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EARLIER TREATMENT OF NMDAR ANTIBODY ENCEPHALITIS IN CHILDREN RESULTS IN A BETTER OUTCOME

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The natural history of NMDA receptor (NMDAR) antibody encephalitis in adults and children is altered by treatment with immunosuppressive therapy or tumor removal.¹ In adult cohorts, early initiation of immunotherapy appears to be beneficial.^{1,2} In the largest series to date, Titulaer et al.¹ demonstrated that earlier treatment was associated with a modified Rankin Scale (mRS) score of 2 or less in a cohort of 501 adults and children (univariate analysis $p = 0.009$, multivariable analysis $p < 0.0001$). Multivariable analysis on 177 children within the cohort showed that earlier treatment was associated with an mRS score of 2 or less, although this did not reach statistical significance ($p = 0.067$).¹ An mRS score of 2 indicates slight disability and that the patient is unable to carry out all previous activities.

We performed a literature review of all first presentation cases of pediatric NMDAR antibody encephalitis to determine whether early treatment with immunomodulatory therapy is associated with a better outcome (see search criteria in appendix e-1 at Neurology.org/nn).

From 43 articles identified (appendix e-1, figure e-1), information was available on 80 children ≤ 17 years of age (56 female, median age 8 years, interquartile range [IQR] 4–14 years, range 1.3–17 years) reported across 34 articles with care from at least 34 institutions (table e-1). We dichotomized outcome into complete recovery (pediatric mRS score = 0) or incomplete recovery (mRS score ≥ 1).

Fifty-seven percent (41) received IV steroids as the first agent, 11.3% (9) received IV immunoglobulin (IVIg), 28.7% (23) had IVIg and methylprednisolone simultaneously, 2 children had tumor removal, and 5 children had no treatment (appendix e-1).

At follow-up (median 12 months, IQR 4.5–24 months, range 1.3–54 months), 33 (41%) children had recovered completely (mRS score = 0), whereas 47 (59%) children had an incomplete recovery (mRS score ≥ 1) based on evaluation by their treating physicians and/or families. There was no difference in median time to follow-up or median age at onset

between children who recovered fully and those who did not (see table 1). There was no difference in median mRS score at nadir between children who made a full recovery (mRS score 5, IQR 4–5, range 3–5) and children who made an incomplete recovery (mRS score 4, IQR 3–5, range 3–5) ($p = 0.2$).

The important finding from this review is that the median time from symptom onset to initiation of treatment was 15 days (IQR 7–21 days, range 3–182 days) in children who recovered completely (mRS score = 0) and 21 days (IQR 15–40 days, range 5–365 days) in those who had not recovered completely at follow-up ($p = 0.014$, Wilcoxon Mann-Whitney nonparametric test).

We illustrate the direct correlation between outcome and days to initiation of treatment as a box plot (see figure e-2).

Discussion. Our retrospective review suggests that earlier treatment of NMDAR antibody encephalitis in children results in better outcomes. This is consistent with a previous report by Titulaer et al.¹ In our study, children who recovered completely at follow-up (mRS score = 0) were treated a median of 15 days from symptom onset vs 21 days in children who did not completely recover. The median time of follow-up was 1 year in all patients, and because recovery from NMDAR antibody encephalitis can be very slow and take 18 months or longer,¹ some patients may recover further. As such, our data may simply reflect an earlier recovery, which nevertheless may have a large benefit on quality of life and educational attainment. Although NMDAR antibody has been shown to mediate its effect by receptor internalization, which is reversible,³ factors such as the extent of secondary disturbance in synaptogenesis as a result of NMDAR binding by antibodies,⁴ manifesting as persisting functional and structural advanced MRI changes,⁵ may exert a larger influence on the developing CNS.

There are limitations to this study. First, selection bias may arise from reporting bias and the subsequent limited author response allowing analysis of only 80 of the potential 300 cases. Single cases are often published because of atypical features, and our study included 23 case reports. Second, 29 of the 80 patients were diagnosed on serum analysis alone, which

Supplemental data
at Neurology.org/nn

Table 1 Comparison of the clinical features between children who recovered completely and those who did not

	Complete recovery at follow-up (n = 33)	Incomplete recovery at follow-up (n = 47)	p Value
Median time of follow-up, mo (IQR)	12 (5-24)	12 (4-24)	0.864
Range, mo	2-54	1.3-36	
Median age at symptom onset, y (IQR)	9 (3.4-14)	8 (5-13)	0.791
Range, y	2.3-17	1.3-16	
Median mRS score at nadir (IQR)	5 (4-5)	4 (3-5)	0.2
Range	3-5	3-5	
Percentage in each group given empiric therapy	89	73	0.175
Median time from symptom onset to treatment, d (IQR)	15 (7-21)	21 (15-40)	0.014 ^a
Range, d	3-182	5-365	
Number of therapies required to induce remission, % (n)			0.968
1	25 (8)	9.5 (4)	
2	40.6 (13)	54.8 (23)	
3	25 (8)	21.4 (9)	
4 or more	9.4 (3)	14.3 (6)	
Median mRS score at follow-up (IQR)	0 (0-0)	2 (1-3)	
Range	0-0	1-5	

Abbreviations: IQR = inter quartile range; mRS = modified Rankin Scale.

^a Significant value.

may yield false-positive results⁶; however, patients included in this study did have a clinical phenotype compatible with NMDAR encephalitis. Third, the outcome is dichotomous—the mRS was designed to describe outcomes in the context of stroke in adults, focusing primarily on physical deficits, and is not a sensitive marker of cognitive deficits.

Prospective longitudinal studies addressing these limitations will be required to confirm whether earlier treatment results in better measurable outcomes.

Early recognition of the variable symptoms of NMDAR antibody encephalitis and more widespread availability of rapid diagnostic tests⁷ will facilitate early initiation of optimal therapy, although empiric therapy may be warranted when children have clinical manifestations that are consistent with NMDAR and other autoimmune encephalitis.

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