

# Long-term neuropsychological outcome following pediatric anti-NMDAR encephalitis

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*Neurology*® 2018;90:e1997-e2005. doi:10.1212/WNL.0000000000005605

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## Abstract

### Objective

To provide detailed long-term outcome data of children and adolescents following pediatric anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis, to identify neuropsychological impairments, and to evaluate the influence of these factors on quality of life (QoL).

### Methods

All Dutch children diagnosed with anti-NMDAR encephalitis were identified. Patients currently aged 4 years or older were included in the follow-up study, consisting of a visit to our clinic for a detailed interview and a standardized neuropsychological assessment. The following domains were included: attention, memory, language, executive functioning, QoL, and fatigue. Primary outcome measures were *z* scores on sustained attention, long-term verbal memory, QoL, fatigue, and working memory.

### Results

Twenty-eight patients were included. Median Pediatric Cerebral Performance Category at last visit was 1 (interquartile range 1–2, range 1–4), and 64% (18/28) of patients returned consistently to their previous school level. Twenty-two patients were included in the cross-sectional part of the long-term follow-up study. Median follow-up time was 31 months (interquartile range 15–49, range 5–91). There were problems with sustained attention ( $z = -2.10$ , 95% confidence interval =  $-2.71$  to  $-1.46$ ,  $p < 0.0001$ ) and fatigue ( $z = -0.96$ , 95% confidence interval =  $-1.64$  to  $-0.28$ ,  $p = 0.008$ ). Cognitive deficits were not correlated with QoL, while fatigue was strongly correlated with QoL ( $r = 0.82$ ,  $p < 0.0001$ ).

### Conclusions

Although follow-up is often reported as “good” following pediatric anti-NMDAR encephalitis, many patients have cognitive problems and fatigue, even up until adolescence, resulting in academic achievement problems and lower QoL. For physicians, it is essential to be aware of these problems, to provide valuable advice to patients and caregivers in the acute and follow-up phase, and to consider early neuropsychological counseling.

## Podcast

Dr. David Lapidés talks with Dr. Maarten Titulaer about his paper on neuropsychological outcome following pediatric anti-NMDAR encephalitis.

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Go to [Neurology.org/N](http://Neurology.org/N) for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

The Article Processing Charge was funded by Erasmus University.

CHANCE Study Group coinvestigators are listed at [links.lww.com/WNL/A496](http://links.lww.com/WNL/A496)

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## Glossary

**anti-NMDAR** = anti-*N*-methyl-d-aspartate receptor; **BRIEF** = Behavior Rating Inventory of Executive Function; **CANTAB** = Cambridge Neuropsychological Test Automated Battery; **HSV** = herpes simplex virus; **ICU** = intensive care unit; **IQR** = interquartile range; **mRS** = modified Rankin Scale; **PedsQL** = Pediatric Quality of Life; **PedsQL-MFS** = Pediatric Quality of Life Multidimensional Fatigue Scale; **PCPC** = Pediatric Cerebral Performance Category; **QoL** = quality of life; **RAVLT** = Rey Auditory Verbal Learning Test.

Anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is an autoimmune disorder, initially described in 2007.<sup>1</sup> Increased awareness has led to more frequent diagnoses, and currently more than 1,000 patients have been reported, of whom 35% are children.<sup>2</sup> The disease course can be severe, with intensive care unit (ICU) admission in 75% of children. Nevertheless, if treated with adequate immunotherapy, outcome is considered favorable in 85% of children.<sup>2</sup>

However, there are signals that actual recovery might be less positive than initially reported. Small studies in both adults and children describe substantial deficits in multiple cognitive domains and also behavioral problems.<sup>3–9</sup> Given these findings, it seems that despite apparent good outcome, full neuropsychological recovery is certainly not always achieved.

Functioning can be studied from different perspectives,<sup>10</sup> including activities and participation. Outcome of anti-NMDAR encephalitis is currently measured in terms of activities with relatively crude measures, such as the modified Rankin Scale (mRS),<sup>11</sup> while participation and quality of life (QoL) are also of major importance, especially in children and adolescents. Neuropsychological deficits can seriously affect participation and career choices as transition into adulthood might call for full cognitive abilities.

Therefore, the aim of this nationwide Dutch cohort study was to provide more insight into long-term outcome following pediatric anti-NMDAR encephalitis, with special emphasis on neuropsychological outcome, and to evaluate whether these neuropsychological factors influence QoL.

## Methods

### Patients

The Departments of Neurology and Pediatric Neurology of the Erasmus University Medical Center–Sophia Children’s Hospital, Rotterdam, the Netherlands, are national referral sites for patients with suspected autoimmune encephalitis. In addition, the Department of Immunology is the national referral site for antineuronal antibody testing of samples from patients with suspected autoimmune encephalitis. Therefore, we had the opportunity to identify all Dutch children diagnosed with anti-NMDAR encephalitis, from January 2008 until March 2017, aged 0 to 18 years at disease onset. NMDAR antibodies were confirmed in serum and/or CSF by both commercial cell-based assay and immunohistochemistry.

### Clinical information

Data about disease course were obtained from medical records and from detailed interviews with patients and caregivers during a visit to our clinic. Neurologic level of function was determined using the Pediatric Cerebral Performance Category (PCPC) scale (table e-1, [links.lww.com/WNL/A495](https://links.lww.com/WNL/A495)).<sup>12</sup>

### Standard protocol approvals, registrations, and patient consents

The institutional review board of the Erasmus University Medical Center approved the study protocol. Informed consent was obtained from adult patients and for children from their parents, and if applicable, also from children aged 12 to 18 years.

