A case of repeated focal motor seizures as expression of an inflammatory cerebral process with suspected dysimmune etiology

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A B S T R A C T

Autoimmune encephalitis (AE) is a condition of severe brain inflammation with a complex differential diagnosis. The identification of a specific neuronal antibody (NA) is not mandatory to diagnose AE. Moreover, even when a NA is detected, the clinical picture can be inconsequential (i.e., GAD-65) and not disease-specific (i.e., LGI1). Peculiar clinical manifestations and specific alterations of conventional tests as cerebral spinal fluid (CSF) and magnetic resonance imaging (MRI) can be sufficient to confirm the diagnostic suspicion of AE. New-onset seizures may be the first manifestation of AE and require immediate treatment. We report the case of a 19-year-old woman with sudden onset of focal motor seizures with unimpaired awareness, resistant to different intravenous antiseizure medications (ASMs). Ancillary tests (MRI, CSF analysis and electroencephalogram) were pathological and compatible with an autoimmune disorder of the brain. A weak positivity of GluR-3 antibody was detected in low serum dilution along with very high levels of angiotensin-converting enzyme in serum. After administration of high-dose corticosteroids, electro-clinical and neuroradiological pictures progressively normalized. This case report suggests that, even without a definite NA positivity, an inflammatory brain disorder of suspected autoimmune etiology should be considered based on clinical assessment and suggestive ancillary tests.

1. Introduction

Autoimmune encephalitis (AE) includes a heterogeneous group of immune-mediated inflammatory disorders of the brain whose estimated incidence is 1.2/100.000 person-years (2006–2015) [1]. Generally, the prevalence of AE is about 13.7/100.000 person-years, varying according to the specific neuronal antibody (NA): MOG (1.9/100.000), GAD65 (1.9/100.000), LGI1 (0.7/100.000), NMDAR (0.6/100.000) and so on [1]. Nevertheless, the prevalence and the incidence of this condition may be underestimated, considering that the number of new NAs and related syndromes is increasing over time [2]. Clinicians should immediately start immune therapies (intravenous steroids/immunoglobulins) or plasma exchange when AE is highly suspected, even when the antibody is not detected or its identification is ongoing [3], because better outcomes have been associated with earlier immunotherapy [4,5].

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seizures, as previously described, with spike and polyspike discharges within theta activity starting from the left temporal regions and spreading to frontal ones bilaterally (Fig. 1). Brain MRI with contrast enhancement (c.e.) was unremarkable. During the hospitalization seizures repeated in cluster and became more frequent and longer; after each cluster a full recovery of the neurological state was observed. Due to the inefficacy of intravenous diazepam (0.15 mg/kg) and midazolam (10 mg), intravenous lacosamide (200 mg) and levetiracetam (40 mg/kg) were sequentially administered, without response. After four days brain MRI with c.e. was repeated, showing T2/FLAIR (fluid attenuated inversion recovery) hyperintense areas of altered signal without c.e. in the left thalamus and homolateral cortical and sub-cortical fronto-parietal regions (Fig. 2). CSF analysis revealed lymphocytic pleocytosis (21 cells/mm³) and four CSF-restricted oligoclonal bands (OCBs). Serum and CSF virological screening (CMV, EBV, HSV1, HSV2, HHV6, HHV7, HH8, VZV) was not suggestive of active cerebral infection. Surface (NMDA, AMPAR, DPPX, IgLON5, LGI1, CASPR2) and intracellular antibodies (anti-Hu, Yo, Ma1-2, CRMP-5, amphiphysin, Ri, GAD65, SOX1, TR, Zic4, CV) were negative both in CSF and serum, even though weak positive GluR3 antibodies were identified in low dilution (1:10). To exclude a paraneoplastic etiology of the disorder, serum tumor markers and a total body CT scan were performed, without pathological findings. Blood tests for autoimmune diseases and thyroid function were in range. An unusual high titer of angiotensin-converting enzyme (ACE) was detected in serum (12.672 pg/ml; normal values: 0–2.600) but was not confirmed in CSF. Neuropsychological assessment demonstrated frontal dysfunction and impairments in working memory, visual and spatial memory and verbal fluency. Intravenous administration of valproate (20 mg/kg) and phenytoin (15 mg/kg) was attempted to stop recurring seizures, without clinical modifications. Intravenous human immunoglobulins (0.4 g/kg/day for 5 consecutive days) were ineffective too.

