Relapse risk factors in anti-N-methyl-D-aspartate receptor encephalitis

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ABBREVIATIONS

CSF	Cerebrospinal fluid
ICU	Intensive care unit
mRS	Modified Rankin Scale
NMDAR	N-methyl-D-aspartate receptor

AIM To identify factors that may predict and affect the risk of relapse in anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis.
METHOD This was a retrospective study of an Italian cohort of patients with paediatric (≤18y) onset anti-NMDAR encephalitis.
RESULTS Of the 62 children included (39 females; median age at onset 9y 10mo, range 1y 2mo–18y; onset between 2005 and 2018), 21 per cent relapsed (median two total events per relapsing patient, range 2–4). Time to first relapse was median 31.5 months (range 7–89mo). Severity at first relapse was lower than onset (median modified Rankin Scale [mRS] 3, range 2–4, vs median mRS 5, range 3–5; admission to intensive care unit: 0/10 vs 3/10). At the survival analysis, the risk of relapsing was significantly lower in patients who received three or more different immune therapies at first disease event (hazard ratio 0.208, 95% confidence interval 0.046–0.941; p=0.042). Neurological outcome at follow-up did not differ significantly between patients with relapsing and monophasic disease (mRS 0–1 in 39/49 vs 12/13; p=0.431), although follow-up duration was significantly longer in relapsing (median 84mo, range 14–137mo) than in monophasic patients (median 32mo, range 4–108mo; p=0.002).
INTERPRETATION Relapses may occur in about one-fifth of children with anti-NMDAR encephalitis, are generally milder than at onset, and may span over a long period, although they do not seem to be associated with severity in the acute phase or with outcome at follow-up. Aggressive immune therapy at onset may reduce risk of relapse.

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is an autoimmune syndrome characterized by rapid onset of symptoms with multistage progression (psychiatric or behavioural changes, movement disorders, epileptic seizures, speech dysfunction, consciousness and vigilance disturbances, sleep-wake cycle disruption, dysautonomias), and the presence of neuronal surface antibodies in the cerebrospinal fluid (CSF) and serum targeting the NMDAR.[1–3]

While outcome is generally favourable,[2] the disease can be very severe in the acute phase, often requiring admission to the intensive care unit (ICU), long hospital stay, and the use of multiple symptomatic medications.[4] Therefore, recurrences represent a worrying prospect in the disease course. After a first episode of anti-NMDAR encephalitis, relapses have been reported in 9 per cent to 23 per cent of patients in the main literature cohorts.[2,5,6] Early immune therapy and second-line treatments have been suggested to favour a good outcome and lower relapse rate,[2,6–9] although data is limited and factors associated with disease recurrence have not been thoroughly clarified yet. In this context, we have studied the Italian multicentre cohort of children with anti-NMDAR encephalitis with focus on relapses and factors that may predict and affect the risk of relapse.

METHOD

This paper presents the Italian cohort of paediatric anti-NMDAR encephalitis, with focus on disease recurrence, with the aim of identifying factors predicting and affecting the risk of relapse.

Inclusion criteria

Inclusion criteria was a diagnosis of anti-NMDAR encephalitis according to the Graus et al.[3] criteria (recently validated in children),[10] with onset in paediatric age (0–18y) in Italy.

Data collection

A questionnaire was prepared ad hoc (MN) and filled in retrospectively by the treating physicians. Data were collected between November 2016 and March 2019 (including updated follow-up data of the previously published patients).[11] Methods are described more extensively in a previous report.[11]

Operational definitions

We categorized symptoms in the first 2 weeks according to the dominant type of presentation, as predominantly neurological onset (seizures, movement disorder, changes in vigilance, autonomic or sleep-wake cycle disturbances), predominantly psychiatric-behavioural onset (unusual behaviour, aggressiveness, irritability, confusion, hallucinations), or mixed onset.

Neurological severity in the acute phase and outcome at last follow-up were assessed via the modified Rankin Scale (mRS).[12] Disease course was categorized as monophasic (one disease event) or relapsing (≥two disease events including onset). Relapse was defined as worsening of symptoms or new onset of symptoms occurring after more than 2 months of stabilization or improvement.[13]

Investigations in the acute phase were assessed based on the reports provided by the treating physicians (brain magnetic resonance imaging [MRI], electroencephalography [EEG], CSF data, and anti-NMDAR antibody search in serum and CSF).