### Cross-sectional follow-up study

All patients currently aged 4 years or older were approached to participate in the follow-up study, as neuropsychological testing and the questionnaires required a minimal age for participation. Patients were invited for a visit to our clinic, in which current complaints and level of functioning were discussed. In addition, patients underwent a standardized neuropsychological assessment. If a visit was not possible, current problems were discussed by phone, and questionnaires were sent to us by mail and checked in additional calls if necessary.

### Neuropsychological assessment

The neuropsychological assessment consisted of a selection of the Cambridge Neuropsychological Test Automated Battery (CANTAB Research Suite 6.0, Cambridge Cognition Ltd., Cambridge, UK), additional neuropsychological tests, and questionnaires (table e-2, [links.lww.com/WNL/A495](https://links.lww.com/WNL/A495)). Tests and questionnaires were selected based on our own experiences and on disorders found in prior studies, were administered in their Dutch versions, and are reliable and validated in the Netherlands. The tests and questionnaires were administered to assess skills in 6 domains:

1. Attention: Reaction Time (CANTAB), Dutch Dot Cancellation Test (Bourdon-Vos).<sup>13</sup>
2. Memory: Paired Associated Learning (CANTAB), Rey Auditory Verbal Learning Test (RAVLT).<sup>14</sup>
3. Language: Boston Naming Test,<sup>15</sup> Token Test.<sup>16</sup>
4. Executive functioning: Intra-Extra Dimensional Set Shift, Spatial Span, Stockings of Cambridge (all CANTAB), Word Generation (NEPSY-II [A Developmental Neuropsychological Assessment, Second Edition]),<sup>17</sup> Behavior

Rating Inventory of Executive Function (BRIEF–Self-Report and BRIEF–Adult) questionnaire,<sup>18</sup> Strength and Difficulties Questionnaire (self-report and parent-proxy report).<sup>19</sup>

5. QoL: Pediatric Quality of Life Inventory 4.0 (PedsQL Self-Report and PedsQL Parent Proxy-Report).<sup>20</sup>
6. Fatigue: PedsQL Multidimensional Fatigue Scale questionnaire (PedsQL-MFS Self-Report and PedsQL-MFS Parent Proxy-Report).<sup>21</sup>

## Statistical analysis

For group comparisons, we used the Mann-Whitney *U* test (age), Fisher exact test (sex, immunotherapy), Fisher-Freeman-Halton extension (PCPC), and the Kruskal-Wallis one-way analysis of variance (character profiles). Results of neuropsychological assessments were compared with normative data of healthy individuals, corrected for age, sex, and educational level. Normative data for the CANTAB were obtained by CANTAB, Cambridge, UK. Scores were converted into standardized *z* scores for comparison. For statistics, *z* scores were set on minimum of –3 and maximum of +3 to prevent statistical differences by outliers (winsorization). In the graphs, the uncorrected *z* scores are shown, but corrected *z* scores were used for statistics. Displayed correlations were also calculated with corrected *z* scores. The *z* scores were analyzed using a one-sample *t* test (test value = 0). Primary outcome measures were sustained attention (Dutch Dot Cancellation Test–attention fluctuations), long-term verbal memory (RAVLT–Delayed Recall), fatigue (PedsQL-MFS Self-Report–Total Score), QoL (PedsQL Self-Report–Total Score), and working memory (BRIEF–Self-Report–Working Memory). Primary outcome measures were considered significant if *p* < 0.017 (Bonferroni). For the secondary outcome measures of the neuropsychological assessment, *p* values < 0.005 were considered significant. Values between 0.005 and 0.05 should be interpreted carefully and considered exploratory. The relationship between our primary outcome measures and QoL were computed with a two-sided Pearson correlation coefficient. SPSS version 21.0 (IBM Corp., Armonk, NY) was used for statistical analyses, as well as GraphPad Prism 7 (GraphPad Software, La Jolla, CA) for Windows.

## Data availability

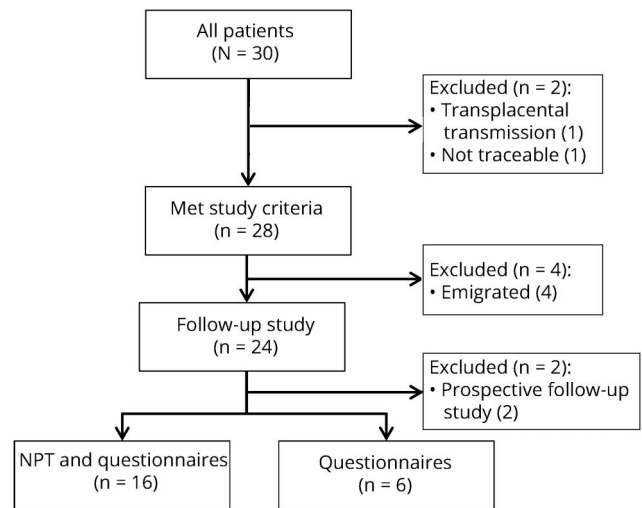
Any data not published within this article are available at Erasmus University Medical Center. Patient-related data will be shared on request from any qualified investigator, maintaining anonymization of the individual patients.

