RESEARCH ARTICLE OPEN ACCESS

Retrospective Pediatric Cohort Study Validates NEOS Score and Demonstrates Applicability in Children With Anti-NMDAR Encephalitis

Marc Nikolaus, MD,* Philipp Rausch, PhD,* Kevin Rostásy, MD, Annikki Bertolini, MD, Ronny Wickström, MD, Jessika Johannsen, MD, Jonas Denecke, MD, Markus Breu, MD, Mareike Schimmel, MD, Katharina Diepold, MD, Martin Haeusler, MD, Annegret Quade, MD, Andrea Berger, MD, Hendrik Rosewich, MD, Claudia Steen, MD, Katja von Au, MD, Mona Dreesmann, MD, Carsten Finke, MD, Frederik Bartels, MD, Angela M. Kaindl, MD, PhD, Markus Schuelke, MD, and Ellen Knierim, MD

Correspondence
Dr. Knierim
ellen.knierim@charite.de

Neurol Neuroimmunol Neuroinflamm 2023;10:e200102. doi:10.1212/NXI.0000000000200102

Abstract

Background and Objectives

Anti-N-methyl-D-aspartate receptor encephalitis (NMDARE) is the most common form of autoimmune encephalitis in children and adults. Although our understanding of the disease mechanisms has progressed, little is known about estimating patient outcomes. Therefore, the NEOS (anti-**N**MDAR **E**ncephalitis **O**ne-Year Functional **S**tatus) score was introduced as a tool to predict disease progression in NMDARE. Developed in a mixed-age cohort, it currently remains unclear whether NEOS can be optimized for pediatric NMDARE.

Methods

This retrospective observational study aimed to validate NEOS in a large pediatric-only cohort of 59 patients (median age of 8 years). We reconstructed the original score, adapted it, evaluated additional variables, and assessed its predictive power (median follow-up of 20 months). Generalized linear regression models were used to examine predictability of binary outcomes based on the modified Rankin Scale (mRS). In addition, neuropsychological test results were investigated as alternative cognitive outcome.

Results

The NEOS score reliably predicted poor clinical outcome (mRS ≥3) in children in the first year after diagnosis ($p = 0.0014$) and beyond ($p = 0.036$, 16 months after diagnosis). A score adapted to the pediatric cohort by adjusting the cutoffs of the 5 NEOS components did not improve predictive power. In addition to these 5 variables, further patient characteristics such as the "*Herpes simplex* virus encephalitis (HSE) status" and "age at disease onset" influenced predictability and could potentially be useful to define risk groups. NEOS also predicted cognitive outcome with higher scores associated with deficits of executive function ($p = 0.048$) and memory ($p = 0.043$).

*These authors contributed equally to this work as first authors.

From the Department of Pediatric Neurology (M.N., A.M.K., M.S., E.K.) and Center for Chronically Sick Children, Charité-Universitätsmedizin Berlin, Corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin Institute of Health (BIH); Institute of Clinical Molecular Biology, Christian-Albrechts-University Kiel, University Hospital Schleswig Holstein, Campus Kiel; Department of Genetics and Bioinformatics (P.R.), Kiel; Department of Pediatric Neurology (K.R., A.B.), Children's Hospital Datteln, University Witten/Herdecke, Datteln, Germany; Neuropediatric Unit (R.W.), Karolinska University Hospital, Astrid Lindgren Children's Hospital, Stockholm, Sweden; Department of Pediatrics (J.J., J.D.), University Medical Center Hamburg-Eppendorf, Hamburg, Germany; Division of Pediatric Pulmonology, Allergology and Endocrinology, Department of Pediatrics and Adolescent Medicine (M.B.), Medical University of Vienna, Austria; Department of Pediatric Neurology (M.S.), University Children's Hospital Augsburg; Division of Pediatric Neurology, Department of Pediatrics (K.D.), Hospital Kassel; Department of Pediatrics (M.H., A.Q.), Division of Neuropediatrics and Social Pediatrics, Medical University Rheinisch-Westfälische Technische Hochschule (RWTH) Aachen; Division of Pediatric Neurology, Department of Pediatrics (A.B.), München Klinik Harlaching, Munich; Department of Pediatrics and Pediatric Neurology (H.R.), Georg August University, Göttingen; Department of Paediatric and Adolescent Medicine (C.S.), St Joseph Hospital, Berlin; Department of Pediatrics (K.v.), Vivantes Hospital Friedrichshain, Berlin; Department of Pediatrics (M.D.), Ernst von Bergmann Hospital, Potsdam; Department of Neurology (C.F., F.B.), Charité-Universitätsmedizin Berlin and Berlin School of Mind and Brain, Humboldt-Universität zu Berlin; Charité-Universitätsmedizin Berlin (A.M.K.), Corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health (BIH), Institute of Cell Biology and Neurobiology; Charité-Universitätsmedizin Berlin (M.S., E.K.), Corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin Institute of Health (BIH), NeuroCure Clinical Research Center Berlin, Germany

Go to Neurology.org/NN for full disclosures. Funding information is provided at the end of the article.

Glossary

AIC = Akaike information criterion; **CSF** = cerebrospinal fluid; **GLM** = generalized linear model; **IV** = Intravenous; **mRS** = modified Rankin Scale; **NMDARE** = N-methyl-D-aspartate receptor encephalitis; **PLEX** = plasma exchange.

Discussion

Our data support the applicability of the NEOS score in children with NMDARE. Although not yet validated in prospective studies, NEOS also predicted cognitive impairment in our cohort. Consequently, the score could help identify patients at risk of poor overall clinical outcome and poor cognitive outcome and thus aid in selecting not only optimized initial therapies for these patients but also cognitive rehabilitation to improve long-term outcomes.

