Case Report

Overlapping demyelinating syndrome and anti-\(N\)-methyl-\(D\)-aspartate receptor encephalitis with seizures

Olga Taraschenko *, Rana Zabad

Department of Neurological Sciences, University of Nebraska Medical Center, Omaha, NE, United States of America

1. Introduction

Anti-\(N\)-methyl-\(D\)-aspartate receptor (anti-NMDAR) encephalitis, an immune-mediated encephalopathy, has been recently reported in association with central nervous system (CNS) demyelinating diseases including acute disseminated encephalomyelitis (ADEM) [1], myelitis [2] and neuromyelitis optica (NMO) [3]. A demyelinating disease can manifest along with anti-NMDAR encephalitis or occur at a distant time [3].

In a recent case series of 691 patients with serologically confirmed anti-NMDAR encephalitis, an antecedent or subsequent episode consistent with NMO spectrum disorder was identified in 12 patients, all of whom had demyelinating or multifocal hemispheric or brainstem lesions [3]. The understanding of the interplay between the adaptive immune system and processes contributing to central demyelination is evolving. We report a patient with an isolated optic neuritis that preceded the manifestation of autoimmune encephalitis and seizure onset by several months. The long-lasting remission of symptoms in both conditions was achieved with immunotherapies.

2. Case report

In January of 2006, a previously healthy 10-year-old right-handed girl developed progressive visual loss which was preceded by a flu-like illness, headaches, and ocular pain. Cerebrospinal fluid (CSF) analysis was normal except for an elevated opening pressure. Magnetic resonance imaging (MRI) of the orbits demonstrated contrast enhancement like illness, headaches, and ocular pain. Cerebrospinal fluid (CSF) analysis was normal except for an elevated opening pressure. Magnetic resonance imaging (MRI) of the orbits demonstrated contrast enhancement and perineural sheath swelling in bilateral optic nerves (Fig. 1); brain MRI was normal. Patient was treated with a 3-day course of intravenous methylprednisolone (IVMP) leading to complete recovery of her vision.

In February of 2007, she developed recurrent episodes of chin quivering, stiffness, and numbness of the left arm and leg followed by an episode of left-sided weakness, speech difficulty, and partial loss of awareness lasting for several minutes. The electroencephalogram (EEG) revealed spike-and-slow wave discharges in the right hemisphere. Brain MRI demonstrated right parietal cortical hyperintensity on fluid-attenuated inverse recovery (FLAIR) sequences consistent with cortical edema (Fig. 1 C, D). The CSF was normal. Patient was treated with IVMP and anticonvulsants with subsequent transition to prednisone for the suspected steroid-responsive inflammatory disease of the CNS. The diagnosis of CNS vasculitis was also entertained, and MRI of the cranial vessels was obtained, but it revealed no abnormalities. Patient’s brain imaging abnormalities resolved in several months. The prednisone was continued for the subsequent 2 years with reemergence of headaches upon weaning trials until a short course of methylprednisolone was administered in October 2009.

In May of 2013, she developed precipitous headache and fever; her examination revealed meningeal signs. Cerebrospinal fluid analysis showed lymphocytic-predominant pleocytosis, elevated protein, decreased glucose, and elevated IgG and albumin (Fig. 1 E, F). There was one oligoclonal band (OCB); infectious pathogens were absent. Brain MRI showed cortical hyperintensity in the right frontal...
region (Fig. 1E, F). She was empirically treated for presumptive viral meningitis with intravenous acyclovir and methylprednisolone as well as oral acetaminophen and prednisone for 40 days. Her headaches resolved in 3 months.

In October of 2015, two weeks following treatment for acute sinusitis, she developed recurrent focal seizures with impaired awareness and precipitous encephalopathy. Cerebrospinal fluid analysis revealed pleocytosis with mixed cellularity, two OCBs, and a minimally elevated titer of anti-NMDAR antibodies (1:1; normal titer is b1:1; Fig. 1G, H).

There were no detectable neuronal autoantibodies in the patient’s serum. Brain MRI revealed two new areas of hyperintense signal abnormalities in the left frontal region (Fig. 1G, H). Pelvic MRI did not reveal ovarian teratoma. She was diagnosed with anti-NMDAR encephalitis and was treated with IVMP leading to the resolution of seizures. She remained on prophylactic prednisone for 3 months and was administered eight doses of intravenous immunoglobulin (IVIG) over 20 weeks. In the months following the discharge, she has had intermittent self-limiting headaches and a single brief focal seizure. The EEG performed at that time was normal while brain MRI revealed a new area of signal change in the right frontal lobe.

Upon presentation to our autoimmune epilepsy clinic one year later, she denied any symptoms. Given her previous history of optic neuritis, she was evaluated for coexisting demyelinating disease. Serum aquaporin-4 (AQP4) and anti-NMDAR antibodies were negative, but serum IgG titer for antibodies against the voltage-gated potassium channel complex (anti-VGKC) was elevated at 0.15 (normal < 0.02). Repeated CSF studies (including the antibodies against NMAD receptors) as well as brain and spinal cord imaging were normal. The CSF paraneoplastic panel (including antiglial nuclear antibody type 1; amphiphysin antibody; antineuronal nuclear antibodies types 1, 2, and 3; collapsin response mediator protein-5 immunoglobulin, Purkinje cell cytoplasmic antibodies types 1 and 2; and Tr) was unrevealing.