## Results

### Clinical characteristics

Thirty children were identified, of whom 28 were included (for patient selection, see figure 1). Twenty-one patients were female (75%), mainly in those aged 12 years or older (89%). Median age at onset was 14 years. Eighteen patients (64%)

**Figure 1** Flowchart of patient selection



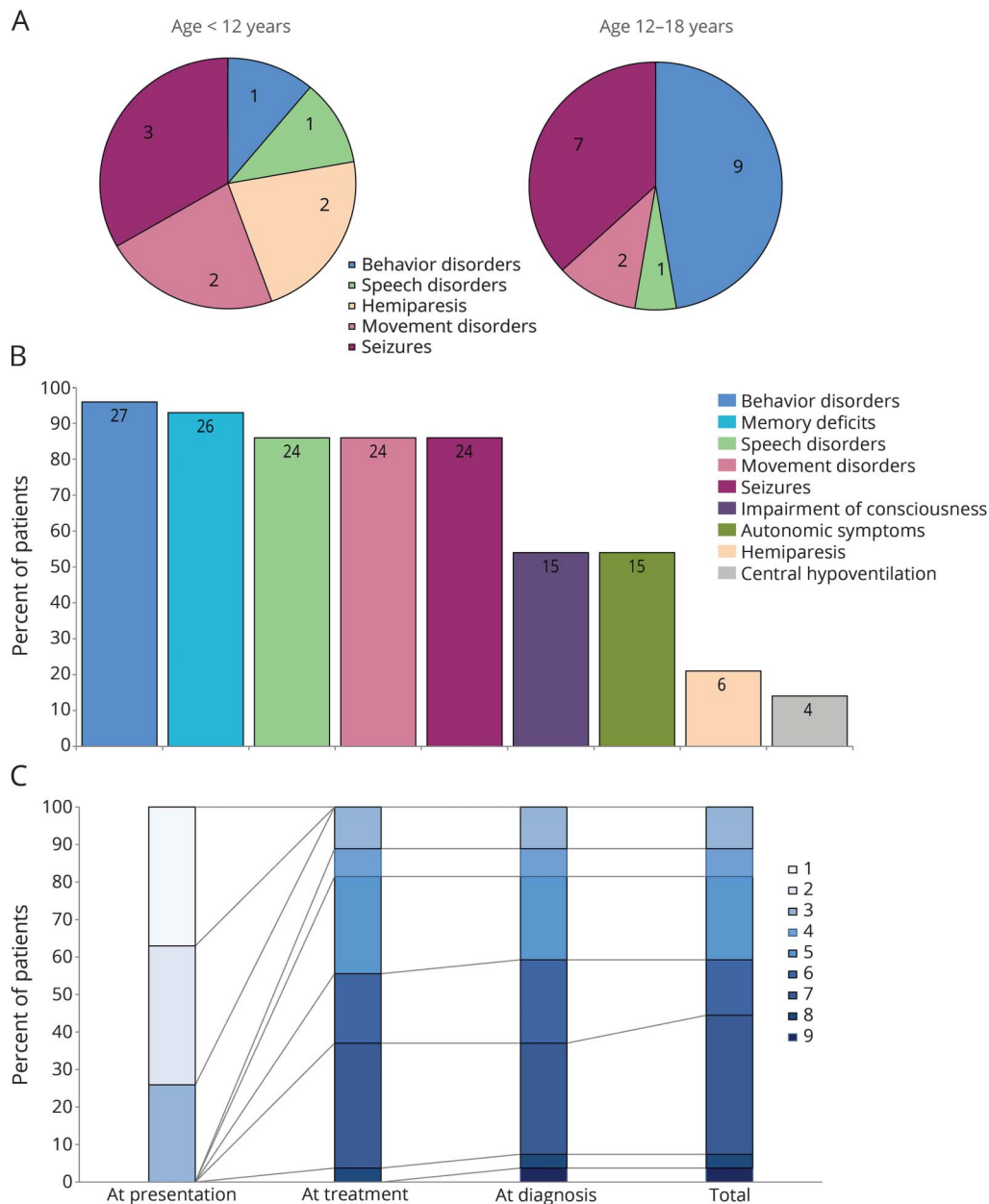
One patient was excluded because he was younger than 4 years (transplacental transmission of anti-N-methyl-D-aspartate receptor),<sup>31</sup> and one patient was untraceable. Twenty-four patients participated in the follow-up study, of whom 2 are followed prospectively. Sixteen of the 22 participants completed the full neuropsychological assessment, 6 patients only completed the questionnaires, 3 visited our clinic, and 3 were contacted by phone because of geographical distance. NPT = neuropsychological testing.

reported a prodromal phase, including headache, blurred vision, or upper respiratory infection. Three children (11%) developed anti-NMDAR encephalitis 3 to 7 weeks after a herpes simplex virus (HSV) type 1 encephalitis. In addition to those 3, one patient had a preexistent mild psychomotor developmental delay. The others were healthy before disease onset.

