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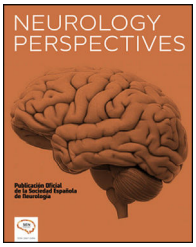

ORIGINAL ARTICLE

Autoimmune-associated epilepsy in an outpatient epilepsy clinic: A retrospective study

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KEYWORDS
Autoimmune epilepsy;
Acute symptomatic seizures secondary to autoimmune encephalitis;
Autoimmune-associated epilepsy;
Isolated autoimmune epilepsy

Abstract
Purpose: To analyse cases with suspected autoimmune-associated epilepsy (AAEp) and to compare them to patients with acute symptomatic seizures secondary to autoimmune encephalitis (ASS-AEn).
Methods: Single-centre retrospective analysis of patients with suspected AAEp seen in an outpatient epilepsy clinic between 2014 and 2021. Differences according to autoimmune testing results and their responsiveness to immunotherapy were assessed and compared with our cohort of patients with ASS-AEn.
Results: A total of 30 patients were included: 18 women (60%); mean age 28.2 years at seizure-onset. AAEp was diagnosed in 14 (46.6%), on the basis of antineuronal antibodies, CSF pleocytosis/OCB (oligoclonal bands), MRI with neuroinflammation, and/or PET hypermetabolism. Thirteen patients (43.3%) received immunotherapy, of whom 5 responded (38.4%). Delay between epilepsy-onset and autoimmune testing was longer in patients with negative autoimmune-testing and in non-responders. Viral prodrome ($P < .035$), associated neurological signs/symptoms and MRI showing neuroinflammation were more common in responders. ASS-AEn patients were older ($P < .019$), and more frequently presented coexisting neurological signs/symptoms ($P < .0001$), antineuronal cell-surface antibodies ($P < .009$), neuroinflammation on MRI, PET hypermetabolism ($P < .01$), CSF pleocytosis ($P < .047$), and higher APE (antibody prevalence in epilepsy)/RITE (response to immunotherapy in epilepsy)-scores ($P < .022$/$P < .004$). Drug-refractoriness ($P < .033$) was more common in AAEp. ASS-AEn received immunotherapy more frequently, with better outcomes. Diagnosis and treatment delay were longer in AAEp ($P < .0001$).

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Conclusion: Isolated/chronic AAEp is a rare, drug-resistant epileptic-disorder. Early diagnosis is essential for immunotherapy. However, diagnostic and therapeutic delay is longer in AAEp than in ASS-AEn. This may indicate that currently there is less capacity to detect AAEp than ASS-AEn.

PALABRAS CLAVE
autoimmune epilepsy;
acute symptomatic seizures secondary to autoimmune encephalitis;
autoimmune-associated epilepsy;
isolated autoimmune epilepsy

Epilepsia asociada a autoinmunidad en consulta monográfica de epilepsia: Estudio retrospectivo

Resumen
Objetivo: Analizar los casos con sospecha de epilepsia asociada a autoinmunidad (EAA). Compararlos con pacientes con crisis epilépticas sintomáticas agudas a encefalitis autoinmunes (CSA-EA).
Métodos: Estudio unicéntrico-retrospectivo de pacientes con sospecha de EAA de una consulta monográfica de epilepsia (2014–2021). Análisis de sus diferencias según resultados del estudio de autoinmunidad y respuesta a tratamiento inmunosupresor. Comparación con una cohorte hospitalaria de pacientes con CSA-EA.
Resultados: Se incluyeron 30 pacientes: 18 mujeres (60%); edad media = 28.2 años al debut. Fueron diagnosticados de EAA 14 (46.6%), en base a anticuerpos antineuronales, pleocitosis/BOC (bandas oligoclonales) en LCR, neuroinflamación en RM y/o hipermetabolismo en PET cerebral. Trece (43.3%) recibieron inmunosupresión, respondiendo 5 (38.4%). El retraso diagnóstico fue mayor en pacientes con resultados negativos y en no respondedores. El pródromos pseudoviral ($p < 0.035$), la coexistencia de signos/síntomas neurológicos y la neuroimagen inflamatoria fueron más frecuentes en respondedores. Los pacientes con CSA-EA fueron mayores ($p < 0.019$) y presentaron más frecuentemente otros signos/síntomas neurológicos ($p < 0.0001$), anticuerpos anti-superficie neuronal ($p < 0.009$), neuroinflamación en RM, hipermetabolismo en PET ($p < 0.01$), pleocitosis ($p < 0.047$) y puntuaciones APE(antibody prevalence in epilepsy)/RITE (response to immunotherapy in epilepsy) más altas ($p < 0.022$/$p < 0.004$). La farmacorrefractariedad ($p < 0.033$) fue más común en EAA. Las CSA-EA recibieron inmunosupresión más frecuentemente, con mejores resultados. El retraso diagnóstico-terapéutico fue mayor en la EAA ($p < 0.0001$).
Conclusión: La EAA constituye una epilepsia infrecuente pero farmacorrefractaria. Su diagnóstico precoz es esencial para su tratamiento; sin embargo, existe un retraso diagnóstico-terapéutico mayor que en las CSA-EA, pudiendo ello indicar que actualmente se dispone de menor capacidad para detectar EAA que CSA-EA.