First-line immune therapy was defined as the use of intravenous or oral corticosteroids, intravenous immunoglobulin, and/or plasma exchange. Second-line immunotherapy included cyclophosphamide and/or rituximab. We considered long-term immune modulation as the protracted (operatively defined as duration ≥5mo) use of immune therapy, such as steroid sparers (mycophenolate mofetil, azathioprine, methotrexate); monthly intravenous immunoglobulin; monthly corticosteroid courses; or repeat rituximab course. We defined the use of three or more different immune therapies as the combination of any three or more treatments among all the above-mentioned agents (intravenous and oral corticosteroids were not regarded as different treatments). Early treatment was defined as initiation of immune therapy 30 days or fewer from onset.[11,14]

Statistical analysis

Data collection was subject to data availability, therefore in the 'Results' denominators may differ. Quantitative variables were expressed as median, mean, and range, whereas categorical variables were reported as the number of participants in each category and the percentage.

According to the main objective of the study, demographics, clinical, and treatment data at disease onset were considered as predictors of time to relapse. In the analysis of survival from first event, the follow-up time was considered as follows: for relapsing patients, the time to first relapse; for relapse-free patients, the time at last follow-up. Median follow-up time for the relapse analysis was calculated with the reverse of the Kaplan-Meier method as described by Schemper and Smith.[15] The factors predictive of survival from first relapse were analysed with a univariate Cox-regression analysis, with Firth adjustment when the number of relapsing patients was zero. A global relapse-free curve was estimated with the Kaplan–Meier method. Multivariable analysis was not carried out in view of the low number of patients with relapses.[16]

The total follow-up time (time from onset to last visit) in the subgroups of monophasic and relapsing patients was compared with the Mann–Whitney *U* test. The mRS at last follow-up was categorized as good (mRS 0–1) versus other (mRS 2–6),[17] and compared in the subgroups of patients with monophasic and relapsing disease using the Fisher's exact test. The significance level was set at 5 per cent (two-tailed). Data was entered in an Excel spreadsheet and analysed with SAS 9.4 (SAS Institute, Cary, NC, USA) for Windows.

What this paper adds

- Relapses of anti-N-methyl-D-aspartate receptor encephalitis may span over a long period.
- Relapses were not associated with severity in the acute phase or outcome at follow-up.
- Aggressive immune therapy at onset appears to decrease risk of relapse.

Ethics

The study complied with the general ethical requirements for retrospective observational studies. In particular, no experimental interventions were performed and patient identity cannot be retrieved from the manuscript.

RESULTS

Study population

Our cohort included 62 patients with anti-NMDAR encephalitis with paediatric onset in Italy (20 of these were described in the first report of the Italian cohort of paediatric anti-NMDAR encephalitis;[11] follow-up data was updated for 14 of these). In total, 88.7 per cent (55/62) of children had definite anti-NMDAR encephalitis according to the Graus et al.[3] criteria, with positive anti-NMDAR antibodies in CSF, whereas the remaining 11.3 per cent (7/62) were tested for anti-NMDAR antibodies only in serum (all positive) and met the Graus et al.[3] criteria for probable anti-NMDAR encephalitis.

Demographics

Disease onset was between 2005 and 2018. Thirty-nine of the patients were female (62.9%), and median age at onset was 9 years 10 months (mean 9y 11mo, range 1y 2mo–18y, data available in 62/62; Table SI, online supporting information). Age at onset was similar in females (median 10y, mean 10y 4mo, range 2y 6mo–18y, data available in

39/39) and males (median 9y 2mo, mean 9y 2mo, range 1y 2mo–17y 8mo, data available in 23/23). In total, 74.2 per cent (46/62) of patients were white. Patients were referred by 27 different Italian centres and were residents of 14 Italian regions (41/62, 66.1%: Northern Italy; 9/62, 14.5%: Central Italy; 12/62, 19.3%: Southern Italy). Five patients had viral encephalitis before anti-NMDAR encephalitis (Table SII, online supporting information).

Clinical data at first disease event

Overall, predominantly neurological presentation was slightly more frequent than behavioural-psychiatric onset (30/61, 49.2% vs 21/61, 34.4%). Behavioural-psychiatric onset was slightly more common among females (16/38, 42%) than males (5/23, 21.7%). Tumour was detected in 6.4 per cent (4/62) of patients. In two of these, tumour was detected during relapse: both patients had negative oncological screening at onset, and had ovarian teratoma removed when detected at relapse; they both received first-line immune therapy at first and second event and had no further relapses (Appendix S2, online supporting information).

Treatment at first disease event

Only two patients did not receive immune therapy at first event (one of these relapsed and was treated after the first relapse). Second-line immune therapy was administered in 48.4 per cent (30/62) of patients and long-term immunemodulation for 5 months or more was used in 41 per cent (25/61) of patients at first event (Table SI). In total, 54.8 per cent (34/62) received three or more immune therapies at first event (including plasma exchange in 20/34 and second-line treatments in 30/34).

In patients with onset between 2005 and 2011 (15/62, 24.2%), as compared to those with onset between 2012 and 2018 (47/62, 75.8%), there was less frequent use of three or more immune therapies (2/15, 13.3% vs 32/47, 68.1%), of second-line immune therapy (1/15, 6.7% vs 29/47, 61.7%), especially of rituximab (0/15, 0% vs 22/47, 46.8%), and of long-term immune modulation (2/15, 13.3% vs 23/46, 50%) at first disease event.