Most children presented with behavioral disorders (36%) or seizures (36%), less frequently with speech disorders and movement disorders. In 2 of 28 patients (7%), hemiparesis was the presenting symptom, only occurring in children younger than 12 years (figure 2A). All patients presented to the initial physician with a maximum of 3 symptoms, while at maximum disease severity, 21 patients had developed more than 4 symptoms (figure 2, B and C). The numbers of symptoms between treatment and diagnosis were often comparable. Four patients developed one additional symptom after start of treatment, i.e., hypoventilation (*n* = 3) and bradycardia (*n* = 1). One patient developed seizures after diagnosis but before treatment, with a delay between diagnosis and treatment of 2 days (patient 16). One patient developed seizures 3 days after diagnosis and 9 days after initiation of treatment (patient 9).

Median time from symptom onset to maximum PCPC (maximum disease severity) was 30 days. Forty-six percent of patients (13/28) were treated in the ICU with a median stay of 13 days. Total hospital stay was more than a month in 78% of patients. All patients were treated with first-line immunotherapy. Forty-six percent of patients received either

**Figure 2** Patient symptoms



(A) Distribution of presenting symptoms of patients younger than 12 years and of patients aged 12–18 years. (B) Cumulative symptoms during disease course. (C) Number of core symptoms at presentation, treatment, and antibody diagnosis, and total number of symptoms.

rituximab ( $n = 12$ ) or cyclophosphamide ( $n = 1$ ). In 14 of 28 patients (50%), treatment was started before diagnosis, in 6 of 28 patients (21%), treatment was initiated on the day of diagnosis, and in 8 of 28 patients (29%), treatment was started after diagnosis. For all clinical characteristics, see table 1 and supplemental material ([links.lww.com/WNL/A493](https://links.lww.com/WNL/A493)).

### Outcome

Three patients had a relapse 3, 5, and 35 months after first symptoms. One patient had a higher PCPC during the relapse than during the initial disease episode, leading to the initiation of rituximab. At hospital discharge, the median PCPC was 3

(interquartile range [IQR] 2–3, range 1–4). Seventeen patients were discharged home, although 10 concurrently started with an outpatient rehabilitation program. Eleven patients (39%) were transferred directly to an inpatient rehabilitation center. Median rehabilitation time was 98 days (IQR 58–194, range 34–578). The median PCPC at last visit was 1 (IQR 1–2, range 1–4). Twenty-six patients (93%) resumed school after admission or rehabilitation. In 6 of the 26 patients (23%) who resumed school, the current educational level was lower, including 5 patients with special educational needs. During follow-up, 3 patients stopped school prematurely because of fatigue ( $n = 2$ ) or anxiety ( $n = 1$ ). Overall,

**Table 1** Patient characteristics

Sex, female	21/28 (75)
Age <12 y	4/9 (44)
Age ≥12 y	17/19 (89)
Age at onset, y	14 (7–17; 1–17)
Prodromal phase	18/28 (64)
Days to start of treatment	21 (9–65; 3–510)
Days to antibody diagnosis	27 (13–61; 13–184)
Days to maximum disease severity	30 (15–43; 2–94)
<b>Maximum PCPC</b>	
3: Moderate disability	1/28 (4)
4: Severe disability	16/28 (57)
5: Coma/vegetative state	11/28 (39)
ICU stay, d	13 (4–34; 1–45)
Hospital stay, d	55 (33–67; 3–141)
MRI abnormal <sup>a</sup>	10/27 (37)
CSF abnormal <sup>a</sup>	21/27 (78)
EEG abnormal at presentation <sup>a</sup>	26/27 (96)
Ovarian teratoma suspected	4/21 (19) <sup>b</sup>
First-line IT	28/28 (100)
Methylprednisolone	27/28 (96)
Plasmapheresis	6/28 (21)
Immunoglobulins	21/28 (75)
Interval between first- and second-line IT, d	18 (14–41; 6–200)
Second-line IT	13/28 (46)
Rituximab	12/28 (43)
Cyclophosphamide	1/28 (4)
Cell-based assay anti-NMDAR serum <sup>a,c</sup>	16/24 (67)
Cell-based assay anti-NMDAR, CSF <sup>a</sup>	27/27 (100)

Abbreviations: anti-NMDAR = anti-N-methyl-D-aspartate receptor; ICU = intensive care unit; IT = immunotherapy; PCPC = pediatric cerebral performance category.

Data are n/n (%) or median (interquartile range; range).

<sup>a</sup> Additional details are shown online.

<sup>b</sup> For girls ≥12 years: 4/19 (21%). All 4 girls underwent resection; 3 had a teratoma, one a follicle cyst.

<sup>c</sup> In one patient, only serum was available; cell-based assay, immunohistochemistry, and live neurons were all positive.

18 of 28 patients (64%) returned consistently to their previous school level.

### Cross-sectional follow-up study

Twenty-two patients participated in the follow-up study, with a median follow-up time after symptom onset of 31 months (IQR 15–49, range 5–91). Nineteen were seen at our clinic, while 3 had an interview by phone. All 22 patients completed

questionnaires, while 16 patients completed the full neuropsychological assessment (figure 1). Individual information is shown online in table e-3 ([links.lww.com/WNL/A495](https://links.lww.com/WNL/A495)). Median age at last visit was 17 years (IQR 12–19, range 4–25). Three patients had post-HSV encephalitis anti-NMDAR encephalitis, 2 with a follow-up PCPC of 3 (patients 14 and 18) and 1 with a PCPC of 4 (patient 19). One patient had a PCPC of 4 because of spasticity and vocal cord paralysis (patient 6).

