Clinical characterisation of patients in the post-acute stage of anti-NMDA receptor encephalitis: a prospective cohort study and comparison with patients with schizophrenia spectrum disorders

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Summary

Background Anti-NMDA receptor (NMDAR) encephalitis is associated with a post-acute stage that is not well known. We aimed to describe the clinical features of this stage, similarities with schizophrenia spectrum disorders, and the factors that predict cognitive–psychiatric outcomes and could serve as prognostic biomarkers.

Methods In this prospective cohort study, participants (aged 12–60 years) with anti-NMDAR encephalitis during the post-acute stage visited Hospital Clínic de Barcelona (Barcelona, Spain) on three occasions (at study entry [V1], at 6 months [V2], and at 12 months [V3]) and underwent comprehensive neuropsychiatric evaluations. Similar evaluations were done in a group of age-matched participants with schizophrenia spectrum disorders and a group of age-matched and sex-matched healthy participants also recruited from Hospital Clínic de Barcelona. We analysed differences between and within groups in the longitudinal follow-up using multilevel linear mixed-effect models, adjusting for group, age, sex, and socioeconomic status to control for possible confounding.

Findings Between Jan 1, 2017, and Sept 30, 2020, 82 participants were recruited, 28 (34%) with anti-NMDAR encephalitis, 27 (33%) with schizophrenia spectrum disorders, and 27 (33%) healthy participants. Although, by V1 (median 4 months [IQR 3–7] from disease onset), many acute-stage symptoms in participants with anti-NMDAR encephalitis had resolved (acute stage median modified Rankin Scale [mRS] score 5 [IQR 4–5] *vs* V1 mRS score 2 [1–2]; p<0·0001), 25 (89%) participants showed deficits in at least one cognitive domain. In this group, 15 (68%) of 22 cognitive domain variables were impaired at V1, whereas only eight (36%) were altered at V3 (p=0·016). In participants with schizophrenia spectrum disorders, 11 (50%) of 22 variables (all shared with participants with anti-NMDAR encephalitis) were impaired at V1, without changes at V3. Two acute-stage features of anti-NMDAR encephalitis (ie, decreased consciousness and no improvement within the first 4 weeks of treatment) predicted cognitive domain outcomes, and a visuospatial task (ie, serial biases) at V1 showed potential in predicting learning and memory outcomes. At V1, all psychiatric symptom clusters were similarly altered in participants with anti-NMDAR encephalitis and in those with schizophrenia spectrum disorders, but only those in individuals with anti-NMDAR encephalitis subsequently improved (p=0·031). The greatest cognitive–psychiatric improvement in participants with anti-NMDAR encephalitis occurred between V1 and V2. During this interval, four (14%) participants with anti-NMDAR encephalitis would have met the diagnostic criteria of schizophrenia if CSF antibody findings had not been investigated.

Interpretation The cognitive–psychiatric symptoms of anti-NMDAR encephalitis in the post-acute stage resembled those of stabilised schizophrenia, but only those in participants with anti-NMDAR encephalitis progressively improved, predominantly during V1–V2. These findings are important for clinical trials on anti-NMDAR encephalitis and suggest that prompt cognitive–psychosocial rehabilitation might be a valuable intervention.

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Introduction

Over the past 15 years, anti-NMDA receptor (NMDAR) encephalitis has transitioned from being an unknown disease to the most common encephalitis that is mediated by neuronal autoantibodies.[1] This change suggests an overall improvement in the diagnosis and treatment of the acute phase of the disease. However, there are symptoms of the disease that persist or develop after hospital discharge (ie, the post-acute stage) that have received less attention. A reason for this scant

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See Online for appendix

Research in context

Evidence before this study

We searched MEDLINE and Embase for articles published in English from date of database inception to April 30, 2022, using the Medical Subject Heading terms: "NMDA receptor encephalitis", "cognitive deficits", "psychosis", "schizophrenia", or "recovery phase". This search showed that anti-NMDAR encephalitis is characterised by a well defined acute phase, during which patients need hospital admission for symptomatic care, immunotherapy, and tumour removal if necessary. Following improvement of this stage, patients are discharged from hospital with residual or emerging cognitive, behavioural, and psychiatric alterations. This second stage is long-lasting, poorly understood, and clinically challenging. Previous reports have described prolonged cognitive deficits; however, to date, the spectrum of symptoms, which might also include psychiatric alterations, has not been comprehensively examined. This knowledge gap, particularly during the first year of the recovery phase, results in uncertainty concerning the treatment approach, in establishing endpoints for clinical trials, and in the differential diagnosis with psychiatric disorders (eg, schizophrenia spectrum disorders).

Added value of this study

This prospective cohort study describes the clinical features of participants with anti-NMDAR encephalitis during the post-acute stage and compares them with both age-matched individuals with stable symptoms of schizophrenia spectrum disorders and age-matched and sex-matched healthy participants. All participants underwent extensive neuropsychiatric evaluations at three follow-up visits over a 1-year period (at study entry, at 6 months, and at 12 months). Two features of the acute stage of anti-NMDAR encephalitis (ie, decreased level of consciousness and no improvement within the first 4 weeks of treatment), as well as a visuospatial task (ie, serial biases) at study entry, predicted cognitive outcomes. This study shows that some patients with anti-NMDAR encephalitis can fulfil the diagnostic criteria of schizophrenia if CSF antibody studies or anti-NMDAR encephalitis are not included in the differential diagnosis.

Implications of all the available evidence

Compared with the acute stage of anti-NMDAR encephalitis, the clinical features of the post-acute stage are substantially different and long-lasting, including cognitive–psychiatric alterations that closely resemble those in individuals with stable symptoms of schizophrenia spectrum disorders. Most cognitive–psychiatric alterations started at presentation of anti-NMDAR encephalitis, preceded all treatments, and continued to improve during the post-acute stage while treatments used in the acute stage were tapered or discontinued. These cognitive–psychiatric alterations and the course of symptoms should be considered when establishing endpoints and outcome measures in clinical trials. The time course of cognitive and psychiatric improvement suggests a time window (the first 6 months), during which intensive cognitive and psychosocial interventions might accelerate recovery and improve cognitive outcomes. Furthermore, the similarity of these alterations with those of individuals with schizophrenia spectrum disorders needs to be considered in the differential diagnosis of patients with psychiatric disorders and when applying the current diagnostic criteria of schizophrenia.

attention is the marked difference in the type and severity of symptoms of the acute stage and the post-acute stage. Whereas the acute stage is associated with rapid onset of behavioural and psychiatric symptoms, along with life-threatening seizures, decreased consciousness, dysautonomia, or hypoventilation,[2] the post-acute stage is characterised by the resolution of many of these symptoms but persistence or emergence of lesser known cognitive, behavioural, sleep, and psychiatric alterations.[3] This post-acute stage is often perceived as a non-active or recovery phase, even though studies suggest that it is associated with cognitive deficits that interfere with patients' academic, occupational, or social interactions.[4–6]

Some previous reports have described protracted cognitive deficits in anti-NMDAR encephalitis; however, further psychopathological changes have not been investigated.[4–7] Otherwise, reports focused on the psychiatric alterations were based on partial aspects of the disease, usually at onset,[8] or reviews of the literature without considering the clinical stage or associated cognitive dysfunction.[9–11] Although some of these reviews suggested similarities with schizophrenia,[9–13] no study has comprehensively addressed and compared the cognitive and psychiatric alterations between individuals with anti-NMDAR encephalitis and those with schizophrenia.

