Long-term outcomes and health-related quality of life in patients with autoimmune encephalitis
An observational study

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Abstract

Autoimmune encephalitis (AE) subacutely causes severe and multiple symptoms; however, most patients achieve neurologically favorable outcomes. Despite the substantial recovery in motor function, persistent impairments in mental/social aspects lasting for several years have been recognized, and its potential effect on health-related quality of life (HRQOL) has been argued. To urgently evaluate the long-term effects of AE on patients' HRQOL, we investigated patient-oriented long-term outcomes and assessed the HRQOL of patients with AE. Data of patients who were diagnosed with probable/definite AE, defined by Graus AE criteria 2016, and treated at our hospital between January 2011 and October 2020 were retrospectively retrieved. Their long-term (≥2 years) outcomes, which included various sequelae and handicaps in social activities such as returning to previous work/school life through structured interview forms, were evaluated, and the HRQOL was assessed using Neuro-QOL battery. We identified 32 patients who met the Graus AE criteria 2016 and eventually enrolled 21 patients in the study. The median interval between disease onset and survey period was 63 (25–156) months, and 43% of the patients had persistent neuropsychiatric symptoms, including memory disorders, personality changes, and seizures. No more than 71% returned to their previous work/school life. Although most of the patients had global QOL within normal limits, 48% had social QOL under normal limits. Patients with sequelae were significantly less likely to return to previous work/school and had worse global/social quality of life than patients without sequelae. In conclusion, nearly half of patients with AE had social QOL under normal limits 5 years after onset. The difficulty in returning to work/school and a worse HRQOL were notable in patients with sequelae.

Abbreviations: ADEM = acute disseminated encephalomyelitis, AE = autoimmune encephalitis, HRQOL = health-related quality of life, mRS = modified Rankin Scale, NMDARE = anti-*N*-methyl-D-aspartate receptor encephalitis.

Keywords: autoimmune encephalitis, anti-*N*-methyl-D-aspartate receptor encephalitis, quality of life, long-term outcome, patient-oriented outcome, sequelae

1. Introduction

Autoimmune encephalitis (AE) causes severe and multiple neuropsychiatric symptoms and can be life-threatening.[1,2] Despite the severity of symptoms in the acute phase, rapid diagnosis and intensive treatment lead to neurologically favorable outcomes, and most patients with AE eventually achieve self-reliance in daily living based on a modified Rankin Scale (mRS).[2–5] Contrary to substantial recovery in motor functions after AE, persistent impairments in mental or social aspects over years after disease onset, which potentially hinder patients from returning to their previous social activity,[6–8] have been recently highlighted.[1,3,8,9] With these findings, researchers argue that the mRS is insufficient to assess potential negative outcomes of AE, including cognitive, behavioral, phycological, or health-related quality of life (HRQOL) outcomes.[8,10]

HRQOL has been commonly used as a primary or secondary endpoint in clinical trials and an important patient-oriented outcome in clinical practice guidelines for various neurological disorders.[11,12] Despite its important role in estimating clinical outcomes, only a few studies have evaluated the potential adverse effects of AE on HRQOL.[3,13,14] Furthermore, no studies have addressed how sequelae and social activity limitations affect the HRQOL of patients with AE over years from disease onset. Thus, to clarify the long-term effects of AE on patients' HRQOL, we investigated long-term outcomes and HRQOL in post-AE patients years after the acute phase, and unveiled that difficulty in return to work/school life and worse HRQOL were tightly associated with sequelae.

YY and SH contributed equally to this work.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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2. Materials and methods

2.1. Protocol approval and patient classification

This study prospectively collected and analyzed data regarding patient-oriented long-term outcomes and HRQOL from a retrospective post-AE cohort of patients at ≥2 years after disease onset. Details of patient selection and classification are presented in Supplementary Figure 1; Supplemental Digital Content 1, http://links.lww.com/MD/K15. Briefly, the clinical records of 111 patients with acute encephalitis[15] who were treated at Nihon University School of Medicine Itabashi Hospital between January 1st, 2011 and October 31th, 2020 were reviewed. In-house antibody screening against a series of neuronal surface antigens (e.g., *N*-methyl-D-aspartate receptor and leucin rich glioma inactivated 1) using patients' cerebrospinal fluid samples was implemented, as detailed in our previous retrospective AE cohort study.[16] We used the Graus criteria 2016[17] as the diagnostic criteria for AE, which emphasize both clinical symptoms and laboratory findings, including antibody test results. Moreover, these criteria cover antibody-negative cases of AE, and currently, they are widely used for the diagnosis of AE.[18,19] Consequently, 40 patients fulfilled the diagnostic criteria for possible AE, and 32 patients were eventually diagnosed with probable/definite AE defined by the Graus AE criteria 2016.[17] The patient classification, which is summarized in Supplementary Methods; Supplemental Digital Content 2, http://links.lww.com/MD/K16 was independently conducted by 2 experts (Y.Y. and M.H.). We tried to contact the 32 patients, but 9 of them were not reachable. On the subsequent postal survey on HRQOL, 2 patients did not respond. Therefore, patient-oriented long-term outcomes and HRQOL were obtained from 21 patients with AE.

Patients with failure in contact or absence of reply were not included in later analysis, and therefore the study size (n = 21) was finally determined by the number of patients from whom we obtained replies to the postal survey on HRQOL. Written informed consent for this study was obtained from all the patients. This study was approved by the Nihon University School of Medicine Itabashi Hospital ethics committee (RK-220614-5).

2.2. Data acquisition

Data were acquired through 3 discrete steps. First, clinical information was obtained by reviewing clinical records during hospitalization, which included age, sex, date of disease onset, hospitalization period, requirements of mechanical ventilation, the mRS[20] at the worst status, and first-line/second-line immunotherapy. Second, patient-oriented long-term outcomes were obtained through a face-to-face or telephone interview. Here, we asked them about their latest status based on mRS, presence of neuropsychiatric sequelae, return to previous work/school activity, self-reliance at home life, and current medication. As regards sequelae, we first asked them about existence of: memory disorder, speech disturbance, delusion or hallucination, mood disorder, personality change, sleep disturbance, seizure, movement disorders, motor impairment, sensory disturbance, or urinary disturbance, and then further obtained detail of them. Patients who continued to attend regular visits to our hospital were administered a comprehensive neuropsychiatric battery, the Wechsler Adult Intelligence Scale-III (WAIS-III). The third step evaluated HRQOL using the Neuro-QOL assessment form for adults.[21] We sent the patients printed short forms of Neuro-QOL in 12 domains; specifically, the domains were upper extremity function (v1.0), lower extremity function (v1.0), fatigue (v1.0), sleep disturbance (v1.0), depression (v1.0), anxiety (v1.0), stigma (v1.0), positive affect & well-being (v1.0), emotional & behavioral dyscontrol (v1.0), cognitive function (v2.0), satisfaction with social roles & activities (v1.1), and ability to participate in social roles & activities (v1.0). Replies from the patients were used in the following HRQOL analysis. Data collection was done between December 1st, 2021 and December 31th, 2022. The authors had access to information that could identify individual participants during data collection.

2.3. Analysis of HRQOL

Raw scores of 12 domains in the Neuro-QOL battery were converted to standardized T-scores,[21] according to Scoring Manual Version 3.0 (https://www.healthmeasures.net/images/neuro_qol/User_and_scoring_guides/Neuro-QOL_Scoring_Manual_26April2021_FINAL.pdf). Average of T-scores of the reference controls is 50; therefore, we could determine whether patients had worse HRQOL than controls or not by comparing the patients' T-scores to 50 for each domain.

