Two Siblings, Two Diagnoses: A Familial Case of MS and AQP4-Positive NMOSD

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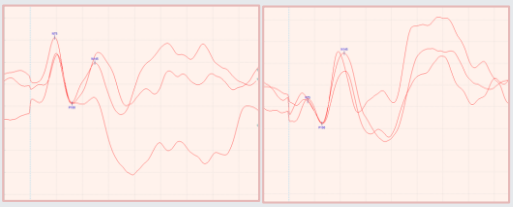
Background

Multiple sclerosis (MS) and aquaporin-4-antibody-positive neuromyelitis optica spectrum disorder (NMOSD-AQP4+) are distinct autoimmune demyelinating disorders of the central nervous system with different immunopathological and genetic profiles. Familial clustering of either disease is rare, and co-occurrence in first-degree relatives is exceptional.

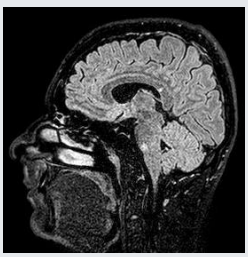
Case presentation

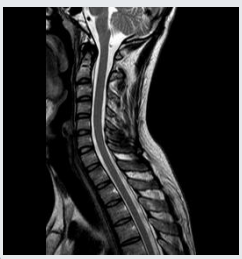
C.C.B.

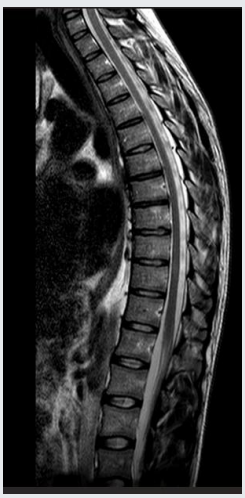
32-year-old man, presented in February 2019 with a transient left-sided sensorimotor syndrome. Brain CT and EEG were normal. His history included a 7-day self-limited vertigo and postural instability episode two years earlier. Brain MRI revealed multiple T2-hyperintense lesions with contrast enhancement in four, fulfilling McDonald criteria for MS. Visual evoked potentials (VEPs) showed bilateral P100 latency delay, more pronounced on the left, consistent with subclinical optic nerve demyelination typical of MS. Autoimmune and thrombophilia panels were negative. He was treated with IV methylprednisolone and started on dimethyl fumarate in April 2019, showing clinical (EDSS 0) and MRI stability until June 2021, when he developed right limb paresthesia and patellar reflex asymmetry. Therapy was switched to cladribine (EDSS 1.0). In December 2024, he experienced right eye visual impairment (EDSS 1.5), treated with corticosteroids with complete recovery. MRI revealed two new brain enhancing lesions, leading to escalation to anti-CD20 therapy.



Right eye Left eye



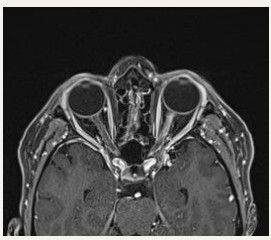


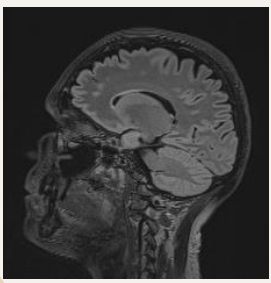


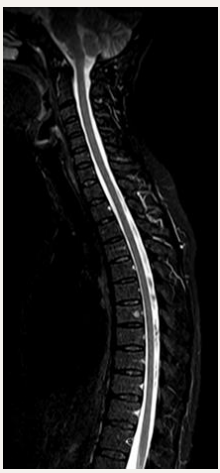
E.B.

C.C.B.'s 49-year-old sister, presented in June 2024 with acute right eye visual loss. MRI showed T2-hyperintense signal, enhancement, and swelling of the right optic nerve. She received IV steroids with poor response, and visual acuity loss persisted (EDSS 3.0). VEPs revealed significant amplitude reduction and latency delay on the right. In May 2025, she developed left eye visual loss, again refractory to high dose of steroids and partially improved after plasma exchange. MRI confirmed bilateral optic nerve enhancement. VEPs showed severe bilateral dysfunction with marked axonal loss. Serum anti-AQP4 antibodies were positive, confirming NMOSD-AQP4+ diagnosis and she started Rituximab.

Right eye Left eye







Discussion

The coexistence of MS and NMOSD within the same family is a very rare event, with few cases reported in the literature, making it challenging to elucidate the underlying mechanisms of this phenomenon. This observation suggests a relationship between the two disorders, potentially involving shared autoimmune susceptibility. Genome-wide studies suggest limited overlap, though both may arise from a predisposition to CNS autoimmunity. The contrasting VEP patterns - mild delay in MS versus severe bilateral axonal loss in NMOSD- reflect divergent pathophysiology and demonstrate neurophysiology diagnostic utility.

Conclusions

This case highlights potential overlapping immunogenetic factors in NMOSD and MS and reinforces the importance of accurate differential diagnosis and appropriate therapeutic choices in familial demyelinating disorders.