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Prognostic Value of Persistent CSF Antibodies at 12 Months in Anti-NMDAR Encephalitis

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Abstract

Background and Objectives

Anti-NMDA receptor (NMDAR) encephalitis is defined by the presence of antibodies (Abs) targeting the NMDAR in the CSF. This study aimed to determine the prognostic value of persistent CSF NMDAR-Abs during follow-up.

Methods

This retrospective observational study included patients diagnosed with anti-NMDAR encephalitis in the French Reference Center for Paraneoplastic Neurological Syndromes and Autoimmune Encephalitis and for whom CSF samples were obtained at diagnosis and >4 months of follow-up to evaluate CSF NMDAR-Ab persistence. Because patients were tested for CSF NMDAR-Abs at different time points, samples were stratified into different periods of follow-up (i.e., 12 months was considered for the 9- to 16-month follow-up period).

Results

Among the 501 patients diagnosed with anti-NMDAR encephalitis between January 2007 and June 2020, 89 (17%) were tested between 4 and 120 months for CSF NMDAR-Abs after clinical improvement and included in the study (75/89 women, 84%; median age 20 years, interquartile range [IQR] 16–26). During follow-up, 21 of 89 (23%) patients had a relapse after a median time of 29 months (IQR 18–47), and 20 of 89 (22%) had a poor outcome (mRS ≥3) after a median last follow-up of 36 months (IQR 19–64). Most patients (69/89, 77%) were tested at the 12-month follow-up period, and 42 of 69 (60%) of them had persistent CSF NMDAR-Abs. When comparing patients with persistent or absent CSF NMDAR-Abs at 12 months, poor outcome at the last follow-up was more frequent in the former (38% vs 8%, $p = 0.01$), who had relapses more often (23% vs 7%), which also appeared earlier in the course of the disease (90% during the following 4 years of follow-up vs 20%), although no significant difference was observed at long-term follow-up ($p = 0.15$). In addition, patients with persistent CSF NMDAR-Abs at 12 months had higher titers of CSF NMDAR-Abs at diagnosis.

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Glossary

CBA = cell-based assay; **CC** = corticosteroids; **ICU** = intensive care unit; **IQR** = interquartile range; **IVIG** = IV immunoglobulin; **mRS** = modified Rankin Scale; **NMDAR** = NMDA receptor; **PE** = plasma exchange; **WBC** = white blood cell.

Discussion

In this study, patients with persistent CSF NMDAR-Abs at 12 months were more likely to have subsequent relapses and a poor long-term outcome. However, these findings should be interpreted with caution because of the variability in the time of sampling of this study. Future prospective studies are required to validate these results in larger cohorts.

Anti-NMDA receptor (NMDAR) encephalitis is an autoimmune neurologic disorder that predominantly affects young women and is characterized by subacute psychiatric symptoms, short-term memory impairment, seizures, and movement disorders.[1] A set of clinical criteria have been proposed to approach the diagnosis, but definite diagnosis is based on the detection of CSF IgG antibodies (Abs) targeting the GluN1 subunit of the NMDAR.[2] Their pathogenicity has been extensively demonstrated in cultured neurons[1,3] and animal models,[4] where they have shown to internalize the NMDAR and disrupt its interaction with ephrin-B2 receptor.[5,6] However, these effects have been proved to be reversible in vitro and in vivo,[1,4] which is also supported by the absence of neuronal loss in histopathologic studies.[7] Consequently, up to 80% of patients improve with immunotherapy and with tumor removal if present, although some cases may require up to 2 years to recover.[8] Nevertheless, 20% of patients remain with cognitive, behavioral, and motor disabilities, and 12%–20% have clinical relapses during follow-up.[8,9]

Several biomarkers have been studied during the acute phase of the disease in an attempt to identify patients at risk of incomplete recovery or relapses, such as cytokine levels, NMDAR-Ab titers, and neuroimaging or EEG features.[10-15] However, the prognostic value of persistent CSF NMDAR-Abs during follow-up remains poorly defined despite being directly pathogenic. Moreover, whether their negativity in CSF should be a therapeutic goal is unclear. Herein, we aimed to define the value of persistent CSF NMDAR-Abs during long-term follow-up to predict outcomes and relapses. In addition, we attempted to identify clinical and immunologic features associated with their persistence.