Most investigators agree on the overall management of the acute stage of anti-NMDAR encephalitis, including escalation of immunotherapy and tumour removal when needed;[2,14] however, the treatment approach for the post-acute stage is less clear. Furthermore, characterisation of this stage during the first year after hospital discharge is needed for the planning and assessment of symptomatic care and to define the endpoints and efficacy of clinical trials.

These gaps in knowledge led us to design a prospective cohort study that included participants with anti-NMDAR encephalitis in the post-acute stage, participants with schizophrenia spectrum disorders, and healthy participants. We aimed to describe the clinical features of the post-acute stage of anti-NMDAR encephalitis, previously unappreciated similarities between anti-NMDAR encephalitis and schizophrenia spectrum

disorders, and the factors that predict cognitive–psychiatric outcomes and could serve as prognostic biomarkers.

Methods

Study design and participants

In this prospective cohort study, patients aged 12–60 years with anti-NMDAR encephalitis in the post-acute stage (ie, within 4 months of hospital discharge from the acute stage) were invited to participate. The study consisted of three visits at Hospital Clínic de Barcelona (Barcelona, Spain): the first at study entry (V1), the second 6 months later (V2), and the third 12 months after V1 (V3). Each visit included 2 days and 1 night of hospitalisation, during which time patients underwent neurological, cognitive, psychiatric, EEG, MRI, and sleep investigations. Similar evaluations were done in a group of age-matched participants with schizophrenia spectrum disorders (schizophrenia: Diagnostic and Statistical Manual of Mental Disorders, fifth edition [DSM-5] 295.90, F20.9; schizoaffective disorder: DSM-5, 295.70, F25.0) with stable symptoms, and a group of sex-matched and age-matched healthy participants, also recruited from Hospital Clínic de Barcelona (appendix p 2).

This study was approved by the Ethical Board Committee of Hospital Clínic de Barcelona. Written informed consent was obtained from participants or their proxies, if patients were younger than 18 years.

Procedures

We obtained demographic information, including years of education, occupation, and socioeconomic status, at all three study visits. For participants with anti-NMDAR encephalitis, we recorded additional information comprising the clinical features of the acute stage, immunotherapy, the modified Rankin Scale (mRS) score,[15] the Clinical Assessment Scale in Autoimmune Encephalitis score,[16] and the anti-NMDAR Encephalitis One-Year Functional Status score.[17]

All participants also underwent structured cognitive and psychiatric evaluations at the three study visits. Cognitive evaluation comprised nine validated tests that measured 22 variables across six cognitive domains: intelligence quotient, working memory, learning and memory, processing speed, executive functions, and attention (appendix pp 3, 13–14). Additionally, the Montreal Cognitive Assessment[18] was used as a screening test of global cognition and to assess language.

We have previously described reduced serial biases during a visuospatial working memory task among participants with anti-NMDAR encephalitis and those with schizophrenia spectrum disorders, compared with healthy participants.[19] Therefore, we assessed the associations between serial biases and cognitive domains.

Psychiatric and functional evaluations comprised structured psychiatric interviews based on either the Structured Clinical Interview guidelines (for adults) or the Kiddie Schedule for Affective Disorders and Schizophrenia guidelines (for children) as per DSM, fourth edition (text revision) criteria (DSM-IV-TR; the translated version of the DSM that is currently available in Spanish); past and current psychiatric disorders as per DSM-5 criteria; level of functioning; suffered stress; and scales quantifying seven variables regarding symptoms of psychosis (Positive and Negative Syndrome Scale [PANSS]), depression (Hamilton Depression Rating Scale), mania (Young Mania Rating Scale), and global psychosocial and occupational disability (Global Assessment of Functioning [GAF] scale (appendix pp 3, 15–16). Basic activities of daily living were defined as self-care activities routinely performed (equivalent to mRS score ≤2).

Statistical analysis

Cross-sectional comparisons between the three groups were done with ANCOVA and χ^2 tests, as appropriate. Analyses were adjusted for age, sex, and socioeconomic status. Post-hoc analyses with Bonferroni correction for post-hoc multiple comparisons were applied to all analyses.

We analysed differences between and within groups in the longitudinal follow-up using multilevel linear mixed-effect models (Lme4 R package [version 1.1.27.1]), with group, age, sex, and socioeconomic status as fixed variables, and the time per group as a longitudinal interaction effect. Residual plots were used to validate these models. Comparisons were done with emmeans library (version 1.7.3) and the Tukey method for post-hoc correction for multiple testing. The global tendency of recovery of cognitive deficits in anti-NMDAR encephalitis (proportion of patients compared with the general population in each domain) was assessed with the Cochran–Armitage test for trend; other comparisons within the group of patients with anti-NMDAR encephalitis were done with the Wilcoxon signed-rank test and McNemar's test. To identify clinical features of the acute stage of anti-NMDAR encephalitis that were associated with cognitive and psychiatric outcomes, simple linear regression analyses were performed. Correlations between serial biases and mean standard T scores for each cognitive domain were done with one-sided Spearman correlation.

All analyses were addressed considering a two-tailed type 1 error of 5% with significance set at $p<0·05$. All analyses were done using SPSS (version 25.0) and R (version 4.1.2). Altered variables are provided with four levels of significance: $p<0·05$, $p<0·005$, $p<0·0005$, and $p<0·0001$.

For more on the **Lme4 R package** see https://cran.r-project.org/web/packages/lme4/lme4.pdf

For more on **emmeans library** see https://cran.r-project.org/web/packages/emmeans/emmeans.pdf

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

	Participants with acute-stage anti-NMDAR encephalitis (n=28)
Age at disease onset, years	27 (21–35; 13–57)
Sex	
Female	22 (79%)
Male	6 (21%)
Time from symptom onset to correct diagnosis, days	31 (17–39)
Cognitive and psychiatric alterations*	
Cognitive deficits	28 (100%)
Behavioural or psychiatric alterations	27 (96%)
General neurological findings†	
Any type	28 (100%)
Language or speech alterations	27 (96%)
Seizures	15 (54%)
Altered level of consciousness	15 (54%)
Abnormal movements	17 (61%)
Sleep disorder	27 (96%)
Autonomic dysfunction	17 (61%)‡
Brainstem or cerebellar symptoms	5 (18%)
Focal deficit (motor or sensory)	4 (14%)
Initially misdiagnosed with a primary psychiatric disorder	15 (54%)
Abnormal brain MRI	7 (25%)§
Abnormal EEG	23 (82%)¶
CSF with pleocytosis	20 (71%)
White blood cell count, cells per mm³	13 (5–28)
NMDAR antibodies	
CSF	28 (100%)
Serum	24 (86%)
Ovarian teratoma	6 (21%)
Stay in ICU	15 (54%)
Duration of ICU stay, days	17 (4–30)
Time from symptom onset to treatment, days‖	24 (17–35)
(Continued from previous column)	
Time from treatment to initial improvement, weeks	2 (2–6)
Antiseizure medication	23 (82%)
Antipsychotic medication	27 (96%)
Immunotherapy	
First-line	28 (100%)**
Second-line	24 (86%)††
First-line only	4 (14%)
Duration of hospital admission, days	46 (24–64)
CASE scale	11 (8–14; 5–23)
Worst mRS score during acute stage	5 (4–5; 3–5)
mRS score at hospital discharge	2 (2–3; 2–4)
NEOS score	2 (1–3; 0–4)