Introduction

Autoimmune epilepsy (AEp) refers to epilepsy of autoimmune aetiology.[1] The link between the immune system and epilepsy has long been described,[2] but AEp was not included in the International League Against Epilepsy (ILAE) seizure classification until 2017.[1] However, the definition of AEp is still highly controversial:[3] AEp is considered a broad term that encompasses different types of conditions, and conceptual distinctions are emerging between acute symptomatic seizures (ASS) secondary to autoimmune encephalitis (AEn) and autoimmune-associated epilepsy (AAEp).[4,5] The first refers to seizures occurring in the setting of the active phase of AEn, while the second refers to chronic seizures which are the unique or the main symptom of a disorder that is caused by autoimmune brain diseases.[4,6] Epilepsy, as defined by the ILAE, is considered a chronic disease.[1] On this basis, AEp should be used to refer to a chronic disorder in which seizures are the most prominent symptom and an autoimmune origin is confirmed by the presence of either antineuronal antibodies or chronic brain inflammation.[3] However, the proposed diagnostic criteria for AEp[7,8] and rating scales predicting antineuronal antibody prevalence in epilepsy (APE-score) and the chance of response to immunotherapy in epilepsy (RITE-score)[9,10] are strongly focused on ASS-AEn.[5] As such, the available diagnostic criteria for AEp as an isolated symptom or as a chronic disorder are inadequate.[5] Moreover, although increasing evidence is emerging on when to suspect AEp in an acute setting,[2,7,10–12] it remains unclear when AEp should be suspected in chronic or isolated epileptic disorders, despite this being the most common scenario in the outpatient care setting. In real-

world practice, most epilepsy experts need to manage chronic seizure disorders of unknown aetiology that might be autoimmune in origin, but no guidelines or recommendations are available on when to perform autoimmune testing or when to start immunotherapy in this setting. In response to this lack of information, this study aimed to provide more data in the area of chronic/isolated AAEp, in order to optimise the selection of patients who would benefit from autoimmune testing and an immunotherapy trial in outpatient clinical practice.

The main objective of this study is to analyse cases in which AAEp was suspected in the outpatient epilepsy clinic of Cruces University Hospital (CUH), a national epilepsy referral centre in Spain, between 2014 and 2021. Primary aims of the study were to determine how many patients with clinical suspicion were finally diagnosed with AAEp and to analyse differences according to autoimmune test results and response to immunotherapy. Understanding these differences could lead to better and earlier identification of patients with AAEp.

A secondary study objective was to assess whether diagnostic, therapeutic, and/or prognostic differences exist between patients with chronic/isolated AAEp and patients with ASS-AEn seen in our hospital.

Materials and methods

We conducted a single-centre retrospective analysis of patients with suspected AAEp who were treated in the outpatient epilepsy clinic of CUH between 2014 and 2021. Patients with a final diagnosis of AAEp were then compared with the cohort of ASS-AEn patients seen in our hospital (data recorded since 2005).

Patients: Inclusion and exclusion criteria

Patients with epilepsy of suspected autoimmune origin were identified. Autoimmune aetiology was suspected based on seizure type and frequency, poor or inexistent response to antiseizure drugs (ASD), and the presence of clinical features suggestive of autoimmunity. Specifically, a diagnostic suspicion of AAEp was established in epilepsies of unknown aetiology despite previous pertinent studies that were associated with drug-resistant epilepsy (DRE) (defined as refractoriness to adequate trials of at least 2 tolerated and appropriately used ASD) and/or high frequency of seizures from onset (defined as $\geq$1 seizure per week) and at least one of the following: (1)medical history of any systemic autoimmune disorder, (2)malignancy, except skin tumours other than melanoma, (3) associated neurological signs or symptoms, such as neuropsychiatric changes (psychosis, delusions), behavioural disorders, dysautonomia, and/or a memory impairment that was worse than that expected from the epileptic disorder. Epilepsy and seizure types were categorised according to the 2017 ILAE seizure classification.[1] Patients were excluded if they had any underlying disorder that would explain epilepsy. The presence of structural brain lesions on magnetic resonance imaging (MRI) that could cause symptomatic seizures, such as stroke, tumour, trauma, heterotopias, vascular malformation, abscess, or congenital malformation, was an exclusion criterion. Patients with idiopathic mesial temporal sclerosis (MTS) were not excluded because MTS has been associated with late stages of autoimmune disorders.[4,6,13–15] Only patients who underwent autoimmune testing, including the determination of anti-neuronal cell-surface and intracellular (antiGAD; onconeural) antibodies, at least in serum samples, were eligible. Antibody determination in cerebrospinal fluid (CSF) was mandatory if a positive result was obtained in serum, and advisable in all patients, although the lack of CSF analysis did not represent an exclusion criterion in patients with negative antibodies in serum.

Autoimmune testing was considered consistent with AAEp if at least one of the following was found: (1) positive anti-neuronal cell-surface or intracellular antibodies in serum and/or CSF, (2) CSF pleocytosis/positive OCB, (3) T2/FLAIR hyperintensity in one/both temporal lobes or in multifocal areas consistent with inflammation in $\geq$2 brain MRIs, or (4) hypermetabolism of one/both temporal lobes in a non-ictal brain PET. An isolated MRI finding following spontaneous resolution was not considered a consistent finding of AAEp in order to prevent over-interpretation of non-specific findings that could be secondary to seizures but not to autoimmunity.[16] Therapeutic response was defined as seizure freedom or a $\geq$50% reduction in seizure frequency after immunotherapy. The immunotherapy trial consisted of methylprednisolone pulses (MTP) (1 g/day for 5 days), intravenous immunoglobulins (IgIV) (0.4 g/kg/day for 5 days monthly for 1–6 months), rituximab (two 1000 mg infusions separated by 2 weeks, following 1–2 additional infusions separated by 6 months) and/or cyclophosphamide (500 mg/day for 5 days), either in monotherapy or in different combinations. Patients with positive autoimmune testing or who showed therapeutic response to immunotherapy were diagnosed with AAEp.

For the secondary study objective, patients with ASS-AEn diagnosed in our hospital were identified. AEn was diagnosed on the basis of clinical syndrome (subacute onset of working memory deficits, altered level of consciousness, psychiatric symptoms, seizures), supported by the presence of antineuronal antibodies or either an altered and congruent brain MRI and/or CSF pleocytosis/positive oligoclonal bands (OCB). MRI was considered congruent with AEn in the presence of hyperintensity on T2-weighted/fluid-attenuated inversion recovery (T2/FLAIR) sequences of one/both medial temporal lobes or in multifocal areas consistent with inflammation. All patients with ASS-AEn satisfied the proposed diagnostic criteria for AEn.[17] The reasonable exclusion of any alternative diagnosis was required for all patients.