Anti-N-methyl-D-aspartate receptor encephalitis (NMDARE) is the most common form of autoimmune encephalitis.[1] It occurs in all age groups, but most often affects young women and children. NMDARE is characterized by a combination of severe neuropsychiatric symptoms, seizures, and autonomic dysregulation.[2] IgG autoantibodies to NR1 subunits of NMDARs lead to receptor internalization and cause the disease.[3,4] Tumors, usually ovarian teratomas, are found in up to 50% of adult patients with NMDARE.[5] Children with NMDARE are less likely to have tumors, although ovarian teratomas are found in up to 30% of adolescents.[6,7] Pediatric patients present with seizures and movement disorders and only rarely develop autonomic dysfunction.[8,9] Overt psychosis is also less common, while subtle behavioral changes such as irritability, insomnia, or mutism may indicate NMDARE in infants.[10,11] Children respond well to immunotherapy, especially when initiated without delay.[6] Intravenous (IV) steroids, immunoglobulins, and plasma exchange (PLEX) represent first-line therapies, intensified in refractory cases by rituximab or cyclophosphamide as second-line and sometimes long-term treatment.[5] In contrast to the well-established diagnostic criteria for NMDARE[2] which allow rapid diagnosis and treatment, less is known about the clinical course and long-term prognosis of children with NMDARE. Functional neurologic outcome improves with treatment and is favorable in 80–90%, surpassing that of adults.[5,12,13] Yet, many patients endure unpredictable periods of failing treatment response or protracted recovery with cognitive deficits and 10–20% relapse.[5,13-15]

In recognition of this prognostic uncertainty, the NEOS (anti-**N**MDAR **E**ncephalitis **O**ne-Year Functional **S**tatus) score was developed,[16] a tool to predict the one-year outcome of NMDARE. It includes 5 independent predictors of poor functional status: (1) need for ICU admission, (2) treatment delay within the first 4 weeks after symptom onset, (3) lack of clinical improvement 4 weeks into treatment, (4) abnormal cranial MRI, and (5) cerebrospinal fluid (CSF) white blood cell count more than 20 cells/μL. While NEOS has been developed in a large mixed-age cohort[16] and was validated in adult patients,[17] there is only 1 brief report of assessing it in a small group of children.[18] In this study, we aimed to validate the NEOS score in a larger pediatric-only cohort and analyze its predictive value taking into account the particular characteristics of NMDARE in children.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

The ethics committee of Charité-Universitätsmedizin Berlin approved this study (EA2/121/17). Patients' parents gave their written informed consent for the storage and use of samples and clinical information for research purposes. In this retrospective observational study, we contacted 23 sites in Germany and Europe and collected records of children with confirmed NMDARE from the following 12 sites, both university and district hospitals, between 2020 and 2021: In Berlin and surrounding areas of our hospital (Charité), Vivantes Klinikum Friedrichshain, St-Joseph Klinikum, and Klinikum Westbrandenburg Postdam; across Germany, from Aachen University Hospital, Augsburg University Hospital, Children's Hospital Datteln, University Witten/Herdecke, Göttingen University Hospital, Hamburg University Hospital, and Nordhessen Klinikum Kassel; and in Europe, from Medical University of Vienna (Austria) and Karolinska University Hospital, Stockholm (Sweden).

Inclusion Criteria

Patient data were accepted according to the following inclusion criteria: (1) Patients had to be younger than 18 years at the time of diagnosis; (2) patients had to be positive for anti-NMDAR autoantibodies in CSF and meet clinical criteria for autoimmune encephalitis (Graus criteria[2]); and (3) sufficient clinical information had to be available to complete at least the 5 items of NEOS at the time of diagnosis and the modified Rankin Scale (mRS)[19] after 1 year. There was one exception: Completed cases with full restitution or fatal outcome within the first 12 months were also included. In these cases, the mRS of the last available time point was taken as one-year mRS.

Calculation of the NEOS Score and mRS

We used the original NEOS score[16] recomposed in a multivariable logistic regression model. The score includes 5 independent predictors of poor functional status (mRS ≥3): (1) need for ICU admission, (2) treatment delay within the first 4 weeks after symptom onset, (3) lack of clinical improvement 4 weeks into treatment, (4) abnormal cranial MRI, and (5) CSF white blood cell count more than 20 cells/μL. Each variable is scored with 1 point. The score ranges from 0 to 5 and is

calculated at bedside (eTable 1, links.lww.com/NXI/A813). For an adapted NEOS score tailored to our pediatric cohort, we defined cutoff points of the continuous variables following the original methodology[16] as the median of measures 1 year after diagnosis (between 6 and 18 months) in healthy/unaffected individuals (mRS = 0).

The mRS is a descriptive measure of global disability after stroke but is widely used to assess patients with autoimmune encephalitis. It comprises 6 categories of severity ranging from "no symptoms at all" to "severe disability" (grades 0 to 5), with the additional category "6" for death. The categories essentially cover activities of daily living and focus on motor function. The score was determined by physicians during physical examination at follow-up visits (eTable 1, links.lww.com/NXI/A813).

Analysis of the Clinical Variables and Evaluation of the NEOS Score

Each clinical record collected included demographic information, date of onset, age and clinical characteristics at admission, type of hospitalization, laboratory, electrophysiologic and radiologic findings, detailed information on treatment procedures, time from onset of symptoms to initiation of treatment, time from initiation of treatment to clinical improvement, and functional status during the course of disease. Data were collected from admission, first discharge, and up to 9 follow-up visits ranging between 1 and 52 months after diagnosis. Owing to the retrospective nature of the study, there was a wide variation in follow-up intervals. Individual follow-up visits clustered around 2, 5, 9, 12, and 16 months after diagnosis (eTable 2, links.lww.com/NXI/A813). To better reflect the time frame used in the original study[16] and consider as many patients as possible for the assessment of outcome after 1 year without pseudoreplication, we used data points from individuals recorded at follow-up visits between 6 and 18 months after diagnosis. If individuals were measured more than once during this period, only the visit closest to the 12-month mark after discharge was used. Status and outcome were quantified using the mRS. Cognitive test scores were collected at follow-up whenever possible.

Neuropsychological Assessment With Various Test Batteries

Data collected on cognitive tests were very heterogeneous, and the test batteries used in this retrospective study varied widely. Therefore, because of the general problem of comparability between these tests, we decided to divide the various quantitative results, including percentile ranks and numerical subscale scores, into a binary measure of "normal" and "pathologic" findings and to broadly assign them to the main categories of neuropsychological assessment: intelligence, memory (including working and episodic memory), language, executive function (including attention span, concentration, processing speed), and visuospatial perception. Given the encephalopathy symptoms of most patients, we included behavior as an additional category, including fatigue, emotional instability, aggression, and hyperactivity. These items were used as an alternative outcome reference to examine the predictive power of NEOS.

