Acta Neurologica Belgica
https://doi.org/10.1007/s13760-023-02241-x

LETTER TO THE EDITOR

Anti-NMDA-receptor encephalitis, a challenging case leading to the discovery of a rapidly growing tumor

Julie Wénin[1] · **Maroussia Bronchain**[1] · **Amina Sellimi**[1] · **Vincent van Pesch**[1]

Received: 30 December 2022 / Accepted: 10 March 2023

Keywords Auto-immune encephalitis · NMDA receptor · Teratoma · Relapse

Short statement

Anti-N-Methyl-D-Aspartate Receptor (anti-NMDAR) encephalitis is the most frequent autoimmune encephalitis mediated by antibodies against cell surface neuronal receptors. Its prognosis is favorable if treated timely and adequately. It may be in relation with underlying neoplasia, most frequently teratomas. Because the tumor can appear several months after the onset, oncological follow-up is crucial. We report here the case of an anti-NMDAR encephalitis with an unusual oncological course. A short-term clinical worsening, lead to the discovery of a rapidly growing tumor, that was not present at disease onset.

Concise clinical description

We report the case of a 16-year-old female of Brazilian origin, without any medical history or chronic medication. She was admitted to the emergency department for a first tonic–clonic seizure. During hospitalization, she developed psychiatric symptoms such as impulsivity and anxiety. Anti-epileptic treatment with levetiracetam was started. Brain magnetic resonance imaging (MRI) showed bilateral temporal hyperintensity on T2/ Fluid-attenuated inversion recovery (FLAIR) sequences. Lumbar puncture demonstrated lymphocytic pleocytosis (48 cells/µL). Other cerebrospinal fluid (CSF) parameters were normal, including the absence of CSF-specific IgG oligoclonal bands. Bacterial culture and PCR for HSV1, HSV2, and VZV were negative. Anti-NMDAR antibodies were present in CSF. Diagnostic criteria for anti-NMDAR encephalitis were fulfilled [1] and a course of high-dose intravenous methylprednisolone (ivMP) and plasma exchanges were administrated with favorable clinical outcome. Upon discharge, the patient and her mother did not mention any behavioral or cognitive difficulties. No epileptic seizure recurred under treatment. The recovery was total (mRS 0). She was discharged with oral tapering of MP. A full body Positron emission tomography–computed tomography (PET–CT) and a pelvic MRI, performed to screen for ovarian teratoma, were unremarkable (Fig. 1A).

Eight weeks after the first seizure, 2 weeks after stopping MP intake, she relapsed a tonic–clonic seizure. She also presented severe psychiatric disorder as emotional lability, anxiety, and euphoria. Because of the severity of these symptoms, a neuroleptic treatment with Olanzapine was started. In addition, cognitive impairment was confirmed through neuropsychological testing, showing executive slowness and language difficulties. Brain MRI was unchanged and lumbar puncture showed reduced lymphocytic pleocytosis (9 cells/µL). Anti-NMDAR antibodies were still detected in the CSF. We repeated a high-dose ivMP course and plasma exchanges, with slower clinical improvement. An induction regimen with Rituximab was administered.

Due to this unusually early relapse, we repeated the paraneoplastic screening. A two-centimeter left ovarian teratoma was detected by total body PET–CT and pelvic MRI (Fig. 1B). Anatomopathological result following surgical resection confirmed a mature teratoma.

Discussion

We report the case of a young female patient with a diagnosis of anti-NMDAR encephalitis, who relapsed very rapidly with detection of a fast-growing ovarian teratoma, which could not be detected at disease onset.

✉ Julie Wénin
julie.wenin@gmail.com

[1] Cliniques Universitaires Saint Luc, UCLouvain, Neurology Departement, Brussels, Belgium

