

# AQP4+ NMOSD: Characteristics and Prognostic Factors in a Diverse Chilean Longitudinal Cohort

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## Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is associated with severe relapses and significant disability. The increased availability of aquaporin-4 (AQP4) antibody testing in regions like Latin America has improved clinical characterization and reduced diagnostic delay. However, further studies are needed to understand the long-term outcomes in this population.

**Objective:** To describe the clinical characteristics and determine prognosis factors in a cohort of pediatric and adult patients with AQP4+ NMOSD in Chile

## Methods

Multicenter, longitudinal, retrospective, and prospective study of patients diagnosed with AQP4+NMOSD. Demographic, clinical, paraclinical, treatment, and disability data were collected from medical records and through ongoing follow-up. Serum AQP4 was determined using a commercial fixed cell-based assay. Multivariate analysis was performed to identify potential prognostic factors.

## Results

The study included 89 patients, of which 81% were women. 7% had pediatric onset, 11% had Mapuche ancestry, and 63% were receiving care in the public health system. The median follow-up period was 3 years (0-21), 64% had a relapsing course with a median relapse number of 2 (1-10), and the median diagnostic delay was 0 years (0-34). The median age at disease onset was 48 years (7-84), and the median age at the last visit was 54 years (13-85). The most frequent initial presentations were myelitis (39%, 83% longitudinally extensive transverse myelitis LETM), optic neuritis (37%, 84% unilateral), and Area Postrema Syndrome (APS) (21%), with multifocal onset in 7%. In pediatric patients, APS was the most common presentation (67%). The median EDSS during the first attack was 4.0 (0.0-8.5). Oligoclonal bands were positive in 26%. Autoimmune comorbidity was observed in 34%; the most common was Sjögren syndrome (14%), then Systemic lupus erythematosus (8%), and celiac disease (6%). Thyroid disease is also a common finding (23%). Tonic spasms were present in 28%. Most patients received intravenous methylprednisolone for initial attacks and relapses; plasmapheresis was used in 10% and 9% of these episodes, respectively. Chronic therapy predominantly consisted of rituximab (63%) as monotherapy or in combination with mycophenolate mofetil (20%) or azathioprine (17%). The median annualized relapse rate was 0.67 (0.1-4.0). We analyzed potential prognostic factors associated with worse outcomes (defined as EDSS  $\geq 4$ ). The factors examined included enrollment in a public healthcare system, Mapuche ancestry, the time of diagnostic delay, LETM as the first attack, Sjögren's syndrome comorbidity, whether the patient had received high-efficacy therapy immediately after the first attack (in our cohort was Rituximab), and the age at disease onset. Our findings demonstrated that only older age at the onset of the disease was independently linked to worse EDSS (OR: 1.08; 95% CI 1.02-1.15,  $p=0.0237$ ).