Methods

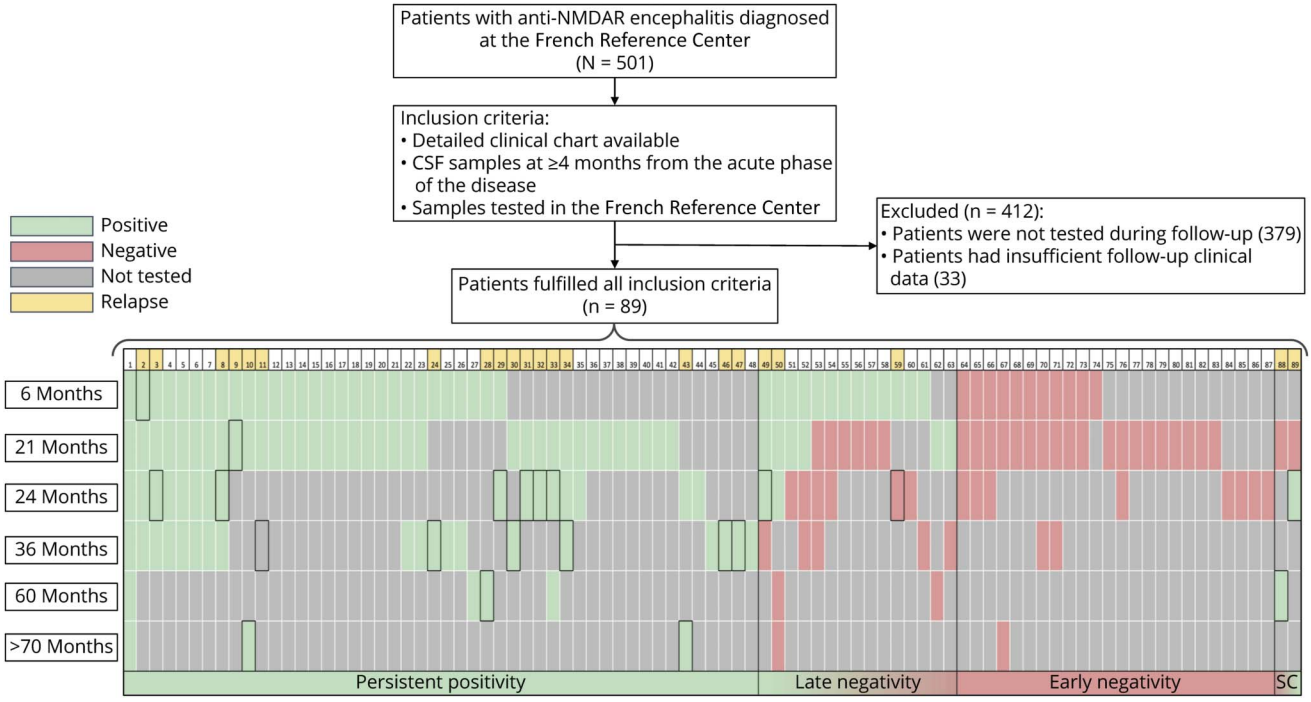
Study Design, Patient Selection, and Clinical Data

All patients diagnosed with anti-NMDAR encephalitis in the French Reference Center for Paraneoplastic Neurological Syndromes and Autoimmune Encephalitis from January 2007 to June 2020 were retrospectively studied. Then, only patients fulfilling the following inclusion criteria were included: (1) full clinical chart available, (2) CSF samples obtained at diagnosis and ≥4 months of follow-up to evaluate CSF NMDAR-Ab persistence and not for diagnostic purposes (patients with samples sent for a suspicion of disease recurrence were excluded), and (3) all samples tested in the French Reference Center (Figure 1). Most patients were tested following our recommendations to systematically control CSF NMDAR-Ab status at recovery to be able to interpret the results in case of relapse. However, some patients were only tested when considered appropriate by the referring physician.

Demographic and clinical data were retrospectively collected from hospital charts, including age; sex; ethnicity; date of clinical onset; first clinical symptom; disability at onset assessed by the modified Rankin Scale (mRS); diagnostic delay; CSF analysis (white blood cell [WBC] and protein content); EEG (normal, epileptic activity, or diffuse slowing); MRI (normal, white matter lesions, medial temporal hypersignal, or other pattern); associated tumor if present; intensive care unit (ICU) admission; total days in the ICU; tracheostomy; days of ventilation; NEOS score; first-line treatment (corticosteroids [CC], IV immunoglobulin [IVIG], and plasma exchange [PE]); second-line treatment (rituximab and cyclophosphamide); treatment duration; mRS at 3, 6, 9, 12, 18, 24, 36, and 60 months of follow-up; relapses; and CSF NMDAR-Ab status during follow-up.

