Clinical/Scientific Notes

Alejandro Sánchez-Carteyron, MD
Raquel Alarcia, MD, PhD
José Ramón Ara, MD, PhD
Jesús Martín, MD, PhD

POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME AFTER RITUXIMAB INFUSION IN NEUROMYELITIS OPTICA

The first complete description of the posterior reversible encephalopathy syndrome (PRES) was made in 1996.[1] Its initial description has been amplified by several atypical or additional clinical and radiologic findings. Throughout the last few years, this syndrome has been presented as a neurologic complication associated with various medical diseases in the context of rapid-onset hypertension or immunosuppressive treatments; its association with neuromyelitis optica (NMO) spectrum disorders has recently been suggested, with series of PRES in NMO cases recently published, implicating a possible role for aquaporin-4 channelopathy in the pathogenesis of some cases of PRES.[2] We present a case of PRES in a patient with an established NMO diagnosis happening after rituximab infusion (anti-CD20 monoclonal antibody), a treatment that has just recently been introduced for severe forms of the disease.[3] We underline the fact that PRES secondary to rituximab may be responsible for neurologic worsening that can simulate a demyelinating relapse.

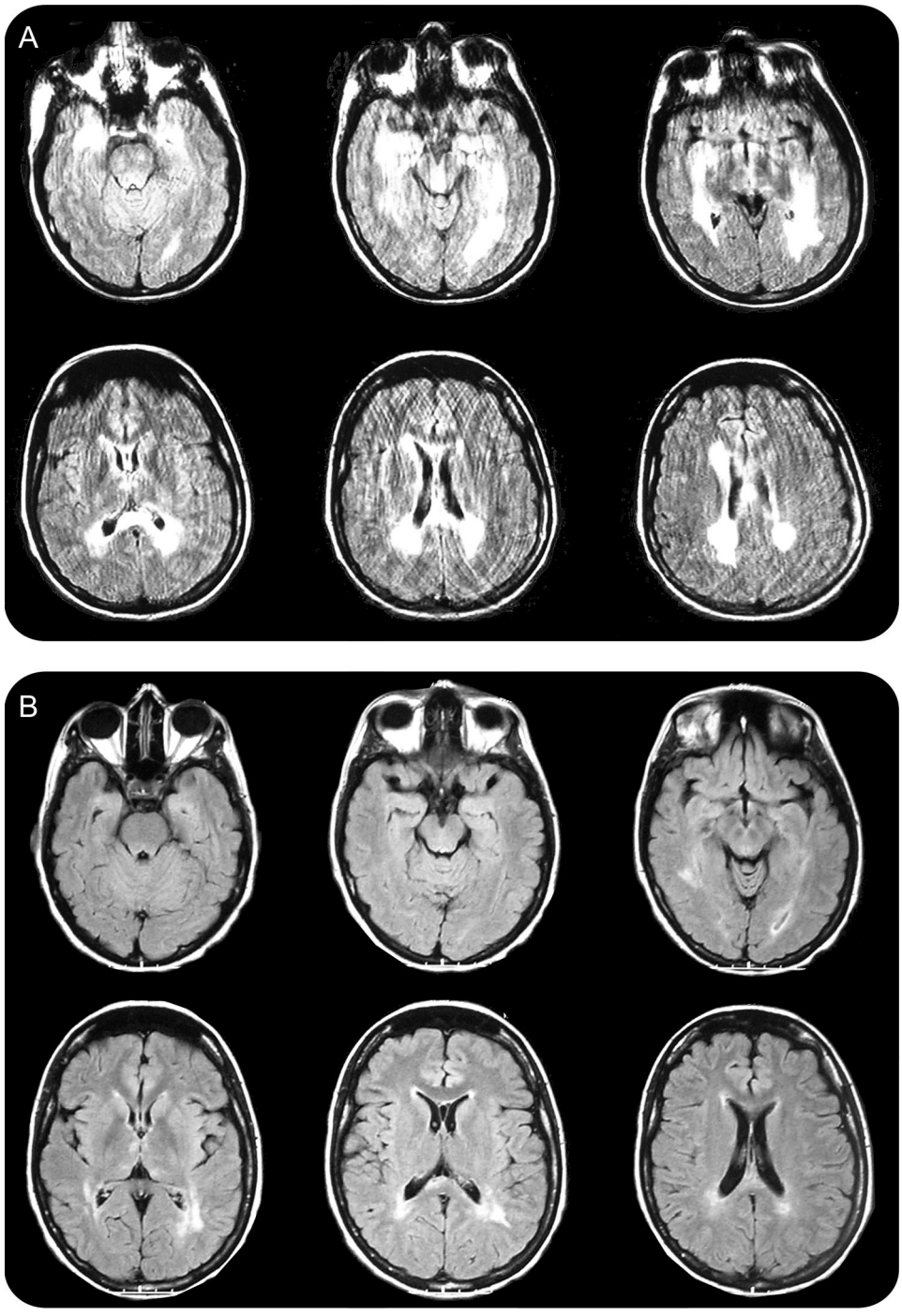
Case report. We report a 35-year-old woman who exhibited mild myelitis in 2006 and right optic neuritis (ON) in 2007. New ON and C3-C6 posterior cord myelitis was noted in February 2008. Cerebral MRI was normal. NMO diagnosis was made on the basis of the current diagnostic criteria.[3] She received IV corticotherapy and IV immunoglobulins. In March 2008, a new episode of transverse myelitis occurred. The following treatments were successively administrated: 1 g of IV methylprednisolone for 5 days, 5 plasma replacements on alternate days with a minimum replacement volume of 40 mL/kg, and, finally, IV immunoglobulins (0.4 g/kg/day), all with a poor clinical response. The cerebral magnetic resonance study showed multiple periventricular T2 signal alterations, enhancement following contrast administration and diffusion changes, about 12 being counted, in addition to multiple hyperintense T2 lesions in the cervical and dorsal spinal cord with posterior and central distribution, some of them with contrast enhancement, suggesting acute demyelinating-type spinal cord affection. In April 2008, she developed an internuclear ophthalmoplegia, which led to the start of treatment with rituximab (375 mg/m^2 for 4 weeks). Twenty-four hours after the first infusion, she exhibited cerebral affection symptoms, consisting of drowsiness, confusion, visual hallucinations, and incoercible nausea and vomiting, progressively resolved in 5–8 days, with blood pressure measurements within the normal range at any time. The magnetic resonance study performed after the onset of these symptoms showed a marked progression of the hyperintense cerebral lesions, with predominant temporal lobe affection; the cervical spinal cord affection did not show a significant variation. The radiologic control performed in July 2008 showed a significant regression of the cerebral lesions (figure). Four determinations of anti-aquaporin-4 antibodies by NMO-immunoglobulin staining pattern on immunohistochemistry were positive, from April 2008 to January 2009.