Data are median (IQR), median (IQR; range), or n (%). NMDAR=NMDA receptor. ICU=intensive care unit. CASE=Clinical Assessment Scale in Autoimmune Encephalitis. mRS=modified Rankin Scale. NEOS=anti-NMDAR Encephalitis One-Year Functional Status. FLAIR=fluid-attenuated inversion recovery. *Information provided by physicians involved in the acute stage of anti-NMDAR encephalitis. †Findings present any time during the acute stage. ‡Ten (35%) participants had more than two signs of autonomic instability, needed vasoactive drugs, or both. §Five (18%) participants had increased non-contrast enhancing T2 or FLAIR signal involving the right cortical temporal lobe (n=2), the right mesial temporal lobe (n=2), and the right insula and frontobasal region (n=1). One (4%) participant had increased T2 or FLAIR signal in the right cortical temporal lobe with mild gyral enhancement, and one (4%) participant had increased T2 or FLAIR signal with leptomeningeal enhancement in the right mesial temporal lobe. ¶Slow background activity (n=14), interictal epileptiform activity (n=4), and electrographic seizures, status epilepticus, or both (n=5). ||Immunotherapy, tumour treatment, or both. **Steroids (n=27), intravenous immunoglobulins (n=24), and plasma exchange (n=7). ††Rituximab (n=24) and cyclophosphamide (n=7).

Table 1: **Neurological features of participants during the acute stage of anti-NMDAR encephalitis**

Results

Between Jan 1, 2017, and Sept 30, 2020, 82 participants were enrolled in the study: 28 (34%) with anti-NMDAR encephalitis (22 [79%] women and six [21%] men), 27 (33%) with schizophrenia spectrum disorders (16 [59%] with schizophrenia and 11 [41%] with schizoaffective disorder; 15 [56%] women and 12 [44%] men), and 27 (33%) healthy participants (21 [78%] women and six [22%] men). Five additional patients with anti-NMDAR encephalitis refused to participate; the clinical status of these patients at hospital discharge was similar to that of the recruited patients. 74 (90%) participants completed the study: 26 with anti-NMDAR encephalitis, 22 with schizophrenia spectrum disorders, and 26 healthy participants. One participant with anti-NMDAR encephalitis had a relapse and was excluded from cross-sectional comparisons between groups at V3 but was included in the rest of the analyses. The main reason for missing follow-up visits or abandoning the study was related to logistical difficulties during the COVID-19 pandemic. Overall, the study included 212 visits, representing a total of 424 days and 212 nights in hospital admissions. The first visit (V1) was after a median of 4 months (IQR 3–7) from disease onset for participants with anti-NMDAR encephalitis; V2 was a median of 10 months (9–12) from disease onset; and V3 was a median of 16 months (15–19) from disease onset. For participants with schizophrenia spectrum disorders, V1 was at a median of 40 months (IQR 16–130) of disease duration.

Demographic and psychopharmacological information is shown in the appendix (p 17). Compared with participants with anti-NMDAR encephalitis and healthy participants, participants with schizophrenia spectrum disorders had a lower socioeconomic status and a higher frequency of past and solved psychiatric disorders, and they were receiving a higher dose of antipsychotic medication (appendix p 17). Participants with anti-NMDAR encephalitis reported higher levels of stress during the month that preceded disease onset than did

	V1 (n=28)	V3 (n=26)	p value
Time from disease onset, months	4 (3–7)	16 (15–19)	..
Cognitive and psychiatric alterations*			
Cognitive deficits	25 (89%)	10 (40%)	0·0007
Psychiatric and behavioural alterations†	24 (86%)	11 (44%)	0·0020
General neurological findings			
Any type	16 (57%)	6 (23%)	0·0020
Language or speech alterations‡	7 (25%)	1 (4%)	0·031
Seizures	1 (4%)	1 (4%)	>0·99
Abnormal movements	3 (11%)§	0	0·25
Sleep disorder (with polysomnography)	8 (29%)¶	4 (15%)‖	0·13
Autonomic dysfunction	1 (4%)	0	>0·99
Apraxia or bradypsychia	4 (14%)	1 (4%)	0·25
BMI, kg/m²	24 (21–30)	27 (24–31)	0·12
Abnormal brain MRI	3/26 (12%)**	4/22 (18%)††	>0·99
Abnormal EEG	9 (32%)‡‡	5/22 (23%)§§	0·13
NMDAR antibodies in serum	11/27 (41%)	1/26 (4%)	0·0018
Antiseizure medication	14 (50%)	7 (27%)	0·016
Antipsychotic medication	9 (32%)	0	0·0040
Antidepressant medication	3 (11%)	2 (8%)	>0·99
Benzodiazepines	6 (21%)	1 (4%)	0·063
Immunotherapy	13 (46%)	2 (8%)	0·0010
Symptoms reported by participants and caregivers			
Any type	27 (96%)	16 (62%)	0·0039
Attention or concentration difficulties	21 (75%)	8 (31%)	0·0010
Irritability	15 (54%)	9 (35%)	0·13
Hyperphagia	15 (54%)	5 (19%)	0·021
Hypersomnia	14 (50%)	4 (15%)	0·039
Decreased interest or participation in social activities	12 (43%)	2 (8%)	0·0061
Apathy, avolition, or both	12 (43%)	2 (8%)	0·0080
Memory problems	9 (32%)	5 (19%)	0·45
Depressed mood	9 (32%)	4 (15%)	0·063
Insomnia	2 (7%)	1 (4%)	>0·99
Additional symptoms reported by caregivers			
Impulsivity, compulsivity, or both	6 (21%)	0	0·031
Sexual disinhibition	2 (7%)	1 (4%)	>0·99
Euphoria	1 (4%)	1 (4%)	>0·99
mRS score	2 (1–2; 1–3)	1 (0–1; 0–2)	0·0004
Impairment of basic activities of daily living or mRS score ≥2	20 (71%)	4 (15%)	<0·0001
Severe deficits according to GAF scale score¶¶	20 (71%)	2 (8%)	<0·0001

