CLINICAL/SCIENTIFIC NOTE OPEN ACCESS

Progression Independent of Relapse Activity in Aquaporin-4-IgG–Positive NMOSD

A Decade-Long Cohort Study

You-Ri Kang,[1,2,*] Ki Hoon Kim,[1,3,*] Jae-Won Hyun,[1] Su-Hyun Kim,[1] and Ho Jin Kim[1]

Correspondence
Prof. Kim
hojinkim@ncc.re.kr

Neurol Neuroimmunol Neuroinflamm 2026;13:e200533. doi:10.1212/NXI.0000000000200533

Abstract

Objectives

Disability in neuromyelitis optica spectrum disorder (NMOSD) is traditionally considered relapse-driven, but recent studies have suggested possible subclinical progression. Whether this translates into clinically meaningful disability worsening remains unclear, and quantitative data on progression independent of relapse activity (PIRA) in NMOSD are limited. We investigated the frequency and clinical relevance of PIRA in a large cohort with long-term follow-up.

Methods

We retrospectively analyzed 281 patients with AQP4-IgG–positive NMOSD with ≥2 years of follow-up. Significant Expanded Disability Status Scale (EDSS) worsening occurred following conventional thresholds, using a roving baseline. PIRA was defined as EDSS worsening without relapse between assessments, confirmed ≥6 months later, sustained, and not attributable to confounders. Relapse-associated worsening (RAW) was defined when the best EDSS score assessed ≥6 months after relapse still met the threshold.

Results

The mean follow-up duration was 11.3 ± 5.1 years, and the mean relapse-free duration was 8.3 ± 5.2 years. A total of 1,662 EDSS assessments were performed, with a median of 5 per patient (interquartile range, 4–7). Seven patients (2.5%) met PIRA criteria. Despite no treatment escalation, none worsened further. Among 194 patients with relapses, 70 (36.1%) experienced RAW.

Discussion

PIRA was rare, even with extended observation using a formal framework, reaffirming relapse as the principal driver of disability and supporting continued focus on relapse prevention.

Introduction

The concept of progression independent of relapse activity (PIRA) was introduced in multiple sclerosis (MS) to describe insidious disability worsening unrelated to relapses.[1,2] By contrast, disability in neuromyelitis optica spectrum disorder (NMOSD) has traditionally been regarded as relapse-driven.[3] While this distinction is widely accepted, recent studies have suggested the potential for subclinical disease activity in NMOSD, based on changes observed on advanced imaging and blood biomarkers during relapse-free periods.[4] Brain and spinal cord atrophy on MRI has also raised the possibility of neurodegeneration.[5,6]

Yet, the clinical relevance of these findings remains to be clarified, particularly whether they translate into functional decline, warranting systematic research on PIRA in NMOSD. Although

*These authors contributed equally to this work as co-first authors.

[1]Department of Neurology, Research Institute and Hospital of National Cancer Center, Goyang, Korea; [2]Department of Neurology, Chonnam National University Hospital and Medical School, Gwangju, Korea; and [3]Department of Neurology, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea.

The Article Processing Charge was funded by the authors.

earlier studies suggested that disability progression without relapse is uncommon in NMOSD compared with MS,[3,7,8] they were based on small cohorts and lacked a structured definition of PIRA. A recent study applied a formal PIRA framework[9]; however, approximately 5 years of follow-up, as in previous studies, may still be insufficient to capture slowly evolving or delayed progression, underscoring the need for evaluation using extended longitudinal data. To fill this gap, we investigated the frequency of PIRA in a well-characterized cohort of patients with aquaporin-4-immunoglobulin G (AQP4-IgG)–positive NMOSD with over a decade of follow-up.

Methods

Study Design and Patients

We retrospectively reviewed 387 patients with AQP4-IgG–positive NMOSD who met the 2015 diagnostic criteria[10] from the National Cancer Center Registry in Korea. After excluding 17 patients with fewer than 24 months of follow-up as of March 2025 and 89 with fewer than 3 Expanded Disability Status Scale (EDSS) assessments, 281 patients were included.

EDSS trajectories were examined to identify episodes of significant worsening, defined by the following thresholds[2]: increase of ≥1.5 points from a baseline of 0, ≥1.0 from 1.0 to 5.5, or ≥0.5 from >5.5. A roving baseline approach was applied, resetting the reference EDSS score after relapses, PIRA events, or confirmed improvement. Events meeting thresholds were classified as PIRA or relapse-associated worsening (RAW). PIRA was defined by (1) no relapse between the worsening and previous EDSS, regardless of the interval between assessments; (2) confirmation ≥6 months later; (3) persistence thereafter (until subsequent relapse, if any); and (4) exclusion of confounders. RAW was defined as significant EDSS worsening associated with relapses between assessments, where the best EDSS score assessed ≥6 months later still met the threshold. All events were adjudicated by consensus among 3 neurologists.