Because of the retrospective nature of the study, patients were tested for CSF NMDAR-Abs at different time points. Therefore, to homogenize the CSF NMDAR-Ab testing during follow-up, samples were stratified according to the time of sampling as follows: 6 months of follow-up (samples obtained between 4–8 months), 12 months (9–16 months), 24 months (18–28 months), 36 months (30–42 months), 60 months (45–70 months), and >70 months. Persistent CSF NMDAR-Abs were defined as their detection at diagnosis and at ≥4 months from the onset of the disease. The best time to assess the impact of persistent CSF NMDAR-Abs was considered to be at 12 months because at this point 75% of patients have recovered,[8] and deciding whether these patients should be maintained on immunotherapy may be challenging. The CSF was considered inflammatory when presenting >5 WBC/μL or proteins >0.45 g/L. Relapses were defined as new onset or worsening of any of the major

Figure 1 Flowchart and Graphical Representation of the Study Design



All the patients who fulfilled the inclusion criteria at 6, 12, 24, 36, 60, and >70 months of follow-up were codified according to the presence (green) or absence (red) of CSF NMDAR-Abs. If the patient was not tested, the time point is shown in gray. Patients who had a relapse during the follow-up are depicted in yellow, and the time of relapse was highlighted with a black frame. NMDAR = NMDA receptor; SC = seroconversion.

clinical features of the diagnostic criteria of anti-NMDAR encephalitis, unexplainable by other causes, and occurring after at least 2 months of improvement or stabilization.[2,8] Good outcome was considered as mRS <3, whereas poor outcome was considered as mRS ≥3. NMDAR-Abs in the CSF were detected as previously described.[16] The duration of the biological effect of the different immunotherapies was estimated to be 1 month from last administration for first-line therapies (CC, IVIG, and PE) and 3 months for second-line therapies (rituximab and cyclophosphamide). Briefly, indirect immunofluorescence on rat brain sections was used as a screening technique, further confirmed by a cell-based assay (CBA) using HEK293 cells expressing the GluN1 and GluN2b subunits of the NMDAR. Diagnosis was only established when both techniques were positive, but follow-up evaluations exclusively included in-house CBA. Antibody titers were assessed with endpoint dilutions on CBAs, starting from 1/10.

To ensure that the study cohort was representative of the disease and to reduce selection bias, we compared the clinical characteristics of the patients included in this study with a control cohort of 104 different, randomly chosen, patients with anti-NMDAR encephalitis from the French Reference Center with all the aforementioned data available (eTable 1, links.lww.com/NXI/A821) but without known NMDAR-Ab status during follow-up.

Statistical Analysis

Continuous variables are described by median and range/interquartile range (IQR), whereas qualitative variables are described by absolute and relative frequencies for each category of the variable (missing data not included). Statistical comparisons between the study and control cohorts and between patients with and without persistent CSF NMDAR-Abs at 12 months were performed using the Wilcoxon-Mann-Whitney test for continuous variables and the χ^2 test or the Fisher exact test for qualitative variables. Relapse-free survival was estimated using the Kaplan-Meier method, and Kaplan-Meier curves were generated according to the persistence of NMDAR-Abs at 12 months. Relapse-free survival curves were compared using the log-rank test. In all analyses, a bilateral type I error rate of 5% was applied without correction for multiple testing. All statistical analyses were performed using R software, version 4.1.1 (Free Software Foundation).

Standard Protocol Approvals, Registrations, and Patient Consents

This study titled Bio-NMDAr was approved by the Institutional Review Board of Université Claude Bernard Lyon 1 and Hospices Civils of Lyon (69HCL21-750), as well as the national data protection commission (Commission Nationale de l'Informatique et des Libertés [CNIL], 21-57750). Written informed consent was obtained from all patients for the storage and use of laboratory samples and clinical information

Table 1 Clinical Features of Patients According to CSF NMDAR-Ab Positivity at 12-Month Follow-up