Immunological analysis

The immunology laboratory of CUH analysed anti-neuronal cell-surface and intracellular antibodies in serum and CSF samples. In the case of intracellular antibodies, indirect immunoblot assays (commercial kit, EUROIMMUN-EUROLINE) were used for detection of antiHu, antiYo, antiRi, antiCV2, antiPNMA2(Ma2/Ta), antiamphiphysin, antiRecoverin, antiSOX1, antiZic4, antiGAD, and antiTr(DNER) antibodies. Positive results were confirmed using indirect immunofluorescence assays on

primate nerve, gut, and cerebellar tissue (EUROIMMUN). In the case of antineuronal cell-surface/synaptic proteins, the laboratory performed a cell-based assay on human epithelial kidney transfected cells (commercial kit, EUROIMMUN) to analyse antiNMDAR, antiGABABR, antiAMPA, antiLGI1, antiCASPR2, and antiDPPX autoantibodies.

Data collection

The following data were recorded: gender; age at epilepsy onset; delay between epilepsy onset and autoimmune testing; type of seizures; seizure frequency (seizure record registered and provided by the patient her/himself); drug-refractoriness, number of ASD; status epilepticus; intensive care unit (ICU) admission; associated neurological signs/symptoms; history of autoimmunity/malignancy/viral prodrome prior to seizure onset; antibody determination in serum and/or CSF; antibody type; brain MRI; lumbar puncture; OCB; electroencephalogram; brain fluorodeoxyglucose positron emission tomography (PET); APE- and RITE-scores; immunotherapy trial; responsiveness to immunotherapy; and mortality.

Statistical analysis

Differences between patient subgroups were analysed. On one hand, patients with positive and negative autoimmune testing were compared. On the other hand, patients with and without therapeutic response to immunotherapy were compared. Lastly, the subgroup of patients with a final diagnosis of AAEp was compared with patients with ASS-AEn.

A Chi-squared test or Fisher's exact test was used to compare differences among the subsets of qualitative variables. The independent samples *t*-test and analysis of variance were used to compare differences in continuous quantitative variables. SPSS 24.0 software was used for statistical analysis, with a *P*-value of $<.05$ indicating a significant difference.

Results

Patients

Overall, 1749 patients were seen during the study period. In 30 (1.71%), autoimmune testing was performed due to clinical suspicion of AAEp (Fig. 1), 60% of whom were women, with a mean age of 28.2 years at seizure-onset. Epilepsy was focal in 27 (90%), generalised in 2 (6.7%), and unknown in 1 (3.3%). Seizures were multifocal in 13 patients. In most patients (73.3%), a temporal onset of seizures was identified. Frequency of seizures was between 1 seizure per month and ≥ 1 daily seizure (median = 4/month, range 49.6). All patients had DRE of unknown aetiology. The median number of ASDs was 3. Ten (33.3%) patients presented with status epilepticus, 2 of them (6.66%) at epilepsy onset. Eight patients (23.6%) had medical history of autoimmunity; 1 (3.3%) had a history of malignancy (testicular teratoma) and 6 (20%) of viral prodrome. Twenty-two patients (73.3%) described memory loss and 8 (23.6%) presented associated neurological signs/symptoms (Table 1). Average delay between epilepsy onset and autoimmune testing was 12.4 years.

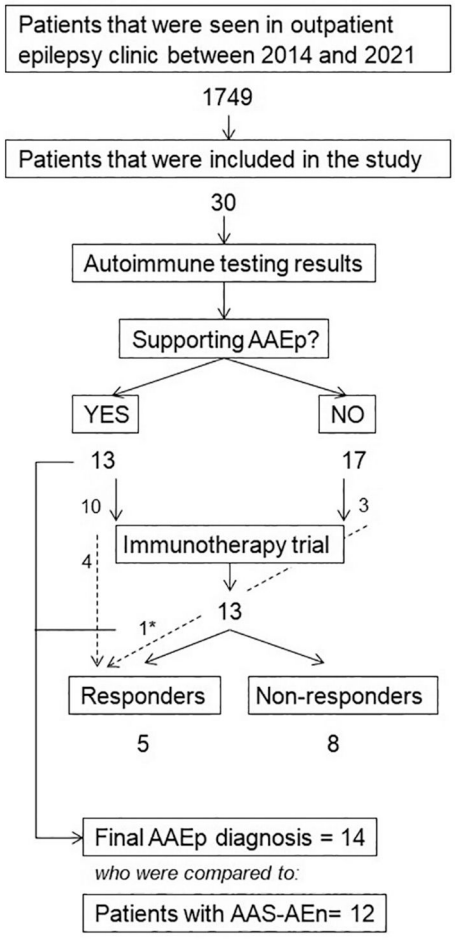

Fig. 1 Flowchart.
A total of 1749 patients were seen in the outpatient epilepsy clinic between 2014 and 2021. In 30 of them, autoimmune testing was performed due to clinical suspicion of autoimmune-associated epilepsy, achieving supporting results in 13. Of the 30 patients with clinical suspicion of autoimmune-associated epilepsy that were included in the study, an immunotherapy trial was performed to 13 (10 of the 13 patients with supporting autoimmune testing and 3 of the 17 patients with normal results). Therapeutic response was obtained in 5 of them, including 4 of the patients with positive autoimmune testing and the 1 patient (*) who had normal results. Eight patients were non-responders. Autoimmune-associated epilepsy was diagnosed in 14 patients: the 13 patients with supporting autoimmune testing and the patient who responded to immunotherapy despite normal results. The 14 patients who were finally diagnosed with autoimmune-associated epilepsy were then compared to 12 patients with acute symptomatic seizures secondary to autoimmune encephalitis.

