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Seeing elephants and drinking water from a porcelain vase - A case of septin-7 antibody-associated encephalitis presenting as a severe disorganized psychosis

Translational Psychiatry (2026)16:71 ; https://doi.org/10.1038/s41398-026-03877-y

Identifying autoimmune encephalitis (AIE) in patients with predominant psychiatric symptoms poses a diagnostic challenge for psychiatrists and neurologists, especially when CSF and MRI findings are inconclusive. We report a case of septin-7 AIE presenting as steroid-responsive psychosis, whose definite diagnosis could only be made years after onset.

CASE REPORT

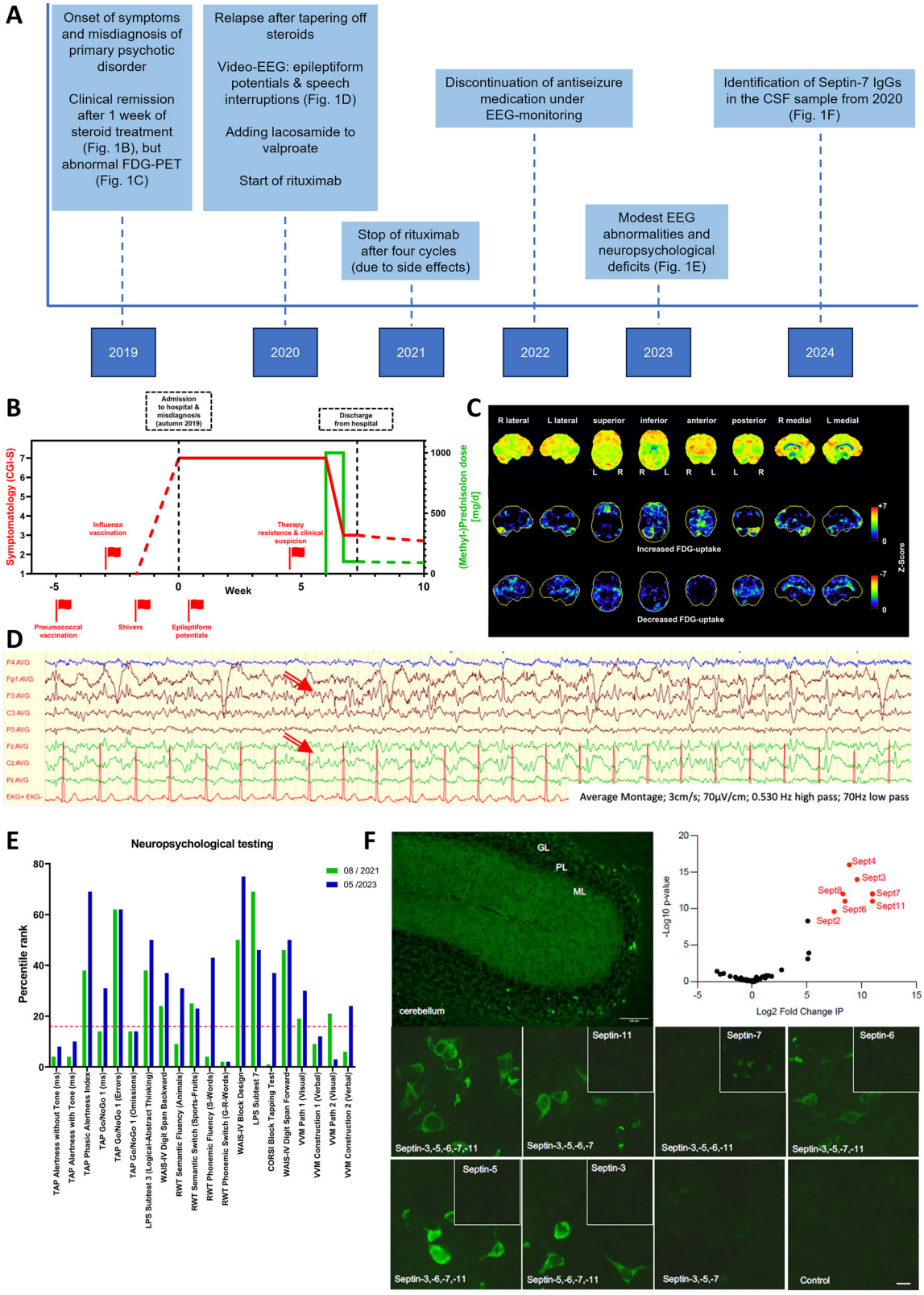
In autumn 2019, a 49-year-old woman was admitted to our neurological clinic with subacute onset of psychosis and cognitive deficits starting two weeks before. She suffered from somatic delusions (having tuberculosis), paranoia, affective lability, logorrhea, visual (elephants) and auditory hallucinations (imperative voices). Her behavior was severely disorganized (showering without undressing, drinking from porcelain vases). She reported shivering and feeling generally ill. There was no history of mental disorders, but different psychosocial stressors were evident. Somatic diagnoses included obesity, hypertension, hypothyroidism, gonarthrosis, atopic dermatitis, asthma and unexplained portal/mesenteric vein thrombosis 10 years earlier causing portal hypertension. She was prescribed phenprocoumon, carvedilol, levothyroxine and pantoprazole. Three and two weeks before admission, she had received vaccination against pneumococci and influenza, respectively.

