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Relapses in Anti-NMDAR Encephalitis

Clinical Characterization and Predictive Features

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Abstract

Background and Objectives

During the recovery phase of anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis, up to 25% of relapses have been reported. Herein, we aimed to clinically characterize these relapses, analyze potential clinical predictors during the first episode, and evaluate the impact of immunotherapy in their occurrence.

Methods

This was a retrospective observational study of patients diagnosed with anti-NMDAR encephalitis relapses between January 2007 and June 2022 at the French Reference Center for Paraneoplastic Neurological Syndromes and Autoimmune Encephalitis with a follow-up longer than 1 year.

Results

Among 507 patients, 49 (9%) presented relapses after a median time of 720 days (range 149–8,280) and a median follow-up of 1752 days (range 390–9,229 days, interquartile range 1760 days). A total of 36 patients (73%) experienced 1 relapse, 9 (18%) had 2, and 4 (8%) had 3 relapses. Most patients presented an isolated core symptom (25/45, 55%). Relapses were less severe than the first episode, as reflected by a lower maximal modified Rankin Scale (median 5, range 3–5, vs median 3, range 0–6; $p = 0.0001$). At the first episode, patients experiencing relapses had shorter intensive care unit stays (22 days; vs 39 days; $p = 0.04$). In addition, presenting CSF pleocytosis >20 white blood cell decreased the risk of relapse by 71% (HR 0.29; CI 0.13–0.66; $p = 0.003$), and having a paraneoplastic etiology decreased the risk by 68% (HR 0.32; CI 0.12–0.87; $p = 0.02$). Moreover, during the first episode, they were treated less frequently with first-line (39/49, 79%, vs 190/197, 96%; $p = 0.0001$) and second-line immunotherapies (20/49, 40%, vs 142/197, 72%; $p = 0.0001$) and more frequently with delay >30 days (20/38, 52%, vs 58/185, 31%; $p = 0.01$) and >60 days (10/20, 50%, vs 39/138, 28%; $p = 0.04$), respectively. In addition, administering rituximab during the first episode with a delay <60 days decreased the risk of relapse by 60% (HR 0.40; CI 0.19–0.84; $p = 0.01$).

Discussion

Relapses of anti-NMDAR encephalitis are uncommon, mostly monosymptomatic, and less severe than the first episode. At onset, presenting CSF pleocytosis or an underlying tumor decreases the risk of relapses. In addition, the early administration of first-line and second-line immunotherapies, particularly rituximab, could protect against further relapses.

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Glossary

HS = hyperintensity; **ICU** = intensive care unit; **IQR** = interquartile range; **mRS** = modified Rankin Scale; **NMDAR** = N-methyl-D-aspartate receptor; **NMO** = neuromyelitis optica; **WBC** = white blood cell.

Introduction

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is an autoimmune neurologic disorder clinically characterized by psychiatric symptoms, speech dysfunction, seizures, memory impairment, and movement disorders, which are frequently followed by dysautonomia and decreased level of consciousness.[1,2] The early administration of immunotherapy and the surgical removal of an ovarian teratoma, if present, are considered essential to achieve good long-term outcomes.[3]

Notably, up to 25% of patients may experience clinical worsening during the recovery phase of the disease, even years after the onset.[4,5] Modest cohorts of patients with relapses have shown that they may either manifest as the full-blown clinical picture or present with only few of the core symptoms; the latter may actually delay the recognition of relapses.[6] Moreover, the mechanisms driving relapses are still poorly understood, although they seem to occur more often in patients who have not been treated with immunotherapy during the first episode of the disease.[3,7] Thus, a better understanding of the underlying mechanisms and the identification of biomarkers able to predict relapse occurrence could facilitate an early diagnosis and even the implementation of preventive strategies.

Herein, we aimed to clinically characterize relapses in patients with anti-NMDAR encephalitis diagnosed at the French Reference Center for Paraneoplastic Neurological Syndromes and Autoimmune Encephalitis, as well as assess potential predictive clinical features and the effect of different treatment strategies on the risk of developing relapses.

Methods

Study Design, Patient Selection, and Clinical Data

Medical charts from all patients diagnosed with anti-NMDAR encephalitis at the French Reference Center for Paraneoplastic Neurological Syndromes and Autoimmune Encephalitis from January 2007 to January 2022 were retrospectively reviewed. Then, only patients fulfilling all following inclusion criteria were included in this study: (1) full clinical chart available, (2) follow-up longer than 1 year, (3) CSF samples tested in the French Reference Center, and (4) occurrence of at least 1 relapse (Figure 1). Relapses were defined as (1) new onset of any of the major clinical features that form the diagnostic criteria of anti-NMDAR encephalitis after at least 4 months of improvement/stabilization or a worsening of symptoms previously observed during the first episode that (2) caused a decline in modified Rankin Scale (mRS) ≥1 or was accompanied by CSF inflammation or CSF NMDAR-Ab.[3,6,8,9] To assess the clinical features during the onset of the disease that may predict further relapses, we compared the study cohort with a control cohort of patients with anti-NMDAR encephalitis from the French Reference Center who fulfilled the first 3 inclusion criteria but did not experience relapses.