Statistical Analysis

All statistical analyses, including the generation of figures, were performed in the statistical programming environment R, version R 3.5.3.[20] Mean differences were assessed using permutative, nonparametric Wilcoxon tests with 10^6 permutations as implemented in the R package *coin*.[21] Differences in frequencies and distribution of variables between this cohort and that in the original study[16] were assessed using Fisher exact tests. The predictability of binary outcomes (mRS ≥3) was assessed using generalized linear models with a binomial error structure and a "clog-log" link function as implemented in MASS.[22] The nonsymmetric complementary log-log link function (clog-log) was chosen because we found in most cases an unbalanced distribution between positive and negative outcomes in the target variables, which is significantly better represented by this link function as compared with *logit*.[23] Models were built individually for each tested covariate and selected to minimize the Akaike information criterion (AIC) and to achieve significant improvement over the less complex null model (mRS ≥ 3∼NEOS). This was achieved by step-wise model selection, testing extended models (i.e., mRS ≥ 3∼NEOS + covariate; mRS ≥ 3∼NEOS + covariate + NEOS:covariate) against the null model, using likelihood ratio tests and AIC calculation, to select the best and most parsimonious model in this comparison and to reduce the potential of overfitting through the inclusion of noninformative variables. Models that were too heterogeneous in fit, had residual patterns, or were too unbalanced or sparse were excluded from further analyses. If applicable, *p*-values were adjusted for multiple testing using FDR/Benjamini-Hochberg correction.[24]

Data Availability

All data are provided in this article and are available in anonymous form on request.

Results

Demographic and Clinical Characteristics of the Pediatric Cohort

We included 59 pediatric patients with confirmed NMDARE from 63 collected records (n = 1 exclusion because of unclear diagnosis, n = 3 exclusions because of incomplete follow-up data). The minimum follow-up period was 12 months. Ten cases (17%) with shorter follow-up time because of early complete restitution (n = 9/10) or fatal outcome (n = 1/10) were included (see inclusion criteria). The median follow-up time was 20 months (12–52 months). Age at disease onset was 8 years (median, 9 months–17 years) and showed a bimodal distribution with maxima at 2 and 16 years, respectively. 44 patients (75%) were female (Table 1, eFigure 1, links.lww.com/NXI/A812). Two cases had preexisting autoimmune comorbidities (Hashimoto thyroiditis, type 1 diabetes). Tumors were found in 3

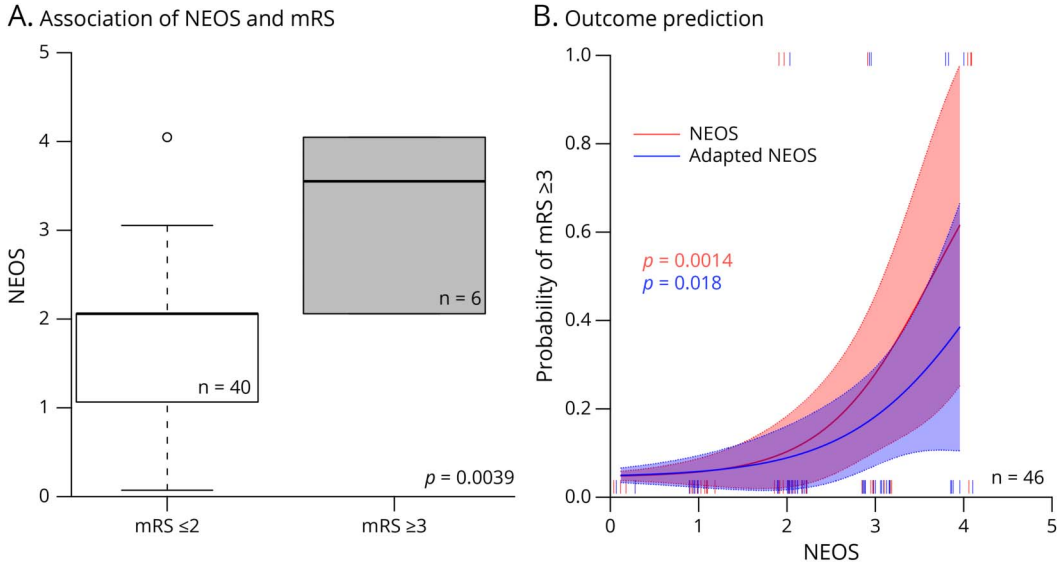
Table 1 Demographic and Epidemiologic Characteristics of Our Pediatric Cohort in Comparison With the Original Cohort[16]

	Pediatric	Original[16]	Comparison
Cohort	**% (N)**	**% (N)**	**Fisher and #Wilcoxon test (FDR adjusted)**
N	59	382	—
Follow-up time [mo]	20	24	—
Sex			
Female	75% (44)	82% (315)	0.3052
Male	25% (15)	18% (67)	
Age [median, range]	8 (9 mo–17 y)	21 (8 mo–85 y)	**#4.7059e-9**
Tumor	5% (3)	42% (159)	**4.1746e-4**
HSV encephalitis before NMDARE	17% (10)	n/a	—
Main symptoms			
Behavior	95% (56)	96% (386)	0.9002
Memory	83% (49)	76% (284)	0.8026
Seizures/therapy refractory	80% (47)/19% (11)	72% (273)	0.8395 (refractory: **7.3860e-4**)
Consciousness	73% (43)	63% (239)	0.7872
Sleep	73% (43)	52% (136)	**0.0072**
Speech	71% (42)	76% (283)	0.9622
Movement	68% (40)	78% (297)	0.8026
Autonomic function	31% (18)	46% (177)	0.3052
Hypoventilation	2% (1)	36% (136)	**1.2821e-4**
NEOS items			
Admission to ICU	59% (35)	77% (291)	0.5271
Disease onset to treatment ≥4 wk	36% (21)	38% (145)	0.9220
Treatment to first improvement ≥4 wk	30% (18)	44% (163)	0.5162
Pathologic MRI findings	47% (28)	31% (112)	0.2179
CSF cell count >20/μL	44% (26)	51% (166)	1.0000
Second-line therapy (rituximab or cyclophosphamide)	41% (24)	27% (102)	0.2936
Outcome after 1 y			
mRS ≤2	88% (49)	74% (281)	0.0991
mRS ≥3	12% (7)	26% (101)	

Cohorts were compared based on the relative frequencies or median differences in characteristics, which were assessed using the Fisher exact test and one-sample Wilcoxon rank test, respectively.
Abbreviations: CSF = cerebral spinal fluid; FDR = false discovery rate; HSV = *Herpes simplex* virus; ICU = intensive care unit; mRS = modified Rankin Scale.