This study aimed not only to estimate patients' HRQOL of each of the 12 domains but also to comprehensively analyze physical, mental, and social health experiences. Thus, we defined "physical QOL," "mental QOL," "social QOL," and "global QOL" based on T-scores of 12 domains, as detailed in the Supplementary methods; Supplemental Digital Content 2, http://links.lww.com/MD/K16 and Supplementary Figure 2; Supplemental Digital Content 3, http://links.lww.com/MD/K17. Briefly, we first classified the 12 domains into "positive categories," where higher T-scores indicate better HRQOL, or "negative categories," where higher T-scores indicate worse HRQOL.[21] Second, we transformed T-scores of negative categories into "inverted T-scores" so that higher scores indicated better HRQOL. Then, we averaged the T-scores of positive categories and inverted T-scores of negative categories across physical, mental, and social domains, which yielded gathered scores of the physical, mental, and social QOL, respectively. The 12 domains were subdivided into physical, mental, and social domains based on the "Neuro-QOL Adult Domain Framework" (National Institute of Neurological Disorders and Stroke User Manual for the Quality of Life in Neurological Disorders (Neuro-QoL) Measures, Version 2.0, March 2015). Then, we averaged the 3 scores of the physical, mental, and social QOL, resulting in a single score of global QOL.

Based on the control group average T-score (i.e., 50), HRQOL of patients were categorized into "within normal limits" or "under normal limits" as follows. First, T-scores ≥ 50 were defined as "within normal limits" and T-scores < 50 were defined as "under normal limits" for each domain of "positive categories" and for physical, mental, social, and global QOL. Similarly, T-scores < 50 were defined as "within normal limits" and T-scores ≥ 50 were defined as "under normal limits" for each domain of "negative categories."

2.4. Statistics

We conducted 3 comparative analyses by dividing patients with AE into 2 subgroups based on HRQOL ("within normal limits" vs "under normal limits"), presence of sequelae, or AE-subtype, namely anti-*N*-methyl-D-aspartate receptor encephalitis (NMDARE) versus all the other types of AE except for NMDARE (other AEs). In these comparative analyses, the statistical significance of differences in clinical features, long-term outcomes, and Neuro-QOL T-scores between groups was tested using Fisher exact test for categorical data and the Mann–Whitney *U* test for numerical data. All statistical analyses were implemented by using GraphPad Prism software (Version 9.5.1; GraphPad Software Inc., San Diego, CA). *P* values of <.05 were considered statistically significant. We obtained data of all items of clinical features, long-term

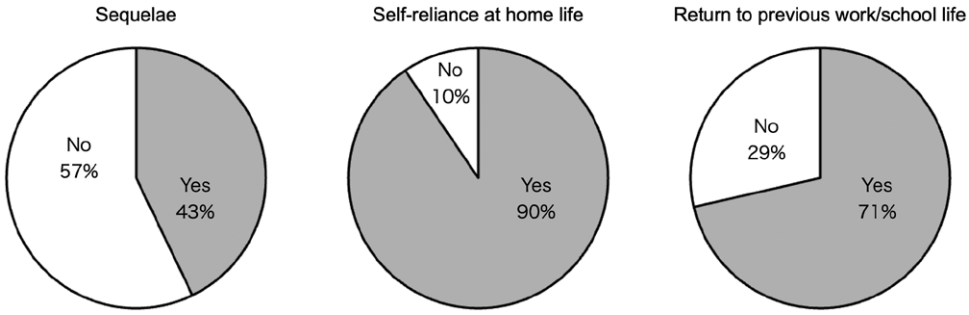

Figure 1. Patient-oriented real-life index and sequelae of patients with AE. The left pie chart represents the frequency of patients with any type of sequelae (n = 21). The middle pie chart represents the frequency of patients who achieved self-reliance in their home life (n = 21). The right pie chart represents the frequency of patients who returned to their previous work or school life (n = 21). AE = autoimmune encephalitis.

outcomes, and Neuro-QOL from all 21 patients, and therefore we needed no correction for missing data in statistical analyses.

3. Results

3.1. Participants

Out of 111 patients with acute encephalitis treated in our institute between January 2011 and October 2020, 40 fulfilled the diagnostic criteria for possible AE,[17] and 32 fulfilled diagnostic criteria for probable/definite AE. We could contact 23 of them, and 21 responded to postal survey on HRQOL. Eventually, clinical features, long-term outcomes, and HRQOL of 21 patients who met the Graus AE criteria 2016 for probable or definite AE were obtained. The etiology consisted of definite autoimmune limbic encephalitis (n = 2), definite acute disseminated encephalomyelitis (ADEM) (n = 2), definite NMDARE (n = 10), definite Bickerstaff brainstem encephalitis (n = 1), definite AE (n = 3), probable Hashimoto encephalopathy (n = 1), and autoantibody-negative but probable AE (n = 2) (Supplementary Figure 1; Supplemental Digital Content 1, http://links.lww.com/MD/K15).

3.2. Demographics, clinical features, and long-term outcomes of patients with AE

Clinical data of 21 patients is summarized in Supplementary Table 1; Supplemental Digital Content 4, http://links.lww.com/MD/K18. The median age at disease onset was 26 (15–71) years, and 15 (71%) patients were female. The median interval between the onset and the survey was 63 (25–156) months. The median hospitalization length was 66 (19–210) days, and 12 (57%) patients required mechanical ventilation. All patients received first-line immunotherapy, and the median interval between onset and first-line immunotherapy was 8 (3–29) days. Five (24%) patients received second-line immunotherapy (i.e., cyclophosphamide). Two (10%) patients experienced clinical relapses. The median mRS score was 5 (3–5) at the worst status and improved to 0 (0–2) at the present. The following sequelae remained in 9 (43%) patients: personality change (3/21, 14%), seizures (3/21, 14%), memory disorders (2/21, 10%), sleep disturbance (2/21, 10%), sensory disturbance (2/21, 10%), mood disorders (1/21, 5%), olfactory dysfunction (1/21, 5%), dysuria (1/21, 5%), frailty (1/21, 5%), and speech disturbance (1/21, 5%). Memory disorders were the third most common sequelae after personality change and seizures. The participants were administered WAIS-III—a comprehensive neuropsychiatric battery. Patients whose WAIS-III data were available, both in acute and follow-up phases, were those with NMDARE. Based on the comparison between the acute and follow-up phase scores, we observed a significant improvement in many items, including the Full Scale Intelligence Quotient (IQ; median, acute phase vs follow-up: 78 vs 98, P = .047), Working Memory (median, acute phase vs follow-up: 72 vs 98, P = .016), Performance IQ (median, acute phase vs follow-up: 71 vs 103, P = .031), Perceptual Organization (median, acute phase vs follow-up 75 vs 101, P = .031), and Processing Speed (median, acute phase vs follow-up: 92 vs 110, P = .016) (Supplementary Figure 3; Supplemental Digital Content 5, A, D, E, F and G, http://links.lww.com/MD/K19). Conversely, no significant improvements were found in Verbal IQ (median, acute phase vs follow-up: 85 vs 93, P = .156) or Verbal Comprehension (median, acute phase vs follow-up: 86 vs 104, P = .219) (Supplementary Figure 3; Supplemental Digital Content 5, B and C, http://links.lww.com/MD/K19). Nineteen (90%) patients gained self-reliance in their home life; however, only 15 (71%) returned to their previous work or school life (Fig. 1). We obtained information about every item of demographics, clinical features, and long-term outcomes for all patients, and there was no missing data.

3.3. HRQOL of patients with AE

The raw scores of the 12 domains in the Neuro-QOL battery were converted to standardized T-scores[21] (Supplementary Table 2; Supplemental Digital Content 6, http://links.lww.com/MD/K20), and based on the T-scores of the 12 domains, 4 scores of the physical, mental, social, and global QOL were calculated for each patient. Then, the scores were categorized into "within normal limits" or "under normal limits" based on the controls group average T-score (i.e., 50). As shown in Figure 2, 15 (71%) patients had global QOL within normal limits. Similarly, most of the patients had physical/mental QOL scores within normal limits (86% and 71%, respectively). By contrast, only 11 (52%) patients had social QOL within normal limits, and those of the other 10 (48%) were under normal limits. Based on the social QOL of each patient, they were divided into the "within-normal" group (n = 11) and "under-normal" group (n = 10), and a comparative analysis of the clinical manifestation revealed a higher frequency of sequelae in the "under-normal" group than in the "within-normal" group (90% vs 0%, P < .001) (Table 1). Moreover, the frequency of returning to work/school life was significantly lower in the "under-normal" group than in the "within-normal group" (40% vs 100%, P = .004), and mRS at the present was significantly worse in the "under-normal" group than in the "within-normal group" (1 vs 0, P = .004). No significant between-group differences were found in any other items (Table 1). The Neuro-QOL results in each of the 12 domains are shown in Supplementary Figure 4; Supplemental Digital Content 7, http://links.lww.com/MD/K21, and around 30% to 50% of the patients had HRQOL under normal limits in