Discussion. The clinical-radiologic spectrum of PRES has been widely enlarged during the last few years with atypical or additional findings, which include irreversible clinical manifestations, frontal, temporal, thalamic, basal ganglia, cerebellum, brainstem, and spinal cord radiologic affection, jointly with descriptions of contrast-enhancing, cortical, confluent, unilateral, asymmetric, hemorrhagic, recurrent lesions, often partially or completely irreversible. The optimal radiologic control interval has not been established.[4]

Patients with NMO exhibit an alteration of the aquaporin-4 water channel function in the CNS secondary to the presence of immunoglobulin G anti-aquaporin-4 autoantibodies, considered to be associated with the neuroimaging appearances of vasogenic edema.[2,5] It has been proposed that this disruption in the water flow control in the interface between the parenchyma and the associated liquid spaces (vessels, ventricles, and subarachnoid space) could favor the appearance of PRES.

Several monoclonal antibodies have been the subject of similar publications. These include sunitinib, bevacizumab, infliximab, sorafenib, and rituximab.[6] The latter, directed against the CD20 antigen, has

Figure Fluid-attenuated inversion recovery MRI, April 2008 (A) and July 2008 (B)



been used in lymphoproliferative disorders, systemic lupus erythematosus, and, recently, NMO with recent relapses or resistant to previous treatments.[3] Having demonstrated the expression of CD20 in activated endothelial cells, the hypothesis of direct cell damage and its contribution to the development of PRES seems to be reasonable.