Neurological outcome

At last follow-up (median 36mo from onset, mean 42.8mo, range 4–137mo; data available in 62/62), mRS was: median 1, mean 0.8, range 0 to 6 (mRS 0 in 27/62, 43.5%). At last follow-up, ongoing seizures were reported in 3.4 per cent (2/59). One male with onset at 16 years 2 months, monophasic disease, and mRS 5, died because of sepsis and disseminated intravascular coagulation 6 months after onset, after receiving intravenous methylprednisolone, intravenous immunoglobulin, and rituximab. Further data on neurological outcome at follow-up is provided in Appendix S3 (online supporting information).

Analysis of relapses

Frequency of relapses, number of events, and time to relapse

Altogether, 21 per cent (13/62) of patients relapsed (Fig. 1, Tables I and SIII, online supporting information, and Fig. S1, online supporting information). A total of 31 clinical events occurred in these 13 relapsing patients (including onset events) (median two events per relapsing patient, mean 2.4, range 2–4; data available in 13/13); while nine of these experienced only one relapse (total two disease events), four had two to three relapses each (total 3–4 disease events). The first relapse occurred at median 31.5 months after onset (mean 34.3mo, range 7–89mo; data available in 12/13). In the four patients with multiple relapses, median time between onset and last event was 97 months (mean 98mo, range 68–130mo; Appendix S4, online supporting information).

Clinical data at relapse compared to first event

In relapsing patients with available data both at first and second event, mRS at second event was lower (median mRS 3, mean 3.2, range 2–4) than at onset (median mRS 5, mean 4.5, range 3–5), rate of ICU admission was lower at second (0/10) than at first event (3/10), and symptom expression was overall more limited at second than at first event (Table SIV, online supporting information).

Treatment at relapse

At the second disease event (first relapse), 10 out of 11 patients with available information received immune therapy, although only three received second-line agents (Fig. 1). None of the patients treated with second-line immune therapy at the second event had further relapses, compared to three out of eight of the cases not treated with second-line agents.

Survival analysis of relapses

In the analysis of survival from first event, the median follow-up time was 39 months (95% confidence interval [CI] 28–41.7mo; follow-up time was the time to first relapse for relapsing patients, and the time to last follow-up for relapse-free patients).

Characteristics in patients with monophasic and relapsing disease and results of the survival analysis are presented in Tables I and SIII, and Figure S1.

Demographics, clinical data, and investigations at first event

Demographics, clinical data including disease severity (i.e. mRS or ICU admission), and investigations at first event were not associated with risk of relapsing.

Treatment at first disease event

Risk of relapsing was significantly lower in patients who received three or more different immune therapies at first disease event (hazard ratio 0.208, 95% CI 0.046–0.941; p=0.042).

Outcome in patients with monophasic and relapsing disease

Neurological outcome (mRS) at last available follow-up (last visit) did not differ significantly between patients with