Table 1: Demographic and Clinical Characteristics of the Study Cohort

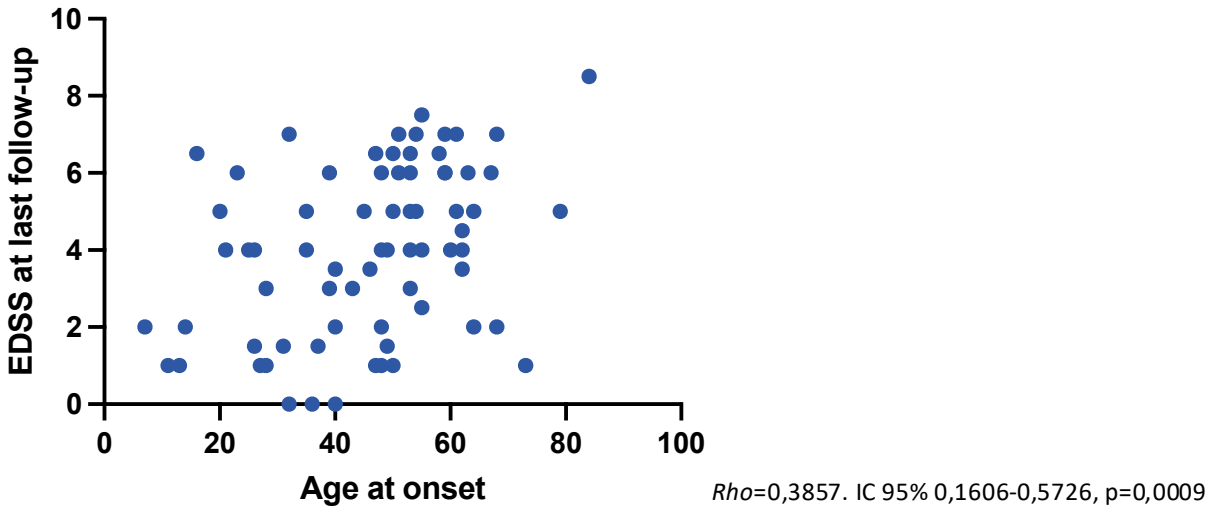
|                                               | Complete Cohort<br>N=89 | Pediatric<br>N=6 | Onset<br>Adult<br>N=83 |
|-----------------------------------------------|-------------------------|------------------|------------------------|
| Median age at onset years(range)              | 48 (7-84)               | 13 (7-16)        | 49 (18-84)             |
| Female sex n(%)                               | 72(81)                  | 6(100)           | 66(92)                 |
| Native chilean indigenous (%)                 | 10(11)                  | 1(17)            | 9(11)                  |
| Healthcare private%/public%/otros             | 34/63/3                 | 83/17/0          | 30/66/4                |
| Median diagnostic delay months (range)        | 0(0-408)                | 0(0-408)         | 0(0-228)               |
| Median disease follow-up period years (range) | 3(0-21)                 | 3(2-16)          | 2(0-21)                |
| Initial symptoms (isolated or multifocal)     |                         |                  |                        |
| Optic neuritis                                | 37% (84% uni)           | 17% (100% uni)   | 36% (84% uni)          |
| Transverse myelitis                           | 39% (83% LETM)          | 33% (100% LETM)  | 39% (81% LETM)         |
| Area Postrema S                               | 21%                     | 67%              | 17%                    |
| Brainstem S                                   | 2%                      | 0%               | 2%                     |
| Diencephalic Syndrome                         | 4%                      | 0%               | 3%                     |
| Symptomatic cerebral S                        | 1%                      | 17%              | 2%                     |
| Multifocal                                    | 7%                      | 33%              | 7%                     |
| Median EDSS at onset                          | 4.0(0-8.5)              | 3.0(0-5.0)       | 4.0(0-8.5)             |
| Median EDSS at last visit                     | 4.0(0-8.5)              | 2.0(1-6.5)       | 4.0(0-8.5)             |
| Median age at last visit                      | 54                      | 24               | 55                     |

S= syndrome, uni=unilateral, LETM= longitudinally extensive transverse myelitis

Table 2: Results of Multivariate Analysis of Prognostic Factors for EDSS  $\geq 4$  in Patients with AQP4+ NMOSD

| EDSS $\geq 4$                              | Odds ratio | 95% CI    |
|--------------------------------------------|------------|-----------|
| Age at onset                               | 1.08       | 1.02-1.15 |
| Myelitis at onset                          | 0.9        | 0.19-4.06 |
| Sjögren's syndrome comorbidity             | 0.94       | 0.13-6.73 |
| Public healthcare system                   | 0.79       | 0.18-3.53 |
| Mapuche ancestry                           | 0.4        | 0.02-4.09 |
| High-efficacy therapy at the disease onset | 1.2        | 0.34-4.45 |
| Diagnostic delay                           | 1.01       | 1.00-1.03 |

Figure 1: Correlation between Age at Onset and EDSS at Last Follow-Up



## Conclusions

APS is a frequent initial manifestation in pediatric NMOSD patients. Older age at disease onset was identified as an independent risk factor for greater disability. The higher proportion of individuals with Mapuche ancestry suggests a need for further investigation into genetic factors influencing NMOSD susceptibility in this population.

### Bibliography

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