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Short communication

NMDAR encephalitis presenting as akinesia in a patient with Parkinson disease

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ABSTRACT

We describe the case of a woman with Parkinson disease who developed an *N*-methyl-D-aspartate receptor antibody-mediated encephalitis. As a novelty, the encephalitis presentation mimicked a worsening of the pre-existing extrapyramidal syndrome, manifesting mainly as severe bradykinesia and, eventually, akinesia. Brain MRI was normal, whereas cerebrospinal fluid (CSF) analysis disclosed unique-to-CSF oligoclonal bands. Prompt identification and timely immunotherapy led to a complete recovery.

1. Introduction

Encephalitis associated with antibodies against the *N*-methyl-D-aspartate receptor (NMDAR-E) is the most common antibody-mediated encephalitis, usually affecting young women in paraneoplastic or non-paraneoplastic forms. NMDAR-E manifests with psychiatric symptoms, encephalopathy, a wide range of movement disorders, and dysautonomia, which often requires intensive care support (Dalmau and Graus, 2018). Milder or incomplete phenotypes are possible but rare (Dalmau and Graus, 2018). Moreover, little is known about the impact of NMDAR-E in patients with other neurological or non-neurological disorders. We describe a case of NMDAR-E in a patient who was suffering from Parkinson disease (PD).

2. Case report

We report on a 71-year-old woman with a 2-year history of PD mainly characterized by bradykinesia affecting the left arm, and well responsive to L-dopa. Previous medical history was remarkable for juvenile poliomyelitis, a diagnosis of dermatomyositis in 2003 (well controlled by low-dose prednisolone over the years), and one major depression *poussè* in 1990. In December 2017, she developed a gradual worsening of the motor performance over 3 months with a generalized slowing that was unresponsive to the increase of L-dopa. In March 2018, after an intercurrent pneumonia with fever, the motor slowing progressed to severe bradykinesia and finally to akinesia (Supplementary Video 1). At admission, in April 2018, the patient was bedridden and incapable of moving her limbs and of swallowing, with preserved tendon reflexes. Mental status examination revealed space-time disorientation, but she was able to understand and execute simple commands. She had a reduction of verbal communication that evolved to complete mutism (Supplementary Video 1). The full clinical picture closely resembled some aspects of catatonia, with only mild rigidity, but without waxy flexibility, stupor or negativism (Tandon et al., 2013). Brain MRI was unremarkable. The progressive evolution of the clinical picture and unresponsiveness to L-dopa led us to perform a lumbar puncture. Cerebrospinal fluid (CSF) analysis showed normal cell count, albumin quotient, and PCR for neurotropic viruses. Agarose isoelectric focusing with immunoblotting revealed unique-to-CSF oligoclonal IgG bands (OCBs). The detection of autoantibodies directed against neuronal cell surface proteins was performed at the Neuroimmunology Laboratory of Pavia, using immunohistochemistry on lightly fixed rat brain tissues, in accordance with a published protocol (Dalmau and Graus, 2018). Both serum and CSF showed a neuropilar staining of the hippocampus (serum titer, 1:200; CSF titer, 1:10). The resulting immunohistochemistry pattern strikingly resembled the typical pattern of NMDAR antibodies (Dalmau and Graus, 2018), which we then identified with a commercial antigen-specific cell-based assay (Euroimmun, Lübeck, Germany; Fig. 1). Interestingly, there was evidence of NMDAR antibody intrathecal synthesis (Antibody Index, 5.0; reference values, ≤4.0) (Reiber and Lange, 1991). A total-body CT performed to exclude an occult cancer was negative. A course of intravenous

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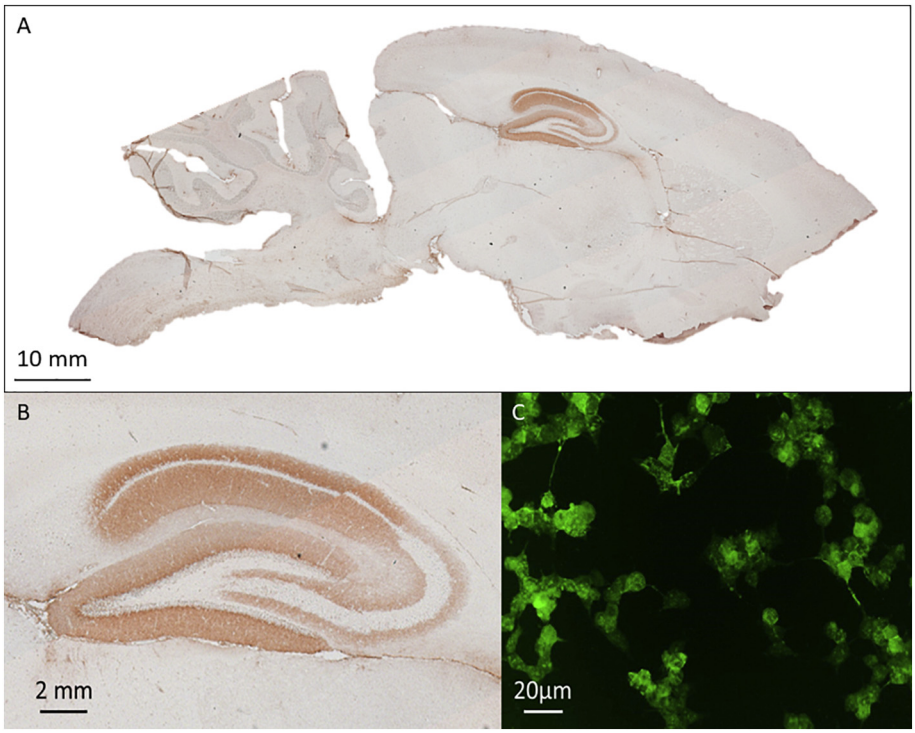

