, Glaser C, Iizuka T, Honig LS, Benseler SM, Kawachi I, Martinez-Hernandez E, Aguilar E, Gresa-Arribas N, Ryan-Florance N, Torrents A, Saiz A, Rosenfeld MR, Balice-Gordon R, Graus F, Dalmau J (2013) Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol 12(2):157–165. https://doi.org/10.1016/S1474-4422(12)70310-1
37. Thaler FS, Zimmermann L, Kammermeier S, Strippel C, Ringelstein M, Kraft A, Sühs KW, Wickel J, Geis C, Markewitz R, Urbanek C, Sommer C, Doppler K, Penner L, Lewerenz J, Rößling R, Finke C, Prüss H, Melzer N, Wandinger KP, Leypoldt F, Kümpfel T; German Network for Research on Autoimmune Encephalitis (GENERATE). Rituximab treatment and long-term outcome of patients with autoimmune encephalitis: real-world evidence from the GENERATE registry. Neurol Neuroimmunol Neuroinflamm. 2021;1;8(6):e1088. https://doi.org/10.1212/NXI.0000000000001088.
38. Rada A, Birnbacher R, Gobbi C, Kurthen M, Ludolph A, Naumann M, Neirich U, von Oertzen TJ, Ransmayr G, Riepe M, Schimmel M, Schwartz O, Surges R, Bien CG (2021) Seizures associated with antibodies against cell surface antigens are acute symptomatic and not indicative of epilepsy: insights from long-term data. J Neurol 268(3):1059–1069. https://doi.org/10.1007/s00415-020-10250-6
39. Ilyas-Feldmann M, Prüß H, Holtkamp M (2021) Long-term seizure outcome and antiseizure medication use in autoimmune encephalitis. Seizure 86:138–143. https://doi.org/10.1016/j.seizure.2021.02.010