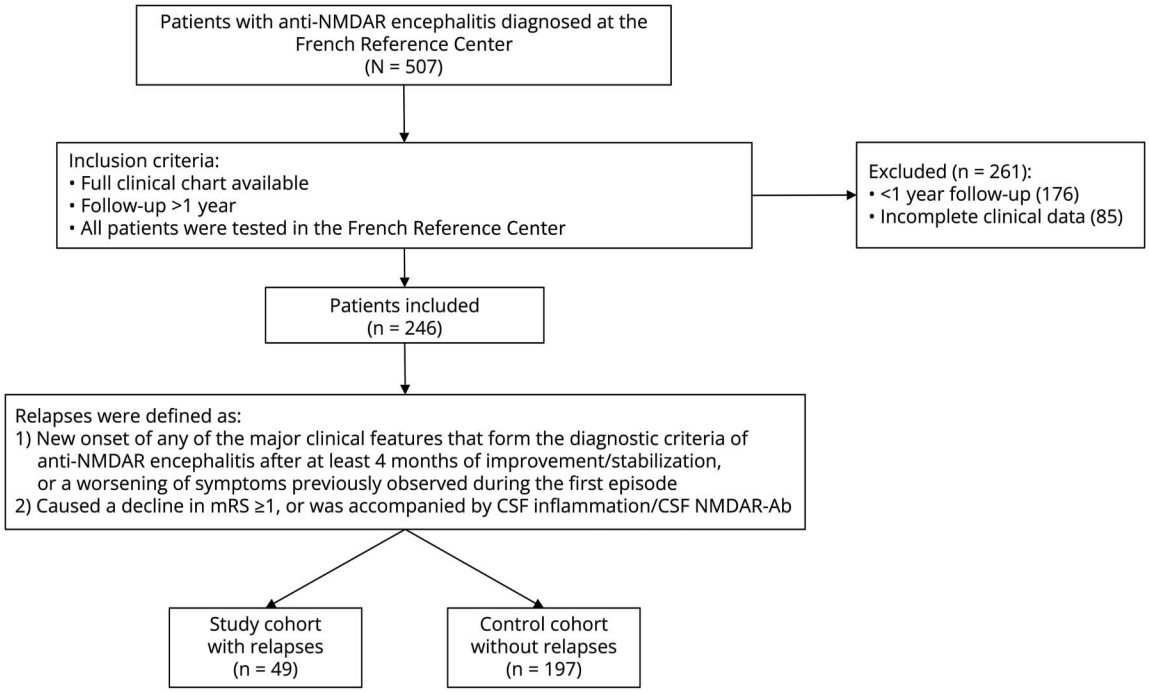
Demographic data were retrospectively collected from the medical charts and included age and sex. In addition, the following clinical features from the first episode and the relapses were retrieved: first clinical symptom, subsequent clinical symptoms, disability at onset and recovery phase assessed by the mRS, 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 ICU, first-line immunotherapies (corticosteroids [CC], IV immunoglobulin, and plasma exchange), second-line immunotherapies (rituximab and cyclophosphamide), and third-line immunotherapies (azathioprine, mycophenolate mofetil, methotrexate, tocilizumab, and bortezomib). The CSF was considered abnormal when WBC >5/μL, oligoclonal bands were present, or protein content >0.45 g/L. Good outcome was defined as an mRS <3. The mRS was retrospectively extracted from clinical charts of the French Reference Center in an heterogenous manner: while some patients, particularly those diagnosed in the past decade, had their mRS consistently documented throughout the follow-up period; for others, the mRS was inferred from clinical information.

The identification of CSF NMDAR antibodies was performed as previously described.[10] First, indirect immunofluorescence on rat brain sections was used as a screening technique, and compatible staining further confirmed by a cell-based assay using HEK293 cells expressing the GluN1 and GluN2b subunits of the NMDAR. Only samples positive by both techniques were considered as NMDAR antibody positive.

Statistical Analysis

Continuous variables are described by median, range, and interquartile range (IQR), whereas qualitative variables are reported as absolute and relative frequencies for each category of the variable (missing data not included). Statistical comparisons between the first episode and the relapses, as well as the relapsing and control cohorts, were performed using the

Figure 1 Flowchart Representing Cohort of Patients Diagnosed at French Reference Center, Inclusion Criteria, and Reasoning for Selecting Study and Control Cohorts



Wilcoxon-Mann-Whitney test for continuous variables and the χ^2 test or the Fischer exact test for qualitative variables. Relapse-free survival was estimated using the Kaplan-Meier method and Kaplan-Meier curves. Relapse-free survival curves were compared using the log-rank test. Then, a Cox regression analysis for survival was performed to evaluate each treatment line as predictors of further relapses. The assumption of hazard proportionality was tested and satisfied. In all analyses, a bilateral type I error rate of 5% was applied without correction for multiple testing. Patients with missing data were excluded from each analysis. All statistical analyses were performed using R software, version 4.1.1 (Free Software Foundation).

