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Case Report

Overlapping demyelinating syndrome and anti-*N*-methyl-D-aspartate receptor encephalitis with seizures

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ABSTRACT

Anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis, the most recognized type of autoimmune encephalitis, manifests with rapid cognitive decline, psychosis, and seizures that develop in 78–86% of patients. Recently, anti-NMDAR encephalitis was reported in association with demyelinating diseases which are accompanied by a characteristic clinical phenotype, imaging abnormalities, and the presence of antibodies against myelin oligodendrocyte glycoprotein (MOG-IgG) in bodily fluids. The patient presented herein suffered from bilateral optic neuritis followed by recurrent encephalitis with focal seizures and demonstrated anti-NMDAR and MOG-IgGs in the cerebrospinal fluid and serum, respectively. Her symptoms responded to immunotherapy and antiseizure medication. The recognition of the novel syndrome of MOG antibody-associated demyelination (MOGAD), encompassing the overlapping anti-NMDAR encephalitis and other MOG-IgG associated disorders, is important for the successful management of these patients.

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 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 methotrexate 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

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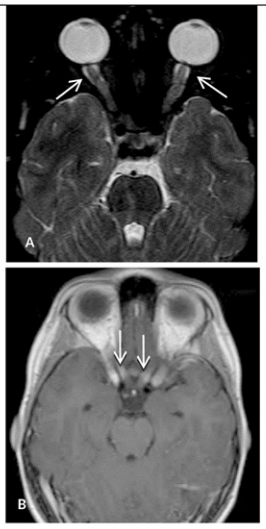
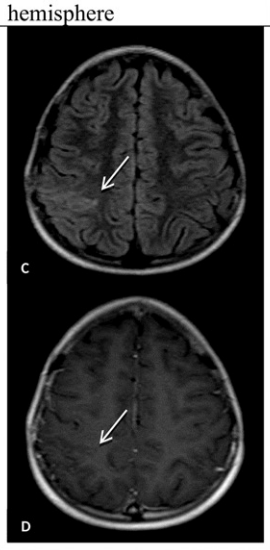
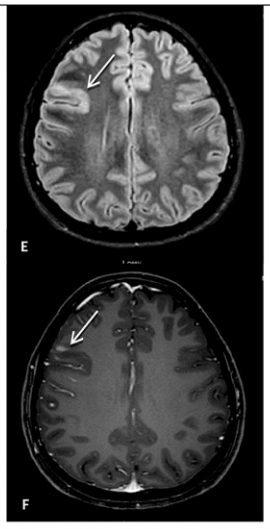
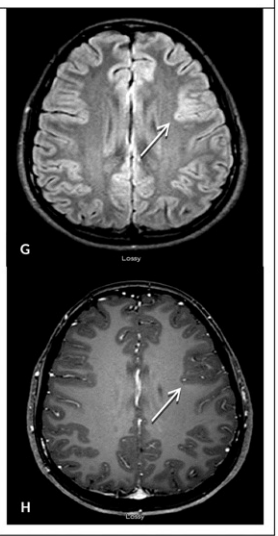
	January 2006	February 2007	May 2013	October 2015
Clinical presentation	Bilateral optic neuritis	Focal seizures	Encephalitis	Encephalitis
Paraclinical investigations	CSF: increased opening pressure at 36 mm H_20; WBC 1, protein 32 mg/dL , glucose 77 mg/dL , MBP 1.97 ng/mL (reference range 0.07-4.10).	CSF: WBC 1, protein 27, glucose 57, MBP 1.28 ng/mL (reference range 0.07-4.10), EEG: spike-and-slow wave discharges in the right hemisphere	CSF: WBC 576 (lymphocytes 99%), protein 94 mg/dL; glucose 35 mg/dL; CSF IgG 6.9 (normal 0-6.0 mg/dL), CSF albumin 58 mg/dL, OCB: 1	CSF: WBC 21 (lymphocytes 49%), protein 35, glucose 48, OCB: 2, NMDAR antibodies titer of 1:1 (normal <1:1).
MRI findings				