Standard Protocol Approvals and Patient Consents

The study was approved by the institutional review board. Informed consent was not required because anonymized patient data were used.

Data Availability

The data from this study are available from the corresponding author on reasonable request.

Results

Among 281 patients, 253 (90.0%) were female, and the mean age at onset was 36.9 ± 14.0 years (Table 1). The median number of attacks was 4 (interquartile range [IQR], 2–7) over a mean disease duration of 14.9 ± 7.6 years. The mean follow-up duration was 11.3 ± 5.0 years. At the last visit, the mean relapse-free duration was 8.3 ± 5.2 years, and all but 1 patient were on immunotherapy.

A total of 1,662 EDSS assessments were performed across the cohort, with a median of 5 per patient (IQR, 4–7) and a median interval of 1.6 years between assessments (IQR, 0.6–2.9 years). The median EDSS score changed from 3.5 (IQR, 2.5–6.0) at baseline to 3.0 (IQR, 2.0–4.0) at the last follow-up. We identified 171 episodes of EDSS worsening. Of these, 16 episodes occurred without relapse. Seven events in different patients (2.5% of the entire cohort) fulfilled the criteria for PIRA. The remaining 9 events in 8 patients were attributable to noninflammatory causes: 2 deaths and 6 comorbidities (musculoskeletal problems, Parkinsonism, heart failure, and cerebral infarction). Among 155 RAW events, 76 in 70 patients (36.1% of those with at least 1 relapse during follow-up; 24.9% of the entire cohort) met RAW criteria; the remainder showed partial or complete recovery. At the time of RAW occurrence, 14 events (18.4%) were observed in untreated patients, 6 (7.9%) in those receiving interferon-beta, 38 (50.0%) in those receiving conventional immunosuppressive therapies (oral corticosteroids, azathioprine, mycophenolate mofetil, or mitoxantrone), 17 (22.4%) in rituximab-treated patients, and 1 (1.3%) in a patient on inebilizumab.

Details of the 7 patients with PIRA are provided in Table 2. PIRA events occurred a median of 6.2 years (range, 2.0–17.5) after the last relapse. Among the 4 patients who underwent MRI, no new lesions were identified. In 2 patients, decreased visual acuity in a previously affected eye was detected during routine examination, without symptoms. Six patients on rituximab maintained B-cell depletion at the event (median 8.4 years). No patients escalated treatment after the event. Disability remained stable for a median of 8.9 years (range, 1.1–13.1), without further EDSS worsening or relapses.

Discussion

In this study, PIRA was identified in only 2.5% of patients over a mean follow-up of 11.3 years. Notably, the average relapse-free duration of 8 years alone exceeded total follow-up periods in prior studies.[3,7-9] This prolonged observation, combined with a formal PIRA framework, offers a more precise characterization of the relapse-driven trajectory of disability in NMOSD.

While the definition of PIRA has varied across studies, how it is defined influences sensitivity and specificity of detection.[2] A recent international study reported a 2.2% frequency of PIRA in NMOSD, applying an operational definition requiring EDSS worsening within 24 months of a roving baseline.[9] This temporal constraint may reduce the detection of more insidious or delayed progression. In this study, we did not impose a specific time window between assessments, aiming to enhance sensitivity in detecting PIRA.[2] Even with this approach and extended follow-up, PIRA remained rare.

Table 1 Demographic and Clinical Characteristics of the Patients

Characteristic (N = 281)	n (%), mean (SD), or median [IQR]
Sex, female	253 (90.0)
Age at onset, y	36.9 (14.0)
Pediatric onset	22 (7.8)
Manifestation at onset	
Myelitis	112 (39.9)
Optic neuritis	107 (38.1)
Brain	49 (17.4)
Multiple sites	13 (4.6)
Number of attacks	4 [2–7]
Disease duration, y	14.9 (7.6)
Follow-up duration, y	11.3 (5.0)
Relapse-free duration, y	8.3 (5.2)
Treatment at the last visit	
Azathioprine	12 (4.3)
Mycophenolate mofetil	50 (17.8)
Rituximab	187 (66.5)
Inebilizumab	8 (2.8)
Interleukin-6 receptor inhibitors[a]	15 (5.3)
C5 inhibitors[b]	8 (2.8)
Number of recorded EDSS assessments per patient	5 [4–7]
First recorded EDSS score of the entire follow-up	3.5 [2.5–6.0]
First recorded EDSS score during the relapse-free period	4.0 [3.0–6.5]
Last recorded EDSS score	3.0 [2.0–4.0]
Change in EDSS score during the entire follow-up	−0.5 [−2.0 to 0.5]
Change in EDSS score during the relapse-free period	−0.5 [−2.0 to 0.0]

Abbreviations: EDSS = Expanded Disability Status Scale; IQR = interquartile range; n = number; y = years.
[a] Interleukin-6 receptor inhibitors include satralizumab and tocilizumab.
[b] C5 inhibitors include eculizumab and ravulizumab.

