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RESEARCH ARTICLE

Disease progression and brain atrophy in NMDAR encephalitis: Associated factor & clinical implication

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Abstract

Objective: We investigated the longitudinal pattern, determining factors, and clinical implications of brain volume changes in N-methyl D-aspartate receptor-antibody (NMDAR) encephalitis. **Methods**: Baseline clinical profiles, treatment profiles, and outcome measured using the Clinical Assessment Scale in Autoimmune Encephalitis (CASE) and modified Rankin scale (mRS) were obtained from a long-term clinical database documenting an NMDAR encephalitis cohort. In serial MRI, the change in the normalized volume of different brain regions from the baseline evaluation was measured. At each MRI evaluation time point, the cumulative disease burden (CASE score × months) and the cumulative duration of status epilepticus were also evaluated. **Results**: Thirty-six patients were followed-up for 28.5 months (range 12–63 months). The volume ratio at last MRI to baseline was the lowest in the cerebellum (94.4 ± 5.7%, $p < 0.001$). Once developed, cerebellar volume reduction followed a progressive course until 2 years from disease onset. The degree of cerebellar volume reduction was positively correlated with mRS and total CASE scores (all, $p < 0.001$), and CASE scores in the domains of memory, language, and psychiatric problems, gait instability/ataxia, and weakness (all, $p < 0.01$). In linear mixed model analyses, the degree of cerebellar volume reduction was associated with cumulative disease burden up to 2 years ($p < 0.001$) and duration of status epilepticus ($p < 0.001$), and delayed removal of teratoma for ≥1 month ($p = 0.006$). **Interpretation**: In NMDAR encephalitis, cerebellar volume reduction was progressive once developed. Cerebellar volume reduction might reflect disease burden and extent of progression and be associated with poor outcomes in multiple functional domains.

Introduction

N-methyl D-aspartate receptor-antibody (NMDAR) encephalitis is caused by the binding of IgG autoantibodies to the NR1 subunit of the NMDAR, which causes the NMDAR to be internalized from the synaptic surface.[1–5] Approximately 75–80% of patients achieve a good long-term outcome by using a combination immunotherapy and removal of an associated teratoma.[6–9] However, there is substantial heterogeneity in the long-term outcomes, and a considerable number of patients still develop significant neurological sequelae.[5,6,10–13] Therefore, demonstrating the factors associated with permanent neurological deficits and poor long-term outcomes in this reversible disease might be a key to optimize the treatment protocol and to improve the outcome of NMDAR encephalitis.[13,14]

NMDAR encephalitis patients face two types of brain atrophy: diffuse cortical atrophy and cerebellar atrophy. Cortical atrophy is associated with extended periods of hospitalization, increased frequency of using ventilator care, and treatment-related adverse events, but is reversible and has an unclear association with long-term outcomes.[15,16] In contrast, cerebellar atrophy is known to be progressive, irreversible, and associated with poor long-term clinical outcomes.[17] Considering the cephalocaudal progression of NMDAR encephalitis initiating with cortical symptoms and gradually evolve to movement disorder, decreased consciousness, and brainstem and

autonomic dysfunctions,[5] brain volume changes might reflect the disease activity, extent of progression, and the burden of disease. However, previous imaging studies did not demonstrate the time course of these brain volume changes, factors affecting the degree of volume change, or the impact brain volume changes on outcomes in multiple functional domains.

Recently, we constructed a long-term clinical database of a NMDAR encephalitis cohort using a comprehensive scale for evaluating the severity of autoimmune encephalitis, the Clinical Assessment Scale in Autoimmune Encephalitis (CASE).[13,18] In this study, we hypothesized that long-term brain volume changes in NMDAR encephalitis might reflect the extent of progression and the cumulative burden of disease, and be associated with long-term outcomes. Using the clinical database of a NMDAR encephalitis, we evaluated the longitudinal patterns, and affecting factors of brain volume change in NMDAR encephalitis, and its impact on outcomes in multiple domains.

Methods

Study population

This study included all inpatients who participated in the NMDAR encephalitis cohort of a national referral hospital between 1 January 2014, and 31 August 2020; had baseline and follow-up MRI evaluations with at least a 3-month interval between the first and last evaluations; and underwent clinical follow-up for at least 12 months.[13] The diagnosis of NMDAR encephalitis was made by initial screening for autoantibodies in patients' serum and cerebrospinal fluid (CSF) by immunohistochemistry using rat brain sections, followed by a cell-based immunocytochemical assay (Euroimmune Ag, Luebeck, Germany) to detect synaptic autoantibodies against NMDARs.[7,13,19,20] Patients with comorbid neurologic complications that might affect brain volume changes were excluded. This study was approved by an institutional review board. Written informed consent was obtained from each patient or the patient's legal surrogate.

Clinical analysis

The CASE dataset of the NMDAR encephalitis cohort, documenting the serial changes in CASE scores, was also used in the present study. In this dataset, CASE scores were obtained at baseline, every 2 weeks for the first 12 weeks, every month for the next 3 months, and then every 3 months for the remainder of the follow-up period.[13] The CASE score consists of nine items, each scored from 0 to 3, for a total score of 0–27.[18] Two experts in autoimmune encephalitis (W.-J. L. and S.-T. L. or K. C.) independently performed the scoring, blinded to the MRI or other laboratory data.[13] Consensus was achieved for any discrepant cases.

Baseline MRI and CSF parameters included CSF white blood cell levels, protein levels, and the presence of T2 hyperintensities in temporal or extratemporal areas.[6,7,9,19,20] Refractory status epilepticus was defined as persisting status epilepticus despite appropriate doses of ≥2 types of antiepileptic drugs, including intravenous infusion of benzodiazepines or anesthetics.[21] For the patients with status epilepticus, the duration of status epilepticus was measured based on electroencephalography data.[22] For the patients with ovarian teratoma, whether the teratoma removal was delayed for ≥1 month was reviewed, which is associated with poor outcomes.[13]

The combination immunotherapy regimen included steroids, intravenous immunoglobulin (IVIG), rituximab, and tocilizumab. The usage and total cycle of each immunotherapy regimen were reviewed. The detailed protocol for each regimen has been described previously.[13] Because chronic use of antiepileptic drugs phenytoin or valproic acid could provoke cerebellar atrophy, the usage and the total doses of those drugs at the time of each MRI evaluation were measured.[23,24]

For every time point of follow-up brain MRI was performed, the cumulative disease burden was calculated by integrating CASE scores over time from onset to the time point of brain MRI (CASE score × months). To address that the cumulative disease burden could be overestimated in patients with chronic residual symptoms, cumulative disease burden summated up to 6-month, 1-year, 2-year, respectively, were also used in the analyses. Similarly, the cumulative duration of status epilepticus (days) was calculated at the time of each MRI evaluation.