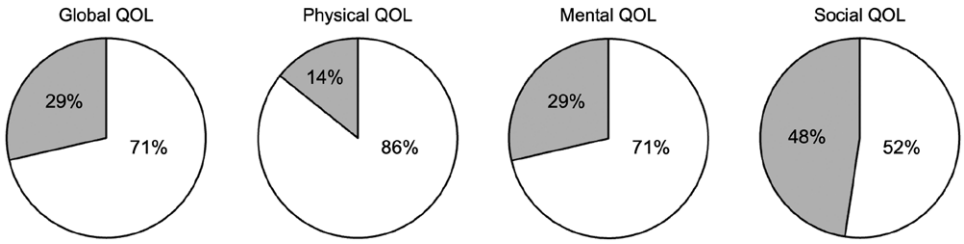

Figure 2. Evaluation of long-term HRQOL of patients with AE. Global, physical, mental, and social QOL were categorized into "within normal limits" or "under normal limits" based on the controls group average T-score (i.e., 50). Pie charts represent the proportions of patients (n = 21) of "within normal limits" and "under normal limits" for global, physical, mental, and social OQL, respectively. White indicates "within normal limits" and gray indicates "under normal limits". AE = autoimmune encephalitis, HRQOL = health-related quality of life, QOL = quality of life.

Table 1

Comparison of the clinical features and outcomes between the patients with social QOL "within normal limits" and "under normal limits".

Social QOL	Within normal group (n = 11)	Under normal group (n = 10)	*P* value
Age at onset, yr, median (range)	24 (15–49)	31 (15–71)	.500
Female, n (%)	8 (72.7)	7 (70.0)	.99
Duration since disease onset to survey (mo), median, (range)	69 (28–156)	57 (25–116)	.426
Acute phase			
Hospitalization, d, median (range)	66 (37–210)	60 (19–186)	.794
Mechanical ventilation, n, (%)	6 (54.5)	6 (60.0)	.99
Peak mRS, median (range)	5 (3–5)	5 (3–5)	.653
Onset to first-line immunotherapy, days, median (range)	7 (3–29)	9 (3–22)	.904
second-line therapy, n, (%)	3 (27.3)	2 (20.0)	.99
Follow-up			
Relapse, n (%)	1 (9.1)	1 (10.0)	.99
mRS at survey, median (range)	0 (0–0)	1 (0–2)	.004*
Sequelae, n (%)	0 (0)	9 (90.0)	<.001*
Self-reliance at home life, n (%)	11 (100)	8 (80.0)	.214
Return to previous work/school life, n (%)	11 (100)	4 (40.0)	.004*

mRS = modified Rankin Scale, QOL = quality of life.
*$P < .05$.

domains of depression, anxiety, affection, cognition, and social role.

3.4. Comparison between patients with and without sequelae

As patients with lower social QOL had a higher frequency of sequelae (Table 1), we divided patients into 2 groups with and without sequelae (n = 9 and 12, respectively), and the clinical features and long-term outcomes were compared between the 2 groups. The frequency of returning to previous work/school life was significantly lower in patients with sequelae than in those without sequelae (33% vs 100%, $P = .002$), although no significant difference was observed in the frequency of self-reliance at home. No significant between-group differences were found in any other items (Table 2). The HRQOL was further compared between the 2 groups, and patients with sequelae had significantly worse global ($P = .002$) and social ($P < .001$) QOL than those without sequelae (Table 3).

3.5. Comparison between patients with NMDARE and those with other AEs

According to previous studies that comparatively analyzed long-term outcomes between those with NMDARE and other AEs,[1,8,22] clinical features and long-term outcomes were further analyzed and compared between patients with NMDARE (n = 10) and other AEs (n = 11) (Supplementary Table 3; Supplemental Digital Content 8, http://links.lww.com/MD/K22). Patients with NMDARE had more favorable neurological outcomes assessed by the mRS ($P = .012$) and less frequent sequelae (10% vs 72%, $P = .008$) than patients with other AEs. The frequency of returning to previous work/school life was higher in patients with NMDARE than in patients with other AEs, although the difference was not significant (90% vs 55%, $P = .149$). Moreover, patients with NMDARE had significantly better social QOL ($P = .018$) than patients with other AEs (Supplementary Table 4; Supplemental Digital Content 9, http://links.lww.com/MD/K23).

4. Discussion

To clarify the long-term effects of AE on patients' HRQOL, this study investigated long-term outcomes and HRQOL in 21 patients with AE at a median of 63 months after disease onset. All patients achieved neurologically favorable outcomes (mRS 0–2); however, 43% had any neuropsychiatric sequelae, and only 71% returned to previous work/school life. Although most of the patients (71%) had global QOL within normal limits, 48% had social QOL under normal limits. Moreover, 60% of the patients with social QOL under normal limits had any type of sequelae, and this rate was significantly higher than that in patients with social QOL within normal limits (27%). As regards the relationship among sequelae, social activity limitations, and HRQOL, this study unveiled a lower number of patients with sequelae who returned to previous work/school life and had worse global/social QOL than patients without sequelae.

Previous studies have reported long-term outcomes of patients with AE measured by the mRS, and they stated that most of the patients eventually achieved favorable mRS scores (mRS ≤ 2) 2.0 to 4.9 years from the onset.[1,5,6,8,22,23] In the present study, all 21 patients showed favorable mRS scores median 5.3 years from the onset. Recently, patients with AE were reported to have persistent symptoms over years after the AE onset.[9] Some studies have revealed that sequelae occur in 52% to 86% of patients after AE onset.[1,8,23] In our AE cohort, 43% (9/21) of the patients had neuropsychiatric sequelae. Moreover, 71% (15/21) of our patients could return to their previous work/school life of patients after AE onset (Fig. 1), whereas Yeshokumar et al reported no more than 50% returned.[8] In summary, after AE onset, patients with favorable outcomes assessed by the mRS frequently had not only persistent neuropsychiatric symptoms but also difficulties in returning to previous social activities. This is not surprising because the mRS is superior to motor function

Table 2

Comparison of the clinical features and long-term outcomes between AE patients with sequelae or not.

	Patient without sequelae (n = 12)	Patient with sequelae (n = 9)	*P* value
Age at onset, yr, median (range)	23 (15–49)	36 (15–71)	.212
Female, n (%)	9 (75.0)	6 (66.7)	.99
Age at survey, yr, median (range)	29 (18–56)	39 (21–76)	.318
Duration since disease onset up to survey, mo, median (range)	60 (28–156)	63 (25–116)	.808
Self-reliance at home life, n (%)	12 (100)	7 (77.8)	.171
Return to previous work/school life, n (%)	12 (100)	3 (33.3)	.002*

AE = autoimmune encephalitis.
*$P < .05$.

Table 3

The difference in Neuro-QOL T-scores between AE patients with sequelae or not.