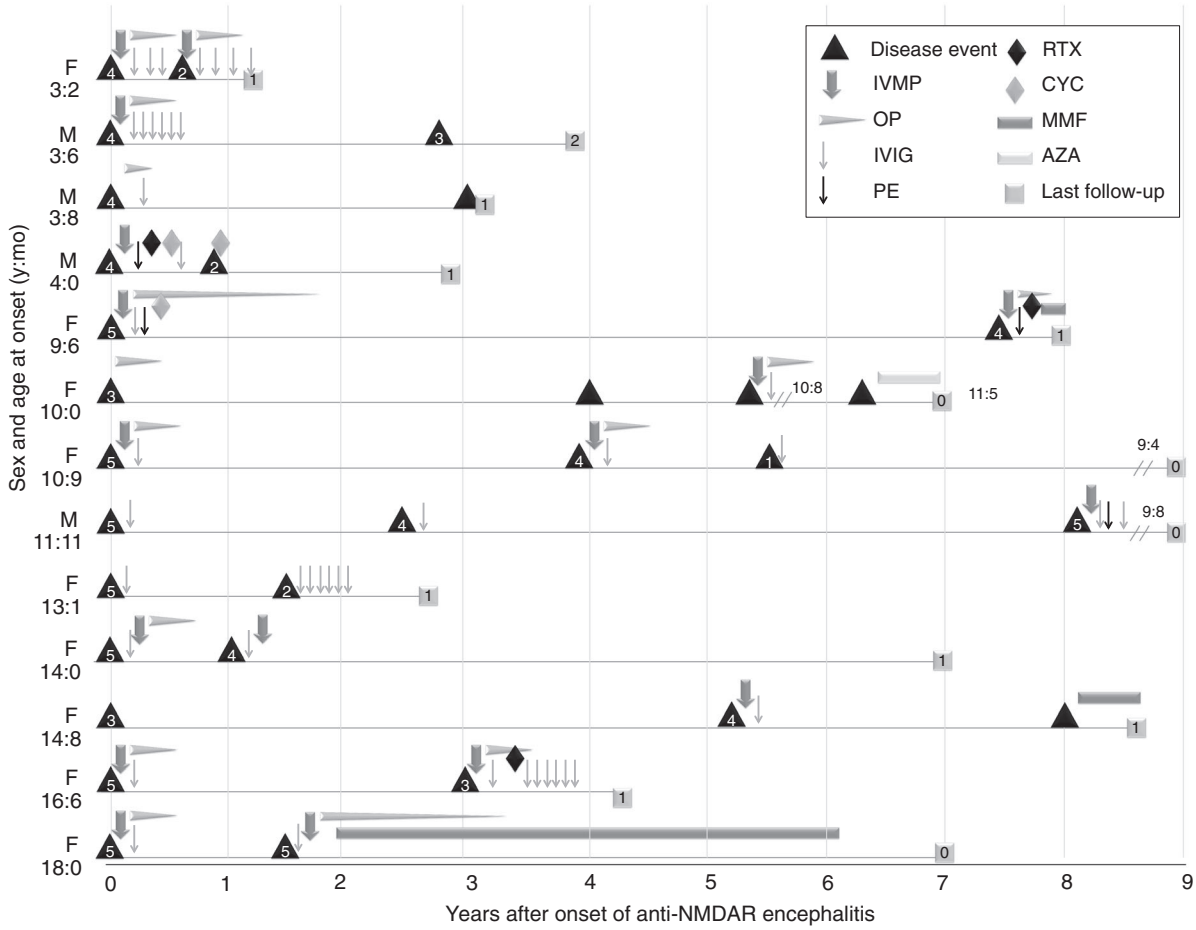

Figure 1: Disease course in 13 patients with relapsing disease. The numbers in the triangles and in the squares represent modified Rankin Scale score during the event and at last follow-up respectively. AZA, azathioprine; CYC, cyclophosphamide; F, female; IVIG, intravenous immunoglobulin; IVMP, intravenous methylprednisolone; M, male; MMF, mycophenolate mofetil; NMDAR, N-methyl-D-aspartate receptor; OP, oral prednisone; PE, plasma exchange; RTX, rituximab.

relapsing and monophasic disease (mRS 0–1 in 39/49 vs 12/13; p=0.431, Fisher's exact test).

Length of follow-up was significantly longer in the subgroup with relapsing disease (median 84mo, mean 72.6mo, range 14–137mo; data available in 13/13) than in patients with monophasic course (median 32mo, mean 34.9mo, range 4–108mo; data available in 49/49; p=0.002, Mann–Whitney U test).

DISCUSSION

We studied the Italian multicentre cohort of children with anti-NMDAR encephalitis with a focus on relapses, with the aim of identifying factors that may predict and affect the risk of disease recurrence.

While anti-NMDAR encephalitis is mostly monophasic, relapses have been described in 8 per cent to 23 per cent of paediatric patients (13/62, 21% in our cohort),[2,5,6] and factors associated with risk of recurrence have not been completely clarified yet. As previously described,[2,17] severity of relapses appeared to be slightly lower compared to disease onset, with higher frequency of ICU admission, higher median mRS score, and broader symptom expression at onset than at relapse (Table SIV). Despite this, it is noteworthy that relapses occurred over a very wide time interval, representing a strikingly long period in a child's lifetime and challenging the concept of anti-NMDAR encephalitis as a mainly monophasic disease (Fig. 1).

There has been emerging evidence in the literature suggesting a possible influence of genetic factors in the predisposition to developing anti-NMDAR encephalitis.[18,19] Hypothetically, this model could be translated into the search of 'constitutional' factors that may affect the predisposition of developing a relapsing, rather than monophasic, course in individuals with anti-NMDAR encephalitis. However, demographic factors did not differ substantially between children with monophasic or multiphasic course in our cohort (Tables I and SIII).

