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Case report

Atypical presentation of MOG-related disease: Slowly progressive behavioral and personality changes following a seizure

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A B S T R A C T

Background: Myelin Oligodendrocyte Glycoprotein (MOG) antibodies-related disease is mainly presented with acute disseminated encephalomyelitis (ADEM), recurrent optic neuritis, and neuromyelitis optica spectrum disorders (NMOSDs), however the complete clinical spectrum has not yet been defined. We describe an unusual presentation of MOG- related disease. A previously well 10-year-old girl admitted with a focal onset seizure. Neurological examination, electroencephalography, and brain magnetic resonance imaging (MRI) were normal. Following seizure episode she developed gradually increased behavioral and personality changes during a period of 2.5 months. Neurological examination was unremarkable except for drowsiness and minimal ataxia on tandem walking. Repeated brain MRI revealed hazy and poorly demarcated lesions with gadolinium enhancement in the basal ganglia, supratentorial white matter, cerebral peduncles, cerebellum, and servical spinal cord. Cerebrospinal fluid analyses (CSF) revealed 10 lymphocytes /μL, normal protein concentration and IgG index, and negative oligoclonal bands. Auto-antibodies against *N*-methyl-D-aspartate receptor and CASPR2 in CSF, and antibodies against aquaporin 4 in serum were negative. Analysis with a cell-based assay identified high serum titer of MOG antibodies (1:320). Following IVIG therapy, the patient showed complete clinical recovery within a week with no further relaps for the following 6-month period.

Conclusion: Slowly progressive behavioral and personality changes following a seizure may be a manifestation of MOG-related disease in children.

1. Introduction

Myelin Oligodendrocyte Glycoprotein (MOG) antibodies-related disease, an increasingly recognized age dependent distinctive disease different from anti-aquaporin 4 (AQP4)-positive neuromyelitis optica spectrum disorders (NMOSDs) and multiple sclerosis, is mainly presented with acute disseminated encephalomyelitis (ADEM) and recurrent optic neuritis (ON), and less frequently NMOSDs, long segment transverse myelitis, brainstem, area postrema, or diencephalic syndrome (Reindl and Waters, 2019; Ramanathan et al., 2018). However recent reports have extended this phenotype, such as extensive brain involvement mimicking diffuse leukodistrophy in very young children, (Hacohen et al., 2018) progressive cognitive deterioration and behavioral changes with primary central nervous system vasculitis, (Baba et al., 2019) isolated seizures (Ramanathan et al., 2019), ocular flutter (Breza et al., 2019), or ADEM with complex movement disorder (Sa et al., 2019).

This report further expands the spectrum describing the unique case of a MOG antibody-positive child who initially presented with an isolated focal-onset seizure and normal brain magnetic resonance imaging (MRI), and subsequently developed slowly progressive behavioral changes mimicking autoimmune encephalitis but typical demyelination for MOG-related disease on MRI.

2. Case report

A previously well 10-year-old girl admitted with a 2-minute-long right-arm onset focal to bilateral tonic-clonic seizure, which was regarded as a first afebrile seizure with a low recurrence risk since electroencephalography and brain MRI were normal. No antiepileptic drug was initiated and she did not have any further seizures. Then she admitted to child psychiatry out-patient clinic for symptoms including reluctance, lack of pleasure from the things she liked before, feeling unhappy, forgetfulness, decreased school performance, deterioration in friendship, intense sleepiness, change in temperament, hitting her sister, unwillingness to speak, occasional stuttering, meaningless wandering in the room, senseless behavior such as hiding fruit peels and seeds, which gradually increased in a period of 2.5 months following seizure episode. During the preceeding week of the last admission, she had vomiting, decreased appetite, weight loss, and difficulty in swallowing.

On neurologic examination, she was drowsy with eye opening to voice and a normal response to pain, slow in conversation but awake and cooperated. Cranial nerve, motor and sensorial examination was normal. She was walking unsupported with minimal ataxia on tandem walking, but no dysmetria. Psychiatric examination revealed behavioral changes including meaningless and excessive fear, lack of interest for anything, and introvert personality.