The clinically dramatic improvement shown by the patient, supported by reversible component of cerebral edema on neuroimaging, led us to consider a PRES diagnosis. This case underlines again the fact that some brain lesions in NMO may be due to vasogenic edema. Given the long list of potential PRES-causing conditions described thus far, this syndrome should be always taken into consideration in patients with NMO, especially those who undergo rituximab administration, as a novel potential PRES-causing factor to be considered. Atypical radiologic findings should be carefully interpreted in such patients, in order to avoid a misleading diagnosis of relapse.

From the Department of Neurology, Miguel Servet University Hospital, Zaragoza, Spain.

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Address correspondence and reprint requests to Dr. Sánchez-Carteyron, Department of Neurology, Miguel Servet University Hospital, Isabel la Católica 1-3, 50009, Zaragoza, Spain; sanchezcarteyron@gmail.com

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NMDA RECEPTOR ENCEPHALITIS MIMICKING SERONEGATIVE NEUROMYELITIS OPTICA

M.C. Kruer, MD
T.K. Koch, MD
D.N. Bourdette, MD
D. Chabas, MD, PhD
E. Waubant, MD, PhD
S. Mueller, MD
M.A. Moscarello, PhD
J. Dalmau, MD, PhD
R.L. Woltjer, MD, PhD
G. Adamus, PhD

NMDA receptor antibody encephalitis typically begins as a fulminant encephalopathy, with prominent neuropsychiatric manifestations, seizures, dyskinesias, and autonomic instability. After this often dramatic presentation, 1–3 relapses may occur. Most patients either die or recover from the disease.[1] We describe a 15-year-old girl who initially presented with encephalopathy, hypoventilation, dyskinesias, and seizures. Her subsequent course was atypical, with more than 10 relapses during the next year, with longitudinally extensive transverse myelitis (LETM) and optic neuritis (ON) in addition to multifocal, contrast-enhancing gray and white matter lesions. These findings have not been previously reported in anti-NMDA receptor encephalitis. Her disease was ultimately controlled on an aggressive combined regimen of monthly plasmapheresis, pulse methylprednisolone and cyclophosphamide, and rituximab.

Case report. A 15-year-old girl presented with headaches, photophobia, complex partial seizures, and encephalopathy dominated by hyporesponsiveness. Orofacial dyskinesias were noted. She required intubation for hypoventilatory failure. Her CSF demonstrated 420 leukocytes/mm^3 (13% neutrophils, 79% lymphocytes, 8% monocytes). Protein was 103 mg/dL; glucose 38 mg/dL. MRI demonstrated a contrast-enhancing periatrial lesion (figure, A). After a 2-week hospitalization, she recovered without residual symptoms.

Profound headaches recurred within 1 month, and she developed right-sided weakness, ataxia, and dysarthria. MRI again demonstrated contrast enhancement, now multifocal. LETM was also noted (figure, B). She began treatment with prednisone, 60 mg/day, for presumed acute disseminated encephalomyelitis with significant improvement.