Volumetric analysis

Baseline and follow-up MRI were performed using 1.5-T or 3.0-T units with protocols that included T1-weighted, T2-weighted, T2 fluid-attenuated inversion recovery, and gradient echo/susceptibility-weighted imaging. T1-weighted images were obtained with spine-echo sequences using the following parameters: number of slices = 25–30, slice thickness/gap size = 4.0–5.0/1.0–1.2 mm, repetition time/echo time = 466–2822/7.8–26 msec, field of view = 185–229 × 220–229 mm, and matrix = 320–352 × 192–256.

For volumetric brain analysis, axial T1-weighted images were anonymized and registered into an offline workstation. Automatic volumetric analysis of the brain segments was performed by a neurology expert (W.-J. L.), blinded to the clinical and outcome data, using FMRIB Software Library according to the following steps: brain extraction; intensity normalization; registration to a template;

segmentation into the cerebellum, cortex, frontal lobe, parietal lobe, temporal lobe, occipital lobe, and brainstem; volume measurement; and normalization to total intracranial volume (TIV) (Fig. S1). Normalization to TIV was to compensate the issue of the low-resolution images, by reducing inter-individual and inter-image variations of volume measurements.[25] Therefore, each volume parameter was expressed as a percentage (%, TIV). As high-resolution MRI images were not used to measure brain volume, volume measurement for the relatively small structures such as brainstem or structure without clear demarcation to adjacent structures, such as frontal, parietal, temporal, and occipital lobes, might have an issue of insufficient accuracy. Therefore, volume parameters in those regions were not included for further analysis for their association with the clinical parameters.

To evaluate the consistency of cerebellar and cortical volume measurements, those volumes were also manually measured. Using a semi-automated freeware NeuRoi software (Nottingham University, Nottingham, UK), cerebellar and cortical borders were identified and semi-automatically designated. The border between the cerebellum and the cerebellar peduncles was designated as the line connecting the posterior-median pole of the fourth ventricle and anterior pole of the cerebellar hemisphere in each side, in each axial cut. The border of cortex was designated as the outer border of caudate, externa capsule, putamen, and thalamus (Fig. S2). The volumes were automatically calculated by adding up the volumes in each axial cut and normalized using the TIV. Paired *t*-test was performed and interclass correlation coefficient was calculated to compare the volume parameters from the automatic and manual methods.

Outcome analysis

For each brain segment, the change in the normalized volume from the baseline evaluation was measured. Due to the lack of a population-based brain volume data covering the entire age-span of the study population, we arbitrarily defined a significant volume reduction as a volume change from baseline for more than 1.96 standard deviation (SD) of the normative baseline volume of the study population, which was 0.86% reduction in the normalized cerebellar volume, 3.79% reduction in the normalized cortex volume, 2.17% reduction in the normalized frontal lobe volume, 1.31% reduction in the normalized parietal lobe volume, 1.02% reduction in the normalized temporal lobe volume, 1.22% reduction in the normalized occipital lobe volume, and 0.03% reduction in the normalized brainstem volume.

Clinical outcomes at the last follow-up were classified according to CASE scores (excellent, 0–4; poor, 5–27) or modified Rankin scale (mRS) scores (favorable, 0–2; poor, 3–6).[6–9,13,20] The scores on the subdomains of the CASE, such as memory dysfunction, language problems, psychiatric symptoms, gait instability/ataxia, and weakness, were also reviewed.[13,18]

Statistical analysis

R version 3.6.0 (R Programming) were used for the statistical analyses. The results are presented as the mean ± standard deviation, median [interquartile range], or number (percentage). Paired *t*-test and interclass correlation coefficient was calculated to compare the volume parameters from the automatic and manual methods. Pearson's *r* or Spearman's rho were used to measure correlations between continuous variables. Paired *t*-test was performed to compare mean values, and the chi-square test was applied to compare frequencies between two groups. Age of onset, sex, and variables with $p < 0.10$ were included in multivariate repeated-measures linear mixed model (RM-LMM) analyses to evaluate the effect of factors on cerebellar or cortical volume changes. RM-LMM analyses were repeated sequentially removing the factors to achieve the lowest Bayesian information criterion value, which represents the best fitness of the model. Among the four cumulative disease burden parameters (disease burden summated up to 6-month, 1-year, 2-year, and without limitation), a parameter that exhibited the best fitness of the RM-LMM was selected. To adjust for the effect of different MRI parameters, RM-LMM analyses were repeated including magnetic field power, gap size, and number of slices. To adjust for the possible effect of high-dose corticosteroid administration on cerebral edema, RM-LMM analyses were repeated excluding patients who includes MRI evaluations performed during or within 2-weeks after high-dose corticosteroid administration.[26,27] Kaplan–Meier curves were generated for the rate of achieving a good clinical outcome based on the CASE scores according to the development of brain atrophy. In every analysis, a two-tailed $p < 0.05$ was considered statistically significant.

Data availability

The datasets generated and/or analyzed during the current study are not publicly available due to the further ongoing studies based on the dataset but are available from the corresponding author on reasonable request.

Results

Patient characteristics

From the 37 patients initially included, one patient with superimposed hypoxic brain damage was excluded and

remaining 36 patients (26 [72.2%] female, mean age of 28.9 ± 15.0 years old) were included in this study (Fig. 1). Thirty patients were reported in our previous study.[13] The median baseline CASE score was 20 [16.5–24] and the median mRS score was 5 [4, 5]. Nineteen (52.8%, all women) had ovarian teratomas, and its removal was delayed for ≥1 month in 7 (36.8%) patients. Twenty-two (61.1%) patients exhibited status epilepticus, with the median duration of 14 [9–33] days. Nineteen (52.8%) patients exhibited refractory status epilepticus. Immunotherapy was initiated 7 [4–32] days from the onset of symptoms.

The median duration of clinical follow-up was 28.5 [21–41] months (range 12–63 months). At the last follow-up, the median CASE score was 3.5 [1–9.5], and the median mRS score was 2 [1–3]. The frequency of excellent outcomes was 22 (61.1%) based on the CASE scores and 23 (63.9%) based on the mRS scores. A total of 6/14 (42.9%) patients with poor outcomes were continuing on immunotherapy schedules at the last follow-up, whereas the remaining patients had ended their immunotherapy schedules. No patient died during the follow-up period. A total of 127 MRI evaluations were included in this study. The median number of MRI evaluations was 3 [2–4], with a median interval of 16 [7.5–29.3] months between the first and last MRI evaluations. The detailed clinical, laboratory, treatment, and outcome profiles are described in Table 1.