### Neuropsychological outcome

Characteristics of the 16 patients who underwent full neuropsychological assessment were similar to those of the other patients (n = 13; table e-4, [links.lww.com/WNL/A495](https://links.lww.com/WNL/A495)). Patients had lower sustained attention scores ( $z = -2.10$ ,  $p_{\text{uncorrected}} < 0.0001$ ; table 2), and these were consistent among almost all patients. The mean score on long-term verbal memory tended to be lower ( $z = -0.68$ ,  $p_{\text{uncorrected}} = 0.031$ ). Patients reported more fatigue ( $z = -0.96$ ,  $p_{\text{uncorrected}} = 0.008$ ), and QoL tended to be lower ( $z = -0.87$ ,  $p_{\text{uncorrected}} = 0.032$ ), while working memory was not different ( $z = 0.24$ ,  $p_{\text{uncorrected}} = 0.23$ ). Results were similar when the 3 patients with anti-NMDAR encephalitis post HSV encephalitis were excluded (1 full neuropsychological assessment, 2 only completed questionnaires; data not shown).

There was a strong correlation between self-reported fatigue and QoL ( $r = 0.82$ ,  $p < 0.0001$ ; figure 3), also as reported by parents (Parent Proxy-Report–Total Score;  $r = 0.70$ ,  $p = 0.004$ ). There were no significant correlations between QoL and fatigue and the cognitive domains sustained attention and long-term verbal memory (figure 3). Treatment delay, follow-up time, age at onset, ICU stay, maximum PCPC, and PCPC at follow-up were not correlated with sustained attention, long-term verbal memory, or fatigue (figure e-1, [links.lww.com/WNL/A494](https://links.lww.com/WNL/A494)). Sustained attention and long-term verbal memory were also not correlated with QoL scores as reported by parents (sustained attention:  $r = 0.20$ ,  $p = 0.62$ ; long-term verbal memory:  $r = 0.45$ ,  $p = 0.27$ ).

Among the secondary outcome measures (tables e-5 and e-6, [links.lww.com/WNL/A495](https://links.lww.com/WNL/A495)), the mean  $z$  score on domain speed was lower (Dutch Dot Cancellation Test–reaction time;  $z = -1.53$ ,  $p_{\text{uncorrected}} = 0.002$ ). Scores on the domains visual memory (Paired Associated Learning–total errors;  $z = -0.90$ ,  $p_{\text{uncorrected}} = 0.016$ ), short-term verbal memory (RAVLT Trials 1–5);  $z = -0.76$ ,  $p_{\text{uncorrected}} = 0.023$ ), and naming (Boston Naming Test–total score;  $z = -0.78$ ,  $p_{\text{uncorrected}} = 0.019$ ) were low, but between 0.05 and 0.005.

Results of the questionnaires completed by parents were comparable to those of children (table e-7, [links.lww.com/WNL/A495](https://links.lww.com/WNL/A495)).

Patients and parents mentioned similar difficulties in the detailed interview (17/22). Regarding school or work performance, the most notable problems were word finding difficulties (24%), dyslexia (12%), and attention and concentration deficits

**Table 2** Results of primary outcome measures

Domain; test; measure	No.	z Score, mean	95% CI	z Score <0, n (%)	z Score <-2, n (%)	p Value
Sustained attention; DDCT; attention fluctuations	16	-2.10	-2.71 to -1.48	15 (94)	10 (63)	<0.0001 <sup>a</sup>
Long-term verbal memory; RAVLT-Delayed Recall	15 <sup>b</sup>	-0.68	-1.29 to -0.07	12 (80)	3 (20)	0.031
Fatigue; PedsQL-MFS; Self-Report; Total Score	21 <sup>c</sup>	-0.96	-1.64 to -0.28	16 (76)	5 (24)	0.008 <sup>a</sup>
Quality of life; PedsQL; Self-Report; Total Score	21 <sup>c</sup>	-0.86	-1.64 to -0.08	15 (71)	7 (33)	0.032
Working memory; BRIEF; Working Memory	19 <sup>c</sup>	0.24	-0.17 to 0.65	8 (42)	0	0.23

Abbreviations: BRIEF = Behavior Rating Inventory of Executive Function; CI = confidence interval; DDCT = Dutch Dot Cancellation Test; MFS = Multidimensional Fatigue Scale; PedsQL = Pediatric Quality of Life; RAVLT = Rey Auditory Verbal Learning Test.

Exclusion of patient 6 (with vocal cord paralysis), patients 14, 18, and 19 (all post-herpes simplex virus encephalitis anti-N-methyl-D-aspartate receptor encephalitis), and patient 16 (with prior mild developmental delay) did not affect results.

<sup>a</sup>  $p < 0.017$  (Bonferroni).