Early clinical data could also represent an interesting element in predicting the subsequent disease course. While differences in the type of presentation (predominantly

Table I: Analysis of survival from relapse

	Monophasic course (n=49)[a]	Relapsing course (n=13)[b]	p	HR (95% CI)
Demographics				
Year of onset 2012–2018	42	5	0.152	0.419 (0.128–1.378)
Age at onset, median; mean; range (y:mo)	9:2; 9:10; 1:4–17:10	10:10; 10:2; 3:2–18:0		
≥12y	21	6	0.220	2.049 (0.652–6.438)
Females	30	9	0.807	1.162 (0.349–3.868)
White	34	12	0.057	7.533 (0.941–60.288)
Clinical data at first event				
Changes in vigilance, hyporeactivity	41	11	0.771	0.796 (0.172–3.691)
Autonomic instability	32	9	0.661	0.762 (0.226–2.567)
mRS in the acute phase, median; mean; range	5; 4.4; 3–5	5; 4.4; 3–5		
mRS 4	9	4	0.459	1.100 (0.226–5.354)
mRS 5	29	7		2.293 (0.411–12.802)
Length of hospitalization, median; mean; range (d)	44.5; 63.2; 6–224[c]	47.5; 58.2; 20–140[d]		
Length of hospitalization ≥4wks	37/45	8/10	0.957	0.957 (0.198–4.640)
Admission to the intensive care unit	22	5	0.657	0.774 (0.250–2.393)
Investigations				
Abnormal brain MRI	27	4	0.190	0.452 (0.138–1.482)
Abnormal EEG[e]	45/48	13	0.565	2.517 (0.109–58.176)
Abnormal CSF[f]	33/44	7	0.345	0.590 (0.197–1.764)
Immune therapy at first event				
First immune therapy ≤30d from onset	35/47	6/10	0.242	0.464 (0.128–1.682)
≥3 different immune therapies	32	2	0.042[g]	0.208 (0.046–0.941)
First-line immune therapy	48	12	0.559	0.539 (0.068–4.285)
Second-line immune therapy	28	2	0.071	0.249 (0.055–1.127)
Long-term immune modulation ≥5mo	22/48	3	0.117	0.355 (0.097–1.294)
First immune therapy ≤30d AND second-line	20	1	0.067	0.148 (0.019–1.139)

For an extended version of this table see Table SIII (online supporting information). [a]All data are for 49 patients, unless otherwise indicated. [b]All data are for 13 patients, unless otherwise indicated. [c]Data available for 36/49 patients. [d]Data available for 10/13 patients. [e]Abnormal electroencephalography (EEG) was considered as presence of slow waves and/or epileptic discharges: slow waves in 49/53 (92.4%); epileptic discharges in 33/54 (61.1%). [f]Abnormal cerebrospinal fluid (CSF) was considered as presence of pleocytosis >4 cells/μL, hyperproteinorrachia >45mg/dL, and/or oligoclonal band: pleocytosis >4 cells/μL in 32/54 (59.2%); hyperproteinorrachia >45mg/dL in 8/49 (16.3%); positive oligoclonal band in 32/52 (61.5%). [g]Statistically significant. HR, hazard ratio; CI, confidence interval; mRS, modified Rankin Scale; MRI, magnetic resonance imaging.

neurological vs psychiatric) have been well associated with characteristics such as the age and sex in large cohorts,[2] the hypothesis of whether different types of presentations may provide early clues on the following course is fascinating, although it was not confirmed by our results and remains to be thoroughly explored. Regarding the florid phase of disease at onset, it is noteworthy, and somewhat counterintuitive, that disease severity did not differ substantially between patients with monophasic and relapsing course in terms of mRS score or ICU admission. Therefore, type of presentation and disease severity in the acute phase did not appear to be reliable predictors of the long-term course of children with anti-NMDAR encephalitis in our cohort. Similarly, abnormal EEG, MRI, and CSF at first disease event did not differ substantially between patients with relapsing and monophasic disease. Long-term neurological outcome (mRS) was not affected by abnormal CSF findings in a published cohort of 43 patients, although CSF data in monophasic and relapsing patients were not provided.[20] While these investigations did not prove useful in predicting the risk of relapse in our cohort, EEG remains a sensitive marker in the early phases of encephalitis,[21] and the relationship between EEG features and disease severity and course is being explored closely in the recent literature.[22–24]

With regards to treatment, relapse risk was higher in patients who did not receive immune therapy in the first episode in the cohort described by Gabilondo et al.[17] This result could not be verified in our cohort in view of the low number of patients who did not receive immune therapy at first episode, possibly given the more recent onset in our patients; although it should be noted that one of the two cases not treated at onset relapsed.

The survival analysis conducted in our cohort showed that the risk of relapsing was significantly lower in patients who received three or more different immune therapies at first disease event (hazard ratio 0.208, 95% CI 0.046–0.941; p=0.042; Table I). In this subgroup, the majority of patients received plasma exchange (20/34), and most received second-line immune therapy (30/34). The use of plasma exchange in this condition is supported by a strong rationale, and anti-NMDAR encephalitis was included in the latest guidelines on the use of therapeutic apheresis in clinical practice by the American Society for Apheresis.[25] However, the literature on the efficacy of plasma exchange compared to other treatments in anti-NMDAR encephalitis is scarce and mainly uncontrolled,[26] and the use of plasma exchange in children may be limited by the low body weight and the potential side effects, and is influenced by the expertise of the treating centres.[27] Rituximab has been shown to be useful and relatively safe in paediatric neurology, although severe adverse reactions including infections are possible;[8] its use has been increasing, as shown by our cohort, and is supported by the demonstration of CD19(+) B-cell expansion in

anti-NMDAR encephalitis.[28] These data suggest a trend towards a beneficial role of aggressive immune therapy with different types of treatments lowering the risk of relapse in paediatric anti-NMDAR encephalitis, and are consistent with previous data in the literature.[2,6]