Evaluation for serum or CSF antileucine-rich glioma inactivated protein 1 (LG1) antibody and anticontactin-associated protein 2 (Caspr2) antibodies was not performed. Additional tests pursued at Mayo Clinic Laboratories revealed the presence of serum antibodies to myelin oligodendrocyte glycoprotein (MOG-IgG). Patient was diagnosed with MOG antibody-positive, unilateral cerebral cortical encephalitis with epilepsy [4]. Based on the findings of recurrent encephalitis for 8 years and the requirements for prolonged immunotherapy, she was started on prophylactic therapy with rituximab which is ongoing. She has had no recurrences of encephalopathy or seizures in the past 20 months.

3. Discussion

It has been recognized that anti-NMDAR encephalitis and demyelinating disease can coexist in the same patients who also develop serological markers of both autoimmune disease (e.g., neuronal autoantibodies) and demyelination (AQP4 or MOG antibodies) [3]. The pathogenesis remains unclear though may be autoantibody-related [4]. However, it is unclear whether antibodies against neuronal receptors are causative for demyelination or develop as a consequence of it. In our patient, isolated optic neuritis preceded the manifestation of autoimmune encephalitis by several months; however, the evaluation for encephalitis and autoimmune antibodies was not undertaken until she developed seizures. Seizures have been previously reported in very few patients with this syndrome [3,11].

The patient underwent lumbar punctures in January 2006, February 2007, May 2013, October 2015 (Fig. 1), and March 2017 (data not shown). The autoimmune antibody assessments in CSF were requested for the last two procedures and were limited to the anti-NMDAR receptor antibody assays. In addition, the paraneoplastic antibody panel was obtained during the latest CSF examination. Our patient was also found to have elevated serum anti-VGKC autoantibodies; however, the
4. Conclusion

We report a rare case of recurrent unilateral alternating cerebral cortical encephalitis associated with MOG antibodies which presented with encephalopathy and seizures and was preceded by optic neuritis. In contrast to the previous findings that MOGAD in patients with overlapping syndrome are more difficult to treat than anti-NMDAR encephalitis, our patient recovered from both demyelinating and autoimmune diseases without any residual deficits. Based on the limited number of case reports of this syndrome, its diagnosis may be challenging, and prognosis for future relapses remains unknown.

Ethical statement

Our article submitted to Epilepsy & Behavior Reports entitled “Overlapping demyelinating syndrome and anti-N-methyl-D-aspartate receptor encephalitis with seizures” has not been published in whole or in part elsewhere. The manuscript is not currently being considered for publication in another journal. All authors have been personally involved in substantive work leading to the manuscript.

Declaration of competing interest

Authors report no conflict of interest.

Acknowledgments

Olga Taraschenko received funding from the American Epilepsy Society Junior Investigator Research Award.

References

[1] Lekoubou A, Viozco A, Dideot A, et al. Anti-N-methyl-D-aspartate receptor encephalitis with acute disseminated encephalomyelitis-like MRI features. Eur J Neurol 2012;19:e15–7.
[2] Pennington C, Livingstone S, Santosh C, Razvi S. N-methyl-D-aspartate receptor antibody encephalitis associated with myelitis. J Neurol Sci 2012;317:151–3.
[3] Titulaer MJF, Hofberger R, Iizuka T, et al. Overlapping demyelinating syndromes and anti-n-methyl-D-aspartate receptor encephalitis. Ann Neurol 2014;75:411–28.
[4] Ogawa R, Nakashima I, Takahashi T, et al. MOG antibody-positive, benign, unilateral, cerebral cortical encephalitis with epilepsy. Neurol Neuroimmunol Neuroinflamm 2017;4:e322.
[5] Lee SK, Lee SH. The laboratory diagnosis of autoimmune encephalitis. 6; 2016.
[6] Sailer MC, Fern R. NMDA receptors are expressed in developing oligodendrocyte processes and mediate injury. Nature 2005;438:1167–71.
[7] Hacoben Y, Absoud M, Woodhall M, et al. Autoantibody biomarkers in childhood-acquired demyelinating syndromes: results from a national surveillance cohort. J Neurol Neurosurg Psychiatry 2014;85:456–61.
[8] Zabrd RK, Stewart R, Healey KM. Pattern recognition of the multiple sclerosis syndrome. Brain Sci 2017;7. https://doi.org/10.3390/brainsci7100138.
[9] Kaneko K, Satoko D, Nakashima I, et al. Myelin injury without astrocytopathy in neuroinflammatory disorders with MOG antibodies. J Neurol Neurosurg Psychiatry 2016;87:1257–9.
[10] Dalmaz J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDA encephalitis. Lancet Neurol 2011:10;63–74.
[11] Fan S, Xu Y, Ren H, et al. Comparison of myelin oligodendrocyte glycoprotein (MOG)–antibody disease and AQP4-IgG-positive neuromyelitis optica spectrum disorder (NMO-S) when they co-exist with anti-NMDA (N-methyl-D-aspartate) receptor encephalitis. Mult Scler Relat Disord 2018;20:144–52.
[12] Kaneko K, Satoko D, Misu T, et al. Anti-N-methyl-D-aspartate receptor encephalitis with multiphasic demyelination. Ann Neurol 2014;76:462–4.
[13] Yokoyama K, Hori M, Yoshida A. Anti-myelin oligodendrocyte glycoprotein antibody neuritis optica following anti-NMDA receptor encephalitis. Pediatr Int 2016;58:963–4.
[14] Sarigacci E, Cohanogullari MD, Komur M, Okuyaz C. A rare concurrence: antibodies against myelin oligodendrocyte glycoprotein and N-methyl-D-aspartate receptor in a child. Mult Scler Relat Disord 2019;28:101–3.