Autoimmune testing

Of the 30 patients with clinical suspicion of AAEp, findings were consistent with AAEp in 13 (43.3%). Antineuronal antibodies were positive in 5 (16.6%): 1 antiNMDAR, 3 antiGAD (titters = 0.6284, 0.2917, 0.244 [normal value <0.02]), and 1 antiSOX1. Lumbar puncture was performed in 22 patients, showing CSF pleocytosis in 4. OCB were

Table 1 Main characteristics of patients with suspected autoimmune-associated epilepsy.

Patients with suspected autoimmune-associated epilepsy	Number (Total *n* = 30)	%
Sex	Female 18	Female 60%
Age at epilepsy onset (mean +/- SD)	28.2 years (+/-12.7 SD)	
Epilepsy type		
Focal	27	90%
Generalised	2	6.7%
Unknown	1	3.3%
Seizure-onset		
Temporal	22	73.3%
Frontal–temporal	3	9.6%
Parietal–occipital	1	3.3%
Unknown	4	13.3%
Frequency of seizures	1 seizure per month to ≥1 daily (median = 4/month, range 49.6)	
DRE	30	100%
Median number of ASD	3 (range 1–5)	
Median number of previously tried ASD	5 (range 0–12)	
Carriers of vagus nerve stimulator	5	16.7%
Status epilepticus	10	33.3%
Status at seizure onset	2	6.7%
ICU admission	9	30%
History of:		
Autoimmunity	8	26.60%
Systemic erythematous lupus associated with antiphospholipid syndrome	4	13.30%
Antiphospholipid syndrome	1	3.30%
Crohn disease	1	3.30%
Sarcoidosis	1	3.30%
Thrombocytopenic purpura	1	3.30%
Malignancy	1	3.30%
Viral prodrome	6	20%
Associated neurological signs/symptoms		
Neuropsychiatric symptoms	7	23.30%
Parkinsonism	1	3.33%
Memory loss	22	73.30%

Abbreviations: ASD: antiseizure drug, ICU: intensive care unit, SD: standard deviation.

assessed in 17, resulting positive in 4, who had otherwise normal CSF analysis. Brain MRI showed neuroinflammation in 4 cases (13.3%). Three patients (10%) had idiopathic MTS. Non-ictal brain PET showed left temporal hypermetabolism in 1 case/patient (3.33%) (Fig. 2), and hypometabolism of various regions in 12 (40%). Mean rating on APE- and RITE-scores were 3.43 (SD = 1.73) and 3.56 (SD = 1.77) respectively, with APE ≥4 (predictor of antineuronal antibody positivity) in 10 cases and RITE ≥7 (predictor of immunotherapy response) in 2.

Immunotherapy trial

Immunotherapy was attempted in 13 patients (43.3%). Immunotherapy consisted of IgIV in 7 cases, rituximab in 1, cyclophosphamide in 1, IgIV followed by MTP in 1, IgIV followed by rituximab in 1, and a combination of IgIV, MTP, and rituximab in 2. Positive therapeutic response was obtained in 5 patients, who had received IgIV, rituximab, and MTP plus IgIV; including 1 patient with normal autoimmune testing. Hence, 38.4% of patients who received immunosuppressants and 16.7% of clinically suspected AAEp improved after immunotherapy. Seizure freedom was achieved only in 1 case. All patients continued treatment with ASD. Among the 4 patients showing neuroinflammation in brain MRI, findings persisted unchanged in 2, neuroinflammation evolved in one case to MTS and in another one to gliotic changes.

Eventually, 14 patients (46.6%) were diagnosed with AAEp: the 13 patients with supporting autoimmune testing and the patient who responded to immunotherapy despite normal results. The median time of patient follow-up after autoimmune testing was 4.7 years.

Differences between patients with positive and negative autoimmune testing

Patients with positive and negative autoimmune testing were compared (Table 2). History of autoimmunity and viral prodrome were more common among patients with positive findings than in those with negative results, although no statistical significance was found. Likewise, associated

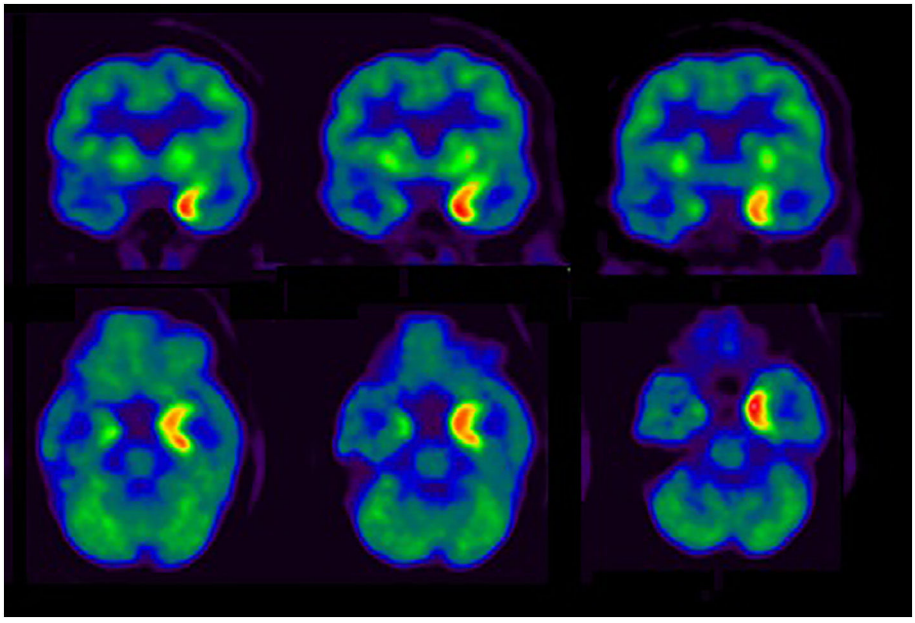

Fig. 2 Hypermetabolism of left temporal lobe in a non-ictal brain 18FDG-PET.
Coronal (figure, top) and axial (figure, bottom) slices of a non-ictal brain 18-fluorodeoxyglucose positron emission tomography (18FDG-PET) are shown. Left temporal lobe hypermetabolism can be seen, with left amygdalar and left hippocampal involvement, revealing an increased glucose uptake (represented as red, orange, and yellow areas) in the left temporomesial structures. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