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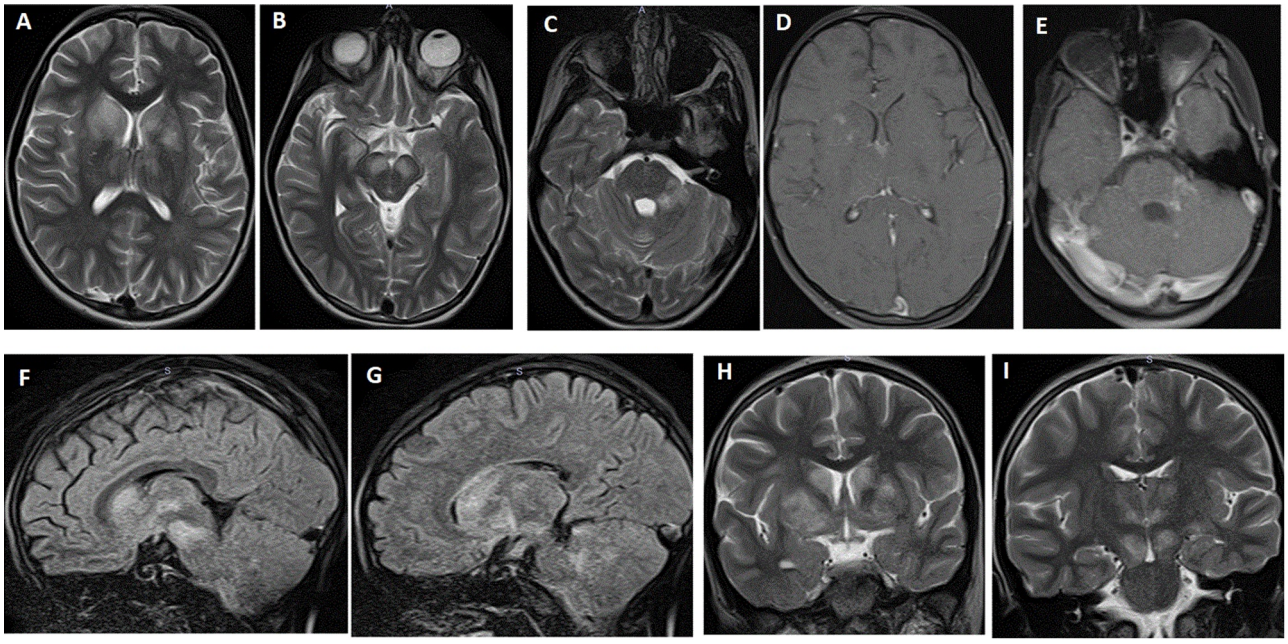

Fig. 1. Brain MRI (2,5 Months after the seizure epizode).
(A–C) Axial T2-weighted images, showing several large, hazy lesions in the bilateral caudate nucleus, putamen, globus pallidus, cerebral and cerebellar peduncles.
(D–E) Gadolinium-enhanced axial T1-weighted MRI of the brain, showing several enhancing lesions.
(F–I) Sagittal FLAIR and Coronal T2-weighted images showing intense involvement of basal ganglia, brain-stem, and cerebellum.

The patient was the first child of nonconsanguineous parents. No family history of neurological or metabolic disorders was reported. The mother's pregnancy and delivery were uncomplicated. Her developmental milestones were normal.

Repeated brain MRI at the last admission revealed multiple hazy and poorly demarcated T2A and FLAIR high signal intensity lesions with gadolinium enhancement predominantly in the basal ganglia, and to lesser extent in supratentorial white matter, cerebral peduncles, cerebellum, and servical spinal cord, which were suggestive of ADEM. (Fig. 1) Electroencephalography showed minimal generalized slowing. Complete blood count and serum chemistry were generally normal with no evidence of infection, metabolic disorders, or autoimmune diseases. Cerebrospinal fluid (CSF) analyses revealed mild lymphocytic pleocytosis with 10 lymphocytes/μL, and normal protein concentration (40 mg/dL). Oligoclonal bands were negative and IgG index was normal. CSF culture and viral polymerase chain reaction for Herpes simplex virus-1/2 and enterovirus were negative. Although history and clinical findings were suggestive of antineural autoimmune encephalitis including anti-*N*-methyl-D-aspartate receptor (NMDAR) or anti-contactin-associated protein 2 (CASPR2) encephalitis, MRI findings were highly compatible with ADEM. Therefore we analyzed anti-MOG antibodies with a cell-based assay which identified high serum titers of MOG antibodies (1:320). Auto-antibodies against NMDAR, CASPR2, a-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor 1 and 2, leucine-rich glioma-inactivated protein 1, and g-aminobutyric acid receptor type A and B receptor in CSF, and antibodies against aquaporin 4, nuclear, double-stranded DNA, anti-Sjögren's-syndrome-related antigen A/B, and thyroid peroxidase in serum were all negative. Based on these findings, the patient was diagnosed with MOG-related disease presenting clinically with seizure and slowly progressive behavioral changes, and radiologically with ADEM-like lesions. The patient was initially treated with IV ceftriaxone and IV acyclovir which were stopped after negative culture and virology results. Following IVIG therapy, the patient showed complete clinical recovery within a week, and had no further clinical relaps for the following 6 months.