Neuro-QOL domain	Patient without sequelae (n = 12)	Patient with sequelae (n = 9)	*P* value
Global QOL, median (range)	57.7 (44.7–61.7)	49.8 (40.2–56.1)	.002*
Physical QOL, median (range)	58.8 (51.5–62.7)	55.3 (45.2–62.7)	.114
Mental QOL, median (range)	56.9 (42.3–64.6)	48.8 (37.8–59.3)	.096
Social QOL, median (range)	56.1 (40.4–60.4)	44.8 (26.3–50.0)	<.001*

AE = autoimmune encephalitis, QOL = quality of life.
*$P < .05$.

assessment that shows comfortable recovery in patients with AE,[5,6,24] whereas it is not likely to be suitable for evaluating mental or social domains.[8,10]

Regarding sequelae in AE, various symptoms persist for many years, including cognitive impairment, mood dysfunction, seizures, sleep disturbances, fatigue, and behavioral impairment.[3,6,9] A study evaluated sequelae in 11 preset categories and revealed a higher frequency of cognitive dysfunction and mood dysfunction than other types of sequelae.[9] Regarding psychiatric symptoms, contrary to the common occurrence of behavioral and personality changes at disease onset, psychosis resolved after the acute stage in most patients; however, many patients had residual mood and behavioral symptoms.[9] Another study evaluated long-term neurobehavioral outcomes in patients with AE and described a higher frequency of ongoing impairments in emotional liability and short-term memory than other symptoms.[8] Among sequelae types in our patients, personality changes and seizures were the most common (14% each), followed by memory disorders, sleep disturbance, and sensory disturbance (Supplementary Table 1; Supplemental Digital Content 4, http://links.lww.com/MD/K18). By comparing the acute phase and follow-up WAIS-III scores, we could obtain both acute phase and follow-up scores from patients with NMDARE. There was a significant improvement in Full Scale IQ, Working Memory, Performance IQ, Perceptual Organization, and Processing Speed (Supplementary Figure 3; Supplemental Digital Content 5A, D, E, F, and G, http://links.lww.com/MD/K19); however, Verbal IQ and Verbal Comprehension were not significantly improved (Supplementary Figure 3; Supplemental Digital Content 5B and C, http://links.lww.com/MD/K19). A higher frequency of personality changes and memory disorders was consistent with the results of the aforementioned 2 previous studies.[8,9] A systematic review of 10 studies reported that patients with NMDARE had persistent impairments in verbal memory and executive functions, even during the chronic phase (i.e., more than 12 months after disease onset),[25] consistently to our findings. In addition, the persistency of seizures was discussed; for instance, Yao et al conducted a large-scale retrospective cohort study of 113 patients with AE and reported the occurrence of seizures in 84% of the patients in the acute phase and its remission in 11% of patients during the follow-up.[26] The frequency of persistent seizures in the present study (14%) was similar to that of Yao study.[26] Furthermore, many studies have reported details in sleep disturbances,[27] fatigue,[22] adaptive behavioral impairments,[8] and cognitive impairments,[28] which persisted years after AE onset. Our results also revealed that more than 3-tenths of the patients showed HRQOL under normal limits in the domains of depression, anxiety, affection, cognition, and social role (Supplementary Figure 4; Supplemental Digital Content 7, http://links.lww.com/MD/K21). These findings highlight the importance of comprehensively acquiring patients' health experiences.

HRQOL has been used as a primary or secondary endpoint in clinical trials and an important outcome in clinical practice guidelines for various neurological disorders.[11,12] For example, 1 study evaluated the long-term effects of rehabilitation on HRQOL in patients with multiple sclerosis,[11] and another evaluated changes in HRQOL with immunotherapy in patients with myasthenia gravis.[29] Despite its important role in estimating clinical outcomes, the literature evaluating the potential adverse effects of AE on HRQOL is limited, as mentioned in a recent review on long-term follow-up and management of AE.[3] To the best of our knowledge, only 3 studies that estimated HRQOL after AE onset have been published.[13,14,30] de Bruijn et al revealed worse HRQOL in pediatric patients with NMDARE 30 months after disease onset and its correlation with fatigue,[13] and Suppiej et al revealed overall favorable long-term HRQOL in children after ADEM.[30] The other is a prospective cohort study measuring HRQOL in patients with encephalitis of infectious, immune-related, and unknown causes.[14] They included 2 patients with ADEM, 7 with autoantibody-associated encephalitis, and one with multiple sclerosis; therefore, a total of 10 adult patients with AE. Using Short-Form 36 and Short-Form 10 batteries to measure the HRQOL of patients with encephalitis 6 months after discharge, worse HRQOL was found in patients than in the general population, in association with poor Glasgow outcome scale with poor HRQOL and the propensity of patients with AE to have HRQOL equivalent to the general population in contrast to patients with infectious encephalitis.[14] The present study is the first report to investigate long-term (approximately 5 years) HRQOL of adult patients with AE and revealed their overall propensity to have global QOL within normal limits (15/21, 71%) (Fig. 2) and worse global/social QOL in patients with sequelae than in those without sequelae (Table 3).

In addition, some studies have reported the long-term adverse effects of AE on patients' daily activities, schoolwork, and employment.[6–8,31] A previous study on neurobehavioral long-term outcomes in patients with AE demonstrated that only half of the patients returned to employment and that less than half traveled independently in the community.[8] Another study revealed an association between the presence of ongoing neuropsychiatric issues and worse psychosocial outcomes estimated by the Patient-Reported Outcomes Measurement Information System Psychosocial Impact Illness.[7] Similarly, the frequency of returning to previous work/school life (71%) was not satisfactory for patients with AE even after 5 years, which could be considered an adverse effect of sequelae. Besides, the difficulty in returning to previous work/school life potentially resulted in social QOL under normal limits in nearly half of them (Figure 2 and Table 1).

We also investigated the association between AE etiology and long-term outcomes. A previous study reported that patients

with NMDARE had better outcomes than those with other AEs.[1,8,22] Some studies on the long-term outcomes of AE have revealed better mRS scores, higher adaptive scores, fewer difficulties with emotional liability, and milder fatigue than other AE types.[8,22] We confirmed that the results of the present study were consistent with previously reported findings; patients with NMDARE had better mRS scores, lower frequency of sequelae, and better social QOL than other AEs (Supplementary Table 3; Supplemental Digital Content 8, http://links.lww.com/MD/K22 and Supplementary Table 4; Supplemental Digital Content 9, http://links.lww.com/MD/K23).

Recent studies have suggested the importance of rapid diagnosis and treatment of AE because of the association between decreased sequelae and improvement in returning to work/school activity.[3,5,7,28,32] The significance of various resources such as experienced neurology clinics, psychiatrists, neuropsychologists, physical medicine, and rehabilitation in partnership with neurologic specialists was also advocated.[33] Considering the tight association between sequelae and social activity limitations, timely diagnosis and treatment in the acute phase and appropriate follow-up in the post-acute phase prevent sequelae and reduce difficulty in social activities, which potentially lead to better HRQOL of patients many years after AE onset. Therefore, the establishment of clinical guidelines for AE, which includes recommendations for the treatment and management in the acute phase with high evidence level, is urgently needed to improve the long-term HRQOL of patients.

This study had some limitations. First, the number of patients was relatively small (n = 21), although representative indices such as the mRS, sequelae frequency, and ratio of returning to work/school life were similar to previous studies. Second, the absence of patients with specific antibodies to neuronal surface antigens other than NMDAR antibodies (e.g., antibodies against leucine-rich glioma-inactivated 1, contactin-associated protein-like 2, and dipeptidyl-peptidase-like protein 6) could potentially lead to bias in the long-term characteristics of patients with AE. Finally, because the details of complementary tests, such as cerebrospinal fluid, magnetic resonance imaging, electroencephalography, and positron emission tomography, were limited to those of the acute phase, we cannot investigate the neural mechanisms underlying sequelae and worse HRQOL over years after disease onset.

5. Conclusions

Five years after AE onset, all patients achieved neurologically favorable outcomes (mRS ≤ 2), but nearly half of them had any type of sequelae. No more than 71% returned to their previous work or school life, and nearly half of the patients had social QOL under normal limits. The difficulty in returning to work/school and a worse HRQOL were prominent in patients with sequelae. Therefore, early diagnosis and treatment to prevent sequelae in the acute phase of AE could potentially promote patients' return to previous work/school life and improve their long-term HRQOL several years after onset.