Published online: 20 March 2023

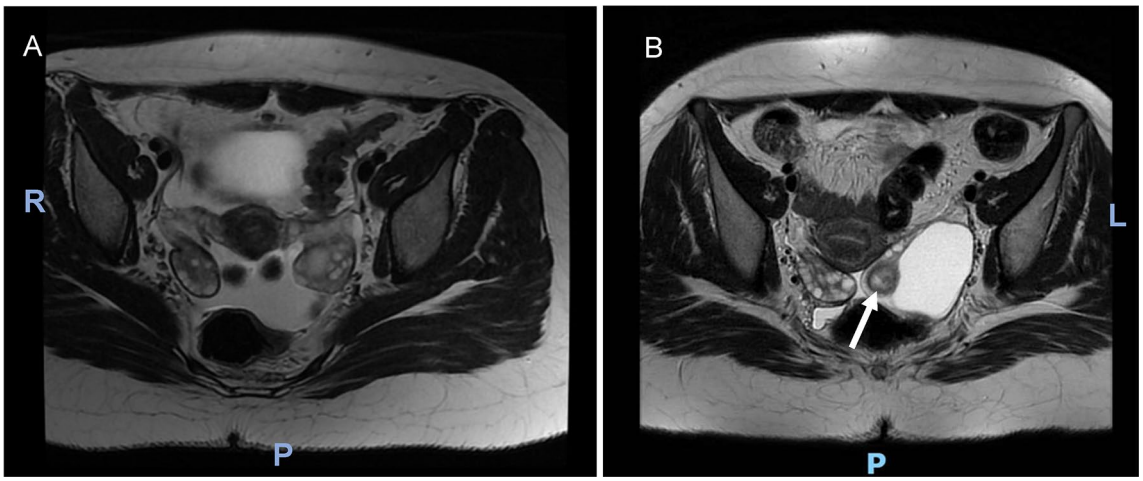

Fig. 1 Axial pelvic MRIs with T2 phase. **A** first MRI performed, with no ovarian abnormalities. **B** Second MRI, performed 68 days later, showed a left ovarian cyst associated with a 2-cm teratoma (arrow)

Underlying neoplasia in anti-NMDAR encephalitis is frequently observed (reported prevalence of 20% [2] to 38% [3]) but varies with age and sex. A higher prevalence of neoplasia is described in patients between 12 and 45 years old, especially women. According to Titulaer et al. [3], 46% of women with anti-NMDAR encephalitis have an underlying neoplasia. In 94% of cases, it is a mature teratoma, except in patients older than 45 years, where carcinomas are more frequent [3].

We found case reports [4] relating development of teratomas several months after onset and without new neurologic symptoms. For this reason, and because of the prevalence of teratomas in this population, a 6-monthly screening is recommended, especially in young female patients in whom initial search for neoplasia is negative, and up to 4 years after onset [3]. Removal of the discovered tumor speeds up recovery and decreases relapses. Our case supports the fact that underlying neoplasia may develop quickly, without gynecological symptoms. A close neurologic and gynecological follow-up is needed but sometimes not sufficient, even with favorable clinical course.

Anti-NMDAR encephalitis is mainly considered as a monophasic disease. However, relapses have been reported with an occurrence between 8 and 36.4% [5]. According to Titulaer et al. [3], the risk of relapse is 12% within 2 years. A relapse is generally defined as the new onset or worsening of symptoms occurring after at least 2 months of clinical improvement or stabilization. Usually, clinical relapses were less severe than the first episode [3] and occurred over a very wide time interval, often of several months. Based on a recent prospective study in China [5], who followed patients with anti-NMDAR encephalitis during a median time of 16 months, median time to first relapse was 8 months with a reported range of 3–54 months. Patients without any underlying neoplasia, had a higher frequency of relapses than did those with a removed tumor [3]. Clinical factors associated with risk of recurrence have not yet been demonstrated, but recurrence risk may be higher in patients with brainstem lesions [5].

In our case, we consider the second episode as a relapse, in view of the complete resolution of symptoms observed between the two episodes. However, it cannot be excluded that the disease flare up was still the first ongoing episode temporarily suppressed by steroids, as can be observed in some paraneoplastic syndromes. This could explain why, surprisingly, the second episode appeared so rapidly and was more severe than the first one. On the other hand, anti-NMDAR encephalitis is not clearly identified as a corticosensitive disease.

To our knowledge, this is the first case of a very early recurrence of an anti-NMDAR encephalitis, leading to the detection of a fast-growing ovarian teratoma, highlighting the need for follow-up and subsequent tumor screening of patients in whom the initial work-up is negative.

Declarations

Conflict of interest The authors have no conflicts of interest to declare.

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