Clinical features	Patients without CSF NMDAR-Abs at 12 mo (n = 27)	Patients with CSF NMDAR-Abs at 12 mo (n = 42)	*p* Value
Women, n (%)	20 (74)	35 (83)	0.53
Age, years, median (IQR)	18 (7–28)	19 (17–25)	0.55
Age >20 y, n (%)	11 (40)	19 (45)	0.90
Ethnicity, n (%)			
Caucasian	15 (60)	17 (43)	0.36
African	4 (16)	11 (27)	
Others	6 (24)	12 (30)	
First symptom, n (%)			
Psychiatric	7 (26)	16 (38)	0.25
Seizures	7 (26)	14 (33)	
Others	13 (48)	12 (27)	
ICU admission, n (%)	17 (63)	31 (73)	0.49
ICU stay, days, median (IQR)[a]	26 (15–49)	49 (33–99)	0.02
ICU stay >30 d (%)	7 (43)	21 (75)	0.08
Tumor, n (%)	4 (15)	10 (25)	0.53
Abnormal MRI, n (%)	8 (29)	14 (33)	0.95
Abnormal EEG, n (%)	25 (92)	35 (85)	0.46
Slowing	19 (70)	25 (61)	
Epileptic discharges	6 (22)	10 (24)	
Inflammatory CSF, n (%)	25 (92)	40 (97)	0.55
CSF WBC, cells/μL, median (IQR)	11 (6–76)	40 (15–98)	0.04
CSF WBC >20 cells/μL, n (%)	10 (40)	25 (62)	0.13
CSF proteins, g/L, median (IQR)	0.32 (0.20–0.37)	0.33 (0.26–0.49)	0.18
CSF proteins >0.45 g/L, n (%)	3 (14)	11 (36)	0.14
NEOS score >3, n (%)	5 (18)	13 (31)	0.38

[a] The time in the ICU was censored at 12 months for patients in the ICU at this time point.
Abbreviations: ICU = intensive care unit; IQR = interquartile range; WBC = white blood cell.

for research purposes, and none of them explicitly opposed his/her participation in the study.

Data Availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

Results

Main Clinical Features of the Study Cohort

Among the 501 patients with anti-NMDAR encephalitis diagnosed between 2007 and 2020 in the French Reference Center, 89 (17%) met the inclusion criteria (75/89 women, 84%; median age 20 years, IQR 16–26 years). An underlying teratoma was found in 15 patients (18%), abnormal MRI findings were observed in 29 (32%), and EEG abnormalities were observed in 78 (88%). The initial CSF analysis was inflammatory in 71 (79%) cases, with a median CSF WBC of 28 cells/μL (range 8–79 cells/μL) and a median CSF protein content of 0.32 g/L (IQR 0.24–0.46 g/L). Overall, 61 (68%) patients were admitted to the ICU for a median time of 40 days (IQR 21–76 days). All patients were treated with first-line immunotherapy with a median delay of 20 days (IQR 11–39 days), whereas 64 (72%) patients were also treated with second-line immunotherapies with a median delay of 45 days (IQR 27–84 days). A total of 21 (23%) patients had clinical relapses during follow-up with a median delay of 29 months (IQR 18–47 months). After a median follow-up of 36

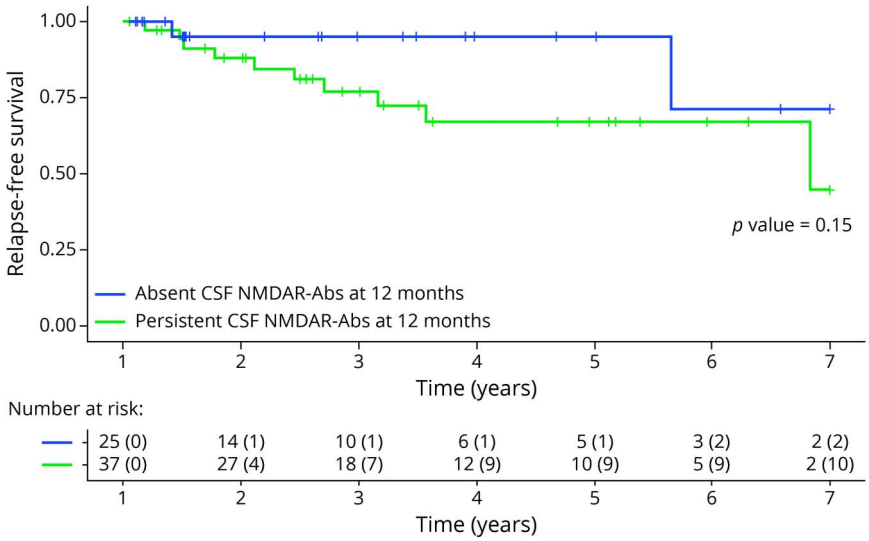
Table 2 Management During the First 12 Months of the Disease According to CSF NMDAR-Ab Status at 12-Month Follow-up

