Received: 17 July 2021 | Revised: 9 October 2021 | Accepted: 31 October 2021

DOI: 10.1002/epi4.12558

Epilepsia Open®
Open Access

LETTER

The grey zone between autoimmune encephalitis and autoimmune-associated epilepsy

To the Editors,

In October 2020, a 45-year-old man came to our outpatient service complaining about "having chills". He reported that seven years before he developed a serious mood disorder following a distressful job experience. Contemporarily, chills began, which the patient described as prolonged episodes (even 30-min long) characterized by a shiver with goosebumps involving his left forearm and rapidly spreading to the ipsilateral arm and back, associated with anxiety and fear "that it might get out of control". Since these phenomena were attributed to stress, he was prescribed anti-psychotics. However, the chill frequency gradually increased, up to several times a day, and eventually they affected the patient's daily life so badly that he was advised to seek medical attention. The description of these episodes was suggestive for pilomotor seizures, a rare epileptic manifestation whose association with autoimmune encephalitis (AE) has been consistently demonstrated over these past years.[1] Indeed, upon further questions, our patient also revealed mild memory impairment, hyposmia, burning feet, and leg pain. The neurological examination was normal, as were neuropsychological assessment, brain MRI, and cerebrospinal fluid analysis. Conversely, the EEG exams showed bilateral asynchronous interictal epileptiform abnormalities over the temporal derivations. Autoantibodies (Abs) directed against amphiphysin were detected in the patient's serum through tissue-based indirect immunofluorescence techniques and immunoblotting, performed in a research laboratory. Although not typical,[2] limbic encephalitis has been reported in a minority of subjects with anti-amphiphysin Abs, in whom underlying neoplasms were rarely found[3] and immunotherapy proved beneficial. We performed a thorough tumor screening (including whole-body contrast-enhanced CT scan, prostate, testicular and thyroid ultrasound, dermatological consultation), which was negative. Before the results of the autoantibody search, our patient received a course of intravenous methylprednisolone (1 g/day for 5 days) followed by oral prednisone (50 mg/day), slowly tapered over 6 months, and reported a steady reduction in seizure frequency to once/twice a week, along with improvement in mood and memory. No clinical worsening was observed overall after steroid withdrawal. Although anti-epileptic therapy was suggested to achieve complete seizure control, the patient refused not to increase his medication burden.

We think this case is paradigmatic in several ways. First, it provides further demonstration that AE identification can be challenging, especially in cases without an overly dramatic onset, and that the careful evaluation of clinical features is always the key to diagnosis. The peculiar semiology (ie piloerection) of our patient's seizures, although not exclusively observed in association with AE, was an important clue, confirming the need for an extensive phenotyping of the various AE forms. Second, this case well exemplifies the complex relationship between immunity and epilepsy and the challenging management of seizures in the context of immune-mediated brain disorders. In 2020, the International League Against Epilepsy (ILAE) Autoimmunity and Neuroinflammation Taskforce addressed the crucial distinction between acute symptomatic seizures (ASS) secondary to AE and autoimmune-associated epilepsy (AAE),[4] defined as the "persistence of seizures despite immunotherapy", possibly related to both structural and immune factors. By doing so, the Taskforce set some conceptual milestones, but applying them into practice can be particularly difficult at times, and the line between ASS and AAE particularly thin, as this case demonstrates. Indeed, considering the exceptionally long diagnostic delay, it could be hypothesized that our patient's AE, left untreated, had determined permanent structural damages leading to long-term sequelae, ie mood disorder and temporal lobe epilepsy.[5] This appeared even more likely since Abs directed against intracellular antigens – such as amphiphysin – are associated with T cell–mediated immune processes, which can cause neuronal loss and gliosis and result in post-encephalitic epilepsy more commonly than B cell–mediated ones, according

to recent evidence. However, the partial response our patient reported to steroids suggests that some immune mechanisms were, in fact, still ongoing, and leaves several unanswered questions, including when and for how long immunotherapy should be tried before relying on anti-seizure medications only. This observation confirms the urgent need for reliable and accessible biomarkers of inflammation, which would greatly help physicians in the daily management of patients diagnosed with AE.

FUNDING INFORMATION

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTERESTS

No conflict of interest to disclose.

ETHICAL APPROVAL

The authors confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Alessandra Morano[1]
Emanuele Cerulli Irelli[1]
Martina Fanella[2]
Luigi Zuliani[3]
Anna Teresa Giallonardo[1]
Carlo Di Bonaventura[1]

[1]*Epilepsy Unit, Department of Human Neurosciences, "Sapienza" University of Rome, Rome, Italy*
[2]*Neurology Unit, "San Camillo de' Lellis" Hospital, Rieti, Italy*
[3]*Neurology Unit, AULSS8 Berica, Vicenza, Italy*

Correspondence
Alessandra Morano, Department of Human Neurosciences, "Sapienza" University of Rome, Viale dell'Università, 30, 00185 Rome, Italy.
Email: alessandra.morano@hotmail.it

ORCID

Alessandra Morano https://orcid.org/0000-0003-3649-8990
Emanuele Cerulli Irelli https://orcid.org/0000-0003-3906-555X
Luigi Zuliani https://orcid.org/0000-0001-7922-9024
Anna Teresa Giallonardo https://orcid.org/0000-0003-3315-6071
Carlo Di Bonaventura https://orcid.org/0000-0003-1890-5409

REFERENCES

1. Morano A, Fanella M, Cerulli Irelli E, Barone FA, Fisco G, Orlando B, et al Seizures in autoimmune encephalitis: Findings from an EEG pooled analysis. Seizure. 2020;83:160–8.
2. Pittock SJ, Lucchinetti CF, Parisi JE, Benarroch EE, Mokri B, Stephan CL, et al Amphiphysin autoimmunity: paraneoplastic accompaniments. Ann Neurol. 2005;58(1):96–107.
3. Moon J, Lee ST, Shin JW, Byun JI, Lim JA, Shin YW, et al Non-stiff anti-amphiphysin syndrome: clinical manifestations and outcome after immunotherapy. J Neuroimmunol. 2014;274(1–2):209–14.
4. Steriade C, Britton J, Dale RC, Gadoth A, Irani SR, Linnoila J, et al Acute symptomatic seizures secondary to autoimmune encephalitis and autoimmune-associated epilepsy: Conceptual definitions. Epilepsia. 2020;61(7):1341–51.
5. Casciato S, Morano A, Fattouch J, Fanella M, Avorio F, Albini M, et al Factors underlying the development of chronic temporal lobe epilepsy in autoimmune encephalitis. J Neurol Sci. 2019;396:102–7.