

# Accelerating clinical research in neuromyelitis optica spectrum disorders

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## Abstract

Neuromyelitis optica spectrum disorders are rare relapsing inflammatory central nervous system diseases with a heterogenous immunological and clinical spectrum. International collaborations are required to: (i) reach a better understanding of the disease and its subtypes; (ii) develop laboratory and imaging biomarkers; and (iii) ultimately improve treatments.

## KEYWORDS

biomarkers, diagnostic imaging, neuromyelitis optica

## 1 | INTRODUCTION

Neuromyelitis optica spectrum disorders (NMOSD) are rare relapsing inflammatory diseases of the central nervous system, with optic neuritis (ON) and myelitis as clinical hallmarks of the disease.<sup>1</sup> NMOSD were distinguished from multiple sclerosis as a separate disease entity in 2014 after the identification of antibodies against aquaporin-4 (AQP4-IgG), an astrocytic water channel, in up to 80% of patients.<sup>1</sup> However, to date, NMOSD are characterized by a considerable immunological and clinical heterogeneity. The most drastic change in the past decade was probably the further separation of the NMO

spectrum after identification of antibodies against myelin oligodendrocyte glycoprotein (MOG) immunoglobulin G (IgG) in a subset of AQP4-IgG seronegative patients – now termed MOG-IgG-associated disease and regarded as a condition with a pathogenesis and clinical presentation distinct from classical AQP4-IgG-associated NMOSD.<sup>2</sup>

After the initial description of NMOSD, case series and small cross-sectional cohort studies contributed significantly to our understanding of the disease. Key features of NMOSD shown in early research were: (i) the highly injurious effects and repetitive character of attacks, especially of myelitis, ON and brainstem syndromes; (ii) the – often dramatically – negative effects of immunotherapies

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used in multiple sclerosis, such as interferon-beta and natalizumab, whereas in contrast, B-cell depleting drugs are very effective; and (c) the significant heterogeneity of the disease spectrum, including epileptic seizures, narcolepsy and even chronic progressive disease courses.<sup>3,4</sup> In particular, this heterogeneity and the rarity of NMOSD led to many conflicting results on: (i) the expected range of damage for initial and following attacks; (ii) the existence of a progressive disease component; and (iii) the efficacy of off-label treatments for relapse prevention. It is also still unclear, why the incidence differs so dramatically between different geographic regions, with a lower incidence in Europe and North America, and a higher incidence in Eastern Asia.<sup>5</sup> Only larger longitudinal studies can solve these questions. To reach this ultimate goal, national and international collaborations are required.

## 2 | CURRENT COLLABORATIONS

Early in NMOSD research, national registry studies, such as the German Neuromyelitis optica Study Group (NEMOS), were founded to improve research on epidemiology and clinical course in NMOSD, as well as to collect biomaterials and establish common recommendations for diagnosis and treatment.<sup>6</sup> Shortly after, European and international NMOSD networks and registers were founded. These networks contributed extremely valuable work improving our understanding of the disease; for example, by describing the influence of sex on clinical aspects, clinical work-up of attacks and by studying the effects of acute therapy of relapses underlining the importance of early plasma separation/immune adsorption.<sup>7,8</sup> Subsequent to the seminal discovery of AQP4-IgG as a specific biomarker of NMOSD, joint expert statements from these networks on monitoring and treatment, and the increased awareness for the disease have been instrumental for a fast-tracked improvement of clinical care and initiation of clinical trials.<sup>6</sup> However, the mostly cross-sectional character of the studies carried out and their ethnic homogeneity limits the generalizability of these studies. Further problems arise from heterogeneous acquisition protocols and the lack of source data, especially for imaging studies describing lesion sites in the optic nerve, spinal cord and – to a smaller extent – brain.

An international NMOSD network, which has to be mentioned, is the Guthy-Jackson Charitable Foundation, bringing together experts for scientific conferences and projects since 2008. Guthy-Jackson Charitable Foundation fostered international collaborations and made many multicenter studies possible.<sup>9</sup> Two interesting approaches, which we had the honor to participate in, were the collaborative optical coherence tomography (OCT) study in NMOSD (CROCTINO), quantifying damage in the retina, and the parallel study on magnet resonance imaging (PAMRINO), quantifying damage in the brain and spinal cord.<sup>10</sup> CROCTINO included 539 patients at 22 participating centers (North and South America, Europe, Asia), and is thereby the largest image repository in NMOSD required so far. Longitudinal data were available for 157 patients from 11 centers. CROCTINO is the first study in NMOSD including this amount of OCT source

data across multiple nations and ethnicities, and will assist in solving many of the outstanding questions in NMOSD research, such as the exact magnitude of ON-related retinal damage and associated functional changes in different NMOSD subtypes, the existence of ON-independent damage in NMOSD, and the influence of therapies and ethnicities on clinical course and disability accumulation. However, CROCTINO and PAMRINO also have their limitations, including: (i) the retrospective data acquisition in often heterogeneous study protocols, and with different OCT and magnet resonance imaging devices; and (ii) the lack of age- and sex-matched healthy controls from all study sides. However, CROCTINO and PAMRINO established the foundation for future prospective studies of comparable size including the creation of: (i) a strong and productive collaborative research community; (ii) a feasible study protocol adapted to NMOSD patients; and (iii) evidence-based outcome parameters not only for observational, but also for future, therapeutic trials.

## 3 | CONCLUSIONS AND FUTURE ACTION

CROCTINO and PAMRINO have built the basis for an international NMOSD image repository, which is currently being developed. Also, on a national level, prospective collaborative studies have been deployed; for example, the NationNMO cohort in Germany. NMOSD is thereby an example of a rare disease, for which collaborative research can achieve unprecedented scientific progress in a very limited time frame. Last year, three therapeutic targets were approved as the first US Food and Drug Administration-approved treatments for NMOSD, and our joint scientific work not only led to a better understanding of NMOSD as a whole, but also to a further separation of the disease spectrum, including the evidence-based differentiation of AQP4-IgG seropositive patients and MOG-IgG-associated disease patients, which will ultimately allow better care and treatment of the individual patient. In the future, further large collaborative efforts should focus on the acquisition of longitudinal and especially prospective data to: (i) confirm disease characteristics and damage pattern previously shown in retrospective data; (ii) establish NMOSD-specific biomarkers and end-points, including imaging end-points, for clinical trials; and (iii) build the basis for fast and successful multicentric clinical treatment trials to avoid disability accrual and improve the life of patients with NMOSD.

### DISCLOSURE

*Conflict of interest:* The authors declare no conflict of interest in context of this commentary.

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