Clinical examination revealed mild atactic gait and left dysdiadochokinesia. The initial electroencephalogram (EEG) showed right temporal status epilepticus. Under valproate treatment, no further epileptiform activity was detected. MRI showed scattered white matter lesions suggestive of cerebral microangiopathy and an old posterior inferior cerebellar artery (PICA)-infarct of the left cerebellar hemisphere but was otherwise inconclusive. Cerebrospinal fluid (CSF) analysis was normal (cell and protein levels, glucose, lactate, blood-CSF barrier function and neurodegenerative markers within normal range, oligoclonal bands and AIE-antibody panels negative). Accordingly, she was transferred to our intensive psychiatric ward with the presumptive diagnosis of a primary psychotic disorder. Here, additional diagnostic work-up of infectious, (para-)neoplastic and rheumatological encephalopathy remained inconclusive. Even after five weeks of treatment with various antipsychotics at sufficient doses (haloperidol, risperidone, olanzapine), valproate and benzodiazepines, severity of psychopathology necessitated treatment inside a protected psychiatric setting. Despite unfulfilled criteria for autoantibody-negative AIE [1] and in view of therapy resistance, previous epileptic activity, shivering and vaccination shortly before symptom onset [2, 3], we deemed AIE likely. Probatory intravenous methylprednisolone pulse therapy (1000 mg daily for five days) surprisingly resulted in resolution of all behavioral symptoms within one week (Fig. 1B). Already eight days after initiation of steroid therapy, she was discharged home with 100 mg oral prednisolone without psychopharmacological treatment. Despite clinical remission, FDG-PET detected brain areas of hyper- and hypometabolism (Fig. 1C). In March 2020, after tapering off prednisolone, she sustained a relapse with nearly identical symptoms leading to re-admission to our intensive psychiatric ward. Repeated routine EEG, MRI, and CSF diagnostics remained unremarkable. However, tissue-based assays with indirect immunofluorescence on unfixed murine brain tissue revealed neuropil autoantibodies binding to the molecular layer of the cerebellum in serum and CSF (Fig. 1F). After four weeks of steroid therapy, she could be transferred in a psychiatric stable condition to the neurology clinic for long-term EEG recording to assess the possibility of intermittent epileptic phenomena. Indeed, video-EEG-monitoring revealed frequent seizure patterns with left frontocentral onset (Fig. 1D). Moreover, we observed a pathological speech pattern characterized by logorrhea in combination with disturbed intonation and phonation. The hallmark were frequent interruptions, with the speech flow coming to a sudden halt and a stutter, with inability to continue for several seconds. These interruptions correlated partially with epileptic activity in the EEG (Supplementary Video 1). After introducing lacosamide, the speech interruptions regressed. Due to the suspected antibody pathology, rituximab treatment was started. After four cycles in 2021, rituximab was discontinued due to dermatological side-effects (fixed drug reaction). Subsequent video-EEG-monitoring could not detect epileptic activity, leading to discontinuation of valproate in 2021 and lacosamide in 2023. However, both EEG and neuropsychological assessment still suggested modest bifrontotemporal brain dysfunction with slight improvements from 2021 to 2023 (Fig. 1E). In 2024, using an IP-MS based autoantibody target identification pipeline [4], we identified septin-7 IgGs in the patient's CSF from 2020 (Fig. 1F) reinforcing the AIE diagnosis. This finding was verified using prototypic cell-based assays expressing single and different combinations of septins as described elsewhere [5].