Clinical feature	Patients without CSF NMDAR-Abs at 12 mo (n = 27)	Patients with CSF NMDAR-Abs at 12 mo (n = 42)	*p* Value
First-line treatment delay, days, median (IQR)	15 (10–32)	21 (11–46)	0.38
First-line treatment delay >30 d, n (%)	9 (33)	15 (35)	>0.99
First-line treatment, n (%)	27 (100)	42 (100)	>0.99
CC	24 (89)	30 (71)	0.15
IVIG	26 (96)	39 (92)	>0.99
PE	5 (18)	11 (26)	0.61
Second-line treatment delay, months, median (IQR)	1.16 (0.84–1.38)	1.67 (0.91–3.60)	0.12
Second-line treatment, n (%)	16 (59)	32 (76)	0.22
RTX	16 (59)	30 (71)	0.43
CPP	1 (4)	17 (41)	0.002
RTX delay >1 mo, n (%)	10 (62)	21 (65)	>0.99
RTX delay >2 mo, n (%)	2 (12)	13 (40)	0.09
RTX delay >3 mo, n (%)	2 (12)	10 (31)	0.28
Active immunotherapy at 12 mo, n (%)			
CC	4 (14)	1 (2)	0.07
IVIG	7 (25)	4 (9)	0.09
PE	0 (0)	1 (2)	>0.99
RTX	5 (18)	14 (33)	0.28
CPP	0 (0)	12 (28)	0.002
Any immunotherapy	10 (37)	25 (59)	0.11
Total time of administration, months, median (IQR)			
CC	4.49 (0.16–10.90)	1 (0.25–8.44)	0.67
IVIG	6.05 (0.30–10.07)	1.87 (0.19–5.89)	0.24
PE	5.87 (0.42–11.32)	1.11 (0.26–7.80)	0.41
RTX	0.72 (0.46–7.09)	2.56 (0.69–7.80)	0.53
CPP	4.07 (4.07–4.07)	7.79 (1.48–9.66)	0.56
Total time of the biological effect, months, median (IQR)			
CC	5.44 (1.16–10.92)	1.61 (1.24–8.84)	0.66
IVIG	7.69 (1.30–10.73)	2.44 (1.20–6.84)	0.16
PE	6.38 (1.43–11.32)	2.13 (1.28–7.80)	0.41
RTX	4.11 (3.44–9.59)	4.89 (3.51–8.75)	0.98
CPP	7.05 (7.05–7.05)	8.25 (4.31–10.07)	0.56

Abbreviations: CC = corticosteroids; CPP = cyclophosphamide; IQR = interquartile range; IVIG = IV immunoglobulins; PE = plasma exchange; RTX = rituximab.

months (IQR 19–64 months), 22% had a poor outcome at the last follow-up. Persistent CSF NMDAR-Abs were detected in 42 of 53 (79%) patients at 6 months, 42 of 69 (60%) at 12 months, 19 of 33 (57%) at 24 months, 19 of 26 (73%) at 36 months, 5 of 7 (71%) at 60 months, and 3 of 5 (60%) after 70 months of follow-up (range 82–120 months; Figure 1). There

Figure 2 Kaplan-Meier Analysis of Relapses in Patients With Persistent and Absent CSF NMDAR-Abs at 12-Month Follow-up



No significant difference was observed in terms of relapses at long-term follow-up (p = 0.15) among patients with persistent (green) or absent (blue) CSF NMDAR-Abs at 12 months. However, patients with persistent CSF NMDAR-Abs at 12 months relapsed earlier: 9 of 10 (90%) relapsed between 12 months and 5 years of follow-up, whereas only 1 of 5 (20%) patients with absent CSF NMDAR-Abs at 12 months relapsed during the same time interval. NMDAR-Abs = NMDA receptor antibodies.

was no significant difference in terms of demographic and clinical features between the study cohort and the control cohort of 104 random patients with unknown CSF NMDAR-Ab status during follow-up (additional data are listed in eTable 1, links.lww.com/NXI/A821).