Standard Protocol Approvals, Registrations, and Patient Consents

This study entitled *Bio-NMDAr* was approved by the institutional review board of the *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*, Commission Nationale de l'Informatique et des Libertés, 21–57750). Written informed consent was obtained from all patients for the storage and use of laboratory samples and clinical information for research purposes, and none of them explicitly opposed their participation in this 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 Relapses

Forty-nine patients (41/49 women, 83%; median age 19 years, range 1–75 years, IQR 8 years) of 507 (9%) diagnosed with anti-NMDAR encephalitis during the study period experienced at least one relapse (Figure 1). The median time from onset to the first relapse was 720 days (range 149–8,280 days, IQR 1,070 days), and the median follow-up was 1752 days (range 390–9,229 days, IQR 1,760 days). Most patients experienced only 1 relapse (36/49, 73%) while 9 (18%) had 2 relapses and 4 (8%) had 3. The most common core symptom at relapse was seizures (27/45, 60%), including 2 patients who presented nonconvulsive status epilepticus. Seizures were followed in frequency by psychiatric symptoms (23/45, 51%) and cognitive impairment (13/45, 28%), whereas speech abnormalities (3/45, 6%), dysautonomia (2/45, 4%), and movement disorders (1/45, 2%) were seldomly observed. Most patients presented with 1 isolated core symptom (25/45, 55%) while 15 of 45 (33%) experienced 2 symptoms and 5 of 45 (11%) experienced 3 (Table 1). Furthermore, at the time of the relapse, 2 patients (4%) exhibited not only the classic core symptoms of anti-NMDAR encephalitis but also other symptoms that had led to the diagnosis of an overlapping aquaporin-4 antibody–positive neuromyelitis optica (NMO). During the relapse, 6 of 36 (16%) had new MRI findings compared with the first episode such as white matter T2 hyperintensities (3/36, 8%), leptomeningeal enhancement (1/36, 2%), frontal cortex T2 hyperintensity (HS) (1/36, 2%), or limbic T2 HS (1/36, 2%).

Table 1 Clinical and Paraclinical Features at First Episode and at First Relapse of Patients With Relapses of Anti-NMDAR Encephalitis

	Total cohort (n = 49)		
Clinical and paraclinical features	**First episode**	**First relapse**	***p* Value**
Core symptoms, n (%)			
Psychiatric	48 (97)	23/45 (51)	0.001
Cognitive	46 (93)	13/45 (28)	0.001
Seizures	41 (83)	27/45 (60)	0.01
Speech	35 (71)	3/45 (6)	0.001
Movement disorders	34 (69)	1/45 (2)	0.001
Decreased level of consciousness	24 (48)	0 (0)	0.001
Dysautonomia	19 (38)	2/45 (4)	0.001
Number of symptoms, n (%)			
1 symptom	0 (0)	25/45 (55)	0.001
2 symptoms	1 (2)	15/45 (33)	0.001
3 symptoms	4 (8)	5/45 (11)	>0.05
>3 symptoms	44 (89)	0 (0)	0.001
CSF abnormalities, n (%)	37 (75)	22/36 (61)	>0.05
CSF NMDAR-Ab, n (%)	49 (100)	38/42 (90)	0.04
MRI abnormalities, n (%)	17 (34)	6/36 (16)[a]	>0.05
Tumor presence, n (%)	5 (10)	1 (2)	>0.05
Ovarian teratoma	4 (8)	0 (0)	>0.05
Other tumors	1 (2)	1 (2)	>0.05
Max mRS, median (range, IQR)	5 (3–5, 1)	3 (0–6, 1)	0.0001

Abbreviations: IQR = interquartile range; mRS = modified Rankin score; NMDAR-Ab = N-methyl-D-aspartate receptor antibodies.
[a] Including only new MRI abnormalities compared with the first episode.

CSF NMDAR antibodies were detected in 38 of 42 (90%) patients during the relapse. In addition, CSF abnormalities suggesting inflammation were detected in 22 of 36 (61%) patients, and among those with normal CSF analyses, CSF NMDAR antibodies were found in 10 of 14 (71%) patients. Patients with isolated seizures (9/49; 18%) or without CSF NMDAR antibodies (4/42, 10%) presented other clinical or paraclinical features that supported the diagnosis of a relapse, as defined in the inclusion criteria. These 4 patients without CSF NMDAR antibodies initially presented a cluster of seizures that lasted several days and responded well, but transiently, to first-line immunotherapies; subsequently, after months of stabilization, they experienced a second polysymptomatic relapse, 2 of them with CSF NMDAR antibodies. During the relapse, only 1 patient was diagnosed with an underlying malignancy, a recurrence of the endometrial carcinoma with lymph node metastasis, also present at the first episode; none of the patients who had surgically removed an ovarian teratoma at the first episode presented a tumor at relapse (4/49, 8%). Notably, 1 patient gave birth a few days before the relapse, and another patient stopped contraceptive pills less than a month before. During the relapse, 12 of 38 (31%) had a maximal mRS ≥3, including 1 patient who died due to severe dysautonomia.

