

Characterizing pediatric-onset neuromyelitis optica spectrum disorder in British Columbia

A review of patient records at UBC Hospital indicates that more females than males are affected by a rare and debilitating disease that can be mistaken for multiple sclerosis, and that many patients are of Asian descent.

ABSTRACT

Background: Neuromyelitis optica spectrum disorder (NMOSD) has emerged as a disorder distinct from multiple sclerosis, largely due to the discovery in 2004 of a novel disease marker, aquaporin-4 immunoglobulin or AQP4-IgG (also known as NMO-IgG). Differentiating NMOSD from multiple sclerosis has important prognostic and treatment implications. The features of pediatric-onset multiple sclerosis have been reported previously and are known to overlap considerably with adult-onset multiple sclerosis. Less is known about the presentation of pediatric-onset NMOSD.

Methods: Demographic and clinical characteristics of pediatric-onset NMOSD patients in British Columbia were identified using UBC Hospital records. Data from 10 cases were collected and analyzed over 5 years. All cases were diagnosed by a neurologist with expertise in NMOSD.

Results: Cases of NMOSD with AQP4-IgG (30.0%) and without AQP4-IgG (40.0%) were identified, along with cases of longitudinally extensive transverse myelitis (30.0%). A diverse ethnic population was involved in the study, which included

patients of Chinese (50.0%), Korean (20.0%), East Indian (10.0%), and Caucasian (20.0%) descent. More females (70.0%) than males (30.0%) were identified, and more patients experienced optic neuritis (60.0%) than opticospinal attacks (30.0%) or spinal attacks (10.0%) as the first event. Average age of onset was 10.0 years.

Conclusions: In common with findings from studies in Germany, Brazil, and South Korea, female patients outnumbered male patients in BC and a preponderance of patients were of Asian descent. In contrast to findings from France, where similar percentages of patients experienced optic neuritis (50.0%) and spinal attacks (41.7%), more patients in BC were affected by optic neuritis (60.0%) than spinal attacks (10.0%). As well, a lower percentage of patients in BC tested positive for AQP4-IgG (30.0%) when compared with patients in South Korea (66.7%) and France (66.7%). It is essential to raise awareness of pediatric-onset NMOSD and its presenting features in the medical community and to find out more about the disorder so that we can expand on the limited treatment options available.

Background

Neuromyelitis optica spectrum disorder (NMOSD), previously known as neuromyelitis optica (NMO) and Devic disease, is a rare neuroinflammatory disease of the central nervous system.^{1,2} This debilitating disease is clinically and pathophysiologically distinct from multiple sclerosis (MS), and primarily affects the optic nerve and spinal cord, resulting in severe optic neuritis (ON) and transverse myelitis (TM).³ In NMOSD, spinal cord lesions can be seen on MRI to extend over three or more spinal segments.⁴ Defined as longitudinally extensive transverse myelitis

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(LETM), this is a typical feature of NMOSD at the time of an acute TM attack. In contrast to MS, NMOSD attacks tend to be more severe, with complete blindness, paraplegia, and quadriplegia being a consequence.

NMOSD affects more females than males,^{5,6} is seen in mixed ethnic populations, and often involves the autoantibody aquaporin-4 immunoglobulin or AQP4-IgG (also known as NMO-IgG).^{6,7} This serum autoantibody targets the aquaporin-4 water channel and induces a series of biological events that result in tissue inflammation, demyelination, and edema.³

AQP4-IgG is a highly specific disease marker for NMOSD and helps distinguish the disorder from MS. Distinguishing NMOSD from MS is important for both prognosis and treatment because it has been observed that traditional MS immunomodulatory therapy may not be effective and may even worsen NMOSD.^{8,9}

In addition to LETM and severe bilateral blindness, which are both highly suspicious for NMOSD in pediatric patients, cerebral lesions in the hypothalamus, brainstem, or diffuse white matter are found in children with features of NMOSD.^{2,7,10} In

July 2015, the International Panel for NMO Diagnosis published revised diagnostic criteria for NMOSD with positive or negative/unknown AQP4-IgG status.¹¹ The Pediatric Working Group indicated that similar clinical, laboratory, and neuroimaging findings apply in pediatric-onset and adult-onset NMOSD, and noted that adult NMOSD criteria can be used for children.¹¹

NMOSD in BC

A review of the UBC NMO database in 2014 found that 84 British Columbians, including both adult and pediatric patients, were diagnosed with NMO, NMOSD, or clinically isolated syndrome (CIS) of NMOSD using the 2006 NMO diagnostic criteria (unpublished data). There was a preponderance of female patients (73.0%) and a diversity of ethnicities, including Caucasian (46.0%), Asian (Chinese, Filipino, Vietnamese, Korean, Japanese, mixed) (39.0%), South Asian (Indian) (7.0%), and others (Ghanaian, First Nations, Guatemalan, West Indian, Somalian) (7.0%). Even though pediatric-onset NMOSD has previously been studied in south-east Wales,⁴ Germany,⁵ South Korea,⁶ United States,⁷ Brazil,⁸ Martinique,¹² and France,¹³ it is a very rare disease and is understudied worldwide. Currently, 1 to 2 pediatric-onset NMOSD cases and 15 adult-onset NMOSD cases can be expected in BC annually.