neurological signs/symptoms, multifocal seizures, and status epilepticus were more frequent in patients with positive autoimmune testing. All the included patients with status epilepticus at epilepsy onset had positive results. Autoimmune testing delay was, on average, 4.5 years longer among patients with negative results than in those with positive findings. Moreover, delay to testing was shorter in patients with neuroinflammation on MRI and significantly longer in patients with MTS ($P < .013$). Immunotherapy was more often attempted in patients with findings consistent with neuroinflammation ($P < .002$). APE- and RITE-scores were higher in patients with positive results ($P < .005$; $P < .001$, respectively). No other significant differences were found.

Differences between responders and non-responders

Thirteen patients received immunotherapy. Responders and non-responders were compared (Table 3). History of autoimmunity did not predict therapeutic response. Viral prodrome was more common in responders ($P < .035$) than in non-responders, as were associated neurological signs/symptoms except for memory disturbances. Patients with antiGAD antibodies seemed to respond poorly to immunotherapy. Brain MRI showing neuroinflammation was more frequent in responders. Similarly, the patient with temporal lobe hypermetabolism in brain PET responded to immunotherapy, whereas 78% of patients with PET hypometabolism were non-responders. No patient with MTS improved after immunotherapy. Autoimmune testing delay was, on average, 2 years longer in non-responders. There was no association between APE- and RITE-scores and therapeutic response. No other significant differences were found.

Differences between AAEp and ASS-AEn

The 14 patients with a final diagnosis of AAEp, were compared to the patients with ASS-AEn that were diagnosed in our hospital (Table 4), where a total of 12 patients with ASS-AEn had been admitted since 2005, being women a 50%, with a mean age of 46.4 years. Patients with ASS-AEn were significantly older than patients with chronic/isolated AAEp (mean age 27.8 years; $P < .019$). Malignancy was more prevalent in the ASS-AEn subgroup. Coexisting neurological signs/symptoms were significantly more frequent among patients with ASS-AEn ($P < .0001$) than in AAEp subgroup. Regarding seizure type, multifocal seizures were more common among the outpatient subgroup, as was drug-refractoriness ($P < .033$). Status epilepticus at seizure-onset was more frequent in ASS-AEn than in AAEp. Antineuronal antibodies were more prevalent in the ASS-AEn subgroup; particularly in the case of antineuronal cell-surface autoantibodies ($P < .009$). However, antiGAD were slightly more common among patients with isolated/chronic AAEp. Brain MRI evidence of neuroinflammation and temporal lobe hypermetabolism on brain PET was more common in ASS-AEn ($P < .01$), as was CSF pleocytosis ($P < .047$). Whereas, MTS and PET-hypometabolism ($P < .04$) were found only in the outpatient subgroup. APE- and RITE-scores were significantly higher in ASS-AEn ($P < .022$/

Table 2 Autoimmune testing in patients with suspected autoimmune-associated epilepsy: comparison of patients with positive and negative autoimmune testing.

Variable	Patients with positive autoimmune testing (*n* = 13)	Patients with negative autoimmune testing (*n* = 17)	*P* value
Sex (female)	54%	64.7%	.7
Age at epilepsy onset (mean +/- SD)	27.3 (+/-13)	28.8 (+/-12)	.7
Epilepsy type			1
Focal	12 (92.3%)	15 (88.2%)	1
Generalised	0	2 (11.7%)	.4
Unknown	1 (7.7%)	0	.4
Status epilepticus	6 (46.1%)	4 (23.5%)	.2
Status at seizure onset	2 (15.4%)	0	.1
Associated neurological signs/symptoms [a]	4 (30.7%)	2 (11.7%)	.3
Memory impairment	9 (70%)	13 (76.5%)	.6
History of:			
Autoimmunity	4 (30.7%)	4 (23.5%)	.6
Malignancy	1 (7.7%)	0	.4
Viral prodrome	4 (30.7%)	2 (11.7%)	.3
Positive antineuronal antibodies	5 (38.4%)	0	**.009**
Sample			
In serum and CSF	3		
Only in serum			
Only in CSF	2		
Antibody type	0		
Antineuronal cell-surface/synaptic protein	1 (antiNMDAR)		
Onconeural	1 (antiSOX1)		
AntiGAD	3		
Brain MRI			
Neuroinflammation	4 (30.7%)	0	**.026**
MTS	0	3 (17.6%)	.2
CSF pleocytosis	4 (30.7%)	0	**.001**
Positive OCB	4 (30.7%)	0	**.001**
Brain PET			
Hypermetabolism in one/both temporal lobes	1 (7.7%)	0	1
Hypometabolism	7 (53.8%)	5 (29.4%)	1
APE- and RITE-scores			
APE-score (mean +/- SD)	4.5 (+/-1.9)	2.5 (+/-0.8)	**.005**
Patients with APE $\geq$ 4	8 (61.5%)	2 (11.7%)	**.007**
RITE-score (mean +/- SD)	4.8 (+/-1.8)	2.5 (+/-0.8)	**.001**
Patients with RITE $\geq$ 7	2 (15.4%)	0	.1
Immunotherapy trial	10 (77%)	3 (17.6%)	**.002**
Responders	4/10	1/3	
Non-responders	6/10		
Delay between epilepsy onset and autoimmune testing (mean +/-SD)	9.8 years (+/-7)	14.4 years (+/-9)	.1

Abbreviations: ASD: antiseizure drug, APE-score: antibody prevalence in epilepsy score, CNS: central nervous system, CSF: cerebrospinal fluid, GAD: glutamic-acid decarboxylase, ICU: intensive care unit, MRI: magnetic resonance imaging, MTS: mesial temporal sclerosis, OCB: oligoclonal bands, PET: positron emission tomography, RITE-score: response to immunotherapy in epilepsy score.