patients (n = 2 ovarian teratomas, n = 1 brain tumor). A subgroup of 17% (n = 10/59) had *Herpes simplex* virus encephalitis (HSE) before NMDARE. Symptoms on admission and NEOS components are listed in Table 1. Almost all patients, 97% (n = 57/59), had 3 or more of these symptoms; 81% (n = 48/59) had at least 5; and 24% (n = 14/59) had all symptoms. Thus, our cohort included a large proportion of severe cases, showing the full picture of NMDARE. Thirty-nine percent (n = 23/59) of patients had pathologic findings in CSF as well as EEG and MRI (83% in CSF, 80% in EEG, and 47% in MRI); 59% (n = 35/59) required ICU treatment; 51% (n = 30/59) were treated with PLEX or immunoadsorption in addition to IV steroids; and 41% (n = 24/59) received second-line therapy (rituximab, additional cyclophosphamide in 3 cases). Most patients showed continuous improvement on therapy; a fluctuating

Figure 1 Validation of the NEOS Score in Children



(A) Association of the original NEOS score with mRS-based outcomes (good outcome mRS ≤ 2, poor outcome mRS ≥ 3) at 1 year after diagnosis. Box plots represent IQR, solid lines mark the median, whiskers display range (upper/lower quartile ± 1.5*IQR), and circles show outliers. "n" indicates the number of subjects included at each time point. (B) Predictability analysis of mRS-based clinical outcomes by the NEOS score with binomial generalized linear models (GLMs). Line plots show association of the original (red curve) and adapted (blue curve) NEOS scores with poor clinical outcome (mRS ≥ 3) at 1 year after diagnosis. Solid lines represent best fit and shadows indicate confidence intervals. tick marks on the upper and lower x axes indicate the number of subjects (also written next to every graph) with each score with a good or poor mRS-based clinical outcome. A small random jitter was added to spread ticks around the discrete NEOS score values, to discriminate single data points. The *p* values were adjusted for multiple testing. NEOS 0: n = 5, NEOS 1: n = 12, NEOS 2: n = 16, NEOS 3: n = 9, NEOS 4: n = 4, NEOS 5: n = 0. For further results (comparison of original and adapted NEOS score, analysis over time), see eFigure 2 (links.lww.com/NXI/A812) and eTable 2 (links.lww.com/NXI/A813).

course with transient deterioration was observed in 22% (n = 13/59); and only 4 children relapsed.

The original NEOS cohort[16] consisted of 382 individuals, of whom 35% (n = 132/382) were younger than 18 years. Our pediatric-only cohort, in comparison (Table 1), more closely represented the spectrum of NMDARE in children. This included a lower tumor prevalence, lower rate of autonomic dysfunction, more frequent use of second-line therapy and, accordingly, shorter time to improvement, and a lower proportion of poor outcomes (mRS ≥3) at 1 year. Otherwise, there were no confounding differences in either group, such as initial disease severity. Our cohort was also comparable with that of the previous pediatric study[18] which reported a test of NEOS in 30 children and whose patients differed only by a higher rate of second-line therapy (70%, n = 21/30).[20]

Validation of the NEOS Score in Pediatric Patients

To examine the association between NEOS and clinical outcomes in our pediatric cohort, we first calculated the score for all patients, dichotomized their functional status by mRS, associated each assessed variable with good (mRS ≤2) or poor (mRS ≥3) status, and rederived the NEOS score based on the original characteristics and cutoff values[16] (eTable 3, links.lww.com/NXI/A813).

To validate NEOS, we grouped all score values to the mRS-based outcome and found that patients with poor functional status (mRS ≥3) consistently had higher NEOS scores than patients with good functional status (mRS ≤2) ($p = 0.0039$, Figure 1A). Using binomial generalized linear models (GLMs), we assessed the relationship between mRS-based outcomes and NEOS, confirming the correlation between the NEOS score and the risk of poor clinical outcome at 1 year after diagnosis ($p = 0.0014$, Figure 1B). In an extended analysis with the multiple follow-up data of readmitted or re-examined patients over time (eTable 3, links.lww.com/NXI/A813), we found robust predictability of mRS even beyond 1 year ($p = 0.036$, 16 months after diagnosis, eFigure 2, links.lww.com/NXI/A812 *p*-values adjusted for multiple testing).

Questioning whether the NEOS score could be further developed to optimize predictive power in children with NMDARE, we recomposed the score by adjusting the population-specific cutoffs of the 5 NEOS components (Table 2). Both scores, the original and the adapted, correlated strongly with each other (eFigure 2, A–D, links.lww.com/NXI/A812); the association between higher adapted NEOS scores and patients with poor status (mRS ≥3) was significant ($p = 0.032$, eFigure 2A, links.lww.com/NXI/A812); and prediction by GLM analysis confirmed this, again up to 16 months after diagnosis ($p = 0.026$, eFigure 2B, links.lww.com/NXI/A812), showing that the adapted NEOS score did not perform better.

To investigate whether additional factors, not included in the 5 NEOS components, might influence the score and

Table 2 Adapted NEOS Score Compiled by Adjusting the Population-Specific Cutoff Median Values of the 5 NEOS Items

NEOS	Original	Adapted
Disease onset to treatment	>28 d	>16 d
Treatment to improvement	>28 d	>15 d
Admission to ICU	Yes/No	Yes/No
MRT pathology	Yes/No	Yes/No
CSF cell count	>20/μL	>13/μL

improve prediction of long-term outcomes, we systematically examined patient characteristics recorded between initial admission and discharge. Of the many factors found (eTable 4, links.lww.com/NXI/A813), 2 patient characteristics seemed of clinical relevance and could be useful to define risk groups: (1) "HSE status", as within the subgroup of individuals with HSE before NMDARE, NEOS predicted an increased risk of poor clinical outcome (mRS ≥3) beyond 1 year after diagnosis and (2) "age at disease onset", as younger individuals showed a persistently higher risk of poor clinical outcome (mRS ≥3) already at lower NEOS scores indicating the effect of age (eFigure 3, links.lww.com/NXI/A812, eTable 4, links.lww.com/NXI/A813).

Overall, our retrospective study confirms that the NEOS score performed very well in children with NMDARE, predicting clinical outcome during the first year and beyond. Adapting the NEOS components did not improve predictive power. Additional items influence the score, but have limited clinical relevance. Yet, HSE status and age at disease onset could complement NEOS and improve its prediction of long-term outcomes.