The role of long-term immune suppression has not yet been clarified in anti-NMDAR encephalitis.[29] In our cohort, the use of long-term immune suppression was not a statistically significant protective factor for relapses. The present cohort and other literature data suggest that long-term immune suppression is currently used only in a limited proportion of cases in anti-NMDAR encephalitis, and often only after disease relapse.[29] Recent surveys have also documented a considerable heterogeneity in the approach to long-term treatment in this condition.[30] Indeed, it is unclear how long the inflammatory component of disease lasts. In this respect, the correlation between anti-NMDAR antibodies and clinical course is unclear,[31,32] and the correlation of disease severity and relapse with other markers, such as C-X-C motif chemokine ligand 13 (CXCL13), C-X-C motif ligand 10 (CXCL10), Fas, Fas ligand, T-helper cell 17 (Th17), B cell activating factor from the tumor necrosis factor family (BAFF), and a proliferation-inducing ligand (APRIL) is being investigated.[33–39]

This dissociation between disease course (monophasic vs relapsing) and neurological outcome (mRS) at final follow-up is an interesting and counterintuitive finding. This result is limited by the statistically different length of follow-up between monophasic and relapsing patients (median 84mo and 32mo respectively), although it is mirrored by a previous analysis of relapses in anti-NMDAR encephalitis, with similar discrepancies in the length of follow-up in the two subgroups.[17] In this regard, it is possible that the good outcome generally associated to anti-NMDAR encephalitis (in the earlier cases, sometimes even without immune therapy) is retained also in case of subsequent disease relapses. On the other hand, most of the available data on outcome in relapsing patients is based on neurological scores (i.e. mRS) that are probably not ideal for detecting non-motor sequelae, such as neuropsychological sequelae. Recently, a score that predicts 1-year functional status in patients with anti-NMDAR encephalitis has been proposed, although it does not take into consideration relapsing versus monophasic disease.[40]

Limitations

The main limitations of our work are the restricted number of patients and the retrospective design, which accounted for the heterogeneous availability of data. Neuroimaging and neurophysiologic data were not reviewed centrally, impeding a more accurate description of EEG and MRI abnormalities detected. Moreover, CSF neuroinflammatory biomarkers were inconsistently available, and data on newer markers whose utility has been suggested in the literature, such as neopterins and cytokines, were not collected.[32–34,41] The study of these markers with regards to disease course and the occurrence of relapses would be of utmost clinical interest. Moreover, the correlation of relapses and outcome was limited by the very different length of follow-up in patients with relapsing and monophasic disease, and may have been affected by the intrinsic limitations of the coarse neurological score used (mRS), which is not ideal to detect non-motor manifestations and neuropsychological sequelae.[42–44]

CONCLUSION

Despite these limitations, the present study focuses on a not fully understood aspect of paediatric anti-NMDAR encephalitis, disclosing modifiable treatment-related factors that may affect the disease course in these patients. In particular, the use of aggressive 'multimodal' therapies at first disease event was a protective factor for relapsing in our cohort, suggesting the utility of lowering the threshold for use of combined and second-line agents, although a tailored and risk versus benefit approach should always be adopted. The identification of clinical, paraclinical, or treatment factors in the early stages of disease that could correlate with higher risk of recurrence may assist and guide appropriate counselling, disease monitoring, and support the use of a more targeted aggressive immune suppression.

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SUPPORTING INFORMATION

The following additional material may be found online:

Appendix S1: Members of the Italian Working Group on paediatric anti-N-methyl-D-aspartate receptor encephalitis.

Appendix S2: Data on two patients in whom tumour was detected at relapse.

Appendix S3: Data on neurological outcome at follow-up.

Appendix S4: Data on one patient with the longest time span between onset and last relapse.

Table SI: Demographics, data in the acute phase (relative to the first event), disease course, and outcome in the whole population

Table SII: Demographics, data in the acute phase of anti-NMDAR encephalitis, disease course, and outcome in the subset of patients with anti-NMDAR encephalitis preceded by viral encephalitis

Table SIII: Analysis of survival from relapse (full version)

Table SIV: Clinical data, mRS, and rate of admission to the ICU at first and second event in patients with relapsing anti-NMDAR encephalitis

Figure S1: Survival from relapses (survival analysis).