Volume change profiles in brain segments

The mean normalized volumes by automatic and manual measurements at baseline were 8.40 ± 0.33% versus 8.42 ± 0.34% ($p = 0.280$) in the cerebellum and 54.15 ± 1.72% versus 54.06 ± 1.80% ($p = 0.171$) in the cortex, and at last follow-up were 7.89 ± 0.58% versus 7.90 ± 0.58% ($p = 0.385$) in the cerebellum and 52.44 ± 2.64% versus 52.51 ± 2.69% ($p = 0.408$) in the

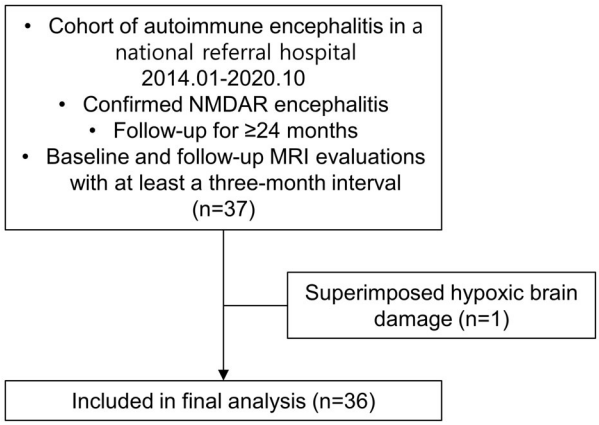


Figure 1. Flow diagram for the study population. From the initially included 37 patients, one patient with superimposed hypoxic brain damage was excluded, considering that those comorbidities might affect the brain volume changes.

Table 1. Clinical, laboratory, treatment, and outcome profiles of the study population.

	N = 36
Demographic & clinical profiles	
Male sex (%)	10 (27.8)
Age of onset (years)	28.9 ± 15.0
Initial CASE scores	20 [16.5–24]
Initial mRS scores	5 [4–5]
Teratoma association (%)	19 (52.8)
Total duration of teratoma presence[1] (days)	18 [9–60]
Refractory status epilepticus (%)	19 (52.8)
Total duration of status epilepticus[1] (days)	14 [9–33]
Use of ventilator care (%)	26 (72.2)
CSF/MRI profiles	
CSF protein level (mg/dL)	54.8 ± 51.8
CSF leukocyte level (cells/μL)	72.9 ± 99.4
T2 hyperintensities in temporal area (%)	13 (36.1)
T2 hyperintensities in extratemporal area (%)	11 (30.6)
Treatment profiles	
High-dose steroid treatment (%)	31 (86.1)
IVIG treatment (%)	34 (94.4)
IVIG cycles[1]	4 [1–12.5]
Rituximab treatment (%)	34 (94.4)
Rituximab cycles[1]	11 [5–14]
Tocilizumab (%)	29 (80.6)
Tocilizumab cycles[1]	3 [1–7.5]
Use of phenytoin	8 (22.2)
Total dose of phenytoin[1] (g)	29.7 [3.6–69]
Use of valproic acid	13 (36.1)
Total dose of valproic acid[1] (g)	61.2 [4.5–218.7]
Outcome profiles	
Follow-up duration (month)	16 [7.5–29.3]
Number of MRI evaluations	3 [2–4]
Cumulative disease burden at last MRI (CASE score × months)	147.8 [45.5–328]
Clinical follow-up duration (month)	28.5 [21–41]
CASE scores at last follow-up	3.5 [1–9.5]
Excellent (scores 0–4, %)	22 (61.1)
Memory dysfunction scores	1 [0–2]
Language problem scores	0 [0–2]
Psychiatric symptoms score	1 [0–2]
Gait instability/ataxia score	0 [0–0.3]
Weakness score	0 [0–0]
mRS scores at last follow-up	2 [1–3]
Favorable (scores 0–2, %)	23 (63.9)

Data are reported as mean ± standard deviation, or as median [interquartile range, IQR]. CASE, Clinical Assessment Scale in Autoimmune Encephalitis; mRS, modified Rankin scale; CSF, cerebrospinal fluid; IVIG, intravenous immunoglobulin.
[1]Data measured from subgroups with non-zero values.

cortex. The interclass correlation coefficients between the automatic and manual volume measurements were 0.902 (95% confidence interval [CI] 0.860–0.917) for cerebellum and 0.939 (95% CI 0.887–0.956) for cortex. Due to the high correlation, we used volume parameters from automatic measurement in the following analyses.

In follow-up MRI evaluations, cerebellar volume reduction of ≥0.86 (%, TIV), which corresponds to the volume reduction for more than 1.96 SD of the baseline volume in the study population, was identified in 10 (27.8%) patients and cortex volume reduction of ≥3.79 (%, TIV) was identified in in 6 (16.7%) patients. At last MRI follow-up, the mean brain volumes were significantly reduced from the baseline in every brain segment, although the volume ratio was the lowest in the cerebellum (94.4 ± 5.7%, $p < 0.001$) (Table 2). There was no statistically significant difference in the cerebellar and cortex volume parameters at baseline and at follow-up, among the different magnetic field power, gap size, or number of slices (Table S1).

When the serial volume changes were plotted over time, the group with cerebellar volume reduction of ≥0.86 (%, TIV) exhibited a trend of progression for up to 2-year and then stabilized (Fig. 2A), whereas the group with cortical volume reduction of ≥3.79 (%, TIV) did not show a progressive trend (Fig. 2B). The frontal lobe, parietal lobe, temporal lobe, occipital lobe, or brainstem did not exhibit progressive volume trends (Fig. 3). The degree of cerebellar volume reduction correlated with the degrees of volume reduction in all other brain segments except for the occipital lobe (Fig. S3).

Clinical implications of cerebellar and cortical volume reduction

The groups with cerebellar volume reduction of ≥0.86 (%, TIV) was associated with a higher frequency of delayed removal of teratoma and refractory status epilepticus; a longer duration of status epilepticus; a higher frequency of tocilizumab use; more cycles of IVIG, rituximab, and tocilizumab; and a higher cumulative disease burden at last MRI. At last follow-up, the CASE total and subdomain scores; and the mRS score were higher, whereas the frequencies of excellent CASE scores and favorable mRS scores were lower, in the patients with cerebellar volume reduction of ≥0.86 (%, TIV) (Table 3). The degree of cerebellar volume reduction also correlated with the CASE total score; the CASE subdomain scores; and mRS score (Table S2).

The group with cortical volume reduction of ≥3.79 (%, TIV) was associated with a higher cumulative disease burden at last MRI; and higher total CASE score; higher CASE subdomain scores for language problems and gait instability/ataxia; and lower frequency of favorable mRS scores at last follow-up (Table 3). In the correlation analysis, the degree of cortical volume reduction correlated with the CASE total and the subdomain scores; and mRS score (Table S2).

When the CASE score changes were plotted over 2 years, the group with cerebellar volume reduction of ≥0.86 (%, TIV) exhibited a slowed rate and restricted degree of recovery compared to the group without a significant cerebellar volume reduction (Figs. 2C, 4 for representative cases), whereas the difference in the disease course was less pronounced between the groups with and

Table 2. Volume changes of the segments in the brain.

