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LETTER TO THE EDITORS

Aquaporin-4 antibody neuromyelitis optica following anti-NMDA receptor encephalitis

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Dear Sirs,

Encephalitis associated with anti-*N*-Methyl-D-Aspartate Receptor (NMDAR) antibodies is an autoimmune encephalopathy often associated with teratoma [1]. Neuromyelitis optica (NMO) is an inflammatory demyelinating disorder of the central nervous system (CNS) associated with antibodies against aquaporin 4 (AQP4) [2]. Here, we report the case of a patient who developed limbic encephalitis (LE) followed by NMO, whose serum harbored anti-NMDAR and anti-AQP4 IgG antibodies.

A 50-year-old woman presented with subacute, short-term memory loss, confusion, and behavioral changes. Routine blood tests, an infectious disease screening, an electroencephalogram (EEG) and cerebral spinal fluid (CSF) tests were all negative, whereas a brain MRI showed a T2-weighted, hyperintense medial temporal cortex. A pelvic mass was detected by computed tomography (CT) scan. Two months later, she underwent a hystero-adnexectomy with the removal of an ovarian teratoma. A diagnosis of paraneoplastic LE was made. Tests for classical onconeural antibodies (Hu, Ri, Ma2, CV2/CMRP5, amphiphysin, Yo) proved negative. Her memory deficit started to improve 4 months after surgery, when she received repeated courses of low-dose oral steroids. One month later, she had only residual retrograde amnesia (Fig. 1e).

Five months later, she developed drowsiness, cervical itching, and impaired gait. Within 2 weeks, she had developed paraplegia and MRI showed multiple T2-weighted hyperintense lesions in the pons, hypothalamus, medulla oblongata, and cervical spine (Fig. 1a–c). A CSF analysis proved negative (normal white cell count and proteins, and absence of IgG intrathecal synthesis). Plasma-exchange and high-dose intravenous steroids were initiated, resulting in a slow improvement of strength. Nine months later, she presented with left-eye optic neuritis. High-dose intravenous steroids were partially effective. Three months later, a relapse occurred with weakness of the right limbs. An MRI disclosed new lesions in the pons and dorsal spine (Fig. 1d). Her serum and CSF were tested for AQP4-IgG-Ab by indirect immunofluorescence on a commercial assay (Euroimmun, Lubeck, Germany) [3], proving positive on serum (titer 1:100). The test was extended to NMDAR-IgG-Ab, also proving positive on serum (1:32) and on CSF. The patient was treated with plasma-exchange and oral steroids, with benefit. Three months later, her CSF analysis revealed a normal white cell count and increased protein content (84 mg/dl); matching oligoclonal bands were detected in the CSF and serum. Human leukocyte typing disclosed the presence of the class I allele B8 and class II DR3-DQ2 (DRB1*03-DQB1*02). AQP4-IgG-Ab- and NMDAR-IgG-Ab-positivity were both confirmed, but a decrease in serum Ab titer was shown (both Abs serum titer 1:10; NMDAR-Ab CSF titer 1:3, 2); VGCC-, AMPAR-, GABAbR-, LGI1- and CASPR2-Abs tested negative. Treatment with azathioprine was started. Eight months later, her conditions were stable.

This patient presented with LE followed by NMO 1 year later, and tested positive for AQP4- and NMDAR-Abs. To