DISCUSSION

The present case could have easily been misinterpreted as primary psychotic disorder. Despite unfulfilled criteria for autoantibody-negative AIE, multiple "red flags" (Fig. 1B) made us assume the autoimmune origin of the psychosis. A potential link between vaccination and AIE has been suggested by different case studies

Received: 10 April 2025 Revised: 16 December 2025 Accepted: 28 January 2026
Published online: 11 February 2026



[2, 3, 6], although a causal relationship is not fully established yet. Potential mechanisms include molecular mimicry [7], re-stimulation of pre-existing autoantibody expressing B-lymphocyte clones, and a transient vaccine-induced dysfunction of the blood-brain-barrier [6]. Further corroborating findings that emerged in the later course included steroid-responsiveness, relapse after discontinuing steroids and shifts of epileptic foci [8]. The latter finding was only obtained by long-term EEG monitoring as previous routine recordings missed epileptic activity under valproate treatment. Importantly, the epileptic speech

Fig. 1 Disease course and medical findings. A Schematic overview of the whole disease and treatment course from 2019 to 2024. **B** Schematic overview of the treatment course of the initial manifestation in 2019 and identified red flags of autoimmune encephalitis, which motivated us to start steroid therapy. Quantification of symptomatology was done retrospectively based on the hospital records. Symptomatology before and after the hospital stay (dashed lines) was not assessed and is only included for the purpose of illustration. Note that the positions of red flags were chosen for readability. The patient had received vaccination against pneumococci and influenza three and two weeks before admission, respectively. **C** FDG-PET scan, conducted on the day of discharge in clinical remission. Anatomical standardization of PET data was done using NEUROSTAT (NEUROSTAT/3D-SSP, University of Utah, Salt Lake City, UT, U.S.A) and three-dimensional stereotactic surface projections of cerebral glucose metabolism were generated. Despite nearly complete clinical remission, FDG-PET still detected right cerebellar as well as bilateral orbitofrontal and medial frontal hypermetabolism. On the other hand, hypometabolism was evident in the bilateral temporal and occipital lobes as well as the left cerebellar hemisphere (likely corresponding to the known PICA infarct). **D** 10-20-EEG (micromed®) from 05/2020, excerpt from video-EEG-monitoring, showing the beginning of a seizure pattern with left frontocentral maximum (F3/C3/Cz electrodes) corresponding to stuttering episode. **E** Neuropsychological test results from August 2021 and May 2023. Despite massive clinical improvement, some test results were still deficient indicating modest frontotemporal brain dysfunction as suggested by EEG recordings. Most test results improved from August 2021 to May 2023. The dashed red line indicates the 16th percentile (corresponding to one standard deviation below the mean). **F** *Upper left panel*: Indirect immunofluorescence of patient's CSF on mouse cerebellum showing IgG reactivity against the molecular layer (ML), and less intense the granular layer (GL), PL: Purkinje cell layer. Scale bar in C: 10 µm. *Upper right panel*: Volcano plot representing significantly enriched septin proteins (labeled in red) in the patient's CSF IP compared to other pull down samples with septin-7 showing the highest abundance, the x-axis shows the log2-transformed fold change, and the y-axis represents the log10-transformed p value. *Lower panels*: Cell-based assays with patient's CSF autoantibody reactivity to Septin-complexes in cell-based assays expressing a complex of septin-3,-5,-6,-7 and -11 (upper left panel). Moreover, we tested reactivity against septin-complexes with deletions of single septins from the complex, as well as against septin-monomers (inserts). Single expression of the septin-monomers confirmed binding to septin-7. Accordingly, deletion of septin-7 from the septin-complex lead to loss of reactivity to the complex. Interestingly, combined deletion of septin-6 and septin-11 and deletion of septin-6 alone, led to a significant loss of autoantibody reactivity as well. Thus, our data suggest that the epitope recognized by the antibody contains septin 7 and binding is facilitated by the presence of the proteins septin 6 and septin 11 presumably affecting the spatial conformation of the epitope.