Beyond the PIRA cases, approximately half of the relapse-free disability worsening events in our cohort were found to be attributed to comorbidities on case-level review. Although noninflammatory causes were carefully excluded at the time of EDSS documentation,[11] subsequent re-evaluations revealed that a substantial proportion was confounded. This illustrates the challenges in distinguishing actual progression from PIRA-like events in real-world settings, where confounders are not always apparent at assessment. Accordingly, EDSS changes should be cautiously interpreted within a longitudinal context to avoid overestimating PIRA, particularly in older individuals or those with long-standing disease who are more susceptible to overlapping health issues.

It is important to note that none of the patients with PIRA experienced further disability progression throughout follow-up (up to 13 years), despite no treatment escalation. This contrasts with the typical course of PIRA in MS, where smoldering inflammation underlies gradual deterioration. Although these events technically met PIRA criteria, their long-term stability raises the possibility that they may not reflect genuine disease progression, but rather functional changes influenced by noninflammatory conditions such as spasticity or inactivity from mood or fatigue. Thus, the true incidence of pathologic PIRA may be even lower than observed. Furthermore, the rarity of PIRA questions the clinical significance of subclinical progression signals proposed in NMOSD, such as brain atrophy, retinal abnormalities, and

Table 2 Characteristics of Patients Exhibited PIRA

No.	EDSS change	Time from baseline EDSS to PIRA, y	Onset age group, y	Disease duration at PIRA, y	Number of attacks before PIRA	Prior attack sites (any)	Time from last relapse to PIRA, y	Used immunotherapy (at PIRA*)	MRI at PIRA	Duration of sustained disability, y	Comments
1	6.0–6.5	2.0	20s	23	11	O, B	8	IFN, mitoxantrone, RTX*	Orbit/ brain MRI negative	3	Decreased walking distance
2	3.5–4.5	2.1	10s	25	26	O, M, B	1	IFN, AZA, RTX*	Spine/ brain MRI negative	1	Increased gait instability
3	3.5–4.5	4.5	30s	22	5	O, M	18	IFN, mitoxantrone, RTX*	Not performed	1	Increased gait instability
4	3.0–4.5	1.2	40s	8	6	O, M, B	4	IFN, MMF*	Spine/ brain MRI negative	11	Decreased visual acuity in the affected eye and cognitive impairment
5	3.0–4.0	1.6	20s	5	6	O	2	IFN, AZA, RTX*	Not performed	13	Decreased visual acuity in the affected eye. No subjective symptom
6	2.0–3.0	3.7	30s	8	5	O, M, B	5	MMF, RTX*	Not performed	9	Decreased visual acuity in the affected eye. No subjective symptom
7	6.0–6.5	1.5	40s	8	6	M	6	RTX*	Brain/ spine MRI negative	9	Decreased walking distance

Abbreviations: AZA = azathioprine; B = brain; EDSS = Expanded Disability Status Scale; IFN = interferon; M = myelitis; MMF = mycophenolate mofetil; O = optic nerve; PIRA = progression independent of relapse activity; RTX = rituximab; y = years.
* Immunotherapy in use at the time of PIRA is marked with an asterisk.

elevated fluid biomarkers,[4] highlighting the need for caution when incorporating subclinical indicators into treatment decisions. Future research is warranted to correlate subclinical changes with clinical outcomes to exclude delayed resolution of inflammation and retrograde degeneration.

The frequency of RAW was relatively high in our cohort, but this may have been overestimated given the long-term nature of this cohort, which included patients followed since before the disease was clearly defined. A considerable proportion of RAW events (20/76, 26.3%) occurred in patients who either received inappropriate therapy or were not on maintenance treatment at the time of relapse, and half of those occurred in patients with moderate-efficacy therapies. With the increasing use of biologics, the frequency of RAW is expected to decline substantially.

This study has limitations. First, EDSS may be less sensitive to subtle or nonmotor changes, such as cognitive impairment, pain, or fatigue, and further studies using complementary outcome measures are warranted. Second, nearly all patients received immunotherapy, which does not fully reflect the natural course of untreated disease. Nevertheless, the exceptionally low frequency of PIRA under immunotherapy reinforces the critical role of relapse prevention in minimizing long-term disability. Finally, because this was a single-center study with an ethnically homogeneous population, the generalizability may be limited. However, consistent clinical practice and EDSS assessments within a single-center setting likely minimized inter-rater variability and site-related differences that often confound multicenter studies.

