CASE REPORT

Optic Neuropathy As the Initial Presenting Sign of *N*-methyl-D-aspartate (NMDA) Encephalitis

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ABSTRACT

A 52-year-old woman presented with painless vision loss for 3 months. She was in custody for allegedly robbing a bank and had recently been diagnosed with paranoid schizophrenia. She had 20/100 VA OD, a 2+RAPD, and optic atrophy. Extensive diagnostic workup including MRI, Fluorescein Angiography, Infectious Disease Panel, lumbar puncture, and leptomeningeal biopsy were unrevealing. Vision in her right eye declined to NLP and her left eye declined to 20/200 VA. Anti *N*-methyl-D-aspartate (NMDA) Autoimmune Encephalitis was diagnosed based on CSF serology and clinical suspicion. Her clinical course improved as she was treated with corticosteroids and rituximab.

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Introduction

Although previously described, *N*-methyl-D-aspartate (NMDA) encephalitis was first categorically defined in the literature in 2007.¹ Patients with this condition classically present having had a flu-like prodromal illness with non-specific neurologic findings, including headache, seizures, and movement disorders. The disease can many times be misdiagnosed as a psychiatric illness due to varied neuropsychiatric symptoms such as paranoia, agitation, psychosis, and hallucinations. Approximately half of reported cases are associated with a paraneoplastic process.¹ The commonly proposed mechanism involves production of antibodies against dendrite expression of NMDA receptors, leakage of the blood-brain barrier, and subsequent internalisation of the antigen-antibody complex. This leads to the disruption of neuro-excitatory synaptic connections stimulated by calcium through NMDA receptors.²

Case report

A 52-year-old female presented with painless vision loss in her right eye for approximately 3 months. Medical history was significant for diabetes mellitus, hypertension, and mood disorder.

At the time of her initial examination, she was in police custody for an unknown cause. Later it was discovered that she had allegedly robbed a bank and was reportedly found praying to the devil at the time of arrest. Her examination was difficult due to emotional outbursts, poor cooperation, and memory deficits.

Visual acuity was 20/100 in the right eye (OD) and 20/25 in the left eye (OS) with a 2+ relative afferent pupillary defect (RAPD) and diminished colour vision OD. Motility was full without ocular pain. Her dilated fundus examination showed mild temporal optic nerve pallor OD. A magnetic resonance imaging (MRI) of brain and orbits was ordered, but she was lost to follow-up. One month later she was out of police custody and with a supportive family member. She had recently been diagnosed with paranoid schizophrenia. Her vision was now 20/400 OD and 20/80 OS with a persistent 3+ RAPD OD. A fluorescein angiogram demonstrates normal ocular perfusion and choroidal filling OU. Laboratory testing showed elevated platelets 434,000 (Platelets $\times 10^3$ /per mL), C-reactive protein (CRP) 26.9 mm/hr, and erythrocyte sedimentation rate (ESR) 58 mg/L.

She was admitted to neurology for evaluation of an atypical optic neuropathy with altered mental

Figure 1. MRI T1 with post-contrast axial cuts demonstrating generalised leptomeningeal enhancement of the brain with hyperintensity in the frontotemporal lobes (arrows).

status. A MRI of the brain and orbits with contrast showed widespread leptomeningeal enhancement suggestive of non-specific encephalitis (Figure 1). There was focal increased T1 intensity in the frontal lobe, worse in the right than left. A lumbar puncture showed clear fluid, red blood cells (RBCs) 26×10^6 /per mL, glucose 133 mg/dL, total protein 69, angiotensin-converting enzyme (ACE) 2 units/L (within normal limits), lymphocytes 90×10^9 per L (elevated), and normal immunoglobulin G (IgG) cerebrospinal fluid (CSF) index (mg/dL).

An infectious disease evaluation yielded negative results for human immunodeficiency virus (HIV), rapid plasma reagin (RPR), herpes simplex virus (HSV)-1, HSV-2, voltage-gated calcium channel antibody (VGCCA), Lyme, tuberculosis (TB) quantitative interferon, and *Cryptococcus*. An autoimmune panel revealed normal ACE levels, neuromyelitis optica (NMO)-IgG negative, and antinuclear antibody (ANA) positive 1:40 titre. A brain biopsy of the right frontal lobe demonstrated mild chronic inflammation, increased gliosis based on glial fibrillary acidic protein (GFAP) immunostaining, and no signs of cellular proliferation based on negative Ki-67

markers. Electroencephalogram (EEG) was non-specific, demonstrating mild generalised slow activity without any signs of seizures.

Treatment with methylprednisolone 250 mg intravenously (IV) four times daily (qid) for 5 days improved her mental status and vision in the left eye (20/60), but the right eye declined to no light perception (NLP). Her 2-week hospitalisation was complicated by three attempts to leave against medical advice. She was discharged from the hospital without a clear understanding of the aetiology of her optic neuropathy and not maintained on a prednisone taper.

She was again lost to follow-up and returned to the emergency department 6 weeks later with persistent NLP vision OD and 20/200 OS and was re-admitted to the neurology service. An MRI of the orbits demonstrated hyperintensity in the pre-chiasmatic and canalicular portions of the right optic nerve, with perineural enhancement (Figure 2). Although serum testing for NMDA antibodies had not been performed, enzyme-linked immunosorbent assay (ELISA) testing of the cerebrospinal fluid for NMDA antibodies had returned and was positive. Search for a tumour, including computed tomography (CT) of the chest, abdomen, and pelvis, showed only nodules

Figure 2. A contrast-enhanced STIR (fat-suppressed) axial T1-weighted MRI of the orbits showed enhancement in the pre-chiasmatic and canalicular portions of the right optic nerve.

of the lung, liver, and adrenal gland that were ultimately deemed incidental.