[a] Associated neurological signs/symptoms included delusions, delirium, behavioural changes, and movement disorders.

P < .004). Patients with ASS-AEn received immunosuppression more often than the AAEp subgroup, and better outcomes were reported. The mean number of ASD that were withdrawn after immunotherapy was significantly higher in patients with ASS-AEn (*P* < .012). Notwithstanding, 2 patients with ASS-AEn died while there were no deaths in the AAEp group. Only 3 patients with ASS-AEn developed chronic epilepsy, meaning that 75% of patients with ASS-AEn were seizure-free after the acute phase. Autoimmune testing delay was significantly longer in AAEp (9.7 years) than in ASS-AEn (*P* < .0001).

Discussion

This study analysed 30 patients with suspected AAEp and expands the knowledge available to date in the area of chronic/isolated AAEp management in outpatient clinical practice.

Table 3 Immunotherapy trial: comparison of responder patients and non-responder patients.

Variable	Responders (n = 5)	Non-responders (n = 8)	P value
Sex (female)	80%	62.5%	1
Age at epilepsy onset (mean +/- SD)	30.6 +/-10	23.8 +/-9	.2
Epilepsy type			.1
Focal	4 (80%)	7 (87.5%)	1
Unknown	1 (20%)	1 (12.5%)	1
Status epilepticus	1 (20%)	4 (50%)	.5
Status at seizure onset	1 (20%)	0	.3
Associated neurological signs/symptoms [a]	2 (40%)	1 (12.5%)	.5
Memory impairment	4 (80%)	6 (75%)	1
History of:			
Autoimmunity	2	3 (37.5%)	1
Malignancy	1 (20%)	0	.3
Viral prodrome	3 (60%)	0	**.035**
Positive antineuronal antibodies	1 (20%)	3 (37.5%)	1
Sample			
In serum and CSF			1
Only in serum	1	2	
Only in CSF	0	1	
Antibody type	0	0	
Antineuronal cell-surface/synaptic protein	0	1 (antiNMDAR)	1
Onconeural	1 (antiSOX1)	0	
AntiGAD	0	2	
Brain MRI			
Neuroinflammation	2 (40%)	0	.1
MTS	0	1 (12.5%)	.1
CSF pleocytosis	1 (20%)	2 (25%)	1
Positive OCB	1 (20%)	3 (37.5%)	.4
Brain PET			
Hypermetabolism in one/both temporal lobes	1 (20%)	0	.3
Hypometabolism	2 (40%)	7 (87.5%)	.1
APE- and RITE-scores			
APE-score (mean +/-SD)	4.6 (+/-2.3)	3.2 (+/-1.1)	.1
Patients with APE $\geq$4	3 (60%)	3 (37.5%)	.5
RITE-score (mean +/-SD)	4.6 (+/-2.3)	3.7 (+/-1.3)	.4
Patients with RITE $\geq$7	1 (20%)	0	.3
Type of immunotherapy			.5
IgIV	3 (60%)	4 (50%)	
Rituximab	1 (20%)	0	
Cyclophosphamide	0	1 (12.5%)	
MTP pulses + IgIV	1 (20%)	0	
IgIV + Rituximab	0	1 (12.5%)	
Pulses of MTP + IgIV + Rituximab	0	2 (25%)	
Delay between epilepsy onset and the autoimmune testing (median and range)	10.4 years (+/-7)	12.4 years (+/-6)	.6

Abbreviations: ASD: antiseizure drug, APE-score: antibody prevalence in epilepsy score, CNS: central nervous system, CSF: cerebrospinal fluid, GAD: glutamic-acid decarboxylase, ICU: intensive care unit, IgIV: intravenous immunoglobulins, MRI: magnetic resonance imaging, MTP: methylprednisolone, MTS: mesial temporal sclerosis, OCB: oligoclonal bands, PET: positron emission tomography, RITE-score: response to immunotherapy in epilepsy score.

[a] Associated neurological signs/symptoms included delusions, delirium, behavioural changes, and movement disorders.

The diagnosis challenge

In our study, among 1749 patients that were seen in epilepsy clinic, AAEp was suspected in 1.71% and a diagnosis of AAEp was given in 0.8%. However, this result probably underestimates the real prevalence of AAEp. Although the incidence of AEp remains unknown,[7] some prospective studies have found that 15%–20% of patients with epilepsy of unknown aetiology had autoimmune-mediated epilepsy.[9,10,18] Hence, AAEp is probably underdiagnosed.[7] In this respect, in a previous study, just under half of patients (44%) who were suspected of AEp were eventually diagnosed with AEp.[3] Similarly, 46.6% of our patients were finally diagnosed with AAEp. Antineuronal antibodies are the main diagnostic tool,[3,7] along with CSF biochemistry and brain MRI.[2,7] Additionally, some EEG patterns could also suggest an

Table 4 Comparison of patients with acute symptomatic seizures secondary to autoimmune encephalitis and patients with chronic/isolated autoimmune-associated epilepsy.