BC consists of an ethnically diverse population of more than 4.6 million.¹⁴ The 2011 Household Survey by Statistics Canada found that 67.3% of the BC population was Caucasian.¹⁵ Minority groups identified included Chinese (10.1%), South Asian (7.2%), Filipino (2.9%), Southeast Asian (1.2%), Korean (1.2%), West Asian (0.9%), Japanese (0.9%), Black (0.8%), Latin American (0.8%), and Arab (0.3%).¹⁵

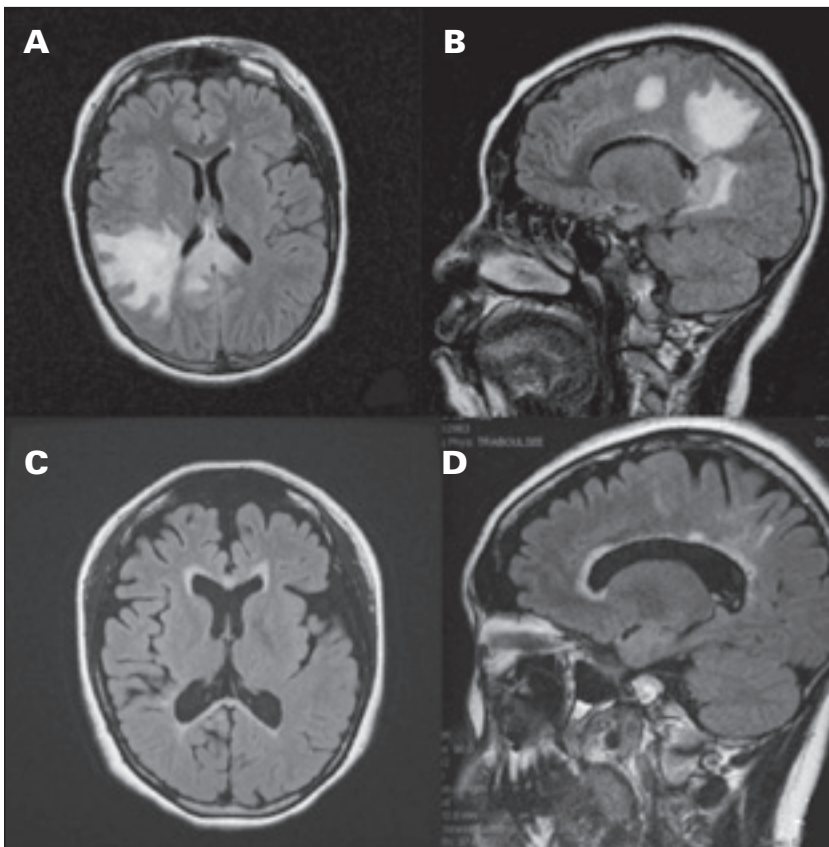


Figure 1. Four images from brain MRI of female patient of Korean descent found to be seropositive for AQP4-IgG and diagnosed with neuromyelitis optica spectrum disorder. Axial (A) and sagittal (B) T2-weighted FLAIR (fluid attenuation inversion recovery) images obtained during a relapsing episode show large, multifocal cerebral lesions. Axial (C) and sagittal (D) T2-weighted FLAIR images obtained 7 years later show shrunken lesion volume, enlarged ventricles, and atrophy.

Case report

The case of one patient eventually found to have neuromyelitis optica spectrum disorder illustrates some demographic and clinical characteristics of the pediatric-onset NMOSD population in British Columbia.

At age 15, a right-handed female of Korean descent presented with weakness in her lower extremities and was diagnosed with transverse myelitis. Within a month she developed bilateral optic neuritis and intractable unexplained nausea and vomiting. This first attack was treated with high-dose intravenous methylprednisolone and her symptoms improved. Based on her presenting symptoms, she was diagnosed with relapsing-remitting MS.

Between age 15 and 19 the patient had recurrent episodes of TM and severe ON. She continued to have attacks despite all conventional forms of MS therapy, including plasmapheresis, steroids, intravenous immunoglobulin, and interferon beta-1a (Avonex). The diagnosis of NMOSD was considered and the patient was treated with mycophenolate mofetil (Cellcept). She also received mitoxantrone for 2 years to prevent the severe relapses she had been experiencing. The medication, while effective, was stopped because of the risk of cardiotoxicity with cumulative doses. Six months later, the patient lost all vision and severe LETM led to near-complete quadriplegia.