Correlation of the NEOS Score With Neuropsychological Test Results

To further evaluate the potential of the NEOS score, we examined cognitive test scores from our patient data sets as an alternative outcome measure to mRS. Quantitative data were grouped into a binary measure (normal vs pathologic) and distributed among categories of neuropsychological assessments: intelligence, memory, language, executive function, and visuospatial function.[25] Taking into consideration the encephalopathy in most patients, we added behavior. A total of 33 children underwent neuropsychological assessments at some time during follow-up. Seventy percent (n = 23/33) of them were tested at 1 year after diagnosis or later. Most patients were tested multiple times. Unfortunately, in one-third of the cases, available data were incomplete. For those complete, 78% (n = 18/23) of the early assessments showed pathologic results in at least one category (Figure 2A). One year after diagnosis, deficits remained in 62% (n = 13/21) of retested patients. Persistent pathologic results frequently concerned executive function and memory (Figure 2B).

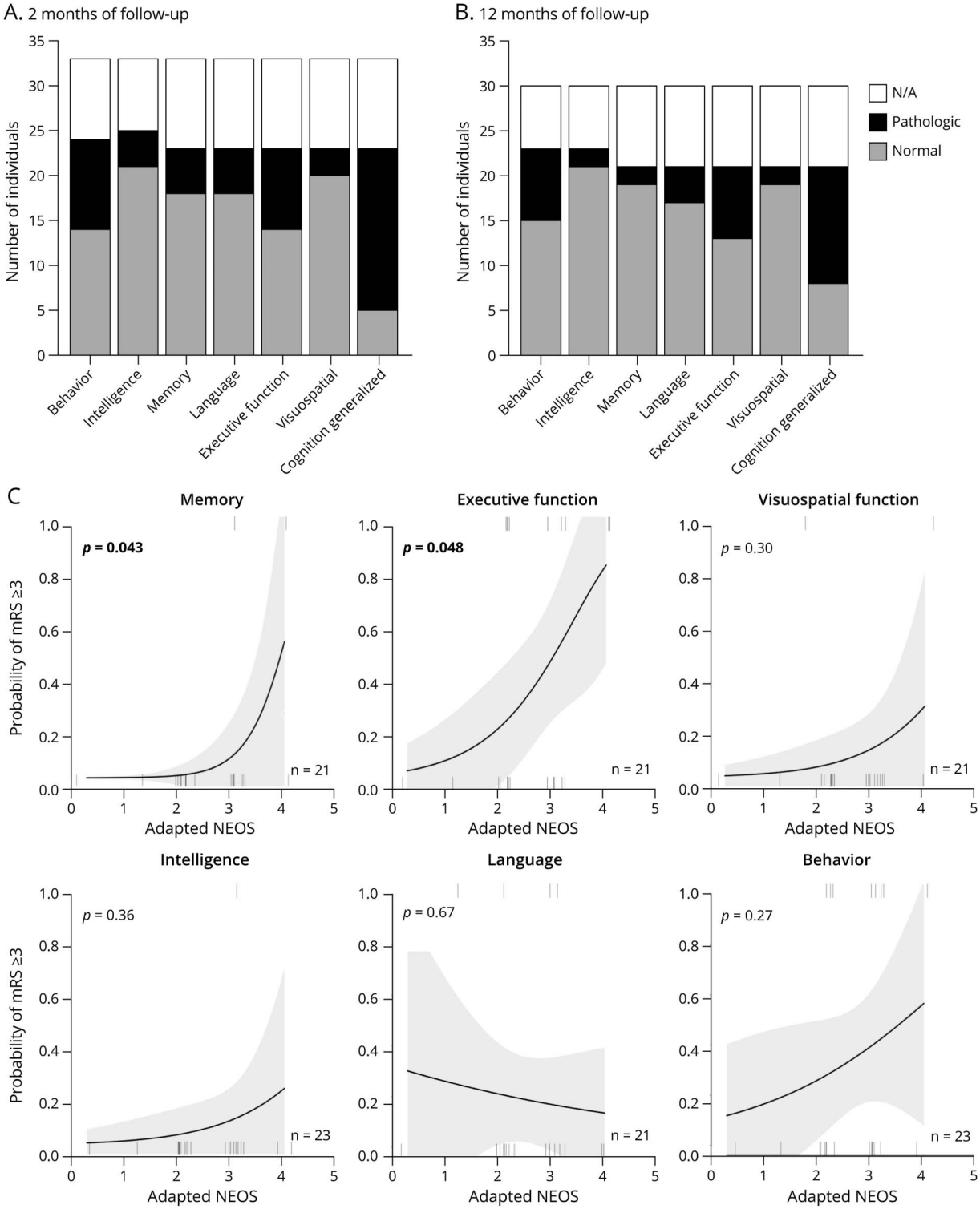
These results were assigned to each patient's NEOS score value. GLM predictive analysis using this cognition-based outcome reference revealed higher NEOS scores in patients with cognitive impairment and particularly an association to deficits in executive function ($p = 0.048$) and memory ($p = 0.043$). This was comparable for both the original and adapted NEOS scores (Figure 2C, eTable 5, links.lww.com/NXI/A813). No significant associations were found with intelligence, behavior, and visuospatial function. In conclusion, these data provide preliminary evidence of the predictive power of NEOS also for cognitive outcomes in children with NMDARE.

Discussion

To provide a predictive tool in NMDARE, the NEOS score was introduced.[16] This score facilitates the estimation of outcome in NMDARE, is expected to identify subgroups with poor prognosis, and can help assign the optimal treatment regimen to the right patient. The score was developed in a mixed-age cohort, which suggested its applicability also to children with NMDARE.[16] A brief evaluation in pediatric patients[18] was promising, although the results were limited by the relatively small sample size and the lack of severe cases. In this study, we present an in-depth analysis of NEOS in a comparatively large pediatric-only cohort. We demonstrate that the NEOS score performs well in children, reliably predicting the mRS-based outcome at 1 year and at least up to 16 months after diagnosis. Beyond, the predictive power gradually decreases. This time dependence is explained in part (1) by sparse data because of the decreasing number of study subjects with increasing follow-up time and selection bias but also (2) by rapid recovery in our pediatric-only cohort—despite severe disease of most patients at baseline, only 12% showed poor functional status (mRS ≥3) at 1 year, compared with 26% in the original mixed-age cohort.[16] Therefore, at least in this study, the NEOS score could not reliably predict long-term outcome.

