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When the mimic meets reality: AQP4-IgG seroconversion in a patient with profound biotinidase deficiency presenting with an NMOSD-like phenotype

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Abstract

Neuromyelitis optica spectrum disorder (NMOSD) is a chronic autoimmune inflammatory disease of the central nervous system. While aquaporin-4 immunoglobulin G (AQP4-IgG) antibodies are detected in most adult patients, seronegativity is common in pediatric and early disease stages, complicating diagnosis. Several metabolic disorders may clinically and radiologically mimic NMOSD in these settings. Biotinidase deficiency is a rare, treatable metabolic disorder reported as an NMOSD mimic. We describe a 16-year-old girl with an NMOSD-like phenotype and longitudinally extensive transverse myelitis who was initially AQP4-IgG–negative and diagnosed with profound biotinidase deficiency. Following clinical improvement with biotin supplementation, she experienced a relapse, and repeat testing revealed AQP4-IgG seroconversion, confirming coexistent seropositive NMOSD. This case illustrates that a metabolic disorder may coexist with, rather than solely mimic, NMOSD.

Keywords: Biotinidase deficiency; Demyelination disorders; Neuromyelitis optica spectrum disorder; NMOSD.

INTRODUCTION

Neuromyelitis optica spectrum disorder (NMOSD) is a chronic autoimmune inflammatory disease of the central nervous system characterized by recurrent attacks of optic neuritis, myelitis, and brainstem involvement.[1] The identification of aquaporin-4 immunoglobulin G (AQP4-IgG) antibodies has been pivotal for diagnosis; however, seronegativity remains common in pediatric patients and during early disease stages, which complicates diagnosis and delays appropriate treatment.[1]

In seronegative presentations, the differential diagnosis broadens considerably, as several metabolic and genetic disorders may clinically and radiologically mimic NMOSD.[1] Biotinidase deficiency (BD), a rare autosomal recessive metabolic disorder, has rarely been reported in the literature as a mimic of NMOSD, presenting with features such as longitudinally extensive transverse myelitis and optic neuropathy.[1-3]

Here, we present a 16-year-old girl with profound biotinidase deficiency who presented with a clinically and radiologically NMOSD-like phenotype. During longitudinal follow-up, she experienced a clinical relapse accompanied by AQP4-IgG seroconversion, leading to a definitive diagnosis of seropositive NMOSD. This case illustrates that a metabolic disorder

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may coexist with, rather than solely mimic, neuromyelitis optica spectrum disorder.

CASE REPORT

A previously healthy 16-year-old girl with no significant personal or family medical history presented with progressive lower extremity weakness following a 15-day history of persistent vomiting. Weakness initially began in the left lower extremity, rapidly involved the right side, and within two days progressed to both upper extremities, accompanied by ascending numbness up to the mid-thoracic level. She had a normal birth history, growth, and development, and no prior neurological or systemic disease.

Neurological examination revealed that the patient was conscious, oriented, and cooperative, with normal cranial nerve functions. Quadriparesis was present. According to the MRC scale, proximal upper extremity strength was 4/5, distal upper extremity strength was 3/5, and both proximal and distal lower extremity strength were 3/5. Deep tendon reflexes were hypoactive, and plantar responses were flexor bilaterally. Sensory examination was normal. No urinary retention was present, and sphincter tone was preserved.

Brain MRI (T2-weighted and FLAIR sequences) demonstrated hyperintense lesions involving the area postrema at the level of the medulla oblongata, periventricular regions surrounding the third ventricle, the hypothalamus, mammillary bodies, and the right parietal subcortical white matter (Figure 1A–D; Figure 2A). These lesions appeared hypointense on T1-weighted images and showed mild nodular gadolinium enhancement on post-contrast imaging. Spinal MRI revealed longitudinally extensive T2-hyperintense lesions extending from the T4 level to the conus medullaris (Figure 2B), with additional T2-hyperintense lesions at the C2–C3 levels in the cervical spinal cord (Figure 2A).