Clinical Features of Patients With CSF NMDAR-Abs at 12 Months of Follow-up

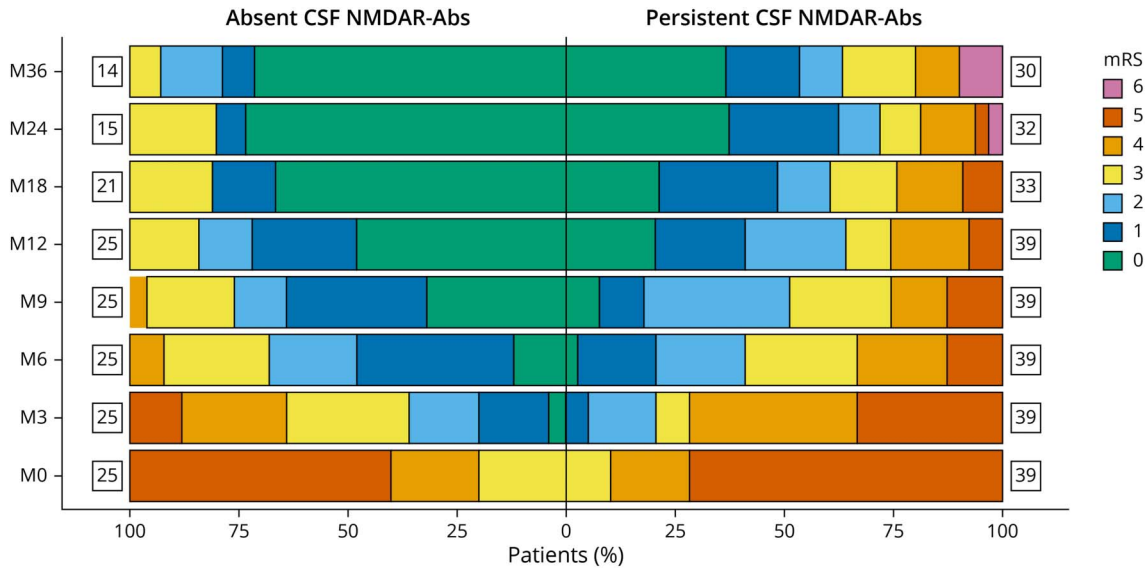
The 12-month follow-up period had the highest number of tested patients (69/89, 77%; Figure 1). Among them, 42 of 69 (60%) had persistent CSF NMDAR-Abs (35/42 women, 83%; median age 19 years, IQR 17–25 years). No significant difference between patients with persistent and absent CSF NMDAR-Abs at 12 months was observed regarding demographic features (Table 1). The rate of ICU admission was also similar between both groups (31/42, 73% vs 17/27, 63%; p = 0.49), although patients with persistent CSF NMDAR-Abs were admitted for a longer time (median 49 days, IQR 33–99 days vs median 26 days, IQR 15–49 days; p = 0.02). Despite both groups being comparable in terms of tumor, MRI, and EEG findings, patients with persistent CSF NMDAR-Abs at 12 months had, at the initial CSF evaluation, a higher number of CSF WBC (median 40 cells/μL, IQR 15–98 cells/μL vs median 11 cells/μL, IQR 6–76 cells/μL; p = 0.04). In addition, no significant difference was observed between both groups regarding their management with first-line therapies and rituximab during the first 12 months of the disease, in terms of the frequency of administration, total time of administration, estimated duration of the biological effect, and active treatment at 12 months (Table 2). However, patients with persistent CSF NMDAR-Abs were more frequently treated with cyclophosphamide (1/27, 4% vs 17/42, 41%; p = 0.002) and more frequently maintained on cyclophosphamide at 12 months (12/42, 28% vs 0/27, 0%; p = 0.002), although the total time of administration and the estimated duration of its effect were similar among both groups (Table 2). All patients were treated because of disability and not because of CSF NMDAR-Ab persistence.