When the patient was 19, serological tests for AQP4-IgG were positive and a diagnosis of NMOSD was confirmed at the Vancouver General Hospital by Dr A. Traboulsee. Tests for antinuclear antibody (ANA) were also positive and the patient was found to have high levels of anti-Sjogren's syndrome antigen A (anti-SS-A/RO) autoantibodies, which are not uncommon in NMOSD. Images from

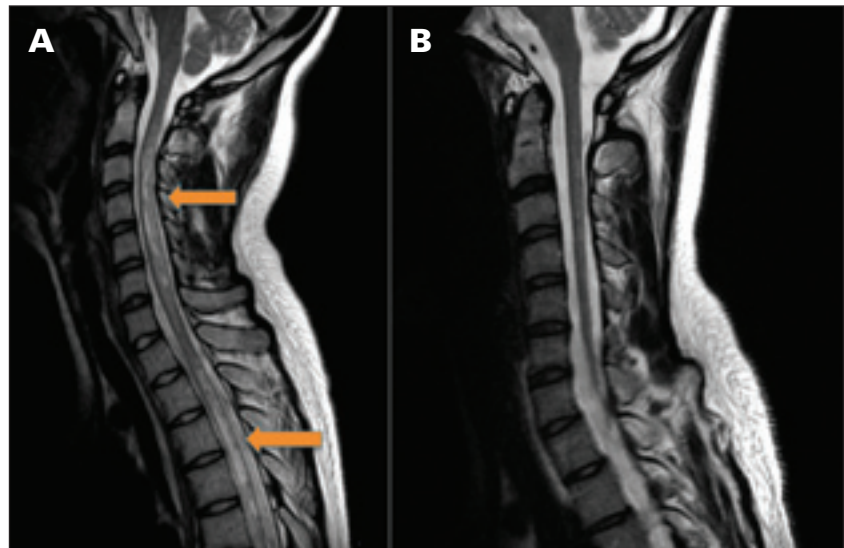


Figure 2. Two images from spinal cord MRI of a female patient of Korean descent found to be seropositive for AQP4-IgG and diagnosed with neuromyelitis optica spectrum disorder. A sagittal T2-weighted image obtained during a relapsing episode (A) shows increased signal intensity in cervical and thoracic vertebrae (arrows) consistent with longitudinally extensive transverse myelitis. A sagittal T2-weighted image obtained 7 years later (B) shows resolved long spinal cord lesions with minor residual lesion. Due to significant atrophy of the spinal cord, the patient currently suffers from partial quadriplegia.

a brain MRI at the time of diagnosis revealed large tumefactive lesions (Figure 1A and Figure 1B), while images from 7 years later revealed shrunken lesion volume and enlarged ventricles (Figure 1C, Figure 1D). Images from a spinal cord MRI at the time of diagnosis revealed a longitudinal lesion extending over several vertebral segments, consistent with LETM (Figure 2A), while images from 7 years later revealed significant atrophy (Figure 2B).

The patient's condition stabilized after a single cycle of intravenous rituximab (two doses of 1000 mg each, 2 weeks apart) and she was discharged to a long-term care facility at age 21 with complete blindness and paraplegia.

Methods

To identify demographic and clinical characteristics of the pediatric-onset NMOSD population in BC, we used

hospital records of patients who presented with initial symptoms at age 18 or younger. It took 5 years to collect data on 10 pediatric-onset cases referred to the NMO Clinic at the UBC Hospital for investigation and management. All cases were diagnosed by a neurologist with expertise in NMOSD using revised diagnostic criteria¹¹ to identify patients with clinical findings highly suspicious for NMOSD.

Results

Seven patients (70.0%) were diagnosed with NMOSD, one patient (10.0%) with recurrent LETM (R-LETM), one patient (10.0%) with clinically isolated syndrome with LETM (CIS-LETM), and one patient (10.0%) with clinically isolated syndrome with optic neuritis and LETM (CIS-ON/LETM). Cases of NMOSD with AQP4-IgG (30.0%) and without AQP4-IgG (40.0%) were

identified. A diverse ethnic population was involved in the study, which included patients of Chinese (50.0%), Korean (20.0%), East Indian (10.0%), and Caucasian (20.0%) descent. Pediatric-onset NMOSD was found to affect more females (70.0%) than males (30.0%), and more patients experienced optic neuritis (60.0%) as the first event than opticospinal attacks

nucleus, cerebellum, optic nerves, and the brainstem. The abnormalities in the spinal MRI were mainly located in the thoracic and cervical vertebrae.