Visual acuity and color vision were normal. Fundoscopic examination was unremarkable. Visual evoked potentials (VEP), optical coherence tomography (OCT), visual field testing, and contrast-enhanced orbital magnetic resonance imaging (MRI) were all within normal limits, and no evidence of optic nerve involvement was detected.

Initial laboratory investigations were unremarkable except for severe hyponatremia (serum sodium: 111 mmol/L). Cerebrospinal fluid (CSF) analysis demonstrated a normal cell count, a mildly elevated IgG index (0.69), and absence of CSF-restricted oligoclonal bands. Serum and CSF AQP4-IgG and MOG-IgG antibodies were negative. Extensive infectious, vasculitic, paraneoplastic, and autoimiotinidasemune evaluations were unremarkable.

Metabolic workup revealed a profound reduction in serum biotinidase enzyme activity (8% of normal). Exome sequencing identified a homozygous pathogenic *BTD* variant (c.1270G>C; p.Asp424His). High-dose intravenous methylprednisolone and intravenous immunoglobulin resulted in limited improvement, after which high-dose oral biotin was initiated, leading to marked clinical and radiological recovery.

At the three-month follow-up, recurrent vomiting prompted reassessment. Repeat testing revealed AQP4-IgG seroconversion (1:32), while MOG-IgG remained negative. The patient

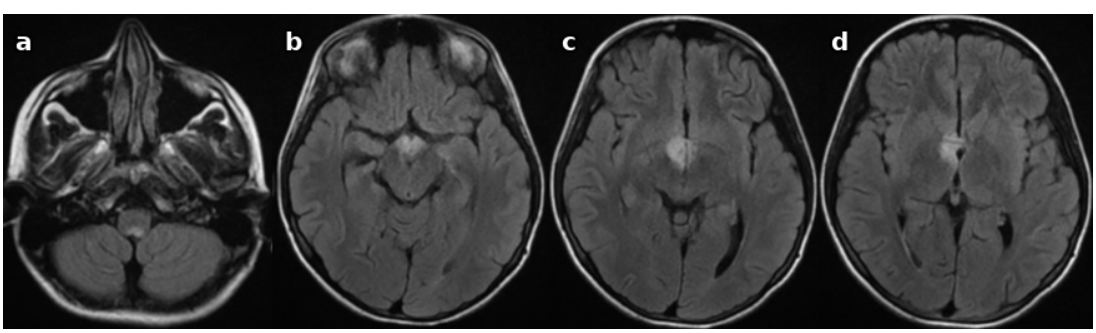

Figure 1. Axial T2-weighted FLAIR brain MRI images demonstrate hyperintense signal changes at the level of the (**a)** area postrema in the medulla oblongata, involving the (**b**) mammillary bodies and adjacent hypothalamic region, and in the (**c,d**) periventricular region surrounding the third ventricle.