Differences Between the First Episode and Relapses

The clinical features of the first episode and those of the relapses were then compared (Table 1). All core symptoms were less frequent at relapse than during the first episode. Furthermore, none of the relapses (0%) consisted of more than 3 symptoms, compared with 44 of 49 (89%) of the first episodes ($p = 0.001$). There was no significant difference in terms of paraclinical features between the first episode and the relapses, including MRI findings, concurrent tumor identification, and CSF analyses, except for CSF NMDAR antibody positivity, which was less frequently observed at relapse (38/42, 90% vs 49/49, 100%; $p = 0.04$). In addition, the maximal mRS at the first episode was higher than at relapse (median 5, range 3–5, IQR 1 vs median 3, range 0–6, IQR 1; $p = 0.0001$).

Clinical Features at the First Episode Associated With Further Relapses

Subsequently, the clinical features at onset of patients with and without relapses were compared with the aim of identifying those that may be associated with the occurrence of future relapses (Table 2). Both groups were similar regarding demographic, clinical, imaging, and electroencephalographic features. Nevertheless, patients who experienced relapses had less frequently a paraneoplastic origin of the first episode (5/49, 10%, vs 57/187, 30%; $p = 0.004$), shorter admissions to the ICU (22 days, range 5–42, vs 39 days, range 18–75; $p = 0.04$), and less WBC per μL of CSF (9 cells/μL, range 4–40, vs 24 cells/μL, range 9–62; $p = 0.014$). Furthermore, patients experiencing relapses had a longer total follow-up period (1,485 days, range 803–2,563, vs 824 days, range 546–1,403; $p = 0.002$), likely attributable to their longer disease activity.

Impact of Immunotherapy During the First Episode on the Occurrence of Relapses

Subsequently, the therapeutic regimens applied during the first episode were compared between patients with and without relapses to evaluate their potential impact on further development of relapses (Table 2). All patients treated with second-line therapies previously received first-line immunotherapies after a median time of 19 days among patients without relapses (range 0–370) and 36 days in those with relapses (range 6–196).

Initially, we analyzed first-line and second-line immunotherapies as groups to understand their global impact on relapses. We observed that patients with relapses were treated less frequently with first-line (39/49, 79%, vs 190/197, 96%; $p = 0.0001$) and second-line (20/49, 40%, vs 142/197, 72%; $p = 0.0001$) immunotherapies. A Kaplan-Meier survival analysis also showed that patients treated with first-line and second-line therapies had fewer relapses at long-term follow-up than patients treated only with first line or patients who did not receive immunotherapy at onset ($p = 0.01$; Figure 2A). Finally, a Cox regression analysis showed that administering first-line and second-line immunotherapies decreases the risk of relapse by 66% (HR 0.34; CI 0.15–0.76; $p = 0.009$; Figure 2B). Furthermore, patients experiencing relapses more often received first-line immunotherapies with a delay >30 days from onset (20/38, 52%, vs 58/185, 31%; $p = 0.01$), as well as second-line therapies with a delay >60 days (10/20, 50%, vs 39/138, 28%; $p = 0.04$). Similarly, a Kaplan-Meier survival analysis only including treated patients found that those who received first-line therapies in the first 30 days of the disease experienced fewer relapses than patients with a delay >30 days ($p = 0.04$; Figure 3A). However, no differences were observed in a Kaplan-Meier survival analysis comparing a delay of second-line therapies >60 days, nor in a Cox regression analysis comparing the impact of a delayed administration of first-line and second-line immunotherapies (Figure 3B).

Next, we evaluated the individual impact of each second-line immunotherapy on relapses. We observed that patients with relapses were less frequently treated with rituximab (19/49, 38%; vs 135/195, 68%; $p = 0.0001$). Then, a Kaplan-Meier survival analysis also revealed a higher frequency of relapses among patients who were not treated with rituximab ($p = 0.04$; Figure 4A), whereas a trend was observed toward a higher frequency of relapses among patients that received rituximab with a delay >60 days ($p = 0.06$; Figure 4B). By contrast, no differences were observed related to cyclophosphamide administration among patients with or without relapses (6/49, 12%; vs 47/197, 23%; $p = 0.07$).

Finally, we performed a multiple Cox regression analysis to evaluate the impact of the aforementioned clinical and therapeutic factors on relapse risk (Figure 5). We observed that presenting CSF pleocytosis of 5–20 WBC per μL during the first episode decreased the risk of relapse by 69% (HR 0.31; CI 0.14–0.69; $p = 0.005$), whereas presenting CSF pleocytosis of >20 WBC per μL decreased the risk by 71% (HR 0.29; CI 0.13–0.66; $p = 0.003$). In addition, presenting a paraneoplastic anti-NMDAR encephalitis decreased the risk by 68% (HR 0.32; CI 0.12–0.87; $p = 0.02$). Finally, administering rituximab during the first episode with a delay <60 days decreased the risk of relapse by 60% (HR 0.40; CI 0.19–0.84; $p = 0.01$). However, no significant differences were observed regarding the time in ICU.