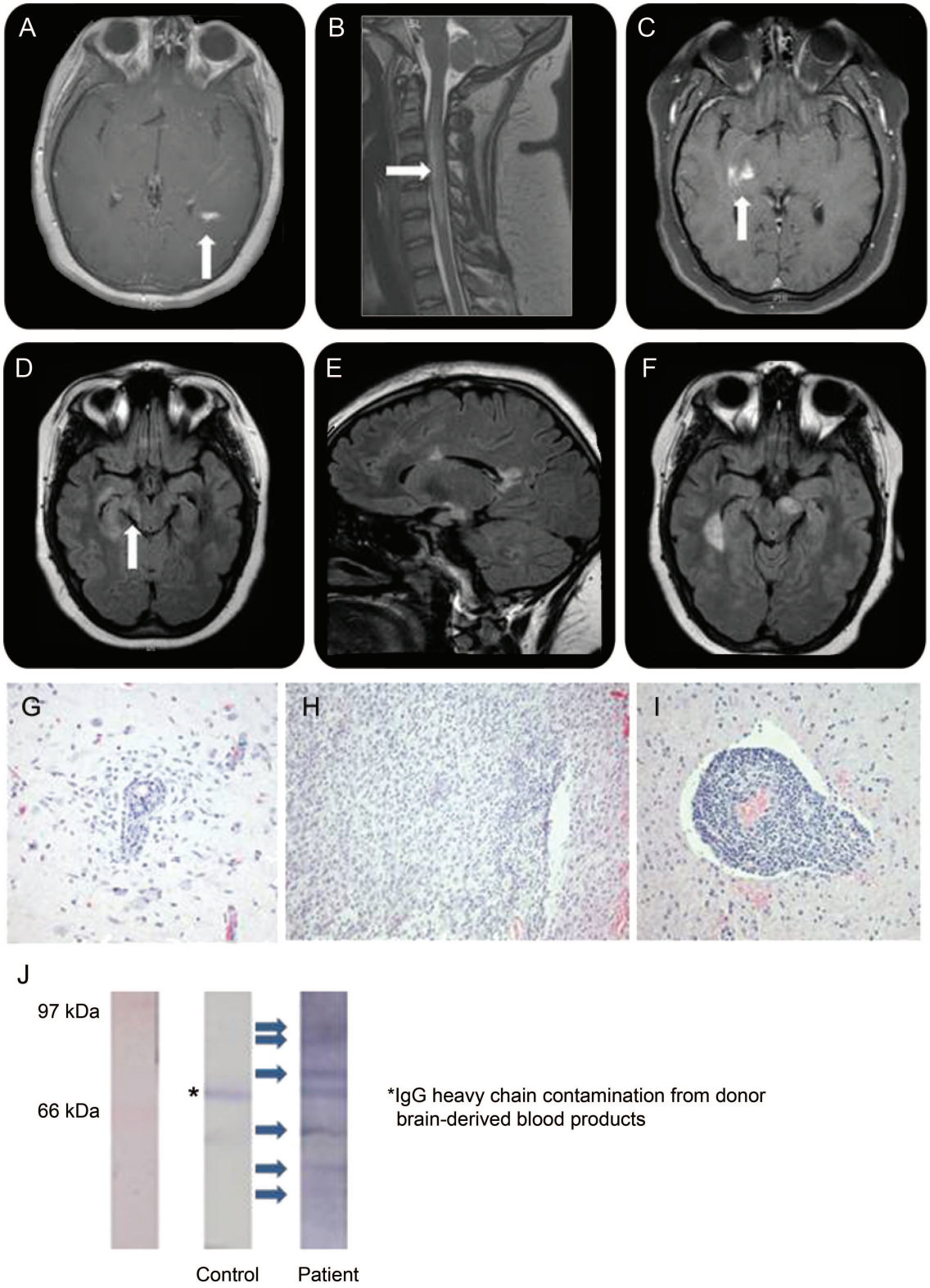
She remained clinically stable on oral steroids for several months before being weaned, without overt clinical symptoms despite the appearance of new enhancing lesions (figure, C). Six months into her course, she developed retrochiasmatic ON (figure, D). LP was repeated, demonstrating 4 leukocytes/mm^3 (94% lymphocytes, 6% monocytes). CSF analysis demonstrated 6 oligoclonal bands absent from serum, consistent with intrathecal immunoglobulin G synthesis. All other CSF indices were normal, as were CSF cytology and flow cytometry. Magnetic resonance angiography was unremarkable. Nutritional studies and testing for chronic meningoencephalitis were unrevealing. Extensive autoantibody testing (including NMO antibody testing; table e-1 on the *Neurology*® Web site at www.neurology.org) was negative.

The patient then developed recurrences at least monthly for the next 6 months (figure, E and F), with ataxia, weakness, sensory loss, internuclear ophthalmoplegia progressing to one-and-a-half syndrome, dysarthria, dysphagia, gait impairment, urinary incontinence, and later, cognitive decline (impaired problem solving, memory, and executive function). Labile emotionality, depression, and panic attacks were prominent later features. New symptoms occurred despite the use of interferon-β therapy for several consecutive months, followed by pulse cyclophosphamide for 2 months. Pulse IV steroid therapy was moderately effective in treating acute attacks. IV immunoglobulin was ineffective, while her response to plasmapheresis was excellent (supporting a role for peripherally produced autoantibodies in her disease), but not sustained for more than a few weeks.