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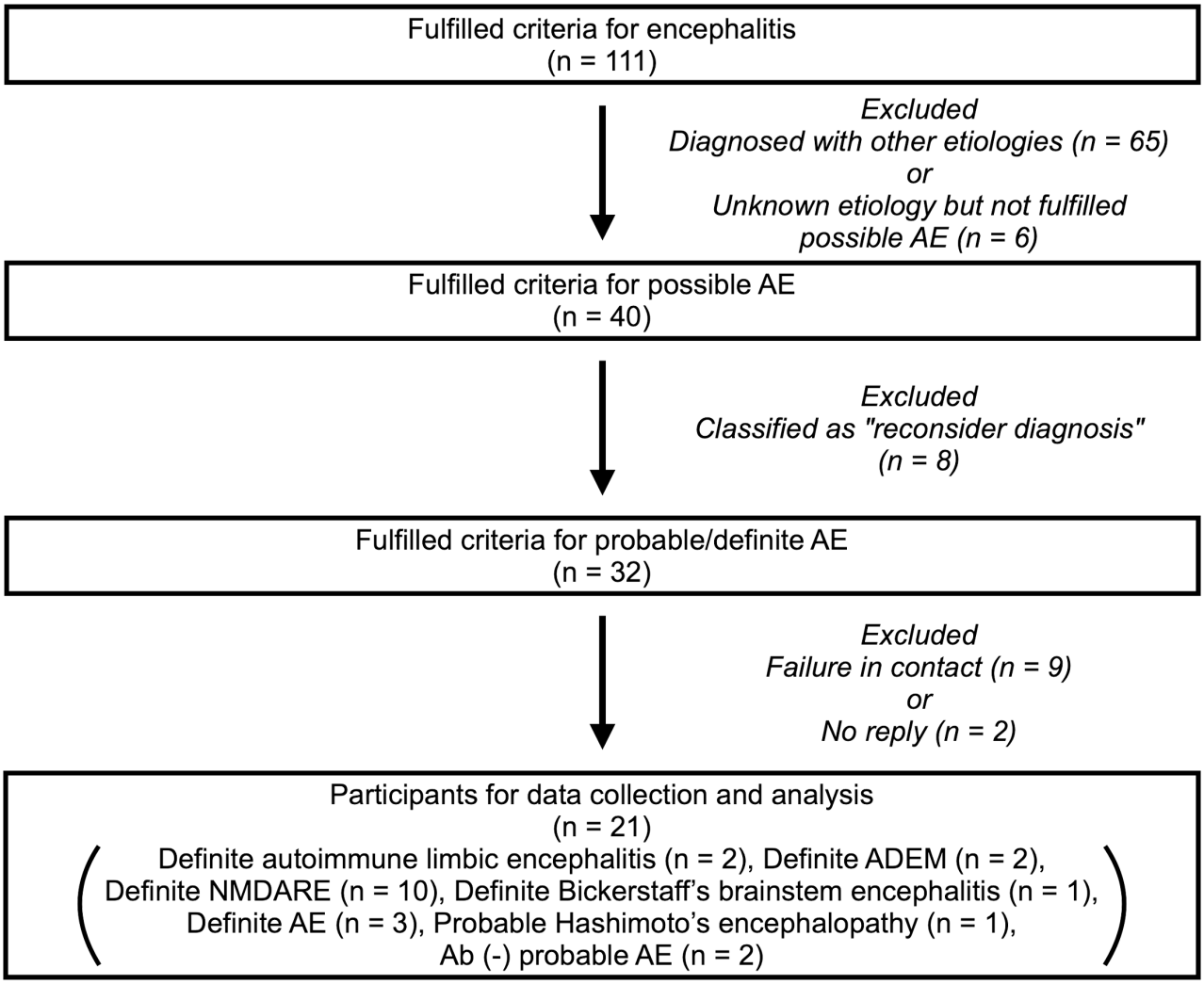
Supplemental Digital Content 1

Long-term outcomes and health-related quality of life in patients with autoimmune encephalitis: An observational study

Yuki Yokota, MD

Supplementary Figure 1. Flowchart of patient selection and classification.



In our clinical records of patients treated between January 2011 and October 2020, 111 patients fulfilled the diagnostic criteria for acute encephalitis.[1] Sixty-five of them were diagnosed with encephalitis of etiologies other than autoimmunity such as infection, vasculitis, or connective tissue disorder. The etiology of encephalitis in six patients could not be determined. Forty patients fulfilled the criteria for possible AE.[2] Furthermore, according to the Graus diagnostic algorithm, eight patients were classified as "reconsider diagnosis," and 32 patients were eventually diagnosed with probable/definite AE. We tried to contact the 32 patients, but 9 of them were not reachable. The long-term outcomes and quality of life of the remaining 21 patients with AE were analyzed. The etiology consisted of

definite NMDARE (n = 10), definite ADEM (n = 2), definite AE (n = 3), definite Bickerstaff's brainstem encephalitis (n = 1), probable Hashimoto's encephalopathy (n = 1), definite autoimmune limbic encephalitis (n = 2), and Ab (-) probable AE (n = 2). Abbreviations: Ab (-) probable AE, autoantibody-negative but probable autoimmune encephalitis; ADEM, acute disseminated encephalomyelitis; AE, autoimmune encephalitis; NMDARE, anti-*N*-methyl-D-aspartate receptor encephalitis.

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Supplemental Digital Content 2

Long-term outcomes and health-related quality of life in patients with autoimmune encephalitis: An observational study

Yuki Yokota, MD

Supplementary Methods. Details of patient classification and HRQOL analysis.

In-house assays for screening of NSAs and onconeural antibodies

A series of NSAs (e.g., antibodies against N-methyl-d-aspartate receptor [NMDAR], leucine-rich glioma-inactivated 1 [LGI1], contactin-associated protein-like 2 [Caspr2], dipeptidyl-peptidase-like protein 6 [DPPX], and immunoglobulin-like cell adhesion molecule 5 [IgLON5]), and onconeural antibodies (e.g., ANNA1, Yo, Ri, Ma, and CV2) for all 111 patients' CSF and serum samples were screened using the following two techniques: tissue-based assay (TBA) with rat brain sections and immunocytochemistry with rat primary cultured neurons (Live-neuron assay).

In-house TBA

TBA, which involved immunohistochemical analyses of rat brain tissue, was implemented as reported.[1] Briefly, adult female Wistar rats were sacrificed without perfusion, and the brain was removed and fixed in 4% paraformaldehyde for 1 h at 4°C, cryoprotected in 40% sucrose for 48 h, embedded in freezing compound media, and snap frozen in isopentane chilled with liquid nitrogen. Thereafter, 6-μm-thick tissue sections were sequentially incubated with 0.3% H_2O_2 for 15 min, 5% goat serum for 1 h, and patients and control CSF (1:2) or serum (1:200) at 4°C overnight. After incubating with biotinylated secondary antibodies against human IgG (1:2000, BA-3000, Vector), the reactivity was developed using the avidin-biotin-peroxidase method. The results of the assay were independently evaluated by two experts (MH and HN) familiar with the immunohistochemical technique, who then classified the samples into "positive (neuropil pattern, astrocytic pattern, white matter pattern, and intracellular pattern)," "negative," or "dubious." The samples categorized into "dubious" required retesting to determine the final TBA results. The samples deemed "positive" were subsequently examined with the confirmation tests described below to determine the specific neuronal antigens.

In-house Live-neuron assay

Rat hippocampal neuronal cultures were prepared as reported.[1] Briefly, matured live neurons grown on coverslips were incubated for 1 h at 4°C with patient or control CSF (1:2) or serum (1:80). After removing the media and extensive washing with PBS, neurons were fixed with 4% paraformaldehyde and immunolabeled with Alexa Fluor® 488 goat anti-human IgG (1:1000, A11013, Invitrogen). The results were photographed using a fluorescent microscope (BZ-X810, KEYENCE, Osaka, Japan). The results of the assay were evaluated by an expert (MH) familiar with the indirect immunofluorescence assay, who then classified the samples into "positive" or "negative." The samples classified as "positive" were subsequently examined with the confirmation tests below to determine the specific neuronal surface antigens.

Confirmation tests of NSAs and onconeural antibodies with commercially available tests

For patients with a positive result during in-house TBA and/or Live-neuron assay, subsequent confirmation tests using commercially available cell-based assay (CBA) for 7 neuronal surface antigens (NMDAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, LGI1, Caspr2, gamma-aminobutyric acid receptor type B, DPPX, and IgLON5) (BIOCHIP, Euroimmun, performed by Labor Berlin) and/or commercially available line blot assays for 12 onconeural antigens (EUROLINE, Euroimmun, Lübeck, Germany) were performed.

Detection of other types of autoantibodies associated with autoimmune encephalitis

Antibodies against aquaporin-4 and myelin oligodendrocyte glycoprotein in the serum were screened using CBA (Cosmic Corporation Co., Ltd., Tokyo, Japan) for all 40 patients who fulfilled the diagnostic criteria for possible AE.[2] Similarly, antibodies against thyroid peroxidase, thyroglobulin, and GQ1b were tested for the serum samples of the 40 patients.