Impact of Persistent CSF NMDAR-Abs at 12 Months of Follow-up on Relapses and Outcomes

Among the 42 patients positive for CSF NMDAR-Abs at 12-month follow-up, 10 (23%) had subsequent relapses during follow-up, in contrast to only 2 of 27 (7%) patients without persistent CSF NMDAR-Abs. Of interest, these last 2 patients were both negative for CSF NMDAR-Abs at 12 months but positive at the time of relapse. To assess the impact of persistent CSF NMDAR-Abs at 12 months on relapses, a Kaplan-Meier survival analysis was performed (Figure 2). Although no significant difference was found in the long-term follow-up (p = 0.15), patients with persistent CSF NMDAR-Abs at 12 months relapsed earlier in the course of the disease: 9 of 10 (90%) relapsed between 12 months and 5 years of follow-up, whereas only 1 of 5 (20%) patients without persistent CSF NMDAR-Abs at 12 months relapsed during the same time interval. Furthermore, poor outcome at the last follow-up (including only patients with follow-up longer than 12 months) was more frequent in patients with persistent CSF NMDAR-Abs at 12 months compared with patients without persistent Abs (15/39, 38% vs 2/25, 8%; p = 0.01). Among all patients tested for CSF NMDAR-Abs at 12 months, only 3 of 64 (4%) patients died during follow-up, and all of them were positive for CSF NMDAR-Abs at 12 months. The functional status during follow-up of patients with persistent and absent CSF NMDAR-Abs at 12 months is presented in Figure 3.

Notably, recovered patients with persistent CSF NMDAR-Abs at 12 months (25/39 [64%]) were more often subsequently retested for CSF Ab persistence (16/25 [64%])

Figure 3 Functional Status of Patients With Persistent or Absent CSF NMDAR-Abs at 12-Month Follow-up



Graphical representation of the mRS of patients with persistent (right) or absent (left) CSF NMDAR-Abs at 12-month follow-up. The vertical axis represents the number of patients included (framed) and the time of follow-up: M0, month 0; M3, month 3; M6, month 6; M9, month 9; M12, month 12; M18, month 18; M24, month 24; and M36, month 36. By contrast, the horizontal axis represents the percentage of patients with a determined mRS. mRS = modified Rankin Scale; NMDAR-Abs = NMDA receptor antibodies.

than recovered patients at 12 months without persistent antibodies (21/25 [84%]; 6/21 [28%]; $p = 0.01$).

A subgroup analysis comparing patients with persistent CSF NMDAR-Abs at 12 months who presented good or poor outcomes at the last follow-up was performed (additional data are listed in eTable 2, links.lww.com/NXI/A821). A significantly lower frequency of Caucasians and a higher frequency of Africans were observed among patients with poor outcomes and persistent CSF NMDAR-Abs at 12 months (Caucasians 3/15 (20%) and Africans 7/15 (46%) vs 14/24 (60%) and 3/24 (13%); $p = 0.002$), whereas other clinical variables were similar among both groups.

CSF NMDAR-Ab Titers

At diagnosis, CSF NMDAR-Ab titers were evaluated in 37 of 89 (41%) patients (median 1/160, IQR 1/20–1/640). A total of 29 of 37 (78%) patients with titers available at diagnosis were subsequently tested at 12-month follow-up. We observed that patients with persistent CSF NMDAR-Abs at 12 months (23/29, 79%) had higher titers at diagnosis (median 1/320, IQR 1/50–1/960 vs median 1/20, IQR 1/12.5–1/20; $p = 0.02$). All patients with CSF NMDAR-Ab titers ≥1/320 at diagnosis subsequently presented persistent CSF NMDAR-Abs at 12 months.

Discussion

The pathogenic role of NMDAR-Abs has extensively been demonstrated,[17] and their persistence at high titers in serum and CSF during the acute phase of anti-NMDAR encephalitis has been associated with poor outcomes, and sometimes death, despite intensive immunotherapy.[1,18] However, it remains unclear whether their persistence in the CSF during the recovery phase of the disease is associated with poor outcomes, therefore warranting maintenance or even more aggressive immunotherapy. In this study, patients with persistent CSF NMDAR-Abs at 12 months had worse long-term outcomes and more relapses in the following 4 years of the disease.

In the past decade, several studies have focused on the identification of clinical and molecular biomarkers in the acute phase to predict outcomes in anti-NMDAR encephalitis.[14] For instance, the NEOS score comprises 5 different variables to predict 1-year outcome, including MRI abnormalities, CSF pleocytosis higher than 20 cells/μL, ICU admission, delay longer than 1 month in the administration of immunotherapy, and lack of response to immunotherapy in the first month.[19] In addition, other EEG, neuroimaging, and molecular biomarkers have been proposed during the acute phase to predict poor outcome, such as an abnormal posterior rhythm on the first EEG,[20] cerebellar atrophy on MRI,[21] and high CSF levels of several cytokines such as CXCL-13, BAFF, APRIL, and IL-17A.[22] However, during the recovery phase, no biomarker has been assessed so far to predict the long-term evolution of patients with anti-NMDAR encephalitis. Herein, we observed that the persistence of CSF NMDAR-Abs at 12 months is associated with a worse outcome at the last follow-up, slower recovery, and higher disability at 18, 24, and 36 months of follow-up, although the small sample size at every time point limited the statistical power.