Data are median (IQR), median (IQR; range), n (%), or n/N (%). NMDAR=NMDA receptor. V1=visit at study entry. V3=visit 12 months after V1. mRS=modified Rankin Scale. GAF=Global Assessment Functioning. FLAIR=fluid-attenuated inversion recovery. *Excluding one participant who had a clinical relapse before V3. Further detail on cognitive and psychiatric features are provided in the appendix (pp 19–20). †Defined by a score of ≥3 in at least one item of the Positive and Negative Syndrome Scale, Hamilton Depression Rating Scale, or Young Mania Rating Scale. ‡Assessed with spontaneous speech and language variables from the Montreal Cognitive Assessment test. §Generalised rigidity (n=1), polymyoclonus movements (n=1), and stereotyped movements (n=1). ¶Confusional arousals (n=7) and rapid eye movement sleep behaviour disorder (n=1). ‖Persisting (n=3) and new (n=1) confusional arousals. **Increased FLAIR signal in left hippocampus (n=1), left mesial temporal sclerosis (n=1), and bilateral hippocampal atrophy (n=1). ††Increased FLAIR signal in left hippocampus (n=1), right mesial temporal sclerosis (n=1), left mesial temporal sclerosis and mild global atrophy (n=1), and bilateral temporal atrophy (n=1). ‡‡Electrographic seizures (n=1), interictal epileptiform activity (n=1), and focal slow activity (n=7). §§Electrographic seizures (n=1), interictal epileptiform activity (n=1), and focal slow background activity (n=3). ¶¶The GAF scale measures psychosocial and occupational disability (score ≤70 denotes disability).

Table 2: **Clinical features identified in participants at examination in the post-acute stage of anti-NMDAR encephalitis, and symptoms reported by participants and caregivers**

healthy participants during the month before V1 (appendix p 17).

Neurological features, frequency of misdiagnosis, and immunotherapy during the acute stage of anti-NMDAR encephalitis are shown in table 1 and in the appendix (pp 4–5). 15 (54%) of the 28 participants with anti-NMDAR encephalitis were initially misdiagnosed with primary psychiatric disorders and 14 (50%) were first admitted to psychiatric wards. The diagnosis of anti-NMDAR encephalitis took a median of 31 days (IQR 17–39) to happen. The clinical features, evaluations, treatments, and symptoms reported by patients and caregivers during the post-acute stage (V1–V3) are shown in table 2. Treatments were progressively tapered or discontinued as per the clinical course and best clinical judgment of clinicians; therefore, at V3, seven (27%) of 26 patients were still receiving antiseizure medication, two (8%) were receiving immunotherapy, and none was receiving antipsychotic medications.

Overall, there was a general improvement of neurological and paraclinical features that was more notable from the acute stage (median mRS 5 [IQR 4–5]) to V1 (2 [1–2]; p<0·0001), and continued from V1 to V3 (1 [0–1]; p=0·0004; tables 1, 2). From the acute stage to V3, 25 (96%) of 26 participants with anti-NMDAR encephalitis became negative for serum NMDAR antibodies (appendix p 29). Two (7%) of 28 participants with anti-NMDAR encephalitis required additional interventions during the V1–V3 period; one had a clinical relapse 11 months after V1 that responded to immunotherapy, and the other had a thymoma that was removed. The brain MRI, EEG, and NMDAR antibody results in participants with schizophrenia spectrum disorders and in healthy participants at V1 are described in the appendix (p 5).

Despite the indicated functional and neurological improvement from the acute stage to V1, 25 (89%) of 28 participants with anti-NMDAR encephalitis showed

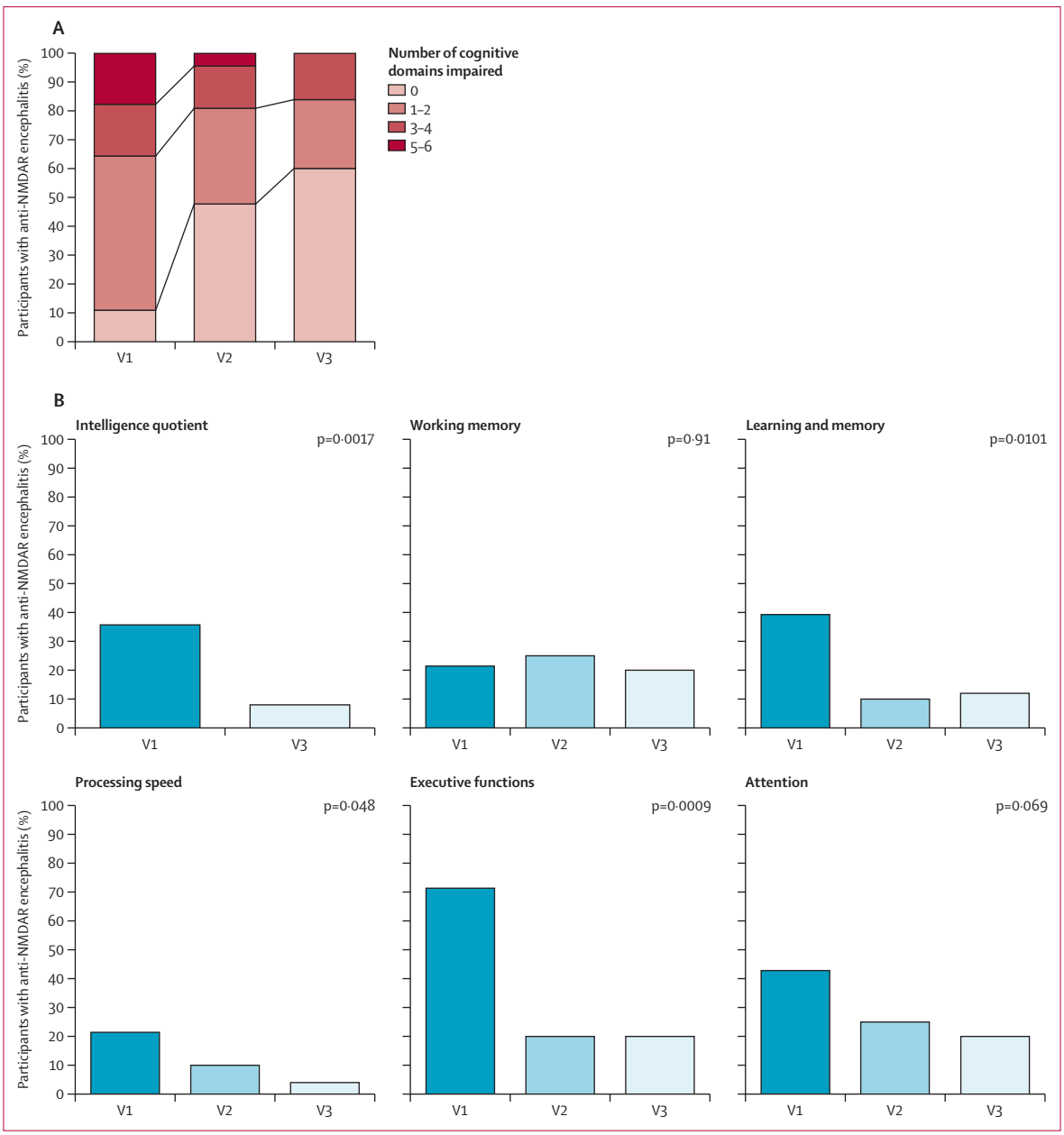

Figure 1: **Follow-up of cognitive domains in the post-acute stage of anti-NMDAR encephalitis**
A) Proportion of patients with anti-NMDAR encephalitis who had impaired cognitive domains at the three study visits (n=28 for V1, n=22 for V2, and n=25 for V3). B) Percentage of participants with anti-NMDAR encephalitis with deficits at a domain level (ie, a score of less than –1·5 SD in at least one test of the corresponding domain) for each of the three study visits. Intelligence quotient was not assessed at V2 to minimise test–retest learning. p values are for global longitudinal comparison between V1 *vs* V2 *vs* V3. NMDAR=NMDA receptor. V1=visit at study entry. V2=visit at 6 months. V3=visit at 12 months.