Definition of physical QOL, mental QOL, social QOL, and global QOL

This study aimed not only to estimate patients' QOL of each of the 12 domains of Neuro-QOL but also to comprehensively evaluate physical, mental, and social health experiences. For this purpose, we defined "physical QOL," "mental QOL," "social QOL," and "global QOL" based on T-scores of 12 domains in the following manner (Supplementary Figure 2). After the transformation from raw scores to T-scores for each of the 12 domains of the Neuro-QOL, we first classified the 12 domains into two categories. A "positive category" included six domains of upper extremity function, lower extremity function, positive affect and well-being, cognitive function, satisfaction with social roles and activities, and ability to participate in social roles and activities, and higher T-scores of these domains indicate better QOL.[3] On the contrary, a "negative category" included the other six domains of fatigue, sleep disturbance, depression, anxiety, stigma, and emotional and behavioral dyscontrol, and higher T-scores of these domains indicate worse QOL.[3] Second, for the six "negative" domains, "inverted T-scores" were defined as 100 minus the original T-score. Consequently, higher scores in inverted T-scores indicate better QOL (similar to the original T-scores of positive domain categories). Here, the controls' average (i.e., 50) and standard deviation (i.e., 10) were preserved through this inversion transformation. Third, we averaged the T-scores of positive categories and inverted the T-scores of negative categories across physical, mental, and social domains, yielding three scores of physical, mental, and social QOL, respectively. Here, the subdivision of the 12 domains into physical, mental, and social domains was based on the "Neuro-QOL Adult Domain Framework" (National Institute of Neurological Disorders and Stroke User Manual for the Quality of Life in Neurological Disorders (Neuro-QOL) Measures, Version 2.0, March 2015). Finally, the three scores of physical, mental, and social QOL were averaged, resulting in a single score of global QOL.

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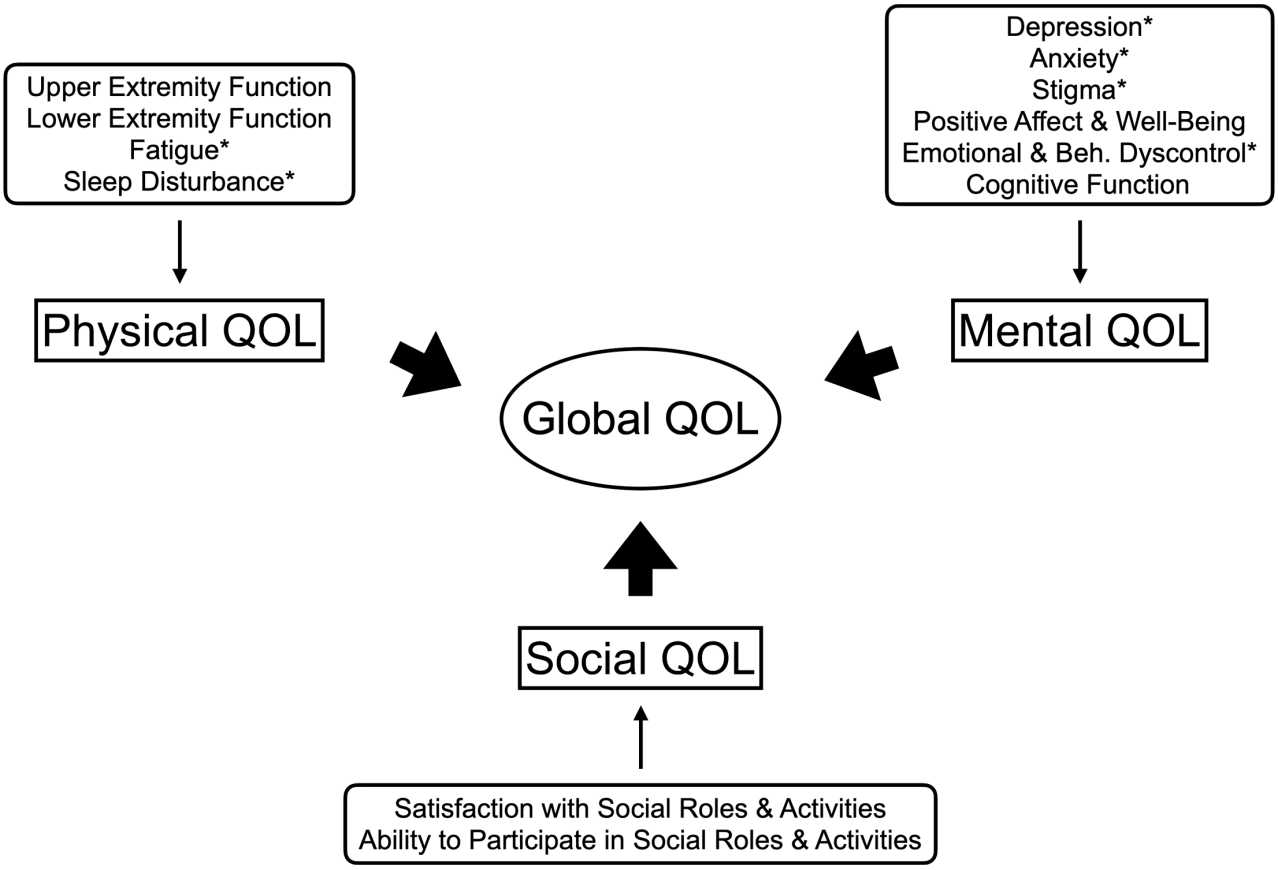
Supplemental Digital Content 3

Long-term outcomes and health-related quality of life in patients with autoimmune encephalitis: An observational study

Yuki Yokota, MD

Supplementary Figure 2. Definition of physical QOL, mental QOL, social QOL, and global QOL.



The T-scores of the positive categories and the inverted T-scores of the negative categories were averaged across four physical domains, yielding a score of physical QOL. Similarly, mental and social QOL were calculated. Finally, the three scores were further averaged into a single score of the global QOL. *Items with an inverted T-score. Abbreviation: Beh, Behavioral.

Supplemental Digital Content 4

Long-term outcomes and health-related quality of life in patients with autoimmune encephalitis: An observational study

Yuki Yokota, MD

Supplementary Table 1. Clinical data of 21 patients with autoimmune encephalitis.

Case	Age		Sex	AE subtype	Follow-up duration	mRS	
	Onset	Follow-up			(months)	Peak	Follow-up
1	34	47	F	NMDARE	156.2	4	0
2	15	25	F	NMDARE	124.3	3	0
3	52	62	F	ALE	116.0	3	1
4	22	31	F	Definite AE	104.1	5	0
5	24	32	F	NMDARE	105.4	5	0
6	31	39	F	NMDARE	102.8	5	0
7	49	56	F	Hashimoto's encephalopathy	82.6	4	0
8	19	25	F	NMDARE	69.4	5	0
9	53	59	F	ALE	74.3	5	2
10	15	21	M	Definite AE	74.4	5	0
11	40	46	M	Ab (-) probable AE	63.0	5	1
12	19	24	F	NMDARE	51.3	5	0
13	71	76	M	ADEM	50.8	3	2
14	31	35	M	Bickerstaff's brainstem encephalitis	49.2	5	0
15	18	22	F	Definite AE	48.1	5	2
16	18	22	M	NMDARE	38.0	5	0
17	21	25	F	NMDARE	39.2	5	0
18	36	39	F	ADEM	32.4	5	1
19	16	18	F	NMDARE	28.5	5	0
20	26	29	F	NMDARE	24.6	5	0
21	44	46	M	Ab (-) probable AE	28.3	4	0

Abbreviations: Ab (-) probable AE, autoantibody-negative but probable autoimmune encephalitis; ADEM, acute disseminated encephalomyelitis; AE, autoimmune encephalitis; ALE, autoimmune limbic encephalitis; NMDARE, anti-*N*-methyl-D-aspartate receptor encephalitis; mRS, modified Rankin Scale.