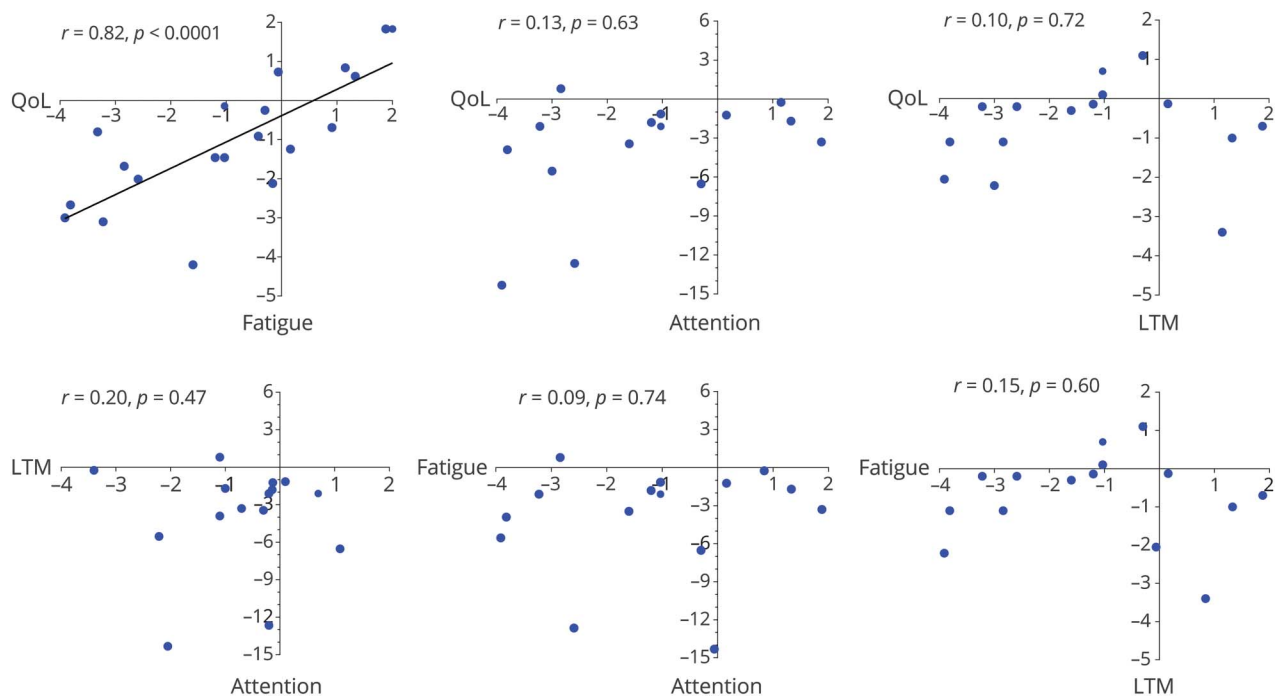
<sup>b</sup> Of one patient (no. 6), no data are shown as the test was aborted because of vocal cord paralysis.

<sup>c</sup> No normative data available for test results of the youngest patient(s).

(18%). Other problems were impulsiveness (18%), anxiety (18%), and indecisiveness (12%). Concerning the disease period, 21 of 22 patients (95%) had a persistent (fragmented or complete) amnesia.

Based on our own observations during the visits to our clinics, we could differentiate 3 frontal lobe syndrome profiles using the character descriptions by parents and the main complaints of the patients themselves. This way, we

allocated the patients visiting our clinic into 3 groups: (1) passive (apathy,  $n = 5$ ), (2) moderate (no signs of a frontal lobe syndrome,  $n = 6$ ), and (3) active (impulsive,  $n = 7$ ). The median scores on QoL and fatigue were compared between these groups (visualized in figure e-2, links.lww.com/WNL/A494). Among the passive patients, the school dropout rate was 80% (4/5), while for the active patients, school resumption was achieved in all 7, of whom 2 did not retain previous school level.

**Figure 3** Overview of correlations between primary outcome measures

Outcome measures: sustained attention (Dutch Dot Cancellation Test-attention fluctuations), long-term verbal memory (RAVLT-Delayed Recall), fatigue (PedsQL-MFS Self-Report-Total Score), QoL (PedsQL Self-Report-Total Score), and working memory (BRIEF-Working Memory). In all graphs, results of uncorrected z scores are shown, but the correlations are calculated with corrected z scores (maximum 3, minimum -3). Anti-NMDAR = anti-N-methyl-D-aspartate receptor; BRIEF = Behavior Rating Inventory of Executive Function; HSV = herpes simplex virus; LTM = long-term verbal memory; MFS = Multidimensional Fatigue Scale; PedsQL = Pediatric Quality of Life; QoL = quality of life; RAVLT = Rey Auditory Verbal Learning Test.

## Discussion

We have demonstrated that, despite good functional recovery (according to the mRS or PCPC), persistent cognitive deficits are common in young children and adolescents following pediatric anti-NMDAR encephalitis, and that important parameters for good outcome, such as treatment delay or age at onset, do not specifically affect neuropsychological outcome. Other interesting and important findings are that patients reported more fatigue, and that patients with fatigue also reported a poorer QoL, while poorer cognitive outcome did not affect QoL.

Fatigue has not been evaluated before in patients with anti-NMDAR encephalitis. However, it is known to be a common disabling symptom in pediatric acquired brain injury,<sup>22,23</sup> making our results that fatigue was associated with poorer QoL plausible. This finding is supported further by the frequent reporting of fatigue by patients as the most disabling symptom often hampering normal participation.

Remarkably, poorer cognitive outcome did not influence QoL, possibly because QoL questionnaires comprise general topics, while patients often reported specific task-related problems, which might be underestimated in current questionnaires. In addition, patients becoming accustomed to a new “stable” situation and reduced awareness might be other explanations. The latter is less likely because parents’ QoL scores were comparable.