Adapting the 5 existing NEOS components to the pediatric cohort did not improve the score. Adding further items influenced its performance. Of clinical relevance here, NEOS predicted a worse outcome beyond 1 year after diagnosis in children with NMDARE after HSE. The entity of NMDARE after HSE[26] was still unknown in the original cohort[16] and was not included in the previous pediatric study[18] This finding is consistent with the clinical course of these patients, whose long-term outcomes remain poor despite complete recovery from NMDARE because of persistent brain damage from viral infection.[27,28] Therefore the HSE status of patients should be considered when applying the NEOS score. Age at disease onset was another clinically relevant patient characteristic associated with NEOS. It is already known as an independent predictor of outcome in children, and within a pediatric cohort, children younger than 12 years tend to recover more slowly than older ones.[29] Consistent with this observation, we found that the NEOS score predicted poorer long-term outcome in children of a younger age. This element, although discussed in

Figure 2 Association of the NEOS Score With Cognitive Outcome



(A) Bar plots display the frequency of pathologic test scores from neuropsychologic assessments early (2 months) in follow-up and 1 year after diagnosis. The categories intelligence, memory, language, executive function, visuospatial function, and behavior contain raw scores of various test batteries grouped into a binary measure—normal (gray bars) vs pathologic (black bars). White bars (N/A) indicate cases with incomplete data. (B) Predictability analysis using binomial generalized linear models (GLMs) with a now cognition-based outcome reference. After assigning cognitive test scores instead of mRS values to each patient's NEOS score, models revealed associations of a poor outcome (mRS ≥ 3) with deficits in executive function and in memory at 1 year after diagnosis, here shown for the adapted NEOS score. No associations were found with intelligence, behavior, language, and visuospatial function. Solid lines represent best fit and shadows indicate confidence intervals. Tick marks on the upper and lower X axes indicate the number of subjects included, also written next to each line plot. A small random jitter was added to spread ticks around the discrete NEOS score values, to discriminate single data points. NEOS 0: n = 5, NEOS 1: n = 12, NEOS 2: n = 16, NEOS 3: n = 9, NEOS 4: n = 4, NEOS 5: n = 0. For further results (original score, analysis over time), see eTable 5 (links.lww.com/NXI/A813).

the original study[16] was not included as a component in the original NEOS score, but may be of greater importance in a pediatric-only cohort. However, both variables HSE status and age were derived from a smaller cohort than in the original study[16] and would have a priori resulted in lower overall validity of a NEOS score modified by them. Future large-cohort studies are needed to evaluate whether these additional patient characteristics should be included in a pediatric NEOS score to further improve predictive power for long-term clinical outcome in children.

The original cohort[16] consisted of patients diagnosed 10–15 years ago, and much has changed in the field of autoimmune encephalitis since then. The frequency of NMDARE is higher than initially suspected and, in children, exceeds that of viral encephalitis.[30] Increasing awareness combined with established diagnostic criteria[2] has led to a rise in anti-NMDAR antibody testing,[31] faster diagnosis, and earlier treatment initiation.[32] Research into disease etiology has resulted in, e.g., rigorous tumor screening to exclude ovarian teratomas and the discovery of HSE-induced NMDARE.[26] Overall, growing clinical experience with NMDARE generated data on treatment response and relapse rates[12,13] and led to rapid treatment escalation, increasing the use of second-line therapy,[33] and most recently, a consensus recommendation for therapy of pediatric NMDARE.[15] Remarkably, NEOS predicted clinical outcome both in patients diagnosed 10–15 years ago[16] and in our current cohort. In this light, our results show considerable robustness of the NEOS score not only across age groups but also over the years.

Cognitive dysfunction is a major cause of long-term morbidity in pediatric and adult NMDARE,[34] and the contrast between good functional neurologic outcomes and persistent severe cognitive impairment has been repeatedly shown.[35,36] While motor function improves rapidly in most patients with NMDARE, cognitive recovery is still incomplete, and deficits in episodic and working memory, executive function,[29,37,38] attention,[35] language,[29,39] or visuospatial function[40] may persist for years, affecting academic performance, social behavior, and overall quality of life (QoL).[35] In our cohort, two-thirds of the patients assessed 1 year after diagnosis had cognitive deficits, despite already showing good functional neurologic outcome (mRS ≤2). Similarly, in most adults with NMDARE persistent cognitive impairment was found more than 2 years after disease onset, while improvement was observed after up to 5 years of follow-up, highlighting the opportunity for cognitive rehabilitation.[36] Most of our patients suffered from memory impairment and executive dysfunction. This reflects impairment in frontal lobe and hippocampal function and is in line with data from adult patients.[36,38,41] In children, fatigue was identified as an additional factor that particularly affects school performance and QoL.[35]

Despite this, assessment of outcomes in NMDARE is still based on the mRS, a score originally developed to evaluate patients with stroke and monitor their recovery. Focusing mainly on walking ability,[19] the mRS was not intended to be a comprehensive assessment that would take into account the wide range of symptoms seen in NMDARE.[5,42] Therefore, we investigated cognitive function as an alternative outcome. Using the cognitive test scores from our cohort instead of mRS, we found an association between persistent deficits in executive function and memory and a poor clinical outcome predicted by NEOS. These preliminary findings extend on previous results on the outcome of NMDARE in children and adults.[29,36-38] Although it remains to be validated by prospective studies, our data suggest that NEOS may also predict cognitive outcome, which is more important in the long term for most pediatric patients with NMDARE.

This study has several limitations, most of which are related to its retrospective design. First, we included data from 12 centers, both university and district hospitals, which differ in size, resources, and expertise. Therefore, selection bias is less of a concern than differences in treatment approaches and monitoring strategies. This resulted in individual follow-up intervals, differing responses in cases of deterioration or relapse, and inconsistencies in the selection of cognitive tests. Second, follow-up data were sometimes incomplete or scattered across follow-up time points and could be susceptible to recall bias. In particular, the neuropsychological assessment protocol was not standardized and raw scores of the various test batteries could not be directly compared with each other. In addition, most cognitive test scores were obtained within a year and a half of diagnosis and, therefore, could not fully reflect persistent deficits in long-term outcome. Third, both our cohort and the original cohort[16] were comparable because there were no confounding differences in clinical characteristics or initial disease severity. However, we were unable to provide a control group to validate the results of additional variables for a pediatric NEOS score. Furthermore, our group was not large enough to be split for cross-validation.

In conclusion, our data demonstrate the applicability of NEOS in children with NMDARE. This score, which can be easily calculated at bedside, could help estimate the clinical course also in children, thereby supporting their families, physicians, and therapists and identifying pediatric patients at risk who could benefit from intensified therapy and novel treatment strategies including individualized cognitive rehabilitation to improve long-term outcome.