A brain biopsy demonstrated a mixed inflammatory infiltrate primarily affecting gray matter (figure, G–I). Significant demyelination was conspicuously absent.

Supplemental data at www.neurology.org

Figure Features of atypical anti-NMDA receptor encephalitis



MRI: (A) Initial contrast-enhancing lesion; (B) longitudinally extensive transverse myelitis; (C) continued development of contrast-enhancing lesions; (D) retrochiasmatic optic neuritis; (E, F) continued accumulation of T2/fluid-attenuated inversion recovery (FLAIR) hyperintense lesion burden, with sagittal FLAIR hyperintensities reminiscent of Dawson's fingers (E). Brain biopsy (from contrast-enhancing frontal lobe lesion): (G) perivascular infiltrate with associated reactive microgliosis; (H) widespread parenchymal destruction mediated by infiltrative lymphocytes and macrophages without selective demyelination; (I) prominent mixed perivascular infiltrate (macrophages, T- and B-lymphocytes with uncommon neutrophils and rare eosinophils). Western blot: (J) Western blot depicting the presence of several additional serum-derived autoantibodies reactive against cerebellar protein extract from control human brain.

Anti-NR1/NR2 heteromer (NMDA receptor) antibody was detected in the CSF (diluted 1:10), but was not detected in any serum samples (diluted 1:10). Western blot of human brain extract probed with patient serum demonstrated several additional antineuronal autoantibodies (figure, J). One of these was identified as anti-myelin basic protein immunoglobulin G, although citrullinated forms (seen in some cases of multiple sclerosis and acute disseminated encephalomyelitis)[2] were conspicuously absent. Chest/abdomen/pelvis CT scan and pelvic MRI failed to demonstrate an occult teratoma.[3] Despite accumulating significant disability early in her course, with a combined regimen of monthly plasmapheresis, pulse methylprednisolone, rituximab, and pulse cyclophosphamide, she became asymptomatic.

Discussion. Our patient was positive for NR1/NR2 antibodies, a highly specific finding that until now has only been identified in patients with a characteristic set of symptoms.[1,4] Although our patient initially exhibited most of the symptoms associated with this disorder, the clinical course was highly unusual. Moreover, her MRI findings of LETM and ON in addition to irregular contrast-enhancing supratentorial and infratentorial lesions were atypical. Her biopsy findings and autoantibody testing did not support a diagnosis of multiple sclerosis, but could be considered consistent with seronegative NMO.[5] Her case thus appears to represent a previously unrecognized overlap syndrome, potentially involving other neuronal autoantibodies, as suggested by her Western blot results. We suggest that her early course was typical for anti-NMDA receptor encephalitis, and that epitope-spreading may have occurred[6] and led to evolution into the syndrome described. The contribution of multiple autoantibodies acting concurrently may be important in the course and evolution of autoimmune encephalitides. CSF autoantibody testing may be crucial in identifying pathogenic autoantibodies. Characterization of these disorders is important because, as shown in our patient, findings may guide treatment strategies, and warrant intensifying immunotherapy. Despite initial accumulation of disability, with aggressive immunotherapy, good outcomes may be possible (table e-2).

From the Department of Pediatrics, Division of Pediatric Neurology (M.C.K., T.K.K.), Child Development and Rehabilitation Center, Division of Developmental Pediatrics (M.C.K.), Department of Neurology, Oregon Multiple Sclerosis Center (M.C.K., D.N.B.), Department of Pathology, Division of Neuropathology (R.L.W.), and Department of Ophthalmology and Program in Neuroscience, Casey Eye Institute (G.A.), Oregon Health & Science University, Portland; Department of Neurology (D.C., E.W., S.M.), Regional Pediatric Multiple Sclerosis Center, Department of Structural Biology and Biochemistry (M.A.M.), The Hospital for Sick Children, Toronto, Ontario, Canada; and Department of Neurology (J.D.), Division of Neuro-oncology, University of Pennsylvania, Philadelphia.

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Address correspondence and reprint requests to Dr. Michael Kruer, Divisions of Pediatric Neurology and Developmental Pediatrics, CDRC-P, 707 SW Gaines St., Oregon Health & Science University, Portland, OR 97239; kruerm@ohsu.edu

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