Conclusions

In this study, there was a preponderance of female patients, a finding in common with Germany (66.6% females),⁵ Brazil (70.0% females),⁸

seropositive for AQP4-IgG (30.0%) compared with patients in South Korea (66.7%)⁶ and France (66.7%).¹³ Additionally, three out of ten patients who experienced ON during the first attack also presented initially with vomiting symptoms. Among these individuals, two patients were found to have cerebral lesions in the brainstem and one patient was found to have three large multifocal lesions at the time of the attack. This could be explained by the possibility that the area postrema is one of the main targeting sites in NMOSD.^{16,17} The area postrema is a circumventricular organ in the brain that is AQP4-rich, chemosensitive, and responsible for emesis.¹⁶ A previous study reported that 40.0% of patients with NMOSD showed lesions on the medullary floor of the fourth ventricle and the area postrema, resulting in intractable nausea, vomiting, and hiccups.¹⁷ This can be explained by the lack of tight endothelial cell junctions in the area postrema, which makes it vulnerable to immunological surveillance and serves as a portal for introducing circulating immunoglobulin G into the central nervous system.^{16,17} Furthermore, three out of ten patients who experienced TM during the first attack also presented with neurogenic bladder problems. All three patients showed long, cervical spinal cord lesions at the time of the attack, suggesting involvement of both the reticulospinal tract and the corticospinal tract.¹⁸

Study limitations

There were limitations to this study. Because NMOSD is rare and often misdiagnosed, the available sample size was small (10 patients). Also, since AQP4-IgG testing was only introduced in 2004, and the NMOSD diagnostic criteria were revised in 2006 and again in July

We found more patients affected by optic neuritis (60.0%) than spinal attacks (10.0%), in contrast to findings from pediatric medical centres in France, where similar percentages of patients experienced optic neuritis (50.0%) and spinal attacks (41.7%).

(30.0%) or spinal attacks (10.0%). Average age of onset was 10.0 years, while the annualized rate of attacks was 0.75 and the average expanded disability status scale (EDSS) score of patients was 2.5. Serological tests for 30.0% of the cohort were positive for AQP4-IgG. Although 30.0% of tests were also positive for ANA, no patients had clinical symptoms of systemic lupus erythematosus. Common symptoms included vomiting, visual disturbances, diplopia, and headaches. Impairment included bilateral blindness (20.0%), quadriplegia (10.0%), and paraplegia (10.0%). Finally, brain MRI findings for 88.9% of the cohort showed abnormalities, and spinal cord MRI findings for 55.6% showed abnormalities. The abnormalities seen on brain MRI were located mainly in the caudate

and South Korea (66.7% females).⁶ Additionally, there was a preponderance of Asian patients. We found more patients affected by optic neuritis (60.0%) than spinal attacks (10.0%), in contrast to findings from pediatric medical centres in France, where similar percentages of patients experienced optic neuritis (50.0%) and spinal attacks (41.7%).¹³ The average age of onset in BC (10.0 years) was similar to the age reported in Germany (9.7 years).⁵ In our study, there was a similar percentage of patients with significant visual disability and mobility disability, in contrast to findings by Banwell and colleagues, who found 12.0% of subjects had limited or significant mobility disability and 71.0% had limited or significant visual disability.⁷ Furthermore, we found a lower percentage of patients were

2015, some patients in the pediatric-onset NMOSD population will reflect recent diagnostic criteria, while the adult-onset population might include misdiagnosed patients. This means it is difficult to pinpoint the exact duration of the disease in the adult population with NMOSD and the rate of change in proportion conversion from acute disseminated encephalomyelitis and MS to NMOSD. Furthermore, the study is based only on the patients who visited the NMO Clinic at the UBC Hospital and the information recorded in their medical charts on their most recent visits.

Summary

Neuromyelitis optica spectrum disorder is a rare disease, and its incidence and prevalence are understudied worldwide. NMOSD often presents with the same clinical features as MS but is distinct from MS in terms of pathophysiology and treatment. Pediatric-onset NMOSD is rarer than adult-onset NMOSD and can be very disabling and debilitating.

In BC the pediatric-onset NMOSD population is characterized by a preponderance of female and Asian patients, a higher rate of optic neuritis at onset, and a higher chance of abnormalities being found on brain MRI than on spinal cord MRI. Common symptoms can include vomiting, visual disturbances, diplopia, and headaches. Impairments can include blindness, quadriplegia, and paraplegia.

It is essential to raise awareness of pediatric-onset NMOSD and its presenting features in the medical community and to find out more about the disorder so that we can expand on the limited treatment options available.

Competing interests

None declared.

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