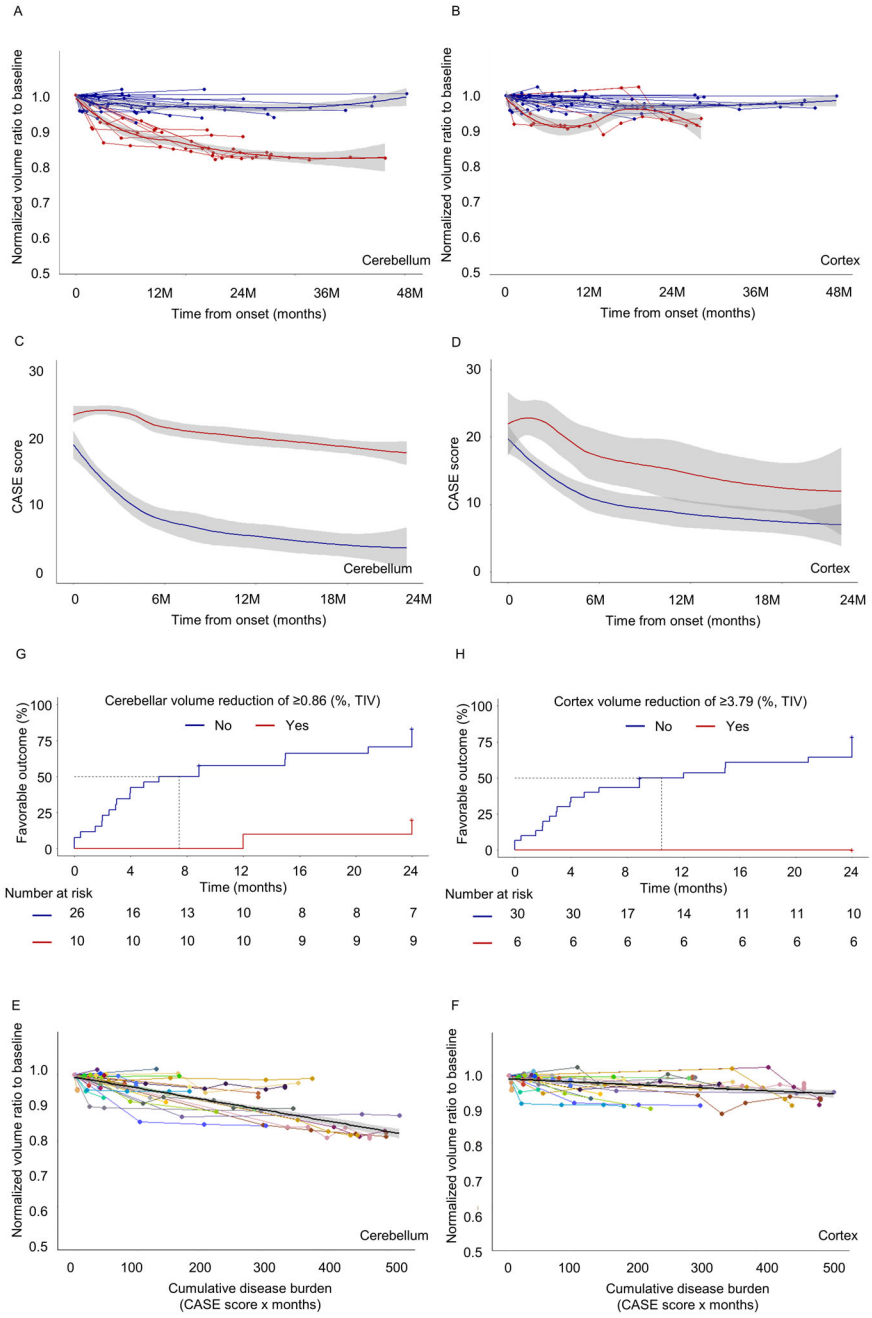
	Volume at baseline[1] (%)	Volume at the lowest during follow-up[1] (%)	*p*	Significant volume reduction at the lowest during MRI follow-up[2] (%)	Volume at last MRI evaluation[1] (%)	Volume change (from baseline to last MRI, %)	Volume ratio (at last MRI to baseline, %)	*p*	Significant volume reduction at last MRI evaluation[2] (%)
Cerebellum	8.4 ± 0.3	7.9 ± 0.6	<0.001**	10 (27.8)	7.9 ± 0.6	0.51 ± 0.51	94.4 ± 5.7	<0.001**	10 (27.8)
Cortex	54.1 ± 1.7	52.2 ± 2.7	<0.001**	6 (16.7)	52.5 ± 2.7	1.65 ± 1.69	97.1 ± 3.2	<0.001**	6 (16.7)
Frontal lobe	20.9 ± 1.1	20.2 ± 1.2	<0.001**	2 (5.6)	20.4 ± 1.2	0.51 ± 0.76	97.5 ± 3.4	<0.001**	2 (5.6)
Parietal lobe	15.3 ± 0.6	15.0 ± 0.7	<0.001**	1 (3.3)	15.0 ± 0.7	0.32 ± 0.47	98.0 ± 3.0	<0.001**	1 (2.8)
Temporal lobe	11.5 ± 0.5	11.0 ± 0.5	<0.001**	3 (8.3)	11.1 ± 0.6	0.34 ± 0.45	96.9 ± 4.0	<0.001**	2 (5.6)
Occipital lobe	8.7 ± 0.4	8.5 ± 0.4	<0.001**	0 (0.0)	8.6 ± 0.4	0.12 ± 0.23	98.6 ± 2.5	0.003**	0 (0.0)
Brainstem	2.0 ± 0.1	1.9 ± 0.1	<0.001**	0 (0.0)	1.9 ± 0.1	0.04 ± 0.08	98.3 ± 3.9	0.006**	0 (0.0)

Data are reported as mean ± standard deviation.

[1]Normalized by total intracranial volume.

[2]Significant volume reduction was arbitrarily designated as the volume reduction >1.96 standard deviation of the baseline volume data of the study population.

**$p < 0.01$.



without cortical volume reduction of ≥3.79 (%, TIV) (Fig. 2D). In the Kaplan–Meier curve analyses, 1/10 (10.0%) of patients who developed cerebellar volume reduction of ≥0.86 (%, TIV) and 0/6 (0.0%) of patients who developed cortex volume reduction of ≥3.79 (%, TIV) achieved an excellent functional outcome during the follow-up of 24 months, whereas 19/26 (73.1%) of patients with cerebellar volume reduction of <0.86 (%, TIV) and 20/30 (66.7%) of patients with cortex volume reduction of ≥3.79 (%, TIV) achieved an excellent functional outcome (both, $p < 0.001$) (Fig. 2E and F).