REFERENCES

1. Dalmau J, Tüzün E, Wu HY, et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. *Ann Neurol* 2007; **61**: 25–36.
2. Titulaer MJ, McCracken L, Gabilondo I, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. *Lancet Neuro* 2013; **12**: 157–65.
3. Graus F, Titulaer MJ, Balu R, et al. A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol* 2016; **15**: 391–404.
4. Mohammad SS, Jones H, Hong M, et al. Symptomatic treatment of children with anti-NMDAR encephalitis. *Dev Med Child Neurol* 2016; **58**: 376–84.
5. Wright S, Hacohen Y, Jacobson L, et al. N-methyl-D-aspartate receptor antibody-mediated neurological disease: results of a UK-based surveillance study in children. *Arch Dis Child* 2015; **100**: 521–6.
6. Nosadini M, Mohammad SS, Ramanathan S, Brilot F, Dale RC. Immune therapy in autoimmune encephalitis: a systematic review. *Expert Rev Neurother* 2015; **15**: 1391–419.
7. Irani SR, Bera K, Waters P, et al. N-methyl-D-aspartate antibody encephalitis: temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes. *Brain* 2010; **133**: 1655–67.
8. Dale RC, Brilot F, Duffy LV, et al. Utility and safety of rituximab in pediatric autoimmune and inflammatory CNS disease. *Neurology* 2014; **83**: 142–50.
9. Hacohen Y, Absoud M, Hemingway C, et al. NMDA receptor antibodies associated with distinct white matter syndromes. *Neurol Neuroimmunol Neuroinflamm* 2014; **1**: e2.
10. Ho ACC, Mohammad SS, Pillai SC, et al. High sensitivity and specificity in proposed clinical diagnostic criteria for anti-N-methyl-D-aspartate receptor encephalitis. *Dev Med Child Neurol* 2017; **59**: 1256–60.
11. Sartori S, Nosadini M, Cesaroni E, et al. Paediatric anti-N-methyl-D-aspartate receptor encephalitis: the first Italian multicenter case series. *Eur J Paediatr Neurol* 2015; **19**: 453–63.
12. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1988; **19**: 604–7.
13. Liu CY, Zhu J, Zheng XY, Ma C, Wang X. Anti-N-methyl-d-aspartate receptor encephalitis: a severe, potentially reversible autoimmune encephalitis. *Mediators Inflamm* 2017; **2017**: 6361479.
14. Armangue T, Titulaer MJ, Málaga I, et al. Pediatric anti-N-methyl-D-aspartate receptor encephalitis-clinical analysis and novel findings in a series of 20 patients. *J Pediatr* 2013; **162**: 850–6.e2.
15. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. *Control Clin Trials* 1996; **17**: 343–6.
16. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. *J Clin Epidemiol* 1996; **49**: 1373–9.
17. Gabilondo I, Saiz A, Galán L, et al. Analysis of relapses in anti-NMDAR encephalitis. *Neurology* 2011; **77**: 996–9.
18. Jones HF, Mohammad SS, Reed PW, et al. Anti-N-methyl-d-aspartate receptor encephalitis in Māori and Pacific Island children in New Zealand. *Dev Med Child Neurol* 2017; **59**: 719–24.
19. Mueller SH, Färber A, Prüss H, et al. Genetic predisposition in anti-LGI1 and anti-NMDA receptor encephalitis. *Ann Neurol* 2018; **83**: 863–9.
20. Wang R, Guan HZ, Ren HT, Wang W, Hong Z, Zhou D. CSF findings in patients with anti-N-methyl-D-aspartate receptor-encephalitis. *Seizure* 2015; **29**: 137–42.
21. Nosadini M, Boniver C, Zuliani L, et al. Longitudinal electroencephalographic (EEG) findings in pediatric anti-N-methyl-D-aspartate (anti-NMDA) receptor encephalitis: the Padua experience. *J Child Neurol* 2015; **30**: 238–45.
22. Mohammad SS, Soe SM, Pillai SC, et al. Etiological associations and outcome predictors of acute electroencephalography in childhood encephalitis. *Clin Neurophysiol* 2016; **127**: 3217–24.
23. Zhang Y, Liu G, Jiang MD, Li LP, Su YY. Analysis of electroencephalogram characteristics of anti-NMDA receptor encephalitispatients in China. *Clin Neurophysiol* 2017; **128**: 1227–33.
24. Sonderen AV, Arends S, Tavy DLJ, et al. Predictive value of electroencephalography in anti-NMDA receptor encephalitis. *J Neurol Neurosurg Psychiatry* 2018; **89**: 1101–6.