Variable	Patients with acute symptomatic seizures secondary to autoimmune encephalitis (*n* = 12)	Patients with chronic/ iisolatedautoimmune-associated epilepsy (*n* = 14[a])	*P*-value
Sex (female)	50%	42.8%	1
Age at epilepsy onset (mean +/-SD)	46.4 (+/-21)	27.8 (+/-13)	**.019**
Epilepsy type			.05
Focal	9 (75%)	13 (92.8%)	.09
Unknown	3 (25%)	1 (7.1%)	.09
Drug-refractoriness	8 (66.6%)	14 (100%)	**.033**
Number of ASD	1.1	2.8	**.002**
Number of previously tried ASD	1.8	6	**<.0001**
Status epilepticus	6 (50%)	6 (42.8%)	1
Status at seizure onset	6 (50%)	2 (14.3%)	.09
Associated neurological signs/ symptoms[b]	12 (100%)	4 (28.5%)	**<.0001**
Memory impairment	9 (75%)	7 (50%)	.4
History of:			
Autoimmunity	3 (25%)	5 (35.7%)	.6
Malignancy	5 (41.6%)	1 (7.14%)	.06
Viral prodrome	4 (33.3%)	4 (28.5%)	1
Positive antineuronal antibodies	9 (75%)	5 (35.7%)	.06
Sample			
In serum and CSF			.1
Only in serum	5	3	
Only in CSF	3	2	
Antibody type	1	0	
Antineuronal cell-surface/synaptic protein	7 (3 antiNMDAR; 1 antiGABAB; 1 antiGABAB + antiNMDAR; 1 antiCASPR2; 1 antiLGI1)	1 (antiNMDAR)	**.009**
Onconeural	1 (antiHu)	1 (antiSOX1)	1
AntiGAD	1	3	.5
Brain MRI			
Neuroinflammation	6 (50%)	4 (28.5%)	.4
MTS	0	1 (7.14%)	1
CSF pleocytosis	9 (75%)	4 (28.5%)	**.047**
Positive OCB	0	4 (28.5%)	**.01**
Brain PET			
Hypermetabolism in one/both temporal lobes	3 (25%)	1 (7.14%)	**.01**
Hypometabolism	0	7 (50%)	**.04**
APE- and RITE-scores			
APE-score (mean +/-SD)	6.5 (+/-2.4)	4.3 (+/-1.9)	**.022**
Patients with APE ≥ 4	10 (83.3%)	8 (57.1%)	.2
RITE-score (mean +/-SD)	7.6 (+/-1.9)	4.6 (+/-1.8)	**.004**
Patients with RITE ≥ 7	8 (66.6%)	2 (14.3%)	**.014**
Immunotherapy trial	11 (91.6%)	11 (78.5%)	.2
Type of immunotherapy			.09
MTP pulses	4 (33.3%)	0	
IgIV	2 (16.6%)	7 (50%)	
Rituximab	0 (16.6%)	1 (7.14%)	
Cyclophosphamide	0 (16.6%)	1 (7.14%)	
Pulses of MTP + IgIV	2 (16.6%)	1 (7.14%)	
IgIV + Rituximab	1 (8.3%)	1 (7.14%)	
MTP pulses + IgIV + Rituximab	2 (16.6%)	2 (14.3%)	

Table 4 (*continued*)

Variable	Patients with acute symptomatic seizures secondary to autoimmune encephalitis (*n* = 12)	Patients with chronic/ iisolatedautoimmune-associated epilepsy (*n* = 14[a])	*P*-value
Outcomes	10 (83.3%)	5 (41.6%)	.08
Mortality	2 (16.6%)	0	.2
Delay between epilepsy onset and the autoimmune testing (mean +/-SD)	At admission	9.7 years (+/-7)	**<.0001**

Abbreviations: ASD: antiseizure drug, APE-score: antibody prevalence in epilepsy score, CNS: central nervous system, CSF: cerebrospinal fluid, GAD: glutamic-acid decarboxylase, ICU: intensive care unit, IgIV: intravenous immunoglobulins, MRI: magnetic resonance imaging, MTP: methylprednisolone, MTS: mesial temporal sclerosis, OCB: oligoclonal bands, PET: positron emission tomography, RITE-score: response to immunotherapy in epilepsy score.

[a] Patients with positive autoimmune testing (*n* = 13) and patients with therapeutic response to immunotherapy despite normal autoimmune testing (*n* = 1).

[b] Associated neurological signs/symptoms included delusions, delirium, behavioural changes, and movement disorders.

autommune aetiology of epilepsy, such as extreme delta brush in antiNMDA-R encephalitis[19] and low-amplitude paracentral electropositive polyspike activity in cortical myoclonus in coeliac disease.[20] Moreover, we found that both brain PET hypermetabolism and OCB might also be helpful in the diagnostic process of AAEp. PET has previously been proposed as a valuable diagnostic tool, and may be more sensitive than MRI in both ASS-AEn and AAEp.[3,21] However, it should be borne in mind that initial hypermetabolic findings could shift to hypometabolism in more advanced phases of the autoimmune-process.[3,15] OCB provided paraclinical evidence to support an AAEp diagnosis in 3 of our patients who had otherwise normal results. Hence, it may be helpful to include OCB and brain PET in the study of suspected AAEp. Multifocal seizures and status epilepticus, particularly at epilepsy onset, were more frequent in patients with AAEp, so these factors, along with viral prodrome[2,11,22] and associated neurological signs/symptoms[11] could point towards a suspicion of AAEp.[2,11] The set of these clinical and paraclinical tools may facilitate an earlier diagnosis of AAEp in the future. However, nowadays, AAEp remains as a diagnostic challenge,[7] leading to a delay of autoimmune testing.