Factors associated with cerebellar and cortical volume reduction

From the univariate analysis, cumulative duration of status epilepticus, cumulative disease burden parameters, refractory status epilepticus, and delayed removal of

Figure 2. Trendlines of serial volume reduction of the brain segments, changes in Clinical Assessment Scale in Autoimmune Encephalitis (CASE) scores over 2 years in patients, and correlations between the cumulative disease burden and the magnitude of brain volume reduction. Panel (A) describes cerebellar volume changes (normalized to total intracranial volume, TIV) over time in each patient, in groups with the cerebellar volume reduction of ≥0.86 (%, TIV) (n = 10, red lines) or of <0.86 (%, TIV) (n = 26, blue lines). Panel (B) depicts normalized cortical volume changes over time in each patient, grouped according to the cortical volume reduction of ≥3.79 (%, TIV) (n = 6, red lines) and <3.79 (%, TIV) (n = 30, blue lines). The gray-filled areas indicate the 95% CI of the trendline. Panel (C) describes the changes in the CASE scores over 2 years in the groups with (red lines, n = 10) or without (blue lines, n = 26) the cerebellar volume reduction of ≥0.86 (%, TIV). Panel (D) shows the changes in the CASE scores over 2 years in the groups with (red lines, n = 6) or without (blue lines, n = 30) the cortical volume reduction of ≥3.79 (%, TIV). The gray-filled areas indicate the 95% CI of the trendlines. Panel (E) describes Kaplan–Meier curve for the rate of achieving an excellent functional outcome according to the CASE score during the follow-up of 24 months, according to the groups with (red lines, n = 10) or without (blue lines, n = 26) a cerebellar volume reduction of ≥0.86 (%, TIV). Panel (F) describes Kaplan–Meier curve for the rate of achieving an excellent functional outcome according to the CASE score during the follow-up of 24 months, according to the groups with (red lines, n = 6) or without (blue lines, n = 30) a cortical volume reduction of ≥3.79 (%, TIV). Panels (G and H) denote correlations between the cumulative disease burden and the magnitude of cerebellar and cortical volume reduction, respectively, normalized by TIV. The gray-filled areas indicate the 95% confidence interval of the linear trendlines.

teratoma were associated with a cerebellar volume change (Tables S2, S3). In subsequent RM-LMM analyses, a model including a cumulative disease burden for up to 2-year showed best fitness, compared to the models including disease burdens summated up to 6-month or 1-year, or without limitation (Table S5). In that RM-LMM model, cumulative disease burden summated up to 2-year (fixed effect [FE] 0.208 ± 0.025, 95% CI 0.159–0.257 percent/score × months, $p < 0.001$), cumulative duration of status epilepticus (FE 0.584 ± 0.114, 95% CI 0.359–0.810 percent/days, $p < 0.001$), and delayed removal of teratoma for ≥1 month (FE 24.895 ± 8.608, 95% CI 7.536–42.255, $p = 0.006$) were positively associated with cerebellar volume reduction at each time of evaluation, whereas time or initial CASE score showed no significant association (Table 4; Fig. 2G). Additional RM-LMM

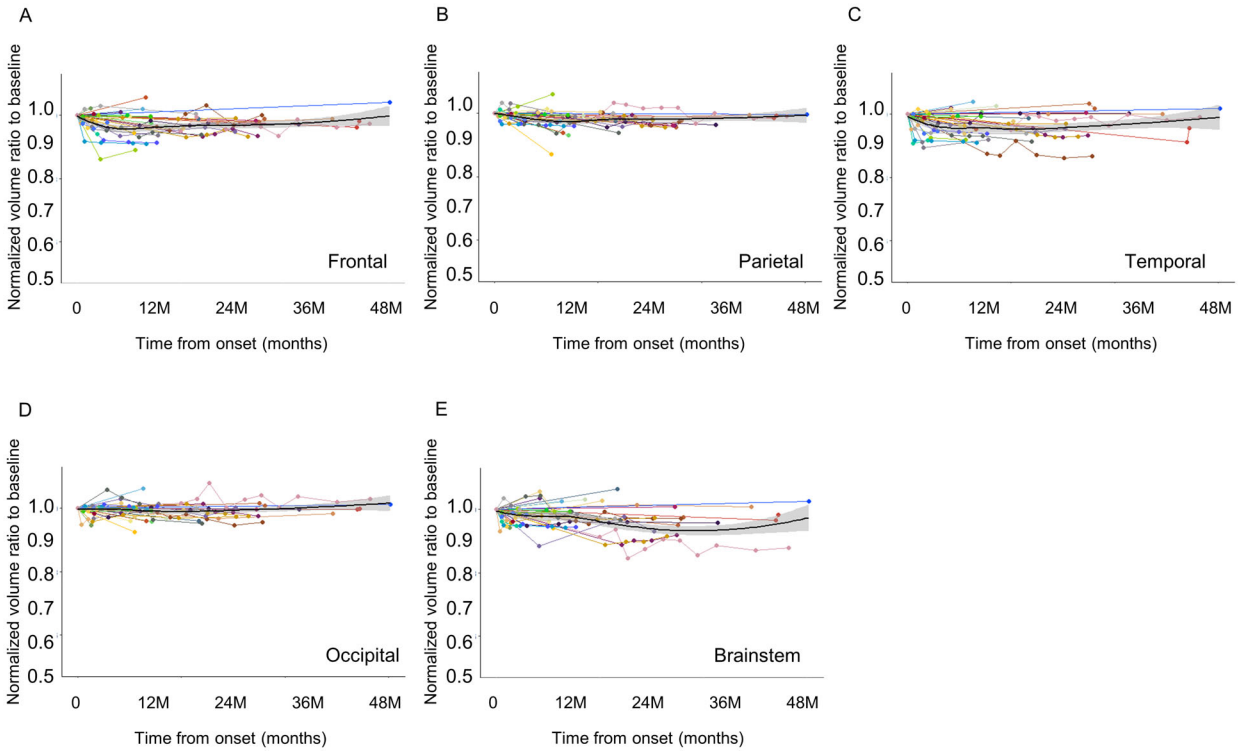


Figure 3. Serial volume changes of the brain segments. Panel (A) describes frontal volume changes over time in each patient, normalized by total intracranial volume (TIV). The gray-filled areas indicate the 95% confidence interval of the trendline. Panels (B–E) describe the changes in the volumes of parietal lobe (panel B), temporal lobe (panel C), occipital lobe (panel D), and brainstem (panel E) over time.

Table 3. Comparison of the profiles among the patients with or without a significant cerebellar/cortical volume reduction.