Fig. 1. Timeline and summary of the clinical, paraclinical, and MRI findings. Orbital MRI demonstrates bilateral optic neuritis with perineural sheath swelling on T2 fat-saturated sequences (arrows, A) and bilateral optic nerve enhancement on T1 sequences with contrast (arrows, B). Brain MRI reveals fluid attenuated inversion recovery (FLAIR) abnormalities (arrows) in the right parietal (C), right frontal (E), and left frontal cortical regions (G) consistent with cortical edema and the corresponding T1 hypointense abnormalities with minimal contrast enhancement in the same regions (D, F, H, respectively). CSF, cerebrospinal fluid; EEG, electroencephalogram; WBC, white blood cells; MBP, myelin basic protein; IgG, immunoglobulin; OCB, oligoclonal bands; NMDAR, *N*-methyl-D-aspartate receptor.

region (Fig. 1 E, 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 <1:1; Fig. 1 G, 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. 1 G, 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 (AQ4) 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 NMDA 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 (LGI1) antibody and anticontactin-associated protein 2 (Caspr 2) 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-NMDA 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

significance of this finding is unclear without the knowledge of patient's LGI1 and Caspr 2 antibody status [5]. The antigenic target for anti-NMDAR antibodies have been identified on oligodendrocyte processes [6], and these antibodies may participate in the process of demyelination. Nonetheless, the detection of these neuronal autoantibodies without an associated encephalitis phenotype appeared to have no effect on the clinical course of the demyelinating diseases [7]. In contrast to that, the demyelinating episodes occurring during the course of anti-NMDAR encephalitis were reported to have a more severe and protracted course than symptoms of the encephalitis alone [3].

While MOG antibodies are commonly associated with a recurrent optic neuritis phenotype and NMO spectrum disorders [8], reports of these antibodies in association with autoimmune encephalitis are uncommon. Only seven out of 691 patients with anti-NMDAR encephalitis demonstrated positivity for MOG-IgG [3]. Patients with MOG-IgG were negative for AQP4 antibodies [3], a diagnostic marker of NMO; the latter were also absent in our patient. Myelin oligodendrocyte glycoprotein antibodies were also recently reported in four out of 24 patients with steroid-responsive autoimmune encephalitis of unknown etiology [4]. Similar to our patient, the patients with MOG antibodies in this cohort also had seizures and optic neuritis. While MOG IgGs can directly contribute to the demyelination in the CNS [9], their potential to serve as a marker of activity in patients with coexistent autoimmune encephalitis is still being investigated [8]. Notably, our patient has never had any radiographic evidence of demyelination outside of that in the optic nerves during the initial presentation. Furthermore, unlike the patients with MOG antibodies who developed only single occurrence of encephalitis with seizures [4], our patient demonstrated recurrent cerebritis and relapsing seizures requiring prolonged multimodal immunomodulatory therapy and anticonvulsants.

Myelin oligodendrocyte glycoprotein IgGs have been recently described in association with cortical encephalitis and seizures [4]; however, patients in that cohort did not have any detectable neuronal autoantibodies in their CSF, and their cerebritis had no further recurrences. On the other hand, the recurrence of anti-NMDAR encephalitis has been reported in patients with and without MOG antibodies [3,10].

According to the results from a systematic review of literature provided in a recent article [11], a MOG antibody-associated demyelination demyelination (MOGAD) and anti-NMDARencephalitis were only reported in less than 20 adult and pediatric patients [3,11–14]; only a few of them had acute seizures. In contrast to our patient, the majority of patients described in the literature had their demyelinating episode and encephalitis in close temporal proximity. Therefore, they could have been diagnosed more easily. The unique feature of the disease history in our patient is a complete recovery from both optic neuritis and encephalitis. This is in contrast to the findings reported by Titulaer et al. who found that patients with MOGAD and antecedent or subsequent anti-NMDA receptor encephalitis have more prolonged recovery from the demyelinating disease and had more significant residual deficits [3].

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.

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