Supplementary Table 1. (continued)

Case	Hospitalization (days)	Mechanical ventilation	Onset to first-line immunotherapy (days)	First-line therapy	Second-line therapy	Relapse
1	78	No	3	Yes	No	Yes
2	66	No	29	Yes	No	No
3	43	Yes	3	Yes	No	No
4	142	Yes	5	Yes	No	No
5	210	Yes	7	Yes	Yes	No
6	37	Yes	6	Yes	No	No
7	54	No	15	Yes	No	No
8	55	Yes	9	Yes	No	No
9	115	Yes	12	Yes	No	No
10	19	No	5	Yes	No	Yes
11	186	Yes	9	Yes	No	No
12	108	No	9	Yes	No	No
13	111	No	8	Yes	No	No
14	37	Yes	3	Yes	No	No
15	33	Yes	11	Yes	No	No
16	128	Yes	6	Yes	Yes	No
17	103	Yes	7	Yes	Yes	No
18	38	No	12	Yes	No	No
19	74	Yes	22	Yes	Yes	No
20	46	No	3	Yes	Yes	No
21	44	No	13	Yes	No	No

Supplementary Table 1. (continued)

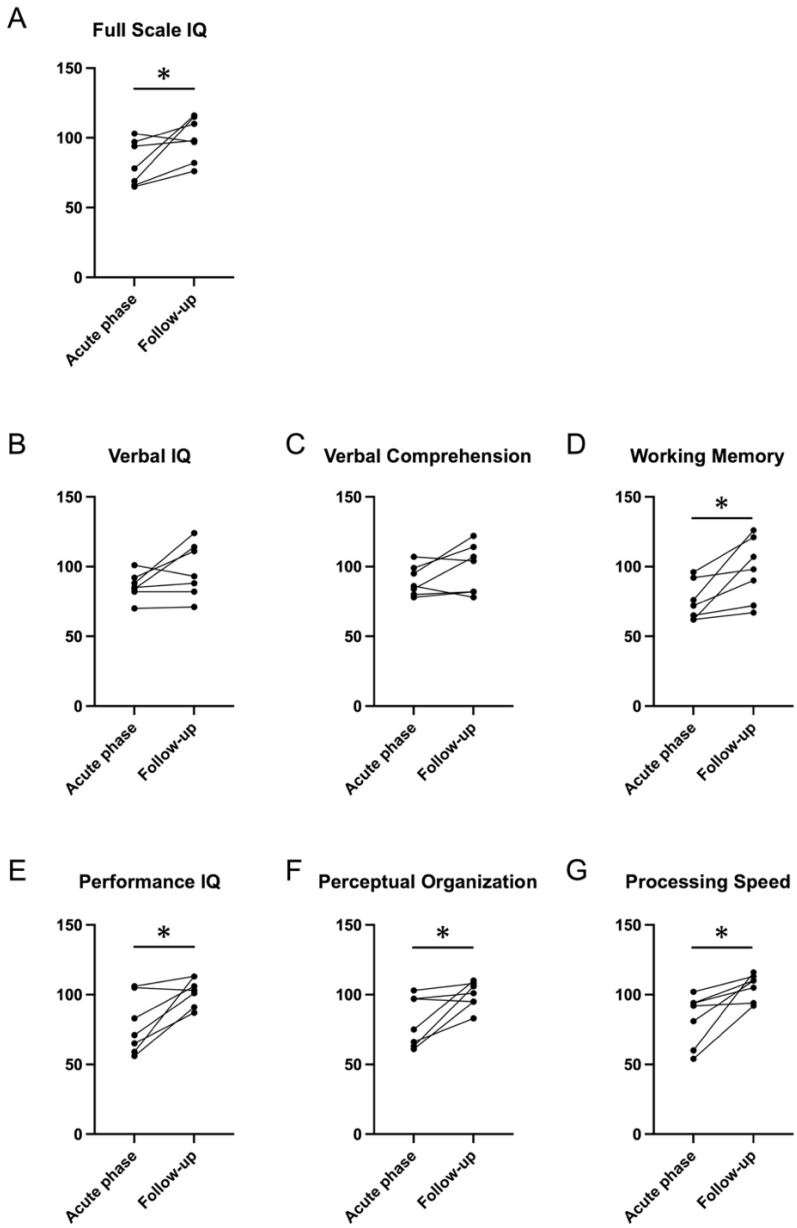
Case	Sequelae		WAIS-III		Return to previous work/school life	Self-reliance at home life
	Symptoms	Medication	Acute phase	Follow-up		
1	None	None	No	No	Yes	Yes
2	None	None	No	No	Yes	Yes
3	Memory disorder (retrograde amnesia)	None	No	No	Yes	Yes
4	Personality change (irritability)	None	No	No	No	Yes
5	None	None	Yes	Yes	Yes	Yes
6	None	None	Yes	Yes	Yes	Yes
7	None	None	No	No	Yes	Yes
8	None	None	No	No	Yes	Yes
9	Memory disorder (severe impairment in short-term memory), personality change (irritability), and olfactory dysfunction	Anti-epileptic drug	No	Yes	No	No
10	Seizure (clonic seizures, once every few years)	Anti-epileptic drug	No	No	Yes	Yes
11	Dysuria, personality change (irritability), and sensory disturbance of the lower right extremity	None	No	No	No	Yes
12	None	None	Yes	Yes	Yes	Yes
13	Mood disorder (apathy), sleep disturbance (insomnia, mid-awakening), and frailty	None	No	No	No	No
14	None	None	No	No	Yes	Yes
15	Seizure (tonic seizures, several times a month)	Anti-epileptic drug	No	No	No	Yes
16	None	None	Yes	Yes	Yes	Yes
17	None	None	Yes	Yes	Yes	Yes
18	Speech disturbance (word-finding difficulty), and sensory disturbance of the lower left extremity	None	No	No	Yes	Yes
19	None	None	Yes	Yes	Yes	Yes
20	Seizure (tonic seizures, once every few years), and sleep disturbance (hypersomnia)	Anti-epileptic drug	Yes	Yes	No	Yes
21	None	None	No	No	Yes	Yes

Supplemental Digital Content 5

Long-term outcomes and health-related quality of life in patients with autoimmune encephalitis: An observational study

Yuki Yokota, MD

Supplementary Figure 3. WAIS-III scores during the acute phase and at follow-up.



We evaluated the WAIS-III scores during the acute phase and at follow-up. There was a significant improvement in Full Scale IQ, Working Memory, Performance IQ, Perceptual Organization, and Processing Speed (A, D, E, F, and G); however, Verbal IQ and Verbal Comprehension were not significantly improved (B and C). The scores of the same patient in the acute phase and follow-up are connected by a line. *$P < 0.05$.

Supplemental Digital Content 6

Long-term outcomes and health-related quality of life in patients with autoimmune encephalitis: An observational study

Yuki Yokota, MD

Supplementary Table 2. Neuro-QOL T-scores of 21 patients with autoimmune encephalitis. (Physical domain)

Case	Upper Extremity Function	Lower Extremity Function	Fatigue	Sleep Disturbance
1	53.8	58.6	43.8	45.6
2	53.8	58.6	29.5	39.1
3	53.8	58.6	43.8	47.3
4	53.8	58.6	29.5	32.0
5	53.8	58.6	38.2	47.3
6	53.8	58.6	29.5	36.3
7	53.8	58.6	39.5	47.3
8	53.8	58.6	29.5	32.0
9	53.8	58.6	29.5	39.1
10	53.8	58.6	29.5	41.7
11	53.8	58.6	46.5	54.4
12	53.8	58.6	29.5	32.0
13	39.3	48.6	45.6	48.9
14	53.8	58.6	40.7	45.6
15	37.1	51.2	48.4	59.2
16	53.8	58.6	29.5	39.1
17	53.8	58.6	41.8	45.6
18	53.8	58.6	36.5	41.7
19	53.8	58.6	47.4	59.2
20	53.8	58.6	53.3	59.2
21	53.8	58.6	29.5	32.0

Supplementary Table 2. (Continued, Mental domain)

Case	Depression	Anxiety	Stigma	Positive Affect & Well-Being	Emotional & Beh. Dyscontrol	Cognitive Function
1	45.3	44.3	47.6	54.9	42.0	59.0
2	45.3	45.9	39.2	51.5	37.2	64.2
3	36.9	48.4	39.2	56.8	43.7	47.1
4	57.4	51.4	81.5	34.3	49.4	64.2
5	52.8	50.5	39.2	41.8	50.7	56.3
6	43.1	36.4	39.2	58.8	45.3	64.2
7	36.9	47.3	39.2	51.5	37.2	64.2
8	36.9	36.4	39.2	54.9	32.2	64.2
9	55.1	51.4	47.6	46.3	46.7	47.1
10	36.9	53.3	39.2	57.8	39.9	59.0
11	43.1	47.3	39.2	58.8	32.2	59.0
12	36.9	42.1	39.2	68.0	37.2	59.0
13	59.8	54.2	57.8	39.4	45.3	42.9
14	36.9	45.9	49.3	55.8	54.5	59.0
15	64.6	64.2	54.6	35.3	58.3	33.0
16	49.8	45.9	45.7	54.0	32.2	50.9
17	47.9	47.3	39.2	49.9	48.1	44.9
18	43.1	36.4	39.2	54.0	42.0	47.1
19	61.4	60.1	47.6	41.8	59.6	40.9
20	63.0	62.6	39.2	49.0	54.5	54.2
21	36.9	36.4	39.2	68.0	32.2	64.2

Abbreviation: Beh, Behavioral.