Implications of delaying autoimmune testing

The delay of autoimmune testing was longer among patients with normal findings and non-responders (4.5 and 2 years, respectively). The sensitivity of autoimmune testing, including antineuronal antibody assays,[23,24] may decrease in the late stages of the disease, possibly as a result of spontaneous fading of the immune response.[23] As such, a delay in testing might produce normal results in tests that could have shown inflammatory findings at an earlier stage of a more active autoimmune disorder. This fact might contribute to the underrecognition of AAEp. Regarding neuroimaging, inflammatory findings could develop into fibrotic changes, misdirecting the aetiological diagnosis of epilepsy towards a structural cause. Indeed, in our study, this time lag was shorter in patients showing neuroinflammation and significantly longer in patients with MTS *(P* < .013). Moreover, 1 patient with inflammatory findings on the first MRI eventually developed MTS. This finding has been described in association with late stages of autoimmune disorders, supporting the hypothesis of a relationship between autoimmune and structural aetiologies of epilepsy.[4,6,13–15] Although this patient initially improved after immunotherapy, he became non-responder during follow-up. Accordingly, the finding of MTS in a patient with suspected AAEp could predict poor therapeutic response. Additionally, therapeutic delay could lead to immunotherapy failure, whereas early initiation of immunotherapy has been associated with favourable outcomes.[25–27]

Limitations of APE-/RITE-scores

APE-score was significantly higher in patients with positive results (*P* < .005). There were no differences in RITE-score between responders and non-responders. Moreover, despite only 2 patients scored RITE$\geq$7, therapeutic response was obtained in 5. Conversely, APE- and RITE-scores were significantly higher in patients with ASS-AEn than in those with AAEp (*P* < .022; *P* < .004). This can be explained by the fact that almost all the items that are scored in both scales (supplementary material)[10,12] were more prevalent in ASS-AEn than in AAEp, such as underlying malignancy, coexisting neurological signs/symptoms (*P* < .0001), positive antineuronal cell-surface antibodies (*P* < .009), neuroinflammation in brain MRI, CSF pleocytosis (*P* < .047), and a shorter delay-time between epilepsy onset and immunotherapy (*P* < .0001). This results from the fact that APE- and RITE-scores are based on the same diagnostic criteria for AEn,[17] being focused on the diagnosis and treatment of ASS in the context of AEn.[5] Therefore, APE- and RITE-score might be inaccurate for guiding AAEp management. Recently, both APE- and RITE-score were updated; leading to antibody prevalence in epilepsy and encephalopathy (APE^2) and response to immunotherapy in epilepsy and encephalopathy (RITE^2) scores,[28] which formed the basis of APE^2-Chinese and RITE^2-Chinese scores later.[29] However, all they are still too reliant on the suspicion of acute/subacute AEn.[30]

Future directions

The lack of proper scales and diagnostic criteria for AAEp[5] as well as the lower diagnostic suspicion of autoimmunity in the absence of additional neurologic manifestations lead to a

significant delay in autoimmune testing in AAEp compared to ASS-AEn ($P < .0001$). Therefore, more specific scales for AAEp are needed. Recently, a promising score was developed to guide autoimmunity screening in patients with epilepsy but without suspicion of encephalitis (antibodies contributing to focal epilepsy signs and symptoms (ACES)) score, achieving high sensitivity and specificity values.[30]

This study has several limitations. It was conducted in a single centre and included a small number of cases ($n = 30$). This study is retrospective, entailing potential bias related to non-systematic data recording. We included only patients who had been studied for AAEp, so it is possible that some patients whose AAEp diagnosis was missed were not included. Additionally, the delay in autoimmune testing might have led to AAEp being underdiagnosed. Furthermore, lumbar puncture was not performed in all study patients. Given the fact that some antineuronal antibodies might be positive only in CSF,[7] we cannot rule out that some results could have been false negatives. Likewise, we are aware that some antibodies were not tested because specific assays were not available or because they were unknown at the time of diagnosis. However, this study does also have some strengths. Focusing on daily clinical practice, this study analyses the longitudinal experience of a tertiary centre in AAEp in outpatient care setting, a quality that makes it of value to the majority of neurologists.

Conclusion

Seizures can be the unique or predominant symptom of CNS autoimmune disorders or a further symptom of already described AEn. Isolated/chronic AAEp is a rare but not unusual DRE disorder that poses a diagnostic and therapeutic challenge, particularly in outpatient care. Lumbar puncture with OCB assessment and brain PET may be useful diagnostic tools. An early diagnosis is essential for providing early aetiological immunosuppressive therapy. Neuroinflammation could lead to MTS, perpetuating an epileptic-disorder that eventually becomes unresponsive to both immunotherapy and ASD. Time to diagnosis and treatment are longer in AAEp than in ASS-AEn. Therefore, efforts should still be made to improve both the diagnosis and therapeutic approaches in AAEp.

Ethical standards statement

This study has been examined and approved by the Clinical Research Ethics Committee of Cruces University Hospital (approval code E21/60). We ensure that ethical standards protecting the confidentiality and anonymity of our patients were upheld. Only clinical data are presented, and no patient personal data or photographs were included.

Assurances

All authors declare that this paper has not been previously published (either in English or in any other language) and that this paper is not under consideration for publication elsewhere.

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Author contribution statement

Ana Moreno-Estébanez, the principal corresponding author of the manuscript, was fully involved in the conception and design of this retrospective study. She played a major role in data collection, methodology, investigation, and statistical analysis, and she led the visualisation and writing of the original version of the manuscript and the review and editing of that first version until the last version. Ainhoa Marinas was fully involved in the conception and design of this retrospective and descriptive study, as well as in data collection. She supported the review and editing of the manuscript from the first version until the final last version. Iñigo Garamendi Ruiz, Amaia González Eizaguirre and Noelia Reurich-Gomez were essential for data collection and provided the main author with necessary resources to write the manuscript. They supported the review and editing of the manuscript from the first version until the last version. Sabas Boyero Durán, Mar Mendibe Bilbao and Alfredo Rodríguez-Antigüedad supported the review and editing of the manuscript from the first version until the final version.

Declaration of Competing Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Appendix A. Supplementary data

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