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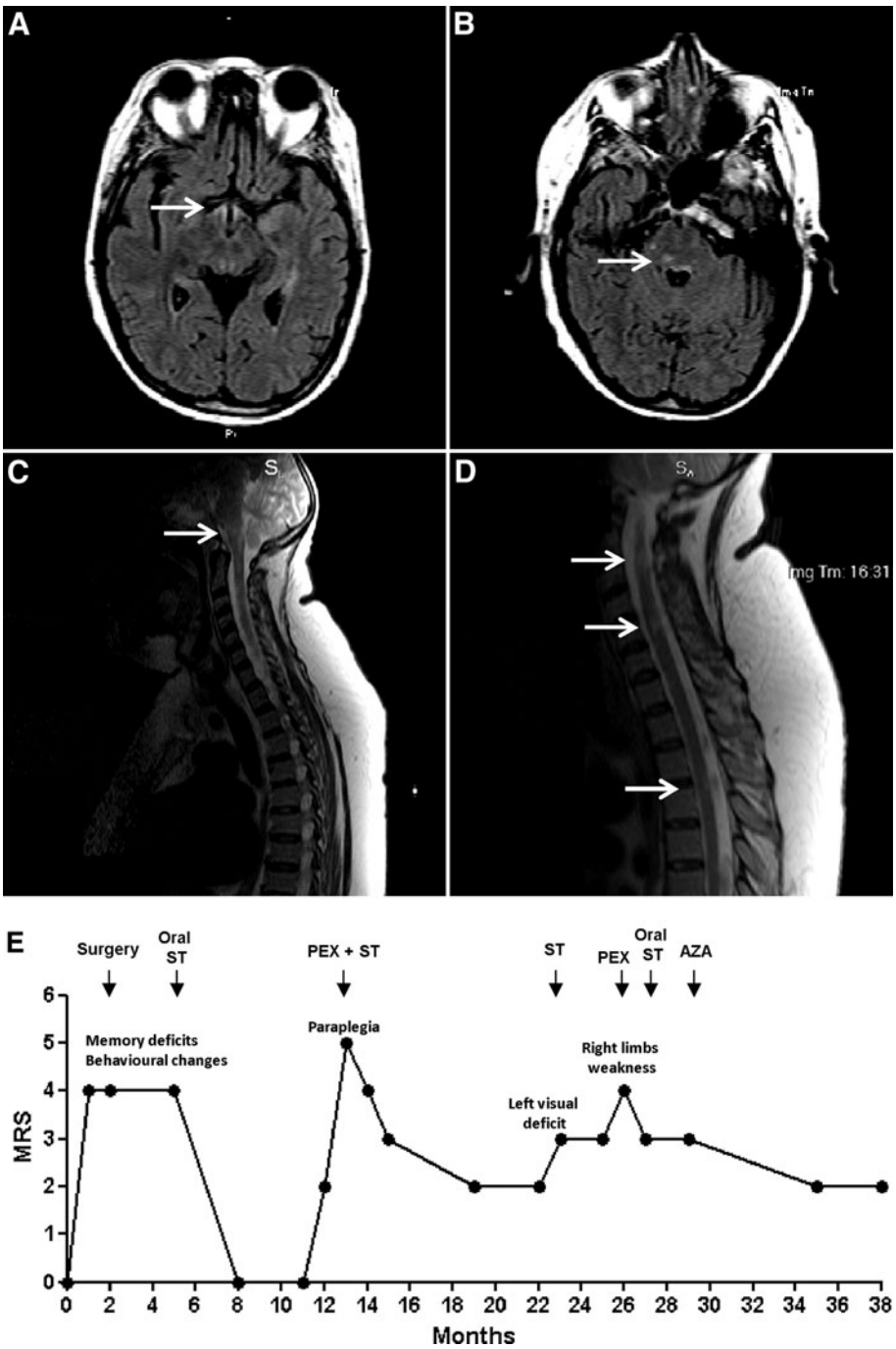

Fig. 1 Brain MRI images (month 12) showing hyperintensity in the hypothalamus (**a**), right pons [FLAIR] (**b**) and medulla oblongata [T2-weighted] (**c**). T2-weighted spine MRI image (month 24) showing hyperintense cervical and dorsal spinal lesions (length $\leq$2 metamers) (**d**). The graph (**e**) shows the clinical course based on the modified Rankin scale (mRS), and treatments. *ST* steroids, *PEX* plasma-exchange, *AZA* azathioprine

our knowledge, this is the first report on NMDAR-encephalitis followed by AQP4-NMO in a single patient. NMDAR-Ab has been reported in a case of AQP4-ab-negative NMO [4]. However, although we were unable to correlate antibody titers with clinical course, our patient did not present with an overlapping syndrome, but rather sequentially with two distinct diseases. LE was associated with teratoma, a typical finding of NMDAR-encephalitis [1], whereas NMO developed 1 year after tumor removal and met the 2006 criteria [2]. Although NMO has been sporadically associated with tumor diagnosis [5], it has never been reported in association with teratoma.

Notably, the patient presented with mild LE, unlike the severe, multistage encephalopathy that is usually observed with NMDAR-Ab [1]; moreover, improvement was not observed after teratoma removal but following repeated courses of steroids. Her NMO was characterized at its onset by pruritus, which is a recently reported manifestation of sensory pathway involvement in NMO [6], and by somnolence, a finding reported in association with bilateral

hypothalamic lesions in only one other seropositive case [7].

The coexistence of multiple autoimmune diseases is increasingly recognized among autoantibody-associated neurological syndromes [8]. However, little is known about the mechanisms that trigger autoimmunity and autoantibody production in neurological syndromes. The HLA typing in our patient resulted in class II DR3-DQ2 (DRB1*03-DQB1*02), already reported in LEMS [9] and NMO [10]. These findings suggest that genetic predisposition may have played a role in the development of these two rare autoimmune disorders.

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Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical standard The manuscript contains original work and has not been published elsewhere. The authors take full responsibility for the data, their analysis and interpretation. All the authors concur with the submission and have full access to all the data. The authors received a patient consent form from the patient prior to the inclusion in the study.

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