Journal of Integrative Neuroscience

J. Integr. Neurosci. **2023**; 22(6): 139
https://doi.org/10.31083/j.jin2206139

Editorial

Neuromyelitis Optica Spectrum Disorder: Redefining an Old Disease. Present and Future Challenges

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Academic Editor: Gernot Riedel
Submitted: 20 August 2023 Accepted: 31 August 2023 Published: 18 October 2023

Introduction

Neuromyelitis Optica Spectrum Disorder presents as an association of acute spinal cord and optic nerve pathology, and has intrigued scholars since the early 19th century. Numerous isolated observations were reported in Western European medical literature, initially from pioneering ophthalmologists since blindness is a dramatic manifestation of the disorder. However, a defined taxonomy for this disorder did not exist until Dr. Julius Sichel, a French ophthalmologist, coined the term "Spinal amaurosis" in 1837. Sir Thomas Clifford Albutt, considered one of the most influential British medical leaders of his time, promoted the use of the recently invented ophthalmoscope by the German physician Hermann von Helmholtz in 1852, in neurological diseases. Albutt described some cases of paralysis associated to blindness (1870) in his voluminous published works [1]. The name of the disorder evolved to Neuromyelitis Optica, following the report from Eugene Devic in 1894, describing the case of a 45-year-old French woman with transverse myelitis and bilateral blindness with papilledema, as well as providing autopsy findings [2]. Devic was professor at Hôtel-Dieu Hospital, Lyon, France and his student, Fernand Gault, had shared the care of this patient and described the case in his doctoral thesis "*Neuromyélite Optique, aiguë*" which was presented to the Faculty of Medicine and Pharmacy, Lyon, in November 1894. Devic's seniority and better-known name prevailed, hence, this disease is also currently recognized by his eponym, specifically, Devic's disease.

For more than 100 years, Neuromyelitis Optica (NMO) was considered a severe subtype of multiple sclerosis (MS), although post-mortem studies available from a few cases demonstrated differing patterns of pathology [3]. Since NMO appeared to notoriously affect people of East Asian ethnicity, during the period prior to establishment of a clinical definition, even such terms as 'Japanese Optic-Spinal MS' were proposed [4]. As unique magnetic resonance (MR) imaging characteristics attributable to NMO, and clinical manifestations were more extensively studied, it became increasingly evident this disease was a distinguishable neurological entity from MS. In 1999, specific diagnostic criteria were proposed [5]; however, the definite distinction from MS was not accomplished until Lennon and co-investigators from the Mayo Clinic (USA), discovered a biomarker of NMO, specifically the presence of Aquaporin-4 (AQP-4) IgG class antibody in the serum. This finding finally provided a molecular and immunologic differentiation between these two major inflammatory and demyelinating diseases of the central nervous system (CNS) [6]. Aquaporins belong to a family of proteins that serve as transmembrane channels of water transport. While having wide distribution within the CNS, aquaporins are especially abundant in structures adjacent to the blood brain barrier (BBB), the ventricles, and the aqueduct. Structures commonly affected in NMO include the cerebrum, periependymal brain stem, diencephalon and the hypothalamus, area postrema, optic nerves involving the entire visual apparatus (including the chiasm), and large segments of the spinal cord. Water channels are present in high density in the foot processes, termed pedicular extensions, of astrocytes resting on vascular spaces of the BBB. Owing to this location, astrocytes in this anatomical region are a favored pathogenic target for aquaporin antibodies. NMO is in fact a CNS channelopathy and astrocytopathy, and manifests as severe tissular damage due to inflammation, demyelination, and necrosis.

NMO is a rare disease. Incidence studies indicate frequencies of 0.037 to 0.73 per 100,000 person-year, while prevalence reports show fluctuations from 0.7 to 10.0 per 100,000 inhabitants [7]. In opposition to MS, NMO predominates in non-Caucasian populations and is more commonly encountered in Asians, people of African ancestry, Middle eastern groups, and Latin Americans. A large retrospective observational study of 2154 subjects contributed by investigators from all twenty-one Latin American countries showed the most affected population were Mestizos (61.4%), and for the first time, a major demyelinating disease was identified in Native Americans (4.0%) [8]. Females are disproportionally affected showing a variable female/male ratio between 5.0 to 9.0 to 1.0, while the clinical relapsing variety is described in over 80% of cases rather than a monophasic form. NMO anatomic lesion distribution reflects in its particular clinical symptomatology. Specifically, the most common presentation is the combination of acute transverse myelitis with magnetic resonance imaging (MRI) typically revealing extensive longitudinal transverse