Eventually, after high-dose intravenous methylprednisolone (1 g/day for 5 days repeated after one week with the same posology upon seizure recurrence), focal motor seizures stopped with progressive normalization of the neuroradiological imaging. After hospital discharge, the patient did not experience other seizures and both the EEG and the serum levels of ACE and GluR3 were negative. Antiseizure therapy consisted of phenytoin 300 mg/day and levetiracetam 3000 mg/day.

3. Discussion

Recognizing AE can be challenging due to the clinical heterogeneity among patients. In some cases, the cerebral autoimmune disorder can be suspected based on specific demographics (age, gender) or clinical clues (movement disorders, such as facio-brachial dystonic seizures characteristic of LGI1 encephalitis), and the diagnostic hypothesis could be confirmed by the NA positivity [5]. In adult people, the most frequent NAs detected in serum and CSF are NMDAR (24.6 %), GAD65 (21.5 %) and LGI1 (20.5 %), with a different distribution according to age and sex [6].

Moreover, it is possible that a patient presents a combined positivity of neuronal and non-neuronal antibodies, making the diagnosis of AE even more difficult. In fact, some authors have demonstrated the presence of high titers of antinuclear antibodies (ANA) in >20% of patients with positivity to anti-Hu or anti-Yo antibodies [7]. It follows that the coexistence between neuronal and non-neuronal antibodies can be possible, considering the high frequency of non-neuronal antibodies in the general population (i.e., prevalence of ANA: 13.8 % [8], prevalence of anti-thyroglobulin antibodies: from 5% to 20% [9]).

However, a specific NA is not detected in up to 50% of cases [10]. Nevertheless, possible AE can be diagnosed, considering suggestive clinical manifestations and ancillary tests alterations. The classical presentation of AE includes subacute onset (<3 months) of altered cognition, sleep disturbances and psychiatric manifestations; seizures are common in the early stages. Steriade et al. [11] identified some clinical features of seizures secondary to AE: they are usually resistant to treatment, with high frequency and perisylvian semiology (i.e., facial clonic seizures) and early occurrence of status epilepticus can be seen. Considering our patient, she had a negative history of epilepsy and presented seizures two weeks after a new-onset condition of cognitive and behavioral dysfunction.

Fig. 1. Electroencephalogram (EEG) and electromyography (EMG) recording. Recording of an electro-clinical seizure originating from left temporal regions. EMG channels positioned on right buccinator muscle.
If the suspicion of AE is high, other possible causes must be ruled out, such as metabolic and toxic disorders and infectious diseases. Brain MRI and CSF analyses are usually the first exams of the diagnostic work-up. According to neuroradiological Graus’ criteria [5], definite AE can be diagnosed only in the presence of bilateral limbic encephalitis; however, T2/FLAIR hyperintense multifocal areas suggestive of brain inflammation can support the diagnosis of probable AE. In some cases, brain MRI can be normal. The brain MRI of our patient presented T2 hyperintense areas of altered signal in cerebral regions corresponding to the seizures’ semiology.

CSF analysis (leukocyte count, total protein, presence of OCBs) can be helpful in the diagnostic process and other useful information can be obtained if broad viral studies, cytology and NA’s panel are performed in CSF as well. Lymphocytic pleocytosis, OCBs and negativity of viral panel are usually expected, as identified in this case, but unremarkable findings do not exclude the diagnosis [12]. Recently, investigators have identified that the subtype of AE could influence some CSF parameters as the leukocyte count, the total proteins’ count and the presence of OCBs [13]. It seems that AEs with NAs against NMDAR, GABABR, AMPAR or DPPX more often present inflammatory pathological changes in all three parameters in opposition to other subtypes of AEs (CASPR2, LGI1, GABAA and Glur) in which CSF abnormalities are less frequent. Nevertheless, AEs in the latter group can rarely show positive OCBs as well as pleocytosis [13].