deficits in at least one cognitive domain at V1. The cognitive impairment involved one to two domains in 15 (54%) participants, three to four domains in five (18%) participants, and five to six domains in five (18%) participants; the other three (11%) participants had healthy cognitive function (figure 1A). The most frequently affected domain was executive functioning (20 [71%] participants; figure 1B). All participants with anti-NMDAR encephalitis had preserved reading and writing. During spontaneous conversation, seven (25%) participants had language alterations (three [11%] had reduced fluency and word finding, three [11%] had dysnomia, and one [4%] had reduced fluency). In the Montreal Cognitive Assessment, language fluency was altered in 16 (57%) participants with anti-NMDAR encephalitis and naming and abstraction tasks in four (14%).

At V3, cognitive deficits remained in ten (40%) of 25 participants with anti-NMDAR encephalitis (one excluded

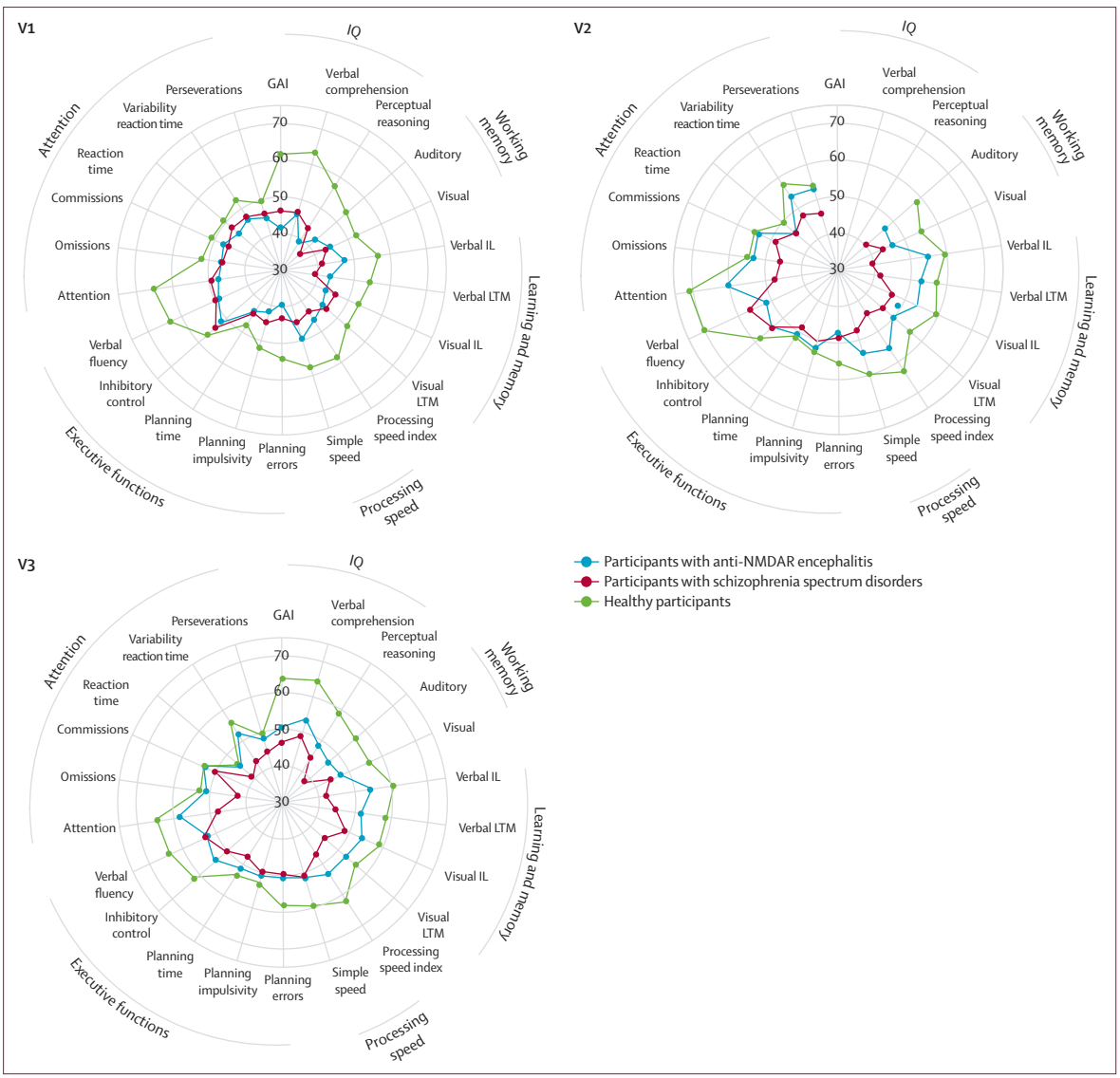

***Figure 2*: Comparison of variables of the six cognitive domains among study participants**
Radar plot comparing all variables of the six cognitive domains among participants with anti-NMDAR encephalitis, participants with schizophrenia spectrum disorders, and healthy participants at V1, V2, and V3. The radial axes show the mean standardised T scores for each neuropsychological variable in the three study groups. Intelligence quotient was not assessed at V2 to prevent test–retest learning. GAI=General Ability Index. NMDAR=NMDA receptor. IL=immediate learning. IQ=intelligence quotient. LTM=long-term memory. V1=visit at study entry. V2=visit at 6 months. V3=visit at 12 months.

because of relapse), which in six (24%) cases involved one to two domains, and in four (16%) cases involved three to four domains; the other 15 (60%) cases had healthy cognitive function (figure 1A). The most frequently affected domains were executive functions (five [20%]), working memory (five [20%]), and attention (five [20%]; figure 1B). During spontaneous conversation, one (4%) participant had difficulties in word finding. In the Montreal Cognitive Assessment, language fluency was altered in nine (36%) participants with anti-NMDAR encephalitis and naming and abstraction tasks in four (16%).

For most domains, the greatest improvement occurred during the interval between V1 and V2, except for working memory, which remained unchanged during the study period (figure 1B, appendix pp 18–20).