Discussion

Despite an extended knowledge about the initial phase of anti-NMDAR encephalitis, the recovery phase of the disease has only been investigated thoroughly recently.[11] Although most patients seem to experience a slowly progressive clinical improvement over 1–2 years, some of them may present relapses, which may add additional disability. Herein, we describe a cohort of 49 patients experiencing relapses, providing a detailed clinical description and analysis of potential risk factors. In our cohort, relapses were slightly less frequent than in the literature[3,12]; however, the clinical characteristics were consistent with previous descriptions, as they may occur more than once, are rarely paraneoplastic, generally monosymptomatic, and milder than the first episode.[3,12] Remarkably, we observed that the administration of first-line and second-line immunotherapies during the first episode decreases the risk of subsequent relapses, especially when given early in the course of the disease.

Anti-NMDAR encephalitis encompasses a well-defined spectrum of clinical features; in the earliest stages, patients predominantly exhibit cognitive impairment, psychiatric symptoms, and seizures, with abnormal movements, dysautonomia, and decreased level of consciousness appearing later in the disease course.[5,13] Thus, as a result of the latter symptoms, patients often require admission to the ICU. Interestingly, most patients in the present series showed a rather mild clinical picture during relapses, usually manifesting with only 1 or 2 core symptoms, chiefly seizures, psychiatric disturbances,

Table 2 Clinical Features at Onset of Patients With and Without Relapses of Anti-NMDAR Encephalitis

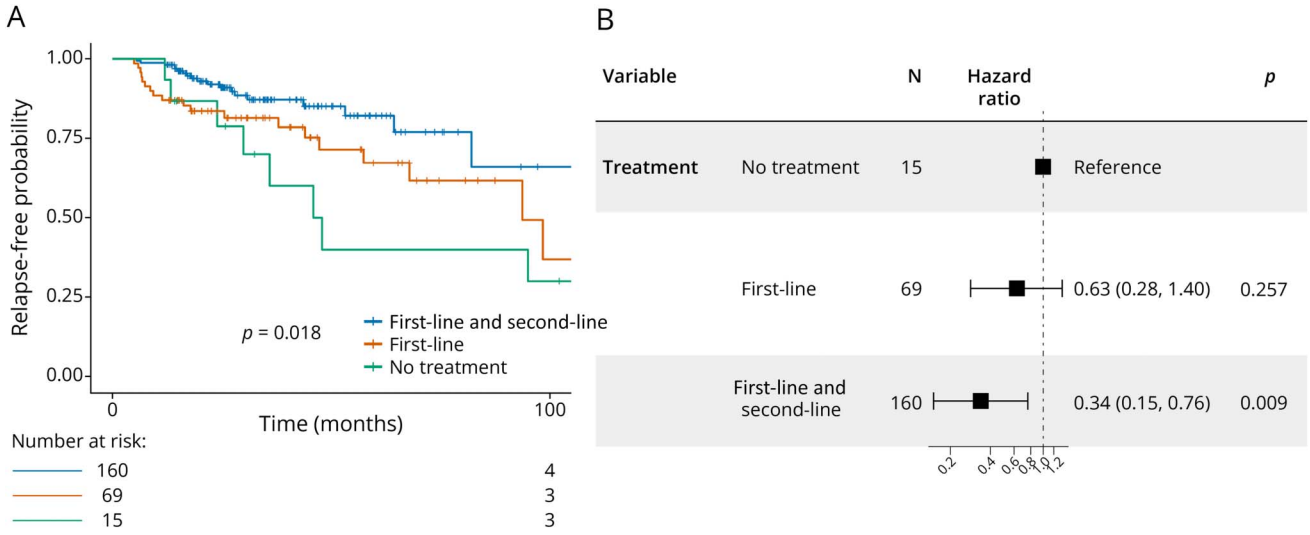
Clinical and paraclinical features	Patients with relapses (n = 49)	Patients without relapses (n = 197)	*p* Value
Women, n (%)	41 (83)	156 (79)	>0.05
Age, y, median (range, IQR)	19 (1–75, 8)	20 (1–66, 13)	>0.05
ICU admission, n (%)	27 (55)	126 (63)	>0.05
ICU stay, d, median (range, IQR)	22 (2–369, 13)	39 (1–299, 57)	0.04
Tumor, n (%)	5 (10)	57/187 (30)	0.004
Abnormal MRI, n (%)	17 (34)	51/184 (27)	>0.05
T2 medial temporal HS	7 (14)	17 (9)	>0.05
T2 extratemporal white matter HS	7 (14)	24 (13)	>0.05
Other	3 (6)	10 (5)	>0.05
Abnormal EEG, n (%)	38 (77)	158/190 (83)	>0.05
Slowing	28 (57)	123 (62)	>0.05
Epileptic discharges	10 (20)	35 (18)	>0.05
CSF abnormalities, n (%)	37 (75)	149/195 (76)	>0.05
CSF WBC, cells/μL, median (range, IQR)	9 (0–290, 36)	24 (0–700, 53)	0.01
CSF protein, g/L, median (range, IQR)	0.32 (0.17–0.72, 0.17)	0.35 (0.11–2.21, 0.25)	>0.05
First-line treatment, n (%)	39 (79)[a]	190 (96)	0.0001
First-line delay >30 d, n (%)	20 (52)[a]	58/185 (31)	0.01
Second-line treatment, n (%)	20 (40)[a]	142 (72)	0.0001
Second-line delay >60 d, n (%)	10 (50)[a]	39/138 (28)	0.04
Rituximab, n (%)	19 (38)[a]	135 (68)	0.0001
Rituximab delay >60 d, n (%)	9 (47)[a]	37/132 (28)	>0.05
Cyclophosphamide, n (%)	6 (12)[a]	47 (23)	>0.05
Cyclophosphamide delay >60 d, n (%)	5 (83)[a]	24/45 (53)	>0.05
Third-line treatment, n (%)	16 (32)[a]	71/197 (36)	>0.05
Max mRS at onset, median (range, IQR)	5 (3–5, 1)	5 (3–6, 1)	>0.05
mRS≥3 at 12 mo follow-up, n (%)	6/45 (13)	33/178 (18)	>0.05
mRS≥3 at last follow-up, n (%)	9 (18)	22 (11)	>0.05
Follow-up, d, median (range, IQR)	1752 (390–9,229, 1760)	824 (375–8,510, 857)	0.02