	Cerebellar volume reduction[1]			Cortical volume reduction[1]		
	≥0.86 (%, TIV) (*N* = 10)	<0.86 (%, TIV) (*N* = 26)	*p*	≥3.79 (%, TIV) (*N* = 6)	<3.79 (%, TIV) (*N* = 30)	*p*
Demographic & clinical profiles						
Male sex (%)	2 (20.0)	8 (30.8)	0.817	1 (16.7%)	9 (30.0%)	0.868
Age of onset (years)	37.3 ± 19.5	25.6 ± 11.8	0.102	40.2 ± 24.6	26.6 ± 11.7	0.238
Initial CASE scores	23 [18–24]	19.5 [15–24]	0.304	17.5 [15–23]	20.5 [17–24]	0.580
Initial mRS scores	5 [4–5]	5 [4–5]	0.666	4 [4–5]	5 [4–5]	0.446
Teratoma association (%)	7 (70.0)	12 (46.2)	0.362	4 (66.7)	15 (50.0)	0.765
Delayed removal of teratoma for ≥1 month (%)	5 (50.0)	2 (7.7)	0.010*	3 (50.0)	4 (13.3)	0.073
Refractory status epilepticus (%)	10 (100.0)	9 (34.6)	0.002**	5 (83.3)	14 (46.7)	0.232
Total duration of status epilepticus (days)	30.5 [16–43]	0 [0–12]	<0.001**	24.5 [5–33]	4.5 [0–19]	0.110
Use of ventilator care (%)	10 (100.0)	16 (61.5)	0.058	6 (100.0)	20 (66.7)	0.244
CSF/MRI profiles						
CSF protein level (mg/dL)	57.8 ± 40.5	53.6 ± 56.2	0.832	56.9 ± 37.1	54.4 ± 54.8	0.916
CSF leukocyte level (cells/μL)	54.3 ± 97.9	80.0 ± 100.9	0.495	86.2 ± 126.6	70.2 ± 95.4	0.725
T2 hyperintensities in temporal area (%)	3 (30.0)	10 (38.5)	0.931	3 (50.0)	10 (33.3)	0.756
T2 hyperintensities in extratemporal area (%)	1 (10.0)	10 (38.5)	0.209	2 (33.3)	9 (30.0)	1.000
Treatment profiles						
High-dose steroid treatment (%)	8 (80.0)	21 (80.8)	1.000	4 (66.7)	25 (83.3)	0.879
IVIG treatment (%)	10 (100.0)	24 (92.3)	0.437	6 (100.0)	28 (93.3)	1.000
IVIG cycles	11 [5–25]	2 [1–5]	0.001**	25 [13.5–26]	3 [1–9.5]	0.079
Rituximab treatment (%)	10 (100.0)	24 (92.3)	0.437	6 (100.0)	25 (93.3)	1.000
Rituximab cycles	16 [14–29]	6 [4–12]	0.001**	29 [17–29]	8 [5–14]	0.155
Tocilizumab (%)	10 (100.0)	19 (73.1)	0.005**	6 (100.0)	23 (76.7)	0.774
Tocilizumab cycles	4 [1–12]	2 [0–5]	0.031*	12 [6.5–13.5]	2 [0.5–4.5]	0.116
Use of phenytoin	2 (20.0)	6 (23.1)	1.000	0 (0.0)	8 (26.7)	0.370
Total dose of phenytoin (mg)	0 [0–0]	0 [0–900]	0.942	0 [0–0]	0 [0–450]	0.351
Use of valproic acid	6 (60.0)	7 (26.9)	0.143	1 (16.7)	12 (40.0)	0.535
Total dose of valproic acid (mg)	43.2 [0–218.7]	0 [0–4.5]	0.685	0 [0–2250]	0 [0–52,200]	0.612
Outcome profiles						
Number of MRI evaluations	4.5 [4–6]	2.5 [2–3]	0.003**	5 [4–5]	3 [2–4]	0.010*
Cumulative disease burden at last MRI (CASE score × months)	412 [298–579]	67.5 [42–168]	<0.001**	390 [227–579]	109.5 [42–298]	0.010*
CASE scores at last follow-up	12.5 [9–19]	2 [0–4]	<0.001**	12 [9–19]	3 [1–6]	0.002**
Excellent (scores 0–4, %)	1 (10.0)	21 (80.8)	<0.001**	0 (0.0)	22 (73.3)	0.004**
Memory dysfunction scores	2 [2–3]	1 [0–1]	0.001**	3 [2–3]	1 [0–2]	0.001**
Language problem scores	2 [1–3]	0 [0–1]	0.001**	3 [2–3]	0 [0–1]	<0.001**
Psychiatric symptoms score	3 [2–3]	0 [0–1]	0.002**	3 [1–3]	0 [0–2]	0.035*
Gait instability/ataxia score	1 [1–3]	0 [0–0]	<0.001**	2 [1–3]	0 [0–0]	0.001**
Weakness score	1 [0–2]	0 [0–0]	0.001**	1 [0–2]	0 [0–0]	0.005**
mRS scores at last follow-up	4 [3–5]	1 [0–2]	<0.001**	4 [4–5]	1 [0–2]	0.001**
Favorable (scores 0–2, %)	2 (20.0)	21 (80.8)	0.003**	0 (0.0)	23 (76.7)	0.002**

Data are reported as mean ± standard deviation, or as median [interquartile range, IQR]. CASE, Clinical Assessment Scale in Autoimmune Encephalitis; mRS, modified Rankin scale; CSF, cerebrospinal fluid; IVIG, intravenous immunoglobulin.

[1]Cut-off values for the volume reduction were designated as the volume reduction ratio that exceeds 1.96 SD of the mean value of the baseline volume in the study population.

*$p < 0.05$.

**$p < 0.01$.

adjusting magnetic field power, gap size, and number of slices (Table S7) and RM-LMM excluding four patients who performed baseline or follow-up MRI during or within 2-weeks from high-dose corticosteroid administration (Table S8) reproduced the same result.