The post-hoc analysis at V1, which compared the cognitive performance of participants with anti-NMDAR encephalitis and participants with schizophrenia spectrum disorders with that of healthy participants, showed that those with anti-NMDAR encephalitis had worse performance in all six domains, whereas those with schizophrenia spectrum disorders had worse performance in five domains (appendix pp 21–23). When considering the 22 variables of the six domains, 11 (50%) variables were altered in participants with anti-NMDAR encephalitis and in participants with schizophrenia

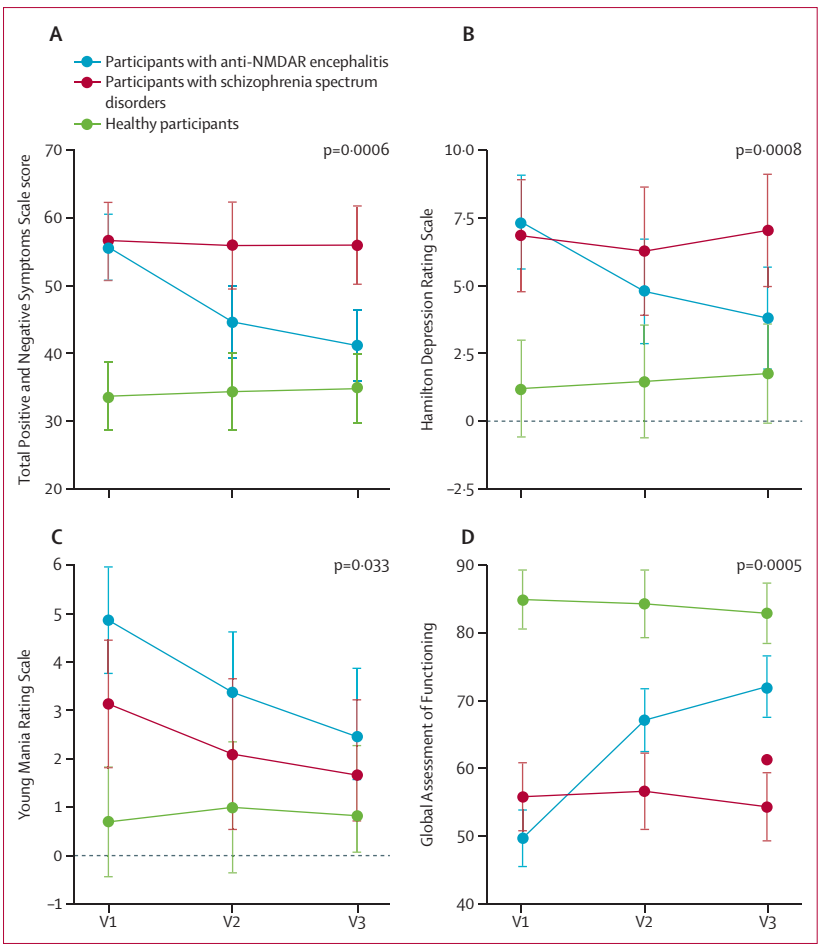

Figure 3: **Comparison of psychosocial function and psychiatric symptoms among study participants**
Longitudinal follow-up of the indicated tests in participants with anti-NMDAR encephalitis, participants with schizophrenia spectrum disorders, and healthy participants. Data are presented as adjusted means and 95% CI for longitudinal time-by-group interaction. NMDAR=NMDA receptor. V1=visit at study entry. V2=visit at 6 months. V3=visit at 12 months.

spectrum disorders. Participants from both groups had similar scores in nine of these variables (one of three intelligence quotient variables, two of two working memory variables, two of four learning and memory variables, two of two processing speed variables, and two of five executive function variables), and participants with anti-NMDAR encephalitis had worse scores in the other two variables than did those with schizophrenia spectrum disorders (two of three intelligence quotient variables). Among the remaining 11 variables, four were only altered in participants with anti-NMDAR encephalitis and the other seven were similar to healthy participants in both groups (figure 2; appendix pp 21–23).

At V3, participants with anti-NMDAR encephalitis still showed worse performance than did healthy participants in four of six cognitive domains (sparing learning and memory, and attention), whereas participants with schizophrenia spectrum disorders showed lower performance in five domains. Participants with anti-NMDAR encephalitis had lower scores than did healthy participants in eight (36%) of 22 variables, seven of which overlapped with deficits identified in those with schizophrenia spectrum disorders (three of three intelligence quotient variables, two of two working memory variables, one of two processing speed variables, and one of five executive function variables; figure 2; appendix pp 21–23).

Longitudinally, 11 (73%) of 15 variables that were initially altered improved in participants with anti-NMDAR encephalitis, representing at least one variable for each domain, except for working memory. Significant improvements were observed in seven (64%) of these 11 variables between V1 and V2, as well as between V1 and V3, and the other four (36%) variables between V1 and V3. No variables showed a significant improvement between V2 and V3 (appendix pp 19–20). Thus, when considering the 15 (68%) of 22 cognitive variables that were impaired at V1 (seven of which subsequently improved during V1–V3), only eight (36%) remained altered at V3 (p=0·016).

Overall, these cross-sectional comparisons and the longitudinal assessment showed a remarkable similarity in cognitive deficits between participants with anti-NMDAR encephalitis and those with schizophrenia spectrum disorders at V1, and a trajectory of progressive improvement in participants with anti-NMDAR encephalitis compared with those with schizophrenia spectrum disorders or healthy participants, who remained mostly unchanged between V1 and V3 (appendix pp 21–23).

Regarding the psychiatric assessment, 24 (86%) of 28 participants with anti-NMDAR encephalitis had psychiatric alterations in at least one test at V1. Participants with anti-NMDAR encephalitis scored a median of 55 (IQR 44–66) in the PANSS (abnormal if score >57), 6 (5–10) in the Hamilton Depression Rating Scale (abnormal if score >7), and 4 (2–7) in the Young Mania Rating Scale (abnormal if score >12) at V1 (appendix pp 24–25). Individual scores were consistent with mild psychotic symptoms in eight (29%) of 28 participants, moderate psychotic symptoms in three (11%), mild depression levels in 11 (39%), and hypomanic symptoms in two (7%).

At V3, participants with anti-NMDAR encephalitis scored a median of 38 (33–45) in the PANSS, 3 (1–6) in the Hamilton Depression Rating Scale, and 2 (0–4) in the Young Mania Rating Scale (appendix pp 24–25). Individual scores were consistent with mild psychotic symptoms in two (8%) of 25 participants and with mild depressive symptoms in three participants (12%). None of the participants had manic or hypomanic symptoms, and none was receiving antipsychotic medications.

At V1, the median GAF score (≤70 denotes disability) among participants with anti-NMDAR encephalitis was 45 (IQR 45–54; appendix pp 24–25), with individual scores consistent with severe disability in 20 (71%) of 28 participants, mild-to-moderate disability in five (18%), and normal functioning in three (11%). By contrast, the median GAF score at V3 was 75 (61–80; appendix pp 24–25), with scores consistent with severe disability in

two (8%) of 25 participants, mild-to-moderate disability in eight (32%), and normal functioning in 15 (60%).