Abbreviations: HS = hyperintensity; ICU = intensive care unit; IQR = interquartile range; mRS = modified Rankin score; NMDAR = NMDA receptor.
[a] Including only treatments given before the relapse.

or cognitive dysfunction, as previously reported by other authors in relapses of anti-NMDAR encephalitis,[5,8] but also in anti-LGI1 encephalitis.[14] Accordingly, most patients presented a less severe disease during relapse compared with the onset, as reflected by a lower maximal mRS, and no additional disability at last follow-up related to the relapse was observed, in contrast to previous studies.[14,15] Nevertheless, a small proportion experienced life-threatening relapses with refractory status epilepticus or severe dysautonomia, which unfortunately led to death in 1 patient. Therefore, early identification and management of anti-NMDAR encephalitis relapses is crucial to prevent these undesired events.

Furthermore, we observed distinctive clinical features during the first episode in patients with relapses when compared with those without them. These clinical biomarkers could potentially serve as a useful tool to identify patients at risk of developing rel with relapses had fewer CSF WBC per μL; interestingly, presenting CSF pleocytosis of 5–20 WBC per μL during the first episode decreased the risk of relapse by 69%,

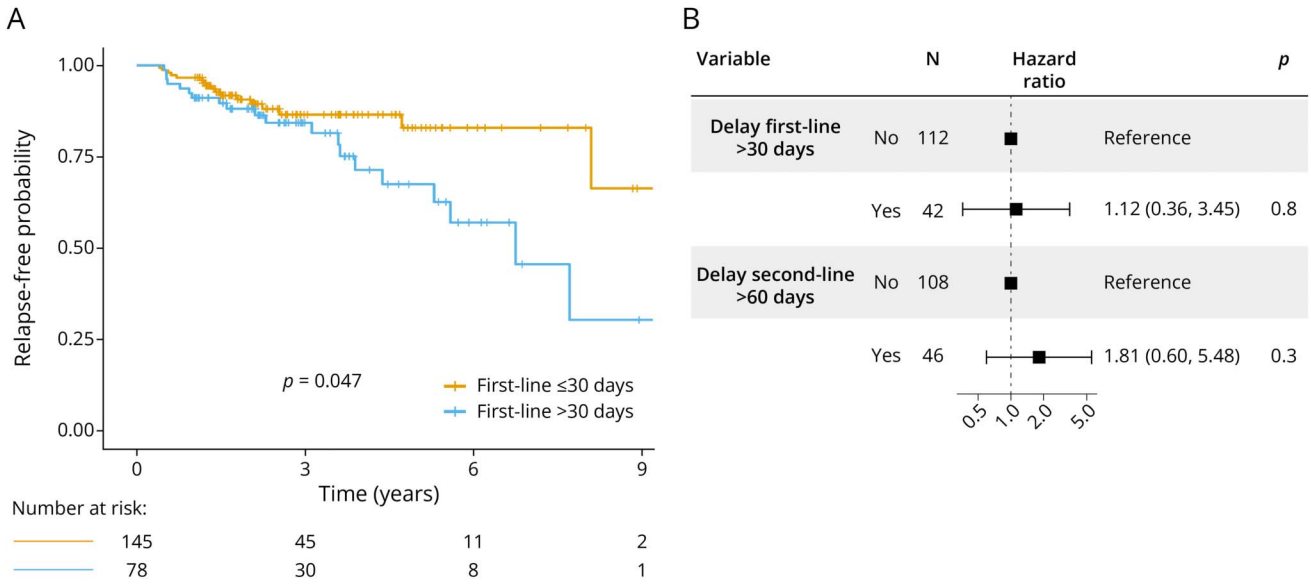
Figure 2 Kaplan-Meier Survival Analysis and Cox Regression Analysis Evaluating Impact of Different Treatments on Further Relapses



(A) Patients treated with first-line and second-line immunotherapies during the first episode of the disease presented less relapses. The abscissa axis represents follow-up time (in months) after disease onset, and the ordinate axis represents the proportion of relapse-free patients over time. Tick marks indicate censored patients, and comparison was made using the log-rank test. (B) Cox regression analysis for survival found a hazard ratio less than 1 for patients who received first-line and second-line immunotherapies, representing a protective effect against relapses. The abscissa axis represents the odds ratio on a log scale with the reference line (dashed), odds ratios (squares), and 95% CI (whiskers).