She was discharged on oral prednisone 60 mg per day and started rituximab 375 mg once per week for 3 weeks. Vision improved in the left eye to 20/25, and her personality returned close to baseline per the family. She is currently maintained on oral prednisone 20 mg per day.

Discussion

NMDA encephalitis is an autoimmune disease that classically manifests with a prodromal headache, fever, prominent psychiatric manifestations, seizures, decreased level of consciousness, and autonomic instability. To our knowledge, there have been three reported cases of patients with NMDA encephalitis with a concomitant optic neuritis.^{3–6} In two of these cases, the visual loss was the presenting symptom.^{4,6} The key findings surrounding their presentation are listed in Table 1. Clearly, the diversity of their clinical course demonstrates a need for additional investigations into the association between optic neuritis and NMDA encephalitis and what role the ophthalmologist might play. Our case is unique in that our patient presented initially to the

ophthalmology clinic and, as best we can tell, is the only one who ended up with complete permanent blindness in an eye.

The differential diagnosis for NMDA encephalitis is extensive, including toxic encephalopathy, porphyria, systemic lupus cerebritis, and herpes simplex cerebritis, among others.⁷ The diagnostic approach to this case involved the same workup as with any patient who presents with altered mental status with non-specific neurologic features, including changes in vision and personality. In our case, the imaging was negative for classic demyelinating disease and suggestive of a non-specific meningo-encephalitis. A spinal tap was performed to test for the presence of well-known infectious pathogens that could explain her clinical presentation, such as herpes simplex virus, HIV, syphilis, tuberculosis, and *Cryptococcus*. Other common autoimmune disorders such as systemic lupus cerebritis, sarcoidosis, and other aetiologies were excluded as well. Ultimately her diagnosis was made by a collection of negative results for common agents that could explain the encephalitis and the presence of NMDA antibodies in the cerebral spinal fluid.

In 2011, Dalmau et al. presented an extensive review of the major diagnostic findings in NMDA encephalitis involving 431 patients.⁸ They report

Table 1. Published case reports of optic neuritis in the setting of NMDA encephalitis.

Case	Presentation	Key laboratory diagnostics	Brain MRI
30-year-old female United Kingdom No. 3	Presented initially with clinical features of optic neuritis without seizures or major behaviour disturbance 3 weeks later developed mood disturbance, pressured speech, and sexually inappropriate behaviour	Aquaporin 4 negative Anti-NMDA positive antibodies in serum No paraneoplastic source	T2 hyperintensity at head of the left thalamus and adjacent internal capsule, hyperintensity in the periventricular white matter lateral to left lateral ventricle, focal lesion in the left frontal lobe
50-year-old female Italy No. 4	Developed episode of optic neuritis 9 months out from established diagnosis of combined NMDA encephalitis and neuromyelitis optica	Aquaporin 4 positive Anti-NMDA positive antibodies in serum and CSF Ovarian teratoma	T2 hyperintensity of the medial temporal cortex Subsequent development of hyperintense lesions in the pons, hypothalamus, medulla oblongata, cervical spine
10-year-old female Japan No. 5	Typical optic neuritis well managed with prednisone Flare and epileptic seizures after attempting withdraw 8 months later	Aquaporin 4 negative Anti-NMDA positive antibodies in the CSF No paraneoplastic source	Multiple cortical, subcortical, leptomeningeal enhanced lesions

that MRI abnormalities are discovered 50% of the time on T2 or FLAIR (fluid attenuation inversion recovery) sequencing with lesions characteristically found in a variety of areas, including the hippocampus, cerebellar or cerebral cortex, frontobasal and insular regions, basal ganglia, brainstem, and infrequently the spinal cord. They also cite the detection of CSF positive antibodies as critical to making the diagnosis, as they were found in all 431 of the patients included in the review. Brain biopsy performed on 15 patients was of low diagnostic yield, showing normal tissue or non-specific inflammatory infiltrates. Electroencephalograms, which typically demonstrated non-specific, slow, and disorganised activity with variable electrographic seizures, were abnormal in almost all patients.

Established first-line treatment of NMDA encephalitis involves the use of high-dose corticosteroids, plasmapheresis exchange, and intravenous immunoglobulin either as individual agents or in combination.¹ A large multicentre review of 577 NMDA encephalitis patients conducted by Titulaer et al. found that 38% of the time, an associated paraneoplastic tumour, most commonly an ovarian teratoma, is discovered.⁹ Thus, routine imaging of the chest, abdomen, and pelvis is recommended. In that study, approximately 53% of patients experienced significant clinical improvement within 4 weeks when they had identified tumours removed and were started on first-line immunotherapy. Independent factors associated with a favorable prognosis include avoiding intensive care unit (ICU) care, lower severity of symptoms at the time of presentation, prompt initiation of immunotherapy, and the removal of identified tumours. The overall mortality rate at 24 months for patients in that study was approximately 7%.⁹

In conclusion, it is still unclear if optic neuritis is part of the disease progression of NMDA encephalitis, but as more cases are reported, one must consider NMDA encephalitis in patients who present with an optic neuritis and psychotic features.

The use of immunomodulatory treatment may preserve vision.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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