Predictors of good functional outcome such as treatment delay, maximum PCPC, and ICU stay were not correlated with QoL, fatigue, or sustained attention. This supports our statement that “good” outcome certainly not always means “good” total recovery. NMDAR antibodies are considered to compromise signal transmission, leading to problems in multiple functional networks, corresponding to the extent of symptoms. Finke et al.<sup>24</sup> showed that a reduced connectivity of the anterior hippocampus and the anterior default mode network was associated with poorer memory in anti-NMDAR encephalitis.<sup>24</sup> In addition, this reduced connectivity is also described in a broad spectrum of other neurologic conditions.<sup>25–28</sup> These connections seem most vulnerable, which may explain the discrepancy between good outcome and poor memory recovery. A follow-up study testing patients by serial neuropsychological tests combined with fMRI will be essential to examine the correlation between cognitive functioning and this reduced connectivity over time, and to examine whether this process is reversible.

Most anti-NMDAR encephalitis follow-up studies concentrate on the neurobehavioral problems of disinhibition. However, frontal lobe syndromes are more widespread, and little is known about passive patients during rehabilitation and follow-up. Our data suggest that these “passive” patients might be more at risk to develop problems with normal participation because these patients showed more school

dropout rates and reported more fatigue. This observation needs confirmation in future research, but may have important consequences for rehabilitation programs.

For cognitive outcome, we particularly observed lower scores in the domain sustained attention and speed. Possibly these cognitive deficits are most prominent and should be considered during cognitive rehabilitation. However, there was no correlation between the different cognitive test results, which underlines that the occurring cognitive deficits are diverse and probably different parts of the brain are affected. Short-term verbal memory and language scores were also lower. Apparently these domains are more vulnerable to dysfunction of the NMDAR. These findings are partially in concordance with earlier findings,<sup>3–9</sup> although these previous published studies describe more diverse cognitive deficits, with additional deficits in executive functioning. However, these studies are difficult to interpret and to compare properly to our results because of limited patient numbers and unstandardized methods and because some patients were assessed in the acute disease phase. By using standardized performance-based measures, such as CANTAB, we found no prominent problems in executive functions. Nevertheless, by using rating measures (questionnaires, interviews), patients reported substantial difficulties in performing activities of daily living. An explanation for this disconnection is that performance-based measures and rating measures do not assess the same aspects in cognitive and behavioral functioning. Rating measures assess whether goals in activities of daily living are reached and have higher ecological validity.<sup>29</sup> Next to the BRIEF (and other rating measures we performed), the BADS-C (Behavioral Assessment of the Dysexecutive Syndrome in Children) might be a useful addition.

The present study, with national coverage, detailed description of clinical data, and the use of a systematic neuropsychological assessment, provides broad, valuable results, likely to be externally valid. This study exclusively pertains to pediatric anti-NMDAR encephalitis, also a valuable aspect, because in comparison to adults, there are differences in disease onset, treatment decisions, and social functioning. First, children present more often with seizures or behavioral changes,<sup>30</sup> whereas adults mostly present with psychiatric symptoms or memory dysfunction,<sup>2</sup> which may lead to different intervals to diagnosis and treatment. Second, treatment decisions can be age-dependent and may affect outcome; i.e., physicians tend to be more aggressive in children, starting immunotherapy early while simultaneously being more careful with cyclophosphamide. Third, neuropsychological problems can seriously affect participation as successful transition into adulthood calls for full cognitive, emotional, and behavioral abilities.

We had the unique opportunity to include all Dutch children with anti-NMDAR encephalitis. Nevertheless, despite national coverage and increasing incidence, anti-NMDAR encephalitis is a rare disease. Therefore, to include a sufficient

number of patients with a reasonable follow-up time, a retrospective study design was inevitable but with the associated problems. The first issue is missing data. The amount of missing data was minimized by contacting treating physicians, parents, and patients. Regarding selection bias (between patients participating and nonparticipating in the follow-up study), we found no difference in clinical characteristics. Furthermore, clinical characteristics are in line with previous studies.<sup>2,30</sup> The results of the participants thus seem to be a good representation for the total group and results are probably generalizable.

Overall, our findings highlight the importance of awareness of persisting neuropsychological deficits and excessive fatigue following pediatric anti-NMDAR encephalitis. With a considerable median follow-up time (almost 3 years), our results clearly indicate that neuropsychological deficits can be prolonged. Currently, disease outcome is assessed with parameters measuring impairment and disabilities (mRS,<sup>11</sup> PCPC), and treatment decisions are based on these parameters. Our results show that neuropsychological parameters measuring participation and QoL are also important and should be considered when assessing outcome, because these factors can substantially affect participation and well-being. Therefore, physicians should inform patients and parents correctly about the occurrence of prolonged neuropsychological problems. In addition, they should provide good accessibility to neuropsychological counseling in rehabilitation centers immediately following the acute disease course and during follow-up.

### Author contributions

M.A.A.M. de Bruijn: study design, acquisition of data, data analysis, medical writing. F.K. Aarsen: study design, acquisition of data, revising the manuscript for content. M.P. van Oosterhout: acquisition of data, revising the manuscript for content. M.M. van der Knoop: acquisition of data, revising the manuscript for content. C.E. Catsman-Berrevoets: revising the manuscript for content. M.W.J. Schreurs: revising the manuscript for content. D.E.M. Bastiaansen: acquisition of data, revising the manuscript for content. P.A.E. Sillevs Smitt: revising the manuscript for content. R.F. Neuteboom: study design, acquisition of data, revising the manuscript for content. M.J. Titulaer: study design, acquisition of data, data analysis, medical writing.