EEG helps to identify subclinical ictal discharges or to monitor drug response in patients with seizures. Abnormalities are common in AE, but a normal EEG is not unusual [11].

The presence of autoantibodies is not mandatory, but their identification supports the diagnosis. We found a weak positivity of Glur3 in low serum dilution. NAs detected only in serum are a laboratory finding reported in previous works [14,15]. The association between Glur3 antibodies and different types of epileptic disorders has been previously demonstrated [16], even though with low specificity and sensitivity [17,18].

However, it has to be underlined that the risk of false-positive diagnoses exists, especially in two situations: 1) when CSF analysis is replaced by the positivity to NA testing in serum or cell-based assays (CBA); 2) when the clinical picture does not fit the NA positivity [5]. In the case of NA positivity in serum/CBA, CSF analysis is strongly suggested due to its higher sensitivity and specificity, as it happens in NMDAR encephalitis, in which the concentration of NA in CSF correlates better with the clinical course [19,20]. In the case of discrepancy between laboratory and clinical findings, sample retesting or use of confirmatory tests (i.e., brain immunohistochemistry or cultured neurons) are needed [5]. On the other hand, high levels of NAs can be identified in CSF without an underlying autoimmune brain disorder, as in the case of the detection of GAD65 antibodies in absence of a suggestive clinical phenotype [21].

A peculiar laboratory finding in our patient is the high title of ACE in serum. ACE levels have been analyzed in serum and CSF of patients affected by different inflammatory neurological conditions, including viral encephalitis, in which ACE levels in CSF were higher compared to healthy controls [22]. The elevation of ACE in CSF was lower if treatment was started [23]. This could be our case in which the determination of ACE in both serum and CSF was conducted when immunotherapy was ongoing, explaining why ACE in CSF was normal.

Based on the existence of paraneoplastic AE, cancer screening should be performed. Small cell lung cancer is the most frequent tumor associated with paraneoplastic syndromes, followed by thymoma, ovarian cancer and teratoma [24]. CT scan and tumor markers resulted negative in our case.

Finally, in addition to the previously described pathological exams, the lack of response to antiseizure medications and the complete recovery after corticosteroids made stronger the diagnosis of probable autoimmune encephalitis for our patient.

It should be underscored that our case presents the limitation of being a single case report and every information should be carefully considered.

4. Conclusion

Diagnostic criteria for definite AE were not met in this patient, given the lack of bilateral involvement of medial temporal lobes. However, considering the subacute clinical presentation with cognitive and behavioral involvement, the new-onset focal seizures, CSF alterations and brain MRI features, a diagnosis of possible AE was made independent of recovering NAs from serum and CSF. Even though the presence of a positive NA is not strictly required [5], a second evaluation of NAs was unrevealing in our patient. When confirmatory results are initially absent to support a clinical diagnosis of AE, repeating NAs may provide further support. Overall, our case illustrates the impact of clinical judgement when making a diagnosis of AE.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:
GB has received speaker’s or consultancy fees from Eisai, Angelini Pharma and UCB Pharma. MT has served on scientific Advisory Boards for Biogen, Novartis, Roche, Merck, and Genzyme; has received speaker honoraria from Biogen Idec, Merck, Roche, Teva, Sanofi-Genzyme, and Novartis; and has received research grants for her Institution from Biogen Idec, Merck, Roche, and Novartis. ALN has received speaker’s or consultancy fees from Eisai, Mylan, Sanofi, Bial, GW, Arvelle Therapeutics, Angelini Pharma and UCB Pharma.

The remaining authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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G. Falciarino, G. Boero, T. Francavilla et al.