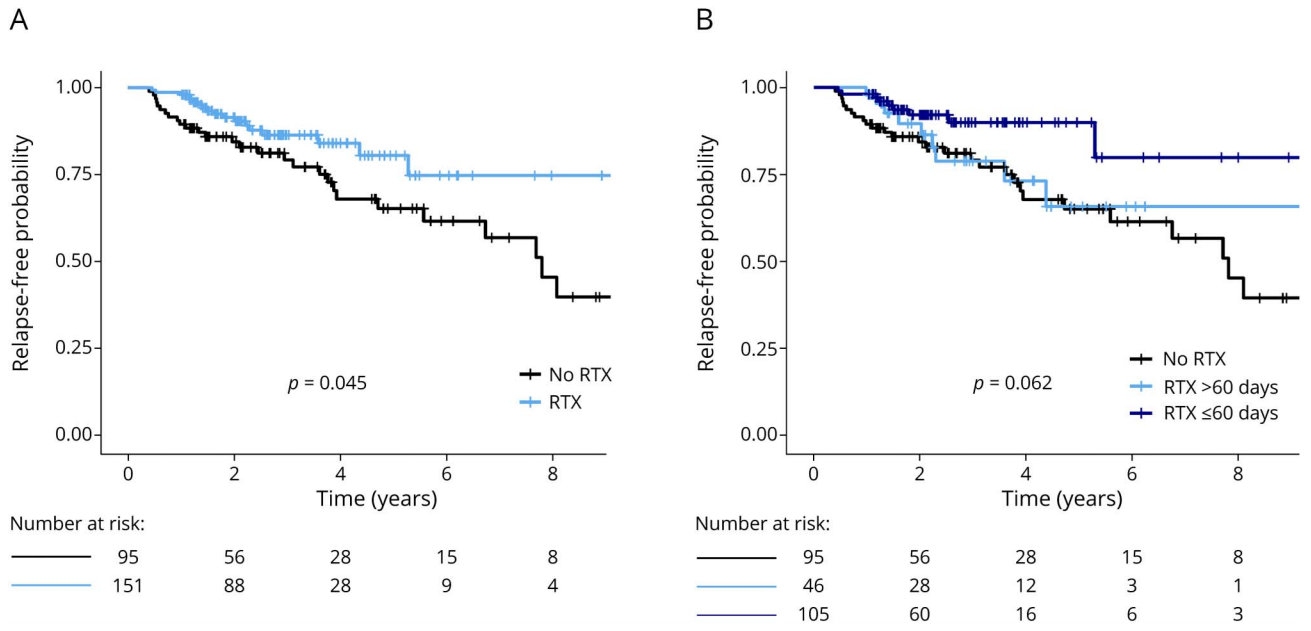
whereas presenting CSF pleocytosis of >20 WBC per μL decreased the risk by 71%. This difference in CSF WBC could simply reflect a different timing of CSF sampling; however, it could also be explained by the lower frequency of an underlying tumor in relapsing cases, as previous studies have shown that paraneoplastic anti-NMDAR encephalitis present more intense CSF inflammation at onset.[2,8] Remarkably, the rare occurrence of relapses among patients with paraneoplastic anti-NMDAR

Figure 3 Kaplan-Meier Survival Analysis and Cox Regression Analysis Evaluating Impact of Administering First-Line Immunotherapies With a Delay Longer Than 30 Days on Further Relapses



(A) Patients treated with first-line immunotherapies with a delay longer than 30 days from onset present more relapses. The abscissa axis represents follow-up time (in months) after disease onset, and the ordinate axis represents the proportion of relapse-free patients over time. Tick marks indicate censored patients, and comparison was made using the log-rank test. (B) Cox regression analysis for survival, including only patients with complete data on the timing of first-line or second-line immunotherapy administration, did not identify an increased risk of relapse associated with delays in treatment. The abscissa axis represents the odds ratio on a log scale with the reference line (dashed), odds ratios (squares), and 95% CI (whiskers).

Figure 4 Kaplan-Meier Survival Analysis Evaluating Impact of Administering Rituximab on Relapses



(A) Patients treated with rituximab presented less relapses. (B) Patients treated with rituximab with a delay <60 days had less relapses than those with a longer delay or who did not receive rixutimab. The abscissa axis represents follow-up time (in months) after disease onset, and the ordinate axis represents the proportion of relapse-free patients over time. Tick marks indicate censored patients, and comparison was made using the log-rank test.

encephalitis support the role of the associated tumors as main drivers of the disease. Interestingly, presenting a paraneoplastic anti-NMDAR encephalitis decreases the risk of relapses by 68%. In this study, only 1 patient was found to have an underlying tumor at relapse, specifically a tumor recurrence with lymph node metastasis of a previously resected endometrial carcinoma. By contrast, nonparaneoplastic cases may relapse after the exposure, or re-exposure, to other unidentified factors that may act as