### Acknowledgment

The authors gratefully thank all patients and their parents for their participation. They thank all referring physicians, with special thanks to Dr. F.M.C. Berkesteijn, Dr. J.M. de Bont, Prof. Dr. K.P.J. Braun, Prof. Dr. O.F. Brouwer, Dr. J.F.H.M. Claes, Dr. K.G.J. van Dijk, Dr. C. Erasmus, Dr. J.G.J. Hoeijmakers, Dr. W. Peper, Dr. J.P.A. Samijn, Dr. R.D. Thijs, Prof. Dr. R.J. Vermeulen. The authors thank Esther Hulsenboom and Mariska Nagtzaam for technical assistance.

### Study funding

M.T. was supported by an Erasmus MC fellowship, has received funding from the Netherlands Organization for Scientific Research (NWO, Veni incentive), from the Dutch Epilepsy Foundation (NEF, project 14-19), and from ZonMw (Memorabel program).

### Disclosure

M. de Bruijn, F. Aarsen, M. van Oosterhout, M. van der Knoop, C. Catsman-Berrevoets, M. Schreurs, and D. Bastiaansen report no disclosures relevant to the manuscript. P. Sillevs Smitt holds a patent for the detection of anti-DNER and received research support from EUROIMMUN. R. Neuteboom reports no disclosures relevant to the manuscript. M. Titulaer has filed a patent for methods for typing neurologic disorders and cancer, and devices for use therein, and has received research funds for serving on a scientific advisory board of MedImmune LLC, for consultation at Guidepoint Global LLC, and an unrestricted research grant from EUROIMMUN AG. Go to Neurology.org/N for full disclosures.

Received September 18, 2017. Accepted in final form March 15, 2018.

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# Long-term neuropsychological outcome following pediatric anti-NMDAR encephalitis

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Cite as: *Neurology*® 2018;90:e1997-e2005. doi:10.1212/WNL.0000000000005605

## Study question

What are the long-term effects of pediatric anti-NMDAR encephalitis on neuropsychologic function and quality of life?

## Summary answer

Many patients experienced cognitive problems and fatigue even after apparent recovery, resulting in decreased quality of life and impaired academic performance.

## What is known and what this paper adds

Anti-NMDAR encephalitis is an autoimmune disorder, and the disease course is severe in 75% of pediatric cases. While previous studies have indicated good outcomes after immunotherapy, new evidence suggests that negative long-term effects may exist. The present study confirms these findings, and provides strong evidence demonstrating the long-term effects of pediatric anti-NMDAR encephalitis. It suggests that academic performance is most affected by passivity as a sign of frontal lobe syndrome.

## Participants and setting

Dutch children (0–18 years of age;  $n = 28$ ) diagnosed with anti-NMDAR encephalitis between January 2008 and March 2017 were included in the initial study. Of these, 22 patients were included in the cross-sectional study.

## Design, size, and duration

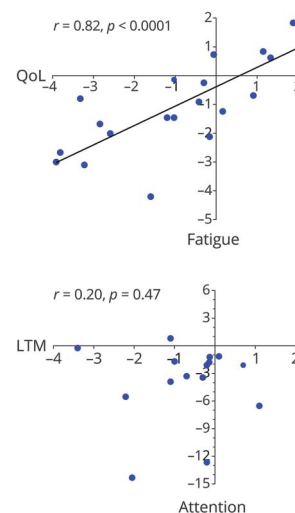
Clinical information was extracted from medical records and detailed clinical interviews. Outcome data were obtained during a cross-sectional follow-up phase in which participants completed an in-clinic standardized neuropsychologic assessment or a mailed questionnaire and telephone interview. Neuropsychologic results were converted into standardized z score and compared to normative data for healthy matched subjects.

## Primary outcomes

Patient functioning was assessed using z scores in 5 domains: sustained attention, long-term verbal memory, working memory, quality of life, and fatigue.

## Main results and the role of chance

The children were predominantly female (75%) and  $\geq 12$  years of age (89%). The median age of onset was 14 years. Sixty-four



percent of patients returned to their previous school level. Sixteen children completed the neuropsychological assessment and showed impairments in sustained attention ( $z = -2.10$ , 95% CI =  $-2.71$  to  $-1.46$ ,  $p < 0.0001$ ) and fatigue ( $z = -0.96$ , 95% CI =  $-1.64$  to  $-0.28$ ,  $p = 0.008$ ). Fatigue, but not cognitive function, was strongly correlated with quality of life ( $r = 0.82$ ,  $p < 0.0001$ ).

## Bias, confounding, and other reasons for caution

The study included a small number of patients, especially in the cross-sectional phase.

## Generalizability to other populations

The results can be generalized to other cases of pediatric anti-NMDAR encephalitis.

## Study funding/potential competing interests

The study was funded in part by the Netherlands Organization for Scientific Research, the Dutch Epilepsy Foundation, and ZonMW. Go to [Neurology.org/N](http://Neurology.org/N) for full disclosures.

A draft of the short-form article was written by A. Symons, a writer with Editage, a division of Cactus Communications. The authors of the full-length article and the journal editors edited and approved the final version.