Atypical Neuromyelitis Optica Spectrum Disorder With Diffuse Cerebral Abnormalities: A Case Report

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ABSTRACT: The recent expansion of the radiological criteria and the use of a highly specific biomarker, anti-aquaporin 4-IgG (AQP4 IgG), has significantly improved the ability of clinicians to provide a timely and accurate diagnosis for neuromyelitis optica spectrum disorder (NMOSD), especially when faced with an abnormal disease presentation. Here, we report on the 5-year clinical experience of a 69-year-old right-handed African American woman who initially presented following symptoms suggestive of transient global amnesia. Her clinical history was only remarkable for a single episode of visual decline with poor recovery experienced 35 years prior, with prior unrevealing serological investigations. Brain MRI features were significant for diffuse, bilateral white matter abnormalities throughout the supratentorial, deep gray matter, and infratentorial regions. Spinal cord imaging studies were within normal limits with no intramedullary high-signal abnormalities identified. Serological studies were significant for the presence of anti-aquaporin 4-IgG. The clinical features were supportive of the diagnosis of NMOSD. The data provided here highlight both the clinical and radiological heterogeneity of NMOSD.

KEYWORDS: Neuromyelitis optica spectrum disorder, MRI, anti-aquaporin 4-IgG, white matter abnormalities, spell

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Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is an inflammatory aquaporin-4 channelopathy of the CNS traditionally characterized by optic neuritis and longitudinally extensive lesions within the spinal cord, although the diagnostic criteria have been recently expanded to include further radiological abnormalities within the brain.[1] Advances in serological testing and the discovery of a biomarker (anti-aquaporin 4-IgG (AQP4-IgG)) have offered improved specificity for the diagnosis particularly when confronted with an atypical disease course, and allowed for the expansion of the NMOSD diagnostic criteria, recognizing the heterogeneity in clinical and radiological presentations.[1]

Here, we describe a patient with AQP4-IgG seropositivity that presented in clinic with an exceptional clinical history of remote disease and striking features on brain MRI, demonstrating the vast spectrum of disease in NMOSD.

Written informed consent was acquired from the patient for clinical information and medical images to be published.

Case Report

A 69-year-old right-handed African American woman was seen in consultation for a recent spell. She experienced an acute episode of confusion and impaired consciousness while pumping gasoline. A prodrome preceding her symptoms was denied. Following symptom incipience, she was unable to operate her car and was taken home by a family member. Difficulties with short-term memory followed and she was observed repeating herself and asking the same questions to family members over the course of a few hours followed by symptom resolution. Her medical history was additionally significant for an episode of visual loss involving the right eye 35 years prior, with no history of repeat neurological events.

On neurological examination, her mental status was intact. Light perception was not described at the right eye. Funduscopic examination revealed right optic disk atrophy without vessel attenuation. A complete blood count and comprehensive metabolic panel were unrevealing. Antinuclear antibody testing was positive (homogeneous and speckled pattern; 1:80) with normal extractable nuclear antigen panel results. Long chain fatty acid analysis was within normal limits and there were no signs of vitamin or mineral deficiencies. A cell-based aquaporin 4-IgG (AQP4) assay revealed a positive test result with an elevated autoantibody titer observed (1:400). Cerebrospinal fluid profile revealed an unremarkable cell count and differential, protein 42 mg/dL, glucose 43mg/dL, myelin basic protein <2.0 µg/L, IgG index <0.7, and 1 unique oligoclonal band. Optical coherence tomography (OCT) using a Spectralis system (Heidelberg Engineering, Heidelberg, Germany) demonstrated severe retinal nerve fiber layer and macular thinning at the affected eye. Brain MRI was significant for diffuse high-signal abnormalities throughout the brain (Figure 1). Cervical and thoracic MRI studies were normal. A routine electroencephalography study was unremarkable for focal abnormalities. The patient was placed on mycophenolate mofetil before transitioning to rituximab for treatment.

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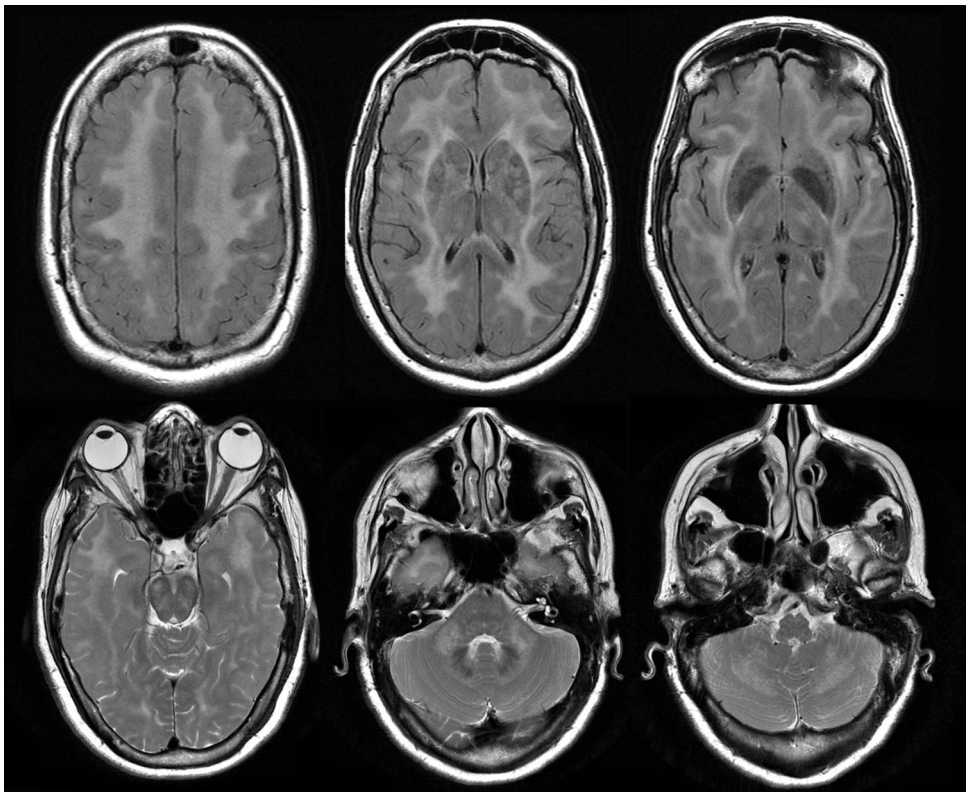