phenomenon is very specific to this case and uncommon as a seizure semiology. Another corroborating finding may be the abnormal FDG-PET pattern, although PET findings in AIEs and their significance for guiding immunosuppressive maintenance therapy remain under investigation [9].

Anti-septin-7 encephalitis was discovered only recently with less than 20 reported cases [10, 11], most of which responded to immunosuppression [11]. While septin-5 and -3 IgGs are associated with cerebellar ataxia [5, 12], septin-7 IgGs are associated with predominant psychiatric symptoms [11]. A peculiarity of this case is that the autoantibody epitope was dependent on the presence of septin-7 and at least one of septin-6 or-11 in the complex of septin-multimers.

Association between septin-7 antibodies and psychosis is particularly important, because reduced septin-7 expression was demonstrated in post mortem brains of patients with schizophrenia [13, 14] and corresponding mouse models [14]. Additionally, under-expression of septin 7 is expected to disrupt synaptic plasticity and reduce dendritic spine density, assumed hallmarks of schizophrenia [15, 16].

Like in our case, the future may reveal new entities of AIE in patients who are currently diagnosed with primary mental disorders. Such discoveries as well as the critical appraisal of potential "red flags" of AIE are crucial for affected patients who require immunosuppression. Moreover, new antibody targets may shed light on the molecular pathophysiology of primary mental disorders.

DATE AVAILABILITY

All relevant data are included in the article or supplementary information. Further clinical data cannot be made available due to patient confidentiality and privacy protection requirements.

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ACKNOWLEDGEMENTS

We would like to thank the patient for the opportunity to publish this case report. Moreover, we would like to thank Katharina Gnatovska, Katharina Zientek and Dr. Kolja Schürmann for the fruitful discussions and inputs in this case.

AUTHOR CONTRIBUTIONS

AJG: patient treatment and clinical data collection, interpretation of findings, writing the manuscript. FAA: laboratory work, data analysis and interpretation, manuscript correction. MS: laboratory work, data analysis and interpretation, manuscript correction. SW: patient treatment and clinical data collection, interpretation of findings, manuscript correction. YW: patient treatment, clinical supervision, interpretation of findings, manuscript correction. ST: patient treatment, clinical supervision, manuscript correction. MK: laboratory work, manuscript correction. PM: laboratory work, manuscript correction. CB: data collection, manuscript correction. IN: clinical supervision, manuscript correction. TF: clinical supervision, manuscript correction. LTVE: clinical supervision, interpretation of findings, manuscript correction. HP: laboratory work supervision, interpretation of findings, manuscript correction. AN: patient treatment, clinical supervision, interpretation of findings, manuscript correction. All authors read and approved the final version of the manuscript.

COMPETING INTERESTS

MS is employee of EUROIMMUN. MS has septin-3 and septin-7 patent applications pending.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The patient has given her signed written informed consent for this publication, including the presented images and video material. All methods were performed in accordance with the relevant guidelines and regulations. Since the present article is a clinical case report, an ethics approval was not required.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41398-026-03877-y.

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