From the univariate analysis for the factors associated with cortical volume change, only the cumulative disease burden parameters were associated with a cortical volume change (Tables S3, S4). In subsequent RM-LMM analyses, a model including a cumulative disease burden for up to

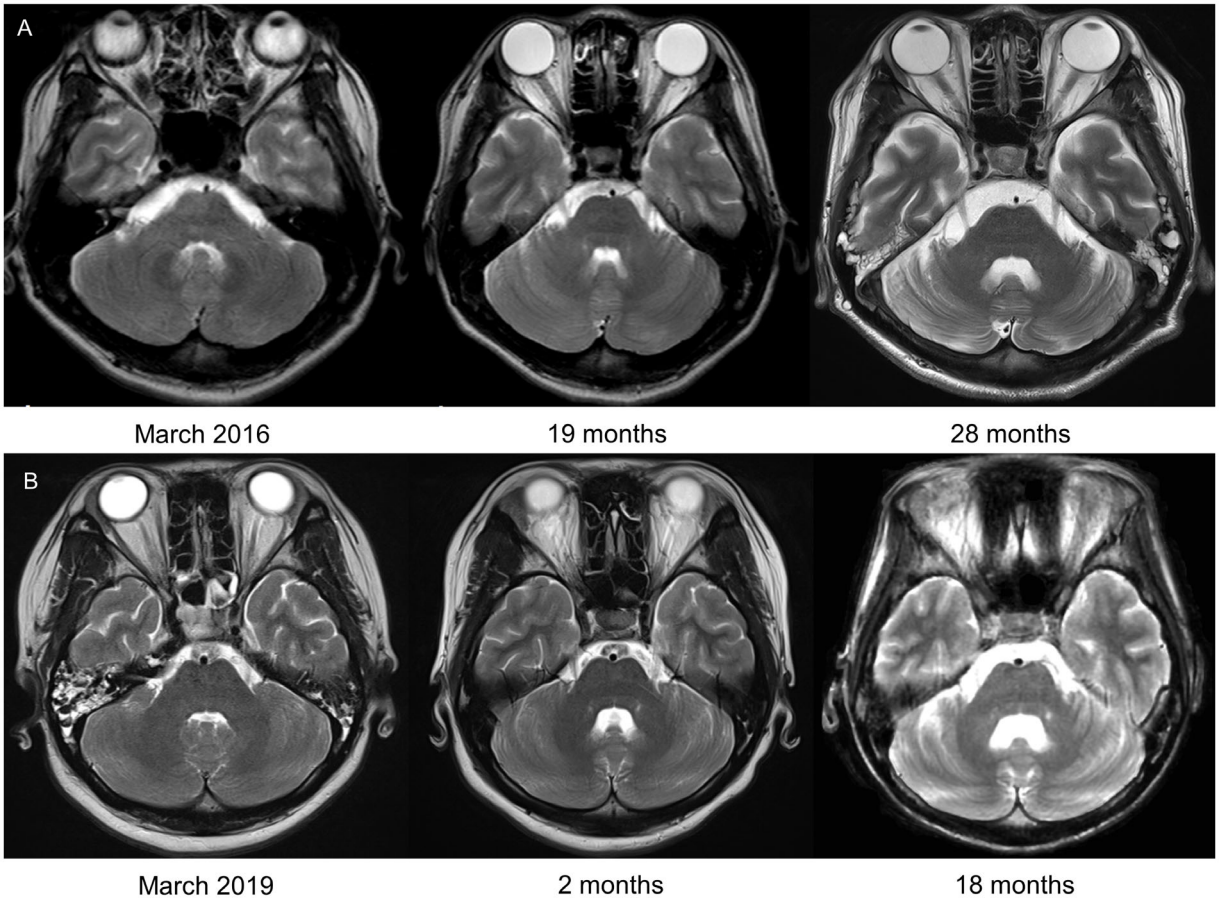


Figure 4. Representative cases. Serial magnetic resonance imaging (MRI) scans of a 28-year-old woman (panel A). The initial Clinical Assessment Scale in Autoimmune Encephalitis (CASE) score was 17, and the mRS score was 4. Nineteen months later, cerebellar sulcal widening, enlargement of the fourth ventricle, and narrowing of the middle cerebellar peduncle were noted, suggesting a cerebellar volume reduction (middle panel); these features had not been evident in the initial image (left panel). The cumulative disease burden was 455 (score × months). Follow-up MRI evaluation at 28 months showed further progression of cerebellar atrophy (right panel). The cumulative disease burden was 595 (score × months), the final CASE score was 13, and the final mRS score was 4. Serial MRIs of a 21-year-old woman with an initial CASE score of 23 and mRS score of 5 (panel B). Two months later, mild cerebellar sulcal widening and enlargement of the fourth ventricle were noted (middle panel); these features had not been evident in the initial image (left panel). The cumulative disease burden was 45 (score × months). Follow-up MRI evaluation at 18 months showed further progression of cerebellar atrophy (right panel). The cumulative disease burden was 308 (score × months), the final CASE score was 12, and the final mRS score was 4.

6-month showed best fitness, compared to the models including disease burdens summated up to 1- or 2-year, or without limitation (Table S6). In that RM-LMM model, cumulative disease burden summated up to 6-month (FE 1.011 ± 0.291, 95% CI 0.436–1.586 percent/score × months, $p = 0.001$) was positively associated with cerebellar volume reduction at each time of evaluation (Table 4; Fig. 2H). Additional RM-LMM adjusting magnetic field power, gap size, and number of slices and RM-LMM excluding four patients who performed baseline or follow-up MRI during or within 2-weeks from high-dose corticosteroid administration reproduced the same result (Tables S7, S8).

Discussion

This study demonstrated the clinical importance of the cerebellar volume reduction in NMDAR encephalitis. Although a significant volume reduction was observed in both cerebellum and cerebrum, cerebellar volume reduction exhibited a higher degree, followed a progressive course until 2-years, and was associated with poor neurological outcomes. The degree of cerebellar volume reduction was positively correlated with total and domain-specific CASE scores; and mRS scores. Cortex volume reduction was also associated with poor outcomes, although the correlations were weaker than those of

Table 4. Repeated-measure linear mixed models for the brain volume change.

	Coefficient for the fixed effect (mean ± standard error)	95% Confidence interval	*p*
Cerebellar volume reduction[1] (%, TIV)			
Intercept	11.574 ± 14.839	−18.344 to 41.491	0.440
Age of onset (years)	0.178 ± 0.240	−0.307 to 0.663	0.463
Male sex	0.639 ± 8.720	−16.965 to 18.243	0.942
Initial CASE score	−1.001 ± 0.573	−2.155 to 0.154	0.088
Time from onset (days)	0.003 ± 0.009	−0.014 to 0.020	0.717
Cumulative disease burden for up to 2-year (CASE score × months)	0.208 ± 0.025	0.159 to 0.257	<0.001**
Cumulative duration of status epilepticus (days)	0.584 ± 0.114	0.359 to 0.810	<0.001**
Delayed removal of teratoma for ≥1 month	24.895 ± 8.608	7.536 to 42.255	0.006**
Cortical volume reduction[1] (%, TIV)			
Intercept	22.749 ± 74.53	−127.131 to 172.629	0.762
Age of onset (years)	1.851 ± 1.215	−0.595 to 4.297	0.134
Male sex	−7.733 ± 44.198	−96.685 to 81.219	0.862
Initial CASE score	−2.604 ± 2.911	−8.452 to 3.244	0.375
Time from onset (days)	0.029 ± 0.043	−0.056 to 0.113	0.502
Cumulative disease burden for up to 6-month (CASE score × months)	1.011 ± 0.291	0.436 to 1.586	0.001**
Cumulative duration of status epilepticus (days)	0.955 ± 0.628	−0.290 to 2.201	0.131
Delayed removal of teratoma for ≥1 month	18.823 ± 40.793	−63.515 to 101.161	0.647

BIC value of the models, a smaller value indicates a better fitness of the model: 61.5 and 459.3. BIC, Bayesian information criterion; CASE, Clinical Assessment Scale in Autoimmune Encephalitis.