25. Schwartz J, Padmanabhan A, Aqui N, et al. Guidelines on the use of therapeutic apheresis in clinical practice-evidence-based approach from the Writing Committee of the American Society for Apheresis: the seventh special issue. *J Clin Apher* 2016; **31**: 149–62.
26. Eyre M, Hacohen Y, Barton C, Hemingway C, Lim M. Therapeutic plasma exchange in paediatric neurology: a critical review and proposed treatment algorithm. *Dev Med Child Neurol* 2018; **60**: 765–79.
27. Suppiej A, Nosadini M, Zuliani L, et al. Plasma exchange in pediatric anti-NMDAR encephalitis: a systematic review. *Brain Dev* 2016; **38**: 613–22.
28. Dale RC, Pillai S, Brilot F. Cerebrospinal fluid CD19 (+) B-cell expansion in N-methyl-D-aspartate receptor encephalitis. *Dev Med Child Neurol* 2013; **55**: 191–3.
29. Nosadini M, Mohammad SS, Toldo I, Sartori S, Dale RC. Mycophenolate mofetil, azathioprine and methotrexate usage in paediatric anti-NMDAR encephalitis: a systematic literature review. *Eur J Paediatr Neurol* 2019; **23**: 7–18.
30. Bartolini L, Muscal E. Differences in treatment of anti-NMDA receptor encephalitis: results of a worldwide survey. *J Neurol* 2017; **264**: 647–53.
31. Zandi MS, Paterson RW, Ellul MA, et al. Clinical relevance of serum antibodies to extracellular N-methyl-D-aspartate receptorepitopes. *J Neurol Neurosurg Psychiatry* 2015; **86**: 708–13.
32. Mariotto S, Andreetta F, Farinazzo A, Monaco S, Ferrari S. Persistence of anti-NMDAR antibodies in CSF after recovery from autoimmune encephalitis. *Neurol Sci* 2017; **38**: 1523–4.
33. Leypoldt F, Höftberger R, Titulaer MJ, et al. Investigations on CXCL13 in anti-N-methyl-D-aspartate receptor encephalitis: a potential biomarker of treatment response. *JAMA Neurol* 2015; **72**: 180–6.
34. Kothur K, Wienholt L, Mohammad SS, et al. Utility of CSF cytokine/ chemokines as markers of active intrathecal inflammation: comparison of demyelinating, anti-NMDAR and enteroviral encephalitis. *PLoS ONE* 2016; **11**: e0161656.
35. Kothur K, Gill D, Wong M, et al. Cerebrospinal fluid cyto-/ chemokine profile during acute herpes simplex virus induced anti-N-methyl-D-aspartate receptor encephalitis and in chronic neurological sequelae. *Dev Med Child Neurol* 2017; **59**: 806–14.
36. Liba Z, Kayserova J, Elisak M, et al. Anti-N-methyl-D-aspartate receptor encephalitis: the clinical course in light of the chemokine and cytokine levels in cerebrospinal fluid. *J Neuroinflammation* 2016; **13**: 55.
37. Deng B, Liu XN, Li X, Zhang X, Quan C, Chen XJ. Raised cerebrospinal fluid BAFF and APRIL levels in anti-N-methyl-d-aspartate receptor encephalitis: correlation with clinical outcome. *J Neuroimmunol* 2017; **305**: 84–91.
38. Ding YW, Pan SY, Xie W, Shen HY, Wang HH. Elevated soluble Fas and FasL in cerebrospinal fluid and serum of patients with anti-N-methyl-D-aspartate receptor encephalitis. *Front Neurol* 2018; **9**: 904.
39. Zeng C, Chen L, Chen B, et al. Th17 cells were recruited and accumulated in the cerebrospinal fluid and correlated with the poor prognosis of anti-NMDAR encephalitis. *Acta Biochim Biophys Sin (Shanghai)* 2018; **50**: 266–73.
40. Balu R, McCracken L, Lancaster E, Graus F, Dalmau J, Titulaer MJ. A score that predicts 1-year functional status in patients with anti-NMDA receptor encephalitis. *Neurology* 2019; **92**: e244–52.
41. Dale RC, Brilot F, Fagan E, Earl J. Cerebrospinal fluid neopterin in paediatric neurology: a marker of active central nervous system inflammation. *Dev Med Child Neurol* 2009; **51**: 317–23.
42. Matricardi S, Patrini M, Freri E, et al. Cognitive and neuropsychological evolution in children with anti-NMDAR encephalitis. *J Neurol* 2016; **263**: 765–71.
43. Cainelli E, Nosadini M, Sartori S, Suppiej A. Neuropsychological and psychopathological profile of anti-Nmdar encephalitis: a possible pathophysiological model for pediatric neuropsychiatric disorders. *Arch Clin Neuropsychol* 2018 Nov 12. https://doi.org/10.1093/arclin/acy088. [Epub ahead of print].
44. de Bruijn MAAM, Aarsen FK, van Oosterhout MP, et al. Long-term neuropsychological outcome following pediatric anti-NMDAR encephalitis. *Neurology* 2018; **90**: e1997–2005.