In conclusion, PIRA was extremely rare in patients with AQP4-positive NMOSD. Extended follow-up and consistent assessments enhanced reliability of the data. These findings reaffirm relapse as a principal driver of disability and support the current therapeutic focus on relapse prevention.

Author Contributions

Y.-R. Kang: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. K.H. Kim: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. J.-W. Hyun: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. S.-H. Kim: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. H.J. Kim: drafting/

revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

Study Funding

This work was supported by the National Research Foundation of Korea (grant no. NRF-2018R1A5A2023127).

Disclosure

Y.-R. Kang, K.-H. Kim, J.-W. Hyun, and S.-H. Kim report no potential conflicts of interest related to this study. H.J. Kim received a grant from the National Research Foundation of Korea and research support from Aprilbio, Eisai, Good T cells, and UCB; received consultancy/speaker fees from Alexion, Altos Biologics, AstraZeneca, Biogen, Daewoong Pharmaceutical, Eisai, GC Pharma, Handok Pharmaceutical, Kaigene, Kolon Life Science, MDimune, Merck, Mitsubishi Tanabe Pharma, Roche, and Sanofi; and is a co-editor for the *Multiple Sclerosis Journal* and an associated editor for the *Journal of Clinical Neurology*. Go to Neurology.org/NN for full disclosures.

Publication History

Received by *Neurology® Neuroimmunology & Neuroinflammation* June 23, 2025. Accepted in final form October 28, 2025. Submitted and externally peer reviewed. The handling editor was Deputy Editor Anne-Katrin Pröbstel, MD.

References

1. Lublin FD, Häring DA, Ganjgahi H, et al. How patients with multiple sclerosis acquire disability. *Brain.* 2022;145(9):3147-3161. doi:10.1093/brain/awac016
2. Müller J, Sharmin S, Lorscheider J, et al. Standardized definition of progression independent of relapse activity (PIRA) in relapsing-remitting multiple sclerosis. *JAMA Neurol.* 2025;82(6):614–625. doi:10.1001/jamaneurol.2025.0495
3. Wingerchuk DM, Pittock SJ, Lucchinetti CF, Lennon VA, Weinshenker BG. A secondary progressive clinical course is uncommon in neuromyelitis optica. *Neurology.* 2007;68(8):603-605. doi:10.1212/01.wnl.0000254502.87233.9a
4. Etemadifar M, Alaei SA, Akaishi T, et al. Relapse-independent disease activity in neuromyelitis optica spectrum disorder: a systematic review. *Mult Scler Relat Disord.* 2024;90:105843. doi:10.1016/j.msard.2024.105843
5. Masuda H, Mori M, Hirano S, et al. Silent progression of brain atrophy in aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder. *J Neurol Neurosurg Psychiatry.* 2022;93(1):32-40. doi:10.1136/jnnp-2021-326386
6. Ventura RE, Kister I, Chung S, Babb JS, Shepherd TM. Cervical spinal cord atrophy in NMOSD without a history of myelitis or MRI-visible lesions. *Neurol Neuroimmunol Neuroinflamm.* 2016;3:e224. doi:10.1212/NXI.0000000000000224
7. Akaishi T, Takahashi T, Misu T, et al. Progressive patterns of neurological disability in multiple sclerosis and neuromyelitis optica spectrum disorders. *Sci Rep.* 2020;10(1):13890. doi:10.1038/s41598-020-70919-w
8. Molazadeh N, Akaishi T, Bose G, Nishiyama S, Chitnis T, Levy M. Progression independent of relapses in aquaporin4-IgG-seropositive neuromyelitis optica spectrum disorder, myelin oligodendrocyte glycoprotein antibody-associated disease, and multiple sclerosis. *Mult Scler Relat Disord.* 2023;80:105093. doi:10.1016/j.msard.2023.105093
9. Siriratnam P, Huda S, Van Der Walt A, et al. Prevalence of progression independent of relapse activity and relapse-associated worsening in patients with AQP4-IgG-Positive NMOSD. *Neurology.* 2024;103(12):e209940. doi:10.1212/WNL.0000000000209940
10. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology.* 2015;85(2):177-189. doi:10.1212/WNL.0000000000001729
11. Kurtzke JF. Rating neurologic impairment in multiple sclerosis. *Neurology.* 1983;33:1444. doi:10.1212/wnl.33.11.1444