Similarly, few biomarkers or clinical features have been associated with an increased risk of further relapse during follow-up, including not giving immunotherapy in the acute phase and a delay in its administration.[1,18,23] Conversely, monthly IVIG for longer than 6 months after the acute phase has been shown to prevent relapses in a recent meta-analysis.[24] Herein, we found that patients with persistent CSF NMDAR-Abs at 12-month follow-up also had an increased risk of relapse, especially in the following 4 years.

Taken together, these findings suggest that the persistence of CSF NMDAR-Abs at 12 months could potentially be used as a prognostic biomarker in the recovery phase. If the findings are confirmed in future prospective studies, the use of immunotherapies that decrease intrathecal antibody synthesis may lead to better long-term outcomes in patients with anti-NMDAR encephalitis. However, although most of the patients with relapse herein had CSF NMDAR-Abs before the relapse, 2 patients without CSF NMDAR-Abs at 12 months subsequently had CSF NMDAR-Abs at the same time they relapsed. Furthermore, it is noteworthy that persistent CSF NMDAR-Abs have been reported in patients with good outcome after more than 15 years from onset,[25] suggesting that their sole presence may not be sufficient to negatively affect patient recovery. Thus, although the present findings support the role of persistent CSF NMDAR-Abs in the development of further relapses, other environmental or immune factors may also play a role.

The mechanism driving the persistence of CSF NMDAR-Abs in patients with good recovery remains unknown. Herein, we observed that patients with persistent CSF NMDAR-Abs at 12 months had higher CSF WBC at diagnosis, had higher CSF NMDAR-Ab titers at diagnosis, had longer ICU admission, and were treated more frequently with cyclophosphamide in the acute phase and at 12 months from clinical onset, suggesting that a more intense initial CSF inflammatory response, and a severe acute phase of the disease, may be related to persistent CSF NMDAR-Abs. Furthermore, higher CSF NMDAR-Ab titers at diagnosis were observed among patients with persistent Abs at 12 months, in line with previous studies proposing an association between high titers, clinical severity, and poor outcome.[1,10,18] However, the early administration of B- and T-cell depletion therapies such as rituximab or cyclophosphamide was not associated with the negativity of CSF NMDAR-Abs at 12 months despite improving outcome. Therefore, other immunotherapies with a broader impact on Ab-secreting cells such as anti-CD19 or anti-CD38 agents could be proposed in early phases of the disease, supported by previous studies reporting their efficacy in refractory cases.[26]

This study has several limitations because of its retrospective nature, mainly regarding the heterogeneity in the time of sampling. The difficulty in obtaining CSF samples during follow-up accounts for the relatively small sample size and decreases the statistical power of the analysis. In addition, one could argue that the inclusion of patients based on the availability of samples may lead to a selection bias by only testing patients persistently disabled. However, most of the patients were tested following our recommendations to systematically control CSF NMDAR-Ab status at recovery, supported by the fact that most patients with persistent CSF NMDAR-Abs at 12 months had good outcomes at this time point, as illustrated in Figure 3. Moreover, we compared the study cohort with a control cohort to reduce the risk of bias, and we found no significant differences regarding outcomes and relapses, in agreement with the results of previous studies.[8,9] Furthermore, recovered patients with persistent CSF Abs at 12 months were more frequently retested during follow-up than recovered patients without persistent Abs, reflecting that patients were not tested based on outcomes and arguing against the aforementioned selection bias. However, we acknowledge that using the mRS to assess outcome may limit the significance of our findings because it does not evaluate cognitive performance.

In conclusion, the present findings suggest that patients with persistent CSF NMDAR-Abs at 12 months are more likely to have subsequent relapses or long-term disability. Nevertheless, these findings should be interpreted very cautiously because of the aforementioned limitations of this study. Future well-designed prospective studies are required to validate these results in larger cohorts of patients and assess the potential impact of novel immunotherapies in CSF NMDAR-Ab synthesis.

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Disclosure

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Continued

Appendix *(continued)*

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