[1]Volume reduction from the baseline, normalized by total intracranial volume (TIV).

**$p < 0.01$.

cerebellar volume reduction. The degree of cerebellar volume reduction was correlated with cumulative disease burden up to 2-year, duration of status epilepticus, and delayed removal of teratoma, whereas cortex volume reduction was associated with cumulative disease burden up to 6-month. Previous studies have evaluated the brain structural changes in NMDAR encephalitis in relation to mRS scores or qualitatively measured functional outcomes,[15–17] but this is the first to demonstrate the associated factors of brain volume changes and their clinical implications using a comprehensive outcome measurement.

Cerebellar volume reduction was irreversible, and its degree was the highest among the brain segments and correlated with the degree of volume reduction in other brain segments. These findings indicates that cerebellum might be especially vulnerable to a mechanism that commonly apply to whole-brain volume reduction in NMDAR encephalitis.[28] Previous studies demonstrated that a physiological level of NMDAR-dependent activation of calcium-mediated signaling pathways, which mediates the downstream activation of brain-derived neurotrophic factor, are crucial to maintain neuronal survival.[29–33] Therefore, a depletion of NMDAR below a certain level might induce ongoing neuronal degeneration and reduction in brain volume. Cerebellum might be the most susceptible to this mechanism, as cerebellar granule cells, the major population of cerebellar neurons, feature highly abundant NMDAR expression.[34] Additionally, considering the cephalocaudal progression pattern of NMDAR encephalitis, cerebellar atrophy might represent the full caudal progression of the disease and fulminant activation of autoimmune mechanism including cytotoxic T-cell and microglia.[5,35]

The degree of cerebellar volume reduction was best associated with cumulative disease burden up to 2-year, whereas the degree of cortical volume reduction was best correlated with 6-month cumulative disease burden. This finding is concordant with the trend that cerebellar volume reduction progressed for up to 2-year and then stabilized, and also reflects the chronically ongoing disease activity due to the persisting antibodies in CSF resulting in long-term NMDAR depletion.[36] In this regard, the degree of cerebellar atrophy might serve as a sensitive biomarker for the cumulative effect of NMDAR depletion and consecutive extent of damage in the brain.[1,4,5]

Additionally, the association with the cumulative duration of status epilepticus and the cerebellar volume reduction might be explained by the effect of prolonged neuronal excitotoxicity and associated activation of microglia and pro-inflammatory cytokines.[1,5,37–39] The association of delayed teratoma removal might also be explained by its deleterious effect on the long-term disease course.[13]

Cerebellar volume reduction was correlated not only with global functional outcomes but also with the severity of memory dysfunction, language problems, psychiatric symptoms, gait instability/ataxia, and weakness. It might be explained by that the cerebellum is highly interconnected with the limbic areas and neocortex and is crucial for emotional and cognitive functions, and also by that cerebellar volume reduction is a marker reflecting the global damage in the brain.[40,41]

The findings of this study have several clinical implications. First, as cerebellar atrophy is irreversible once developed and correlated with poor long-term outcomes, early introduction of the combination immunotherapy might provide additional benefits, as it might promote clinical improvement and minimize the 2-year cumulative disease burden.[13] Second, in patients with ongoing disease activity in the chronic phase, adjuvant immunotherapy within 2-year might be considered to halt the progression of cerebellar atrophy and prevent long-term sequelae.[13,20,42] Third, more active control of symptomatic status epilepticus to minimize its cumulative duration might be beneficial to improve the outcomes.[5,13]

This study has some limitations. First, the lack of high-resolution 3D T1 images prevents precise measurement of the absolute value of the volume changes in brain structures. Second, although RM-LMM adjusting for the MR parameters reproduced the result, heterogeneity in the MR protocols among patients and among evaluations in a same subject. Third, the numbers and intervals of serial MRI evaluations are heterogeneous among the patients, which might be another main methodological limitation. Fourth, the medical indications for taking multiple MRI evaluations might be a source of selection bias. Fifth, brain edema associated with drugs such as high-dose corticosteroid or refractory seizure might have significant effect on brain volume status,[26,27] which were not fully investigated in the current study. Those limitations are mainly due to patients' diminished coordination, unstable medical status, and cohort-based retrospective design, and prevent this study result from being interpreted as representing the clinical and radiological course of the general population with NMDAR encephalitis. Additionally, the serial changes in NMDAR antibody titers in CSF, which might be useful for measuring the burden of active disease activity, were not assessed in this study. To further improve our findings, a prospective cohort study of NMDAR encephalitis with predefined MRI protocols and follow-up schedules might be warranted.

Author Contributions

W.-J.L. acquired study data, performed data analysis and interpretation, and drafted the manuscript. S.-T.L. contributed in the initial conceptualization and design of the study, patient management, acquired study data, performed data interpretation, drafted the manuscript, and managed the entire study cohort. D.-Y.K. and S.K. contributed in the acquisition, analysis, and management of the laboratory data. K.C. contributed in the initial conceptualization and design of the study, patient management, revised the manuscript, and supervised the entire procedures in this study.

Conflict of Interest

S.-T. L. reports advisory roles for Roche/Genentech, UCB, Ono Pharmaceuticals, Biofire Diagnostics, and Advanced Neural Technologies. Otherwise, the authors have no competing interests.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Brain segmental volumetric analysis.
Figure S2. Manual measurement of cerebellar and cortical volume.
Figure S3. Correlations between the degree of cerebellar volume reduction and the degrees of the volume reduction in other brain segments.

Table S1. Profiles of MRI parameters and comparison of the normalized volumes in the cerebellum and cortex according to the MRI parameters.
Table S2. Correlation of brain volume reduction with clinical and functional outcomes.
Table S3. Correlation coefficients of cerebellar/cortical volume reduction with continuous variables.
Table S4. Comparison of mean cerebellar/cortical volume reduction between the groups divided according to the dichotomized variables.
Table S5. Repeated-measure linear mixed models for the cerebellar volume reduction normalized by total intracranial volume.
Table S6. Repeated-measure linear mixed model for the cortical volume reduction normalized by total intracranial volume.
Table S7. Repeated-measure linear mixed models for the brain volume change, adjusting for the MRI power strength, gap size, and number of slices.
Table S8. Repeated-measure linear mixed models for the brain volume change, excepting for the cases with MRI evaluations taken during or within 2-weeks after high-dose corticosteroid administration.