3. Discussion

This case report illustrates an atypical presentation of MOG-related disease with slowly progressive behavioral and personality changes following a seizure with normal brain and spinal cord imaging at onset but ADEM-like lesions 2.5 months later. This clinical presentation which has not been previously described as a presenting feature of MOG-related disease in children, demonstrates a possible overlap in terms of clinical presentation between MOG-related disease and anti-NMDAR encephalitis which typically presents with psychiatric features, agitation, movement disorders, and seizures (Dale et al., 2017). However hazy and poorly demarcated lesions on MRI which developed 2.5 months later after the onset of symptoms, and the quick and dramatic response to IVIG treatment supported the diagnosis of MOG-related disease in the present case since patients affected with anti-NMDAR encephalitis frequently show a slow response to steroid treatment and may require second- or third-line treatment options and have a normal brain MRI in most cases. Although MOG-related disease and anti-NMDAR encephalitis are pathologically and clinically distinct disorders, antibodies against both MOG and NMDAR may rarely be simultaneously detected in children (Sarigecili et al., 2019). Consistently in a recent study, anti-MOG antibodies were detected in 9/23 patients diagnosed with NMDAR encephalitis with prominent clinical and/or MRI findings compatible with MOG demyelination (Titulaer et al., 2014). However the present case supports the notion that MOG-related disease is distinct from NMDR encephalitis despite similar clinical phenotype, since MRI was highly compatible with MOG-related disease and antibodies against NMDAR were not detected in CSF. AQP4, MOG, and NMDAR antibody serostatus and their levels may change during the disease course. Serum titers of antibodies against AQP4 and MOG are significantly higher during acute attack than during remission (Jarius et al., 2016a). While antibodies to AQP4 usually stay detectable with lower titers during remission (Jarius et al., 2008), MOG and NMDAR antibodies may be transient in a substantial proportion of patients (Jarius et al., 2016a; Jitprapaikulsan et al., 2019; Gresa-arribas

et al., 2014). AQP4 and MOG antibodies are produced mainly extrathecally and are therefore less frequent in CSF than in serum (Jarius et al., 2011; Jarius et al., 2016b), in contrast to NMDAR antibodies which were not detected in 14% of patients with positive antibodies in CSF (Gresa-arribas et al., 2014). Therefore we measured antibodies to AQP4 and MOG in serum, and antibodies to NMDAR in CSF in order to avoid misdiagnosis or not to miss possible coexistence.

Seizures may be a component of clinical phenotype such as ADEM, ON, hemiparesis or dyskinesia (Ramanathan et al., 2018; Titulaer et al., 2014; Ogawa et al., 2017; Hamid et al., 2018) or rarely be the sole manifestation in patients with MOG-related disease (Ramanathan et al., 2019), which may therefore be considered a form of autoimmune epilepsy (Ramanathan et al., 2019). Recent reports have identified that seizures were observed in up to 15% of patients with MOG-related disease (Hamid et al., 2018) and also were the presenting phenotype in some adult cases (Ogawa et al., 2017; Hamid et al., 2018). However all patients in these series had cortical brain lesions on MRI in contrast to the present case where MRI was normal at the time of seizure occurence but numerous lesions appeared 2.5 months later when substantial behavioral and personality changes developed. In another recent report, isolated cluster of focal seizures was found to be the presenting feature in four children with normal MRI similar to the MRI findings at the onset of disease in our case (Ramanathan et al., 2019). However an asymptomatic interval between 8 months and 48 months before subsequent clinical episodes were observed in these patients, in contrast to the present case where insidious behavioral change started just following the single focal-to-bilateral seizure.

In a recent report, a 60-year-old biopsy-confirmed CNS vasculitis patient who admitted with progressive cognitive deterioration and behavioral changes over nine months was found to have MOG antibodies (Baba et al., 2019). In contrast to our case, the patient's cognitive deterioration and behavioral changes were not improved, suggesting behavioral changes may not be reversible in elderly patients possibly due to delay in the diagnosis and the irreversible brain damage.

Diagnostic criteria for MOG-related disease include the presence of a typical clinical relapse with positive MOG-IgG detected by cell-based assay, and exclusion of alternate diagnoses (Jarius et al., 2018). We suggest to include atypical clinical phenotypes to the diagnostic criteria since the complete spectrum of the disorder has not yet been elucidated with increasing number of recently reported atypical presentations.

4. Conclusion

This case further expands the clinical spectrum of MOG-related disease and underlines that child neurologists should be aware of MOG-related disease in patients presented with slowly progressive behavioral and personality changes following a seizure and a normal initial brain MRI, since prompt diagnosis has management, treatment and prognostic implications.

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Declaration of Competing Interest

All authors declare that there is no conflict of interest.

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