Figure 1. Diffuse brain T2-hyperintensities related to neuromyelitis optica spectrum disorder.
Axial fluid attenuated inversion recovery (FLAIR) (upper row) and T2-weighted MRI images (lower row) of the brain demonstrating the presence of diffuse high-signal abnormalities involving all lobes, deep gray nuclei, brainstem, cerebellar peduncles, and cerebellum.

Discussion

The reported clinical experience was significant for an isolated remote event of acute vision loss with poor recovery occurring 3 decades earlier, a brief acute episode of impaired consciousness with diagnostic studies demonstrating severe optic neuropathy, and diffuse high-signal abnormalities on brain MRI. Serological testing also indicated the presence of anti-AQP4 serum IgG, a highly specific biomarker for the diagnosis of NMOSD.[1] The diagnostic criteria for NMOSD with anti-AQP4 IgG was fulfilled given the presence of at least 1 core syndrome (i.e. optic neuritis), a positive serum anti-AQP4 antibody test result, and the exclusion of other alternate diagnoses.[1]

Supporting evidence from clinical, para-clinical, or radiological investigations, for other medical conditions was not observed. The patient's history was devoid of chronic headache events or focal neurological deficits, symptoms characteristic of CNS vasculitis. Although the acquired imaging data highlighting diffuse involvement throughout the entire brain requires consideration of an inherited or acquired metabolic disorder, the clinical course and supporting paraclinical data were more representative of NMOSD. The imaging was also non-supportive of other diagnoses, including neurosarcoidosis, and longitudinal investigations were non-suggestive of a progressive disorder. Although the described clinical experience was suggestive of an ictal event or symptoms supportive of transient global amnesia, the etiology was not supported by the other differential considerations provided. In addition, the lack of considerable temporal evolution of the patient's clinical experience and degree of radiological discordance to her clinical status was less supportive of other progressive conditions.

The unique and extraordinary radiological features presented appear to be highly atypical for NMOSD given the extent of brain involvement. The classic longitudinally extensive intramedullary lesion beyond ⩾3 contiguous segments, longitudinally extensive optic nerve lesion, or brain MRI features (in the setting of a recent episode of optic neuritis) non-supportive of multiple sclerosis were not observed.[1] Previously unreported, diffuse, high-signal changes extending far beyond the areas of high anti-AQP4 density were observed in the case presented with involvement appreciated in all lobes of the brain, deep gray matter, as well as the infratentorial region. The presence of T2-weighted hyperintensities in areas with a high-density of AQP-4 channels has been observed in NMOSD.[2] The remarkable involvement appreciated on structural neuroimaging is consistent with the high anti-AQP4 titer obtained from serum contributing to pathology.[3] A high anti-AQP4 titer may lead to greater functional loss in AQP4 channels, resulting in diffuse vasogenic edema, creating spindle-like or radial-like changes that extend along the white-matter tracts.[4]

Recent years have seen the emergence of optical coherence tomography (OCT) as a viable technology for diagnostic and

disease monitoring purposes in NMOSD in patients with at least 1 episode of optic neuritis.[5] While the true benefit as a successful measure for monitoring treatment response remains undetermined, the acquired OCT findings were consistent with identifying the extent of injuries associated with the previous history of an acute visual disturbance at the right eye.

The clinical experience described by the patient also appeared to be highly atypical of NMOSD, remaining asymptomatic for 35 years following her initial episode of optic neuritis and occurring in the setting of a lack of exposure to commonly used treatments. Prior clinical experiences of similar duration have not been described within the scientific literature and benign cases of NMOSD, defined by the lack of acute neurological episodes or progressive decline in neurological dysfunction spanning decades, appear highly uncommon.[6] While clinical syndromes involving the optic nerve, spinal cord, brainstem, diencephalon, or cerebrum are considered typical of the disease course, our patient remained clinically silent over an extensive period of time.[1] About 5 years following her initial presentation, a better explanation for her clinical experience has not been identified. In addition, acute neurological events or a remarkable decline in neurological function was not experienced by the patient. Furthermore, disease advancement on MRI was not observed on repeat studies performed annually following the commencement of treatment.

Conclusion

The clinical case highlights the presence of diffuse white matter abnormalities on brain MRI, in the absence of the traditionally seen longitudinally-extensive transverse myelitis, in an AQP4-IgG seropositive patient with neuromyelitis optica spectrum disorder who suffered a recent spell following more than 3 decades of benign disease activity along with 5-year clinical follow-up data demonstrating stable features. Despite improvements in structural imaging of the central nervous and visual systems, as well as the emergence of highly specific biomarkers for recognized diseases that have been made possible through recent technological advancements, the key principles of neurology involving the proper acquisition of clinical history and physical examination data remain invaluable in directing future medical evaluations, especially in cases where atypical disease behavior or remarkable diagnostic imaging data are obtained.

Author Contributions

DTO and BDN were involved in the data acquisition, clinical data analysis, interpretation, figure design and drafting of the manuscript. OK was involved in the data analysis, interpretation, and critical review of the manuscript.

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