myelitis involving 3 or more spine spaces, and acute optic neuritis frequently simultaneously bilateral in nature. Diencephalic involvement may produce narcolepsy and hypothalamic neuro-endocrine syndromes, and area postrema damage may result in intractable hiccups, nausea, and vomiting. Characteristically, each NMO attack will add neurological deficits to preexisting ones, but a secondary progressive course generally does not occur. Mortality is not uncommon in NMO patients, and fluctuates worldwide in ranges from 9% to 32% with death usually occurring within the first 5 years following disease onset. This outcome appears to be associated to effects developing in the brain stem and upper spinal cord, high relapse rate, lack of therapy, and African ancestry [9].

A Spectrum of Disorders

Over the last three decades, a gamut of autoimmune and neuro-endocrine disorders have been reported as associated with NMO. These pathologies include serological detection of Thyroid Peroxidase, Ro/SSA and antinuclear antibodies, and one third of patients who manifest clinical thyroiditis, systemic lupus erythematosus, myasthenia gravis, Sjögren's syndrome and hypothalamic-pituitary axis disturbances such as Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIAHS) and amenorrhea. The term Neuromyelitis Optica Spectrum Disorders (NMOSD) has been formally adopted since 2015 with the establishment an international diagnostic consensus [10].

The advent of the AQP4-IgG antibody testing for NMOSD disclosed in seronegative individuals another independent classification entity: Anti-Myelin Oligodendrocyte Glycoprotein (MOG) IgG antibody disorder. This neurological disease has distinctive pathology and clinical manifestations and has recently been defined as MOG associated disease or MOGAD. This disorder, initially described in 2012 in children with 'relapsing' acute disseminated encephalomyelitis (ADEM), produces a wide variety of neurological syndromes including optic neuritis and transverse myelitis. Approximately half of sero-negative patients with NMOSD, and one in five of non-MS demyelinating cases, are MOG-IgG positive [11].

Clear Present and Future Challenges

NMOSD have been established as a group of disorders commonly accompanied by aggressive neurological manifestations but constitutes the principal clinical differential diagnosis with MS. Despite NMOSD being a rare disease, its socioeconomic impact is enormous, particularly on health care systems in developing countries. High sensitivity serological testing for AQP4-IgG antibody such as a cell-based assay, is costly and not readily available in many areas of the world. This may potentially lead to inaccurate results from the use of inferior laboratory techniques or an avoidance of the test entirely. While the 2015 international diagnostic consensus considered this eventuality, access to affordable sensitive diagnostic methods remains an unmet need. These needs extend to MR imaging, another expensive technology, that is not generally available in some regions of the world where NMOSD is increasingly identified. Treatment of acute relapses with intravenous steroid pulses, followed, or not, by plasma exchange or intravenous hyperimmune gamma globulin, may produce substantial, albeit temporary, relief. Immunosuppressive therapies are commonly utilized in the long-term management of NMOSD with inconsistent results. The most common, and economically accessible therapies, are periodic intravenous rituximab and oral azathioprine. All these medications lack evidence-based studies and are globally used in an off-label fashion. To date, only three products have been approved by the licensing agencies of the US Food and Drug Administration (FDA), and the European Medicine Agency (EMA). These are eculizumab (a terminal complement inhibitor), inebilizumab (a CD19 inhibitor), and satralizumab (an interleukin-6 inhibitor). The high cost of these therapeutics makes their accessibility extremely limited, particularly to people in countries with economically fragile economies. Effective and accessible treatment for NMOSD remains an elusive reality, raising the concern of potentially affecting the global prognosis of the disease. Without treatment, or suboptimal therapeutic options, about 50% of patients will become blind and wheelchair-bound if they survive longer than 5 years [12]. A coordinated effort between neuroscience clinicians, health officials, and the pharmaceutical industry is imperative to find solutions to mitigate these current challenges.

Author Contributions

VMR-Writing, Conceptualization, Original draft.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The author declares no conflict of interest. Victor M. Rivera is serving as one of the Guest editors of this journal. We declare that Victor M. Rivera had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Gernot Riedel.

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