Study Funding

M.N. and J.K. are participants in the BIH-Charité Clinician Scientist Program funded by Charité - Universitätsmedizin Berlin and the Berlin Institute of Health. This research was also funded by grants from the Deutsche Forschungsgemeinschaft (DFG; German Research Foundation) under Germany's Excellence Strategy—EXC-2049—390688087 to M.S. and E.K. and by the German Ministry of Education and Research (BMBF), grant numbers 01GM1908D and 01 GM2208C (CONNECT-GENERATE), to C.F.

Disclosure

The authors report no relevant disclosures. Go to Neurology.org/NN for full disclosure.

Publication History

Received by *Neurology: Neuroimmunology & Neuroinflammation* September 20, 2022. Accepted in final form January 18, 2023. Submitted and externally peer reviewed. The handling editor was Editor Josep O. Dalmau, MD, PhD, FAAN.

Appendix Authors

Name	Location	Contribution
Marc Nikolaus, MD	Department of Pediatric Neurology and Center for Chronically Sick Children, Charité-Universitätsmedizin Berlin, Corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin Institute of Health (BIH), Berlin, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Philipp Rausch, PhD	Institute of Clinical Molecular Biology, Christian-Albrechts-University Kiel, University Hospital Schleswig Holstein, Campus Kiel, Germany. Department of Genetics and Bioinformatics. Kiel, Germany	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Kevin Rostásy, MD	Department of Pediatric Neurology, Children's Hospital Datteln, University Witten/Herdecke, Datteln, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Annikki Bertolini, MD	Department of Pediatric Neurology, Children's Hospital Datteln, University Witten/Herdecke, Datteln, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Ronny Wickström, MD	Neuropediatric Unit, Karolinska University Hospital, Astrid Lindgren Children's Hospital, Stockholm, Sweden	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Jessika Johannsen, MD	Department of Pediatrics, University Medical Center Hamburg-Eppendorf, Hamburg, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Jonas Denecke, MD	Department of Pediatrics, University Medical Center Hamburg-Eppendorf, Hamburg, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Markus Breu, MD	Division of Pediatric Pulmonology, Allergology and Endocrinology, Department of Pediatrics and Adolescent Medicine, Medical University of Vienna	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Mareike Schimmel, MD	Department of Pediatric Neurology, University Children's Hospital Augsburg, Augsburg, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Katharina Diepold, MD	Division of Pediatric Neurology, Department of Pediatrics, Hospital Kassel, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Martin Haeusler, MD	Department of Pediatrics, Division of Neuropediatrics and Social Pediatrics, Medical University Rheinisch-Westfälische Technische Hochschule (RWTH) Aachen, Aachen, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Annegret Quade, MD	Department of Pediatrics, Division of Neuropediatrics and Social Pediatrics, Medical University Rheinisch-Westfälische Technische Hochschule (RWTH) Aachen, Aachen, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Andrea Berger, MD	Division of Pediatric Neurology, Department of Pediatrics, München Klinik Harlaching, Munich, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Hendrik Rosewich, MD	Department of Pediatrics and Pediatric Neurology, Georg August University, Göttingen, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Claudia Steen, MD	Department of Paediatric and Adolescent Medicine, St Joseph Hospital, Berlin, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Katja von Au, MD	Department of Pediatrics, Vivantes Hospital Friedrichshain, Berlin, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Mona Dreesmann, MD	Department of Pediatrics, Ernst von Bergmann Hospital, Potsdam, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Carsten Finke, MD	Department of Neurology, Charité-Universitätsmedizin Berlin and Berlin School of Mind and Brain, Humboldt-Universität zu Berlin, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Frederik Bartels, MD	Department of Neurology, Charité-Universitätsmedizin Berlin and Berlin School of Mind and Brain, Humboldt-Universität zu Berlin, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Angela M. Kaindl, MD, PhD	Department of Pediatric Neurology and Center for Chronically Sick Children, Charité-Universitätsmedizin Berlin, Corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin Institute of Health (BIH), Berlin, Germany; Charité-Universitätsmedizin Berlin, Corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health (BIH), Institute of Cell Biology and Neurobiology, Berlin, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data

Continued

Appendix *(continued)*

Name	Location	Contribution
Markus Schuelke, MD	Department of Pediatric Neurology and Center for Chronically Sick Children, Charité-Universitätsmedizin Berlin, Corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin Institute of Health (BIH), Berlin, Germany; Charité-Universitätsmedizin Berlin, Corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin Institute of Health (BIH), NeuroCure Clinical Research Center Berlin, Germany	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Ellen Knierim, MD	Department of Pediatric Neurology and Center for Chronically Sick Children, Charité-Universitätsmedizin Berlin, Corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin Institute of Health (BIH), Berlin, Germany; Charité-Universitätsmedizin Berlin, Corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin Institute of Health (BIH), NeuroCure Clinical Research Center Berlin, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data