The post-hoc analysis at V1, which compared the psychiatric scores of participants with anti-NMDAR encephalitis with those of healthy participants, showed that participants with anti-NMDAR encephalitis had higher scores in the total and three subscores of psychosis (PANSS) and on the scores of depression and mania. All psychiatric rating scales scores were similar between participants with anti-NMDAR encephalitis and those with schizophrenia spectrum disorders (appendix pp 24–25). Both groups also had similar GAF scores, which were significantly lower than those of healthy participants (appendix pp 24–25).

At V3, participants with anti-NMDAR encephalitis had higher scores than did healthy participants in the total and general scores of PANSS and in the scale of mania. By contrast, participants with anti-NMDAR encephalitis showed less severe ratings in all subscales of psychosis and depression, and similar ratings in mania symptoms, compared with those with schizophrenia spectrum disorders. At V3, the GAF score in participants with anti-NMDAR encephalitis was higher than in participants with schizophrenia spectrum disorders, but remained lower than in healthy participants and did not reach the pre-morbid GAF score (median 85 [IQR 79–90]; p=0·003).

These findings and the longitudinal psychiatric and functional assessments showed an overall improvement in participants with anti-NMDAR encephalitis: four (57%) of seven psychiatric variables significantly improved between V1 and V2, alongside V1 and V3, but none improved between V2 and V3 (appendix pp 19–20, 24–25), whereas scores did not change among participants with schizophrenia spectrum disorders (p=0·031) and healthy participants (p=0·13) during the follow-up (appendix pp 24–25; figure 3).

Simple linear regression analyses showed that only two acute clinical or paraclinical features of the acute stage of anti-NMDAR encephalitis were associated with poor outcomes in more than two cognitive domains or psychiatric variables at V3: decreased level of consciousness and no improvement within the first 4 weeks of treatment (appendix p 5).

Among participants, reduced serial biases during a visuospatial working memory task were found to be associated in particular with the learning and memory domain (appendix pp 6, 30). In participants with anti-NMDAR encephalitis, serial biases at V1 predicted the outcome of learning and memory at V3 (r=0·34; p=0·054) and showed a positive correlation (r=0·31; p=0·075) with the overall cognitive outcome (appendix pp 6, 30).

Given that most participants with anti-NMDAR encephalitis had cognitive and psychiatric alterations that resembled those of participants with schizophrenia spectrum disorders, we next assessed whether they fulfilled DSM-5 criteria of schizophrenia (appendix pp 26–27) 6 months after disease onset (corresponding to V1 or V2, depending on the participant). 26 (93%) of 28 participants with anti-NMDAR encephalitis fulfilled criterion A related to symptoms of psychosis; all (100%) met criterion B for impaired functioning, and 11 (39%) met criterion C concerning the persistence of psychotic features for at least 6 months. Although some participants developed depressive or manic symptoms, these were short-lasting or not major (criterion D). Thus, 11 (39%) participants met criteria A to D of schizophrenia. After excluding individuals at the acute stage of anti-NMDAR encephalitis with clinical, MRI, or EEG features suggesting autoimmune encephalitis, four (14%) of the 11 participants would have met all of the criteria for schizophrenia if CSF antibody findings had not been investigated (appendix pp 7–12, 26–27). None of the participants with anti-NMDAR encephalitis met the criteria for schizophrenia at V3.

Discussion

In this prospective cohort study, we observed that the post-acute stage of anti-NMDAR encephalitis was characterised by a cognitive–psychiatric syndrome accompanied by residual, often mild, neurological deficits from the acute stage. This post-acute phase was long-lasting, similar across participants with anti-NMDAR encephalitis, and resembled the syndrome of participants with stabilised schizophrenia spectrum disorders. However, although cognitive deficits and psychiatric alterations remained stable in participants with schizophrenia spectrum disorders, those in participants with anti-NMDAR encephalitis gradually improved.

In most respects, the acute phase of anti-NMDAR encephalitis showed the expected spectrum of neurological and psychiatric symptoms.[2] Nevertheless, roughly half the patients were initially misdiagnosed with primary psychiatric disorders and were first admitted to psychiatric wards. These findings, and the reported delay in the diagnosis of anti-NMDAR encephalitis, emphasise the existing problems in recognising the disease.[20]

During the acute phase of anti-NMDAR encephalitis, all participants received immunotherapy and symptomatic treatment that resulted in substantial neurological improvement, similar to that of previous reports.[2,14,21] Thus, at V1 (median 4 months from disease onset), many of the initial neurological symptoms had resolved, and just over half the participants had mild-to-moderate functional deficits (median mRS score 2). Nevertheless, almost all participants had cognitive deficits and psychiatric alterations that were in line with the problems described by participants and caregivers.[6,22] Altogether, these problems affected the basic activities of daily living of just under three-quarters of participants with anti-NMDAR encephalitis, indicating that the mRS should not be used as the primary endpoint for clinical trials in this patient group. During the V1–V3 interval, the general neurological assessment continued to improve, and by V3 (median 16 months from disease onset), about a quarter of participants showed deficits in the neurological

examination, and many of the initial problems described by participants and caregivers had resolved. This improvement was also reflected in the ability to carry out basic activities of daily living, which were impaired for only a few participants at V3.

The presence of persisting cognitive deficits after otherwise considerable neurological recovery from the acute stage of anti-NMDAR encephalitis has been noted previously.[4,6,7,23,24] In the current study, we further investigated cognitive functions and psychiatric symptoms, showing that, besides cognitive deficits, participants with anti-NMDAR encephalitis had poor performance in all psychiatric symptom scales at V1, which subsequently improved at follow-up. These alterations probably contributed to the noted psychological, social, and occupational disabilities, as judged with the GAF score. The observation that the greatest improvement in most cognitive deficits (except for working memory) and psychiatric alterations occurred between V1 and V2 suggests a time window in which intensive cognitive and psychosocial interventions, with a special focus on working memory, could hasten recovery and improve cognitive outcomes.[25]

A notable finding was the similarity of symptoms between participants with anti-NMDAR encephalitis in the post-acute stage and participants with stabilised schizophrenia spectrum disorders. For example, at V1, all psychiatric variables and half the variables of the cognitive domains were similarly impaired in both participant groups. A key difference was that, during the longitudinal assessment, all but two features (ie, working memory and PANSS positive subscore) improved significantly in participants with anti-NMDAR encephalitis, whereas cognitive and psychiatric scores did not change in participants with schizophrenia spectrum disorders.

In this study population, the One-Year Functional Status score, Clinical Assessment Scale in Autoimmune Encephalitis score, and mRS score during the acute phase did not predict cognitive–psychiatric outcomes in participants with anti-NMDAR encephalitis.[15–17] Attempts to identify features of the acute stage as predictors of cognitive–psychiatric outcomes showed that only two features (ie, decreased level of consciousness and no improvement within the first 4 weeks of treatment) were associated with poor performance in at least two cognitive or psychiatric variables. The scores from the serial biases in a visuospatial working memory task[19] obtained at V1 predicted the outcome of learning and memory. However, the relations we noted in reduced serial biases were not significant at the 5% level. Nevertheless, the task holds potential as a simple feasible biomarker and requires validation in larger study populations of patients with anti-NMDAR encephalitis.