Fig. 1. Strong neuropilar hippocampal staining pattern compatible with the presence of *N*-methyl-D-aspartate receptor (NMDAR) antibodies (panel A, whole brain; panel B, detail on hippocampus; brown staining; cerebrospinal fluid, dilution 1:2); no additional staining was found in other brain areas (panel A); the antibody reactivity was confirmed on an NMDAR antibody-specific cell-based assay (panel C; green fluorescence; cerebrospinal fluid, undiluted). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

immunoglobulins (0,4 g/Kg/day for 5 days) led to a gradual and slow improvement of the cognitive and motor symptoms over a few months (Supplementary Video 1). After two months, the patient repeated a lumbar puncture, which disclosed an unmodified CSF OCB pattern, and the persistence of NMDAR antibodies at the same 1:10 titer detected at onset of the disease. Serum antibody titer and Antibody Index were unchanged too. Considering the favorable evolution, no additional treatment was given and the patient reached complete recovery at the 3 months follow-up, with the persistence of the slight left arm bradykinesia that had characterized her PD before the NMDAR-E manifestation. As typical of NMDAR-E (Dalmau and Graus, 2018), the patient had complete amnesia of what occurred during the acute phase of the disease.

3. Discussion

Due to the rapidly progressive manifestation of symptoms, NMDAR-E is usually considered a severe syndrome in differential diagnosis of infectious encephalitis (Dalmau and Graus, 2018). In elder patients, however, NMDAR-E can present with mild or absent inflammatory signs on the brain MRI or CSF analysis, making the diagnosis challenging (Escudero et al., 2017). In our patient NMDAR-E diagnosis was extremely challenging, since her symptoms were interpreted as a deterioration of PD for some months. In this setting, clinical clues, such as a history of autoimmunity, the complete lack of response to L-dopa, and the progressive evolution to frank mutism led us to consider alternative causes, and perform a lumbar puncture, which, in turn, proved to be fundamental to generate the hypothesis of intrathecal immune activation, after the detection of unique-to-CSF OCBs. On the other hand, routine CSF analysis with cell count were normal, with the exception of the presence of OCBs, confirming that autoimmune encephalitis in elder patients can present with few signs of CSF inflammatory signature (Escudero et al., 2017). Ultimately, the presence of disease-specific antibodies in the CSF (100% specificity, using two techniques (Gresa-Arribas et al., 2014)) strongly supported the diagnosis of an NMDAR-E. High NMDAR antibody titers in the CSF, and the decrease of CSF titers during follow-up have been shown to associate with a worse outcome and a higher risk of disability (Gresa-Arribas et al., 2014). Accordingly, the low CSF titer of NMDAR antibodies that our patient presented at onset associated with a favorable outcome. The low CSF titer persisted unmodified at 2 months follow-up, so they did not correlate with the clinical course. In parallel, the slight intrathecal synthesis of NMDAR antibodies was detectable at the two timepoints. Lumbar puncture was not repeated afterward as the patient recovered completely.

In NMDAR-E, PD-like brady – /akinesia has been described rarely in pediatric patients only (Mohammad et al., 2014), whilst NMDAR-E and PD comorbidity has been never reported to our knowledge. NMDAR has a crucial role in synaptic transmission in many CNS networks, including basal ganglia (Ahmed et al., 2011). In NMDAR-E, the autoantibody binding to the brain areas of the highest NMDAR expression causes receptor internalization and synaptic dysfunction, resulting in polymorphic symptoms (Dalmau and Graus, 2018). In our patient, the altered basal ganglia circuitry might likely have represented a *locus minoris resistentiae* where such antibodies might have primarily acted as promoters of the severe worsening of PD. The substantial unresponsiveness to L-dopa further links the worsening with the encephalitis.

In conclusion, our case should alert neurologists that NMDAR-E onset in PD patients could manifest mainly as worsening of PD. Searching for symptoms typical of NMDAR-E and, above all, testing for NMDAR antibodies, preferably with two different techniques, is fundamental for early diagnosis, oncologic follow-up, and administration of therapies that can cure the disease (Dalmau and Graus, 2018; Gastaldi et al., 2018).

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jneuroim.2018.12.002.

Conflict of interest

None.

Informed consent

The patient provided written informed consent for video publication. This study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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