References

1. Dalmau J, Tüzün E, Wuyan H, et al. Paraneoplastic anti–N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. *Ann Neurol.* 2007;61:25-36.
2. Graus F, Titulaer MJ, Balu R, et al. A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol.* 2016;15:391-404.
3. Hughes EG, Peng X, Gleichman AJ, et al. Cellular and synaptic mechanisms of anti-NMDA receptor encephalitis. *J Neurosci.* 2010;30:5866-5875.
4. Mikasova L, Rossi PD, Bouchet D, et al. Disrupted surface cross-talk between NMDA and Ephrin-B2 receptors in anti-NMDA encephalitis. *Brain.* 2012;135:1606-1621.
5. 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 Neurol.* 2013;12:157-165.
6. Armangue T, Petit-Pedrol M, Dalmau J. Autoimmune encephalitis in children. *J Child Neurol.* 2012;27:1460-1469.
7. Cellucci T, Mater HV, Graus F, et al. Clinical approach to the diagnosis of autoimmune encephalitis in the pediatric patient. *Neurol Neuroimmunol Neuroinflamm.* 2020;7:e663.
8. 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;162:850-856.e2.
9. Florance NR, Davis RL, Lam C, et al. Anti–N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. *Ann Neurol.* 2009;66:11-18.
10. Wright S, Vincent A. Pediatric autoimmune epileptic encephalopathies. *J Child Neurol.* 2016;32:418-428.
11. Hacohen Y, Wright S, Gadian J, et al. N-methyl-d-aspartate (NMDA) receptor antibodies encephalitis mimicking an autistic regression. *Dev Med Child Neurol.* 2016;58:1092-1094.
12. Nosadini M, Mohammad SS, Ramanathan S, Brilot F, Dale RC. Immune therapy in autoimmune encephalitis: a systematic review. *Expert Rev Neurother.* 2015;15:1391-1419.
13. Nosadini M, Granata T, Matricardi S, et al. Relapse risk factors in anti-N-methyl-D-aspartate receptor encephalitis. *Dev Med Child Neurol.* 2019;61:1101-1107.
14. 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;100:521-526.
15. Nosadini M, Thomas T, Eyre M, et al. International consensus recommendations for the treatment of pediatric NMDAR antibody encephalitis. *Neurol Neuroimmunol Neuroinflamm.* 2021;8:e1052.
16. 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.* 2018;92.
17. Peng Y, Dai F, Liu L, et al. Validation of the NEOS score in Chinese patients with anti-NMDAR encephalitis. *Neurol Neuroimmunol Neuroinflamm.* 2020;7:e860.
18. Loerinc LB, Blackwell L, Howarth R, Gombolay G. Evaluation of the NEOS score in predicting functional outcomes in pediatric anti-NMDA receptor encephalitis patients. *Pediatr Neurol.* 2021;124:21-23.
19. Swieten JCvan, Koudstaal PJ, Visser MC, Schouten HJ, Gijn Jvan. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke.* 2018;19:604-607.
20. Team RCR. A Language and Environment for Statistical Computing. R Foundation for Statistical Computing. 2022.
21. Hothorn T, Hornik K, Wielvan de MA, Zeileis A. A lego system for conditional inference. *Am Statistician.* 2006;60:257-263.
22. Venables WN, Ripley BD. *Modern Applied Statistics with S. Stat Comput; Springer, New York.* 2002.
23. Zuur AF, Ieno EN, Walker N, Saveliev AA, Smith GM, Walker NJ. Mixed effects models and extensions in ecology with R. Statistics Biology Heal;2009:245-259.
24. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc Ser B Methodol.* 1995;57:289-300.
25. Anderson PJ. Leader of the pack. *J Int Neuropsych Soc.* 2013;19:488-489.
26. Prüss H, Finke C, Höltje M, et al. N-methyl- D-aspartate receptor antibodies in herpes simplex encephalitis. *Ann Neurol.* 2012;72:902-911.
27. Marcus L, Ness JM. Pediatric N-Methyl-d-Aspartate (NMDA) receptor encephalitis, with and without herpes encephalitis. *J Child Neurol.* 2021;36:743-751.
28. Nissen MS, Ørvik MS, Nilsson AC, Ryding M, Lydolph M, Blaabjerg M. NMDA-receptor encephalitis in Denmark from 2009 to 2019: a national cohort study. *J Neurol.* 2022;269:1618-1630.
29. Shim Y, Kim SY, Kim H, et al. Clinical outcomes of pediatric anti-NMDA receptor encephalitis. *Eur J Paediatr Neuro.* 2020;29:87-91.
30. Gable MS, Sheriff H, Dalmau J, Tilley DH, Glaser CA. The frequency of autoimmune N-Methyl-D-Aspartate receptor encephalitis surpasses that of individual viral etiologies in young individuals enrolled in the California encephalitis project. *Clin Infect Dis.* 2012;54:899-904.
31. Erickson TA, Muscal E, Munoz FM, et al. Infectious and autoimmune causes of encephalitis in children. *Pediatrics.* 2020;145:e20192543.
32. Cellucci T, Mater HV, Graus F, et al. Clinical approach to the diagnosis of autoimmune encephalitis in the pediatric patient. *Neurol Neuroimmunol Neuroinflamm.* 2020;7:e663.
33. Nosadini M, Eyre M, Molteni E, et al. Use and safety of immunotherapeutic management of N-Methyl-d-Aspartate receptor antibody encephalitis. *Jama Neurol.* 2021;78:1333-1344.
34. McKeon GL, Robinson GA, Ryan AE, et al. Cognitive outcomes following anti-N-methyl-D-aspartate receptor encephalitis: a systematic review. *J Clin Exp Neuropsyc.* 2018;40:234-252.
35. Bruijn MAAMde, Aarsen FK, Oosterhout MPvan, et al. Long-term neuropsychological outcome following pediatric anti-NMDAR encephalitis. *Neurology.* 2018;90:e1997-e2005.
36. Heine J, Kopp UA, Klag J, Ploner CJ, Prüss H, Finke C. Long-term cognitive outcome in anti–N-Methyl-D-Aspartate receptor encephalitis. *Ann Neurol.* 2021;90:949-961.
37. Matricardi S, Patrini M, Freri E, et al. Cognitive and neuropsychological evolution in children with anti-NMDAR encephalitis. *J Neurol.* 2016;263:765-771.
38. Finke C, Kopp UA, Prüss H, Dalmau J, Wandinger K-P, Ploner CJ. Cognitive deficits following anti-NMDA receptor encephalitis. *J Neurol Neurosurg Psychiatry.* 2012;83:195.
39. Hinkle CD, Porter JN, Waldron EJ, Klein H, Tranel D, Heffelfinger A. Neuropsychological characterization of three adolescent females with anti-NMDA receptor encephalitis in the acute, post-acute, and chronic phases: an inter-institutional case series. *Clin Neuropsychologist.* 2017;31:268-288.
40. McKeon GL, Scott JG, Spooner DM, et al. Cognitive and social functioning deficits after anti-N-Methyl-D-Aspartate receptor encephalitis: an exploratory case series. *J Int Neuropsych Soc.* 2016;22:828-838.
41. Chen Z, Wu D, Wang K, Luo B. Cognitive function recovery pattern in adult patients with severe anti-N-Methyl-D-Aspartate receptor encephalitis: a longitudinal study. *Front Neurol.* 2018;9:675.
42. Lim J, Lee S, Moon J, et al. Development of the clinical assessment scale in autoimmune encephalitis. *Ann Neurol* 2019;85:352-358.

Retrospective Pediatric Cohort Study Validates NEOS Score and Demonstrates Applicability in Children With Anti-NMDAR Encephalitis

Marc Nikolaus, Philipp Rausch, Kevin Rostásy, et al.

Neurol Neuroimmunol Neuroinflamm 2023;10;
DOI 10.1212/NXI.0000000000200102