The difficulty in differentiating anti-NMDAR encephalitis from psychiatric disorders not only occurs at disease onset[10,14,20,26,27] but can also involve the post-acute stage. The similarities of this stage with the cognitive–psychiatric alterations of schizophrenia spectrum disorders led us to assess how the current criteria for diagnosing schizophrenia fared in those cases. Four participants with anti-NMDAR encephalitis would have met criteria for schizophrenia if CSF samples or NMDAR antibodies had not been investigated. It could be argued that the initial episode of encephalitis or detection of NMDAR antibodies readily excludes the diagnosis of schizophrenia; however, this is not so straightforward in practice. First, CSF studies (required for the diagnosis of anti-NMDAR encephalitis) are scarcely obtained in psychiatric facilities,[26] and serum testing is unreliable.[28] A review of case series on first-episode psychosis or antibody-associated psychiatric disorders showed that only four (14%) of 28 series included CSF studies.[1] Second, a misdiagnosed or overlooked initial episode of anti-NMDAR encephalitis could avert recognition of the post-acute stage in individuals with enduring psychiatric–cognitive deficits, or who develop relapses with isolated psychiatric symptoms.[29] Albeit infrequent today, these problems could have been more common a few years ago when anti-NMDAR encephalitis was unknown.[13,30]

This study has several considerations and limitations. First, the different durations of symptoms between participants with anti-NMDAR encephalitis and those with schizophrenia spectrum disorders at V1 was related to the goals of the study and the different clinical course of these diseases. For individuals with anti-NMDAR encephalitis, V1 was dependent on the time of hospital discharge from the acute stage; however, for individuals with schizophrenia spectrum disorders, V1 had to occur any time after 6 months from disease onset (to meet the criteria of schizophrenia and schizoaffective disorders). Additionally, for comparison with participants with anti-NMDAR encephalitis, participants with schizophrenia spectrum disorders had to have stable symptoms (regardless of their duration), be on stable medication, and have a similar age.

Second, in line with previous studies,[7] a cognitive domain was considered to be altered if at least one variable or test was affected. Given that the number of variables is different across domains, in domains with fewer variables, each variable has more diagnostic weight. These considerations suggest that some domains were more robustly altered than others in participants with anti-NMDAR encephalitis (eg, learning and memory were more affected than attention).

Third, the follow-up time of the post-acute stage of anti-NMDAR encephalitis was 1 year (median 16 months from disease onset). It is probable that a longer follow-up would have shown further improvement, although possibly at a lower pace, as suggested by the decelerated improvement when comparing the first and last 6 months of the study. Previous reports have suggested that the process of recovery could take several years;[2,4,7] however, these studies were either retrospective or had a less systematic follow-up (eg, interval from disease onset to

first visit ranged from months to years),[7] did not include comprehensive psychiatric assessment, did not longitudinally evaluate healthy participants to control for test–retest learning effects, and did not interpret cognitive scores according to normative values of the general population.[4–7]

Fourth, although antipsychotic drugs or other medications could be perceived to be contributors to the cognitive deficits observed in participants with anti-NMDAR encephalitis, these deficits preceded the use of all medications, which were tapered or discontinued according to symptom improvement. Thus, we consider that the cognitive deficits observed in participants with anti-NMDAR encephalitis during the post-acute stage were predominantly caused by the disease, as part of its trajectory to improvement.

Fifth, our recruitment could have excluded patients with severe or irreversible deficits who were unable to travel to our centre; however, we are not aware of such cases during the study period.

Finally, although the sample size was relatively small, all participants were consecutively recruited and assessed with well defined neurological and psychiatric tests. All patients met the corresponding diagnostic criteria, and most participants with anti-NMDAR encephalitis received similar immunotherapies currently used to manage this disease. Therefore, the post-acute stage of anti-NMDAR encephalitis observed in this study population can be generalised to other patient populations with the disease.

Overall, compared with the acute stage of anti-NMDAR encephalitis, the clinical features of the post-acute stage are substantially different and long-lasting, including cognitive–psychiatric alterations that closely resemble those of individuals with stable symptoms of schizophrenia spectrum disorders. Most cognitive–psychiatric alterations start at disease presentation, precede all treatments, and continue to improve during the post-acute stage, whereas treatments used in the acute stage are tapered or discontinued. The cognitive and psychiatric features and course of symptoms of the post-acute stage should be taken into account when establishing endpoints and outcome measures in clinical trials. The time course of symptom improvement suggests a period (the first 6 months of the post-acute stage), during which intensive cognitive and psychosocial interventions might accelerate recovery and improve cognitive outcomes. The similarity between the post-acute stage of anti-NMDAR encephalitis and the psychiatric–cognitive alterations of individuals with schizophrenia spectrum disorders needs to be considered in the differential diagnosis of patients with psychiatric disorders and when applying the current diagnostic criteria of schizophrenia. Future work should address whether early cognitive and psychosocial rehabilitation accelerates improvement of cognitive deficits and psychiatric alterations, and leads to better outcomes in patients with anti-NMDAR encephalitis. Furthermore, the value of the indicated predictors of cognitive–psychiatric outcomes should be confirmed and, in particular, the serial biases assessment obtained at the post-acute stage as a predictor of memory and learning should be validated. This test is a simple quantitative visuospatial working memory task with the potential of being a biomarker of cognitive outcome.

Contributors

MG contributed to study design and conceptualisation, data collection, data interpretation, statistical analysis, figures and tables creation, literature search, writing, and critical approval of the final paper. MR-J contributed to study design, data collection, data interpretation, statistical analysis, and critical approval of the paper. AM-L, EM-H, TA, GS, HS, LP, HA, ED-L-S, DE, and SL contributed to data collection, data interpretation, and critical approval of the paper. RB and HS contributed to statistical analysis and critical approval of the paper. JP contributed to the design of the figures. RS-V, JS, AC, and JC-F contributed to study design, data interpretation, and critical approval of the paper. JD contributed to study design and conceptualisation, data interpretation, literature search, writing, and critical approval of the final paper, and obtained funding. MG, JC-F, and JD verified the underlying data. Members of the Spanish Anti-NMDAR Encephalitis Study Group participated in data collection. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

JD holds patents for the use of NMDAR as autoantibody tests. GS received speaker fees from Angelini Pharma. SL received compensation for consulting services and speaker honoraria from Biogen Idec, Novartis, Teva, Genzyme, Sanofi, and Merck. RS-V served in advisory boards meetings for Wave Lifesciences and Novo Nordisk; and received personal fees for participating in educational activities from Janssen, Roche Diagnostics, and Neuroxpharma, and funding to her institution for research projects from Biogen and Sage Pharmaceuticals. All other authors declare no competing interests.

Data sharing

Non-published anonymised data will be shared with qualified investigators on request to the corresponding author.

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