Figure 5 Multiple Cox Regression Analysis Evaluating Impact of Different Clinical Features on Risk of Relapses

Variable		N	Hazard ratio	p
CSF WBC	WBC <5	31	Reference	
	WBC 5–20	70	0.34 (0.15, 0.76)	0.009
	WBC >20	100	0.38 (0.17, 0.86)	0.020
Delay RTX	No RTX	78	Reference	
	RTX >60 days	36	0.76 (0.34, 1.72)	0.516
	RTX ≤60 days	87	0.38 (0.18, 0.80)	0.012
ICU stay	No ICU	98	Reference	
	≤4 weeks	38	1.56 (0.74, 3.28)	0.242
	>4 weeks	65	1.06 (0.45, 2.49)	0.894
Tumor diagnosis	No	147	Reference	
	Yes	54	0.32 (0.12, 0.87)	0.025

The abscissa axis represents the odds ratio on a log scale with the reference line (dashed), odds ratios (squares), and 95% CI (whiskers).

triggers of an autoimmune reactivation. Interestingly, 2 patients experienced a relapse shortly after interrupting contraceptive pills or after giving birth. Although it cannot be definitively suggested that these factors directly influenced the relapse, hormonal transitions are known to significantly influence immune responses,[16] and puerperium is widely recognized as a time of autoimmune flares resulting from the cessation of immunotolerance induced during pregnancy.[17] Moreover, 2 other patients additionally presented other concurrent clinical and MRI findings at relapse that led to the diagnosis of coexisting anti-NMDAR encephalitis and aquaporin-4 antibody–positive NMO, suggesting a common immune background driving this rare but well-known overlapping syndrome.[18]

Yet, the factor most likely to substantially influence the risk of subsequent relapses—and the one more amenable to improvement—is the administration of immunotherapy and its timing. Shortly after the discovery of the disease, a few studies including small cohorts of patients reported that not receiving immunotherapy was associated with a higher risk of developing relapses.[5,6] Later, further research confirmed this finding, and early administration of immunotherapy was reported to be crucial to achieve better outcomes in the acute phase and also to prevent relapses.[3,5] In this study, we confirmed such findings by analyzing the largest cohort of patients with anti-NMDAR encephalitis and relapses reported to date. In addition, we found that the administration of first-line and second-line immunotherapies during the first episode decreased the risk of relapses by 66%, whereas the initiation of first-line immunotherapies with a delay >30 days from onset, or second-line therapies with a delay >60 days, was more frequent among patients with relapses. Specifically, patients with relapse were treated less frequently with rituximab, and its administration during the first episode with a delay <60 days decreased the risk of relapse by 60%. However, we did not observe a change in relapse rate over time potentially related to more frequent use of second-line therapies in the past decade, as previously reported.[12] Taken together, all these findings suggesting a milder clinical course could explain why these patients, despite having a similar mRS, are often treated less aggressively, and may therefore be at a higher risk of relapse. Consequently, it could be recommended that a second line of immunotherapy should be considered regardless of disease severity, rather than only after the failure of first-line immunotherapy, as classically proposed.[7,19]

However, although the aforementioned clinical features might identify patients at risk of relapses, the triggers and underlying immune mechanisms explaining their clinical distinctiveness from the first episode remain largely unknown. Previous studies proved that there is no epitope spreading or change in the main epitope region of NMDAR antibodies during relapses.[8] Nonetheless, we recently described that the persistence of CSF NMDAR antibodies at 12-month follow-up is associated with a higher risk of further relapses.[4] Similarly, the persistence or a secondary elevation of different immune factors, such as CXCL10, CXCL13, and IL-17A, has been associated with relapses.[20–23] Therefore, future prospective studies should aim to define the most significant clinical and soluble biomarkers to predict patients at risk of further relapses who may benefit from a personalized management strategy.

The retrospective nature of this study associates several limitations, particularly concerning the retrieval of clinical data from past medical records and the possibility of misidentifying delayed relapses despite including patients with a follow-up longer than 1 year. In addition, using the mRS to evaluate the clinical status of patients may have minimized the impact of our results, as it underestimates neuropsychiatric and cognitive deficits. Moreover, the diagnosis of anti-NMDAR encephalitis relapses is based only on clinical features, and the identification of NMDAR antibodies at the time of the relapse was not considered as mandatory,[3,6,8,9] increasing the risk of misdiagnosing other entities as relapses. However, long-lasting synaptic and network alterations could make patients vulnerable to present relapses despite negative CSF NMDAR antibodies, or because of low, and unidentifiable, antibody titers. In addition, based on our findings, patients with mild or isolated symptoms suggestive of relapse but negative CSF NMDAR antibodies should be closely monitored to prompt early recognition of new symptoms or even new CSF NMDAR antibody synthesis.

These findings may have meaningful implications in daily clinical practice. The analysis of the present cohort allowed to refine the knowledge about the clinical and paraclinical features of anti-NMDAR encephalitis relapses, prompting early recognition and management. In addition, we confirmed the importance of first-line and second-line immunotherapies during the first episode and reaffirmed the impact of a delay in their administration on the occurrence of subsequent relapses.

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Author Contributions

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