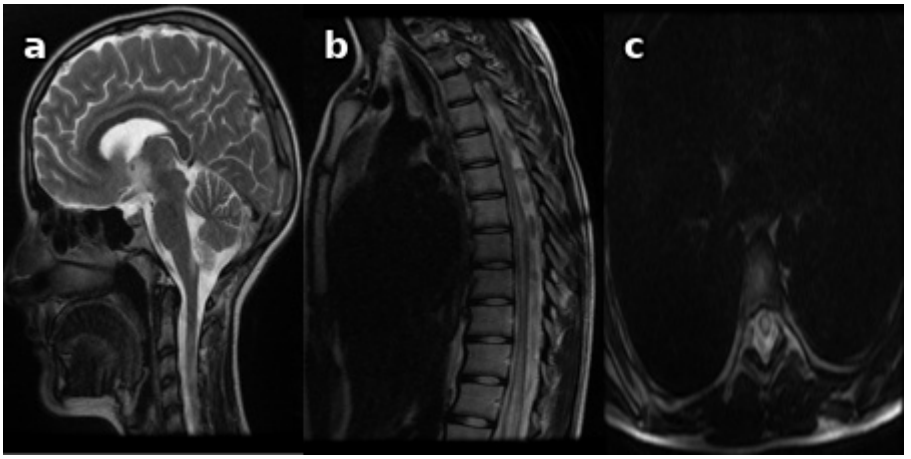

Figure 2. Sagittal and axial T2-weighted MRI images demonstrate hyperintense signal changes involving the (a) hypothalamus, mammillary bodies, periventricular region surrounding the third ventricle, area postrema at the level of the medulla oblongata, and the upper cervical spinal cord; **(b)** longitudinally extensive hyperintense signal changes extending from the T4 level to the conus medullaris on sagittal spinal imaging; and **(c)** central hyperintense signal changes within the spinal cord on axial T2-weighted images.

was reclassified as having seropositive NMOSD, and rituximab therapy was initiated.

DISCUSSION

This case highlights the diagnostic challenges arising from the overlap between treatable metabolic disorders and autoimmune demyelinating diseases in the pediatric population. Although metabolic mimics of NMOSD are rare, the number of reported cases has increased in recent years, likely reflecting improved recognition of metabolic disorders and the use of comprehensive diagnostic evaluations.[1,3-6] In pediatric seronegative presentations, overlap among infectious, autoimmune, and metabolic conditions necessitates a broader and dynamic diagnostic approach.[1]

Profound BD classically presents in early life with neurocutaneous features; however, late-onset cases are uncommon and may present with myelitis and optic neuropathy, thereby mimicking the clinical spectrum of neuromyelitis optica spectrum disorder (NMOSD), especially in the absence of typical systemic features.[2,3] The neuroradiological findings observed in our patient—including longitudinally extensive spinal cord lesions extending from the T4 level to the conus medullaris and involvement of the area postrema, hypothalamus, and mammillary bodies—are consistent with previously reported demyelinating phenotypes associated with BD.[4,6] Current NMOSD diagnostic and management consensus statements emphasize that BD should be considered in the differential diagnosis, particularly in patients presenting with atypical or seronegative demyelinating syndromes.[1]

Existing reports of BD-associated NMOSD-mimicking presentations have largely focused on the identification of the metabolic disorder and the clinical response to biotin therapy. In these cases, AQP4-IgG antibodies were negative at diagnosis, and longitudinal monitoring of AQP4-IgG status during follow-up or clinical relapses has not been systematically described.[1,3-7] In contrast, cohort studies in patients with NMOSD have demonstrated the value of repeated AQP4-IgG testing over time, reflecting the dynamic nature of serostatus in this antibody-mediated disorder. For example, a large Chinese cohort reassessed AQP4-IgG antibodies at regular intervals and during relapses over a 36-month follow-up period, revealing fluctuations in serostatus associated with disease activity.[8]

The lack of structured, longitudinal serological monitoring in patients with biotinidase deficiency presenting with an NMOSD-like phenotype may contribute to underrecognition of potential evolving autoimmune processes during follow-up. The most distinctive feature of the present case is the development of AQP4-IgG seropositivity during follow-up. To our knowledge, this represents the first genetically confirmed case of profound BD in which an

initially seronegative NMOSD-like presentation evolved into seropositive NMOSD through documented AQP4-IgG seroconversion. The predominance of isolated case reports and small case series, rather than systematic longitudinal studies, may explain why such seroconversion has not been previously recognized.

This case underscores the limitations of relying solely on initial serological testing and highlights the diagnostic importance of repeated AQP4-IgG assessment in NMOSD-mimicking presentations, even after an apparent metabolic diagnosis. These observations suggest that metabolic and autoimmune processes are not mutually exclusive but may coexist or emerge sequentially over the disease course.

In conclusion, BD may not only mimic inflammatory demyelinating diseases but may also coexist with autoimmune conditions, including AQP4-positive NMOSD. Accordingly, in patients with BD presenting with seronegative NMOSD-like features, long-term clinical and immunological follow-up with repeated antibody testing should be considered.

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DISCLOSURE

Data availability: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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