Supplementary Table 2. (Continued, Social domain)

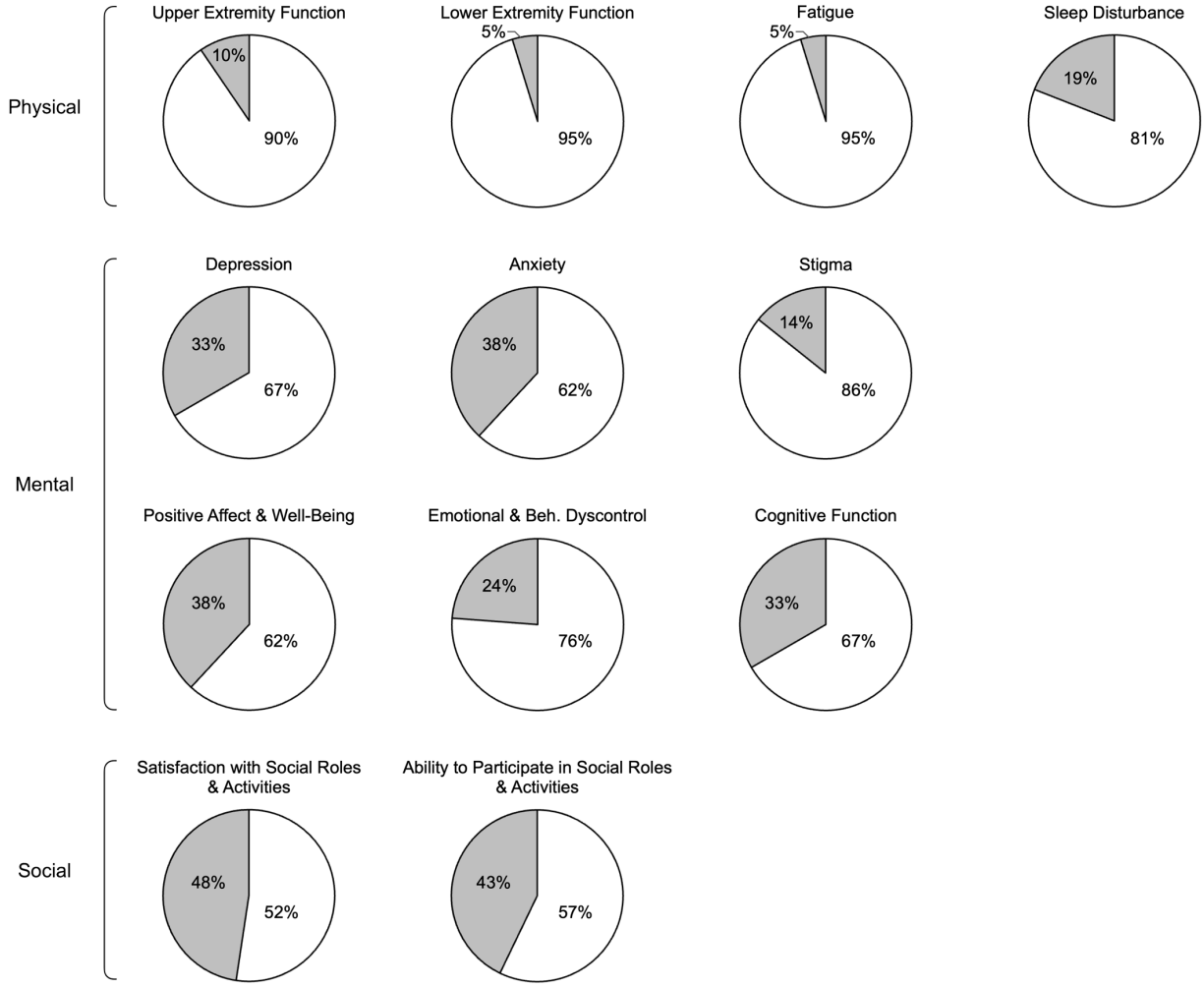
Case	Satisfaction with Social Roles & Activities	Ability to Participate in Social Roles & Activities
1	52.0	60.2
2	50.7	60.2
3	42.7	33.5
4	28.4	24.1
5	52.0	60.2
6	53.7	60.2
7	52.0	60.2
8	49.8	60.2
9	48.9	42.7
10	50.7	49.2
11	42.7	46.8
12	60.5	60.2
13	41.7	39.2
14	52.0	60.2
15	39.1	36.4
16	60.5	60.2
17	52.0	53.4
18	47.5	51.6
19	42.2	38.5
20	46.3	43.4
21	52.0	51.6

Supplemental Digital Content 7

Long-term outcomes and health-related quality of life in patients with autoimmune encephalitis: An observational study

Yuki Yokota, MD

Supplementary Figure 4. Evaluation of long-term HRQOL for each 12 domains.



The Neuro-QOL T-scores of each 12 domains were categorized into “within normal limits” or “under normal limits” based on the controls group's average T-score (i.e., 50). Twelve pie charts represent the proportions of patients (n = 21) of “within normal limits” and “under normal limits” for each Neuro-QOL domain. White indicates “within normal limits” and gray indicates “under normal limits.” Abbreviation: Beh, Behavioral.

Supplemental Digital Content 8

Long-term outcomes and health-related quality of life in patients with autoimmune encephalitis: An observational study

Yuki Yokota, MD

Supplementary Table 3. Comparison of the clinical features and long-term outcomes between the patients with NMDARE and the patients with other AEs.

	NMDARE (n = 10)	other AEs (n = 11)	*P*-value
age at onset, y, median (range)	20 (15–34)	40 (15–71)	.021*
age at survey, y, median (range)	25 (18–47)	46 (21–76)	.041*
duration since disease onset up to survey, month, median (range)	60 (25–156)	63 (28–116)	.918
peak mRS, median (range)	5 (3–5)	5 (3–5)	.580
mRS at survey, median (range)	0 (0–0)	1 (0–2)	.012*
sequelae, n (%)	1 (10.0)	8 (72.3)	.008*
self-reliance at home life, n (%)	10 (100)	9 (81.8)	.476
return to previous work/school life, n (%)	9 (90.0)	6 (54.5)	.149

Abbreviations: AE, autoimmune encephalitis; mRS, modified Rankin Scale; NMDARE, anti-*N*-methyl-D-aspartate receptor encephalitis. *$P < 0.05$

Supplemental Digital Content 9

Long-term outcomes and health-related quality of life in patients with autoimmune encephalitis: An observational study

Yuki Yokota, MD

Supplementary Table 4. The difference in Neuro-QOL scores between the patients with NMDARE and the patients with other AEs.

Neuro-QOL domain	NMDARE (n = 10)	other AEs (n = 11)	*P*-value
global QOL, median (range)	57.0 (44.7–61.7)	52.3 (40.2–59.7)	.115
physical QOL, median (range)	58.8 (50.0–62.7)	56.5 (45.2–62.7)	.544
mental QOL, median (range)	55.5 (42.3–62.4)	56.0 (37.8–64.6)	.756
social QOL, median (range)	55.8 (40.4–60.4)	45.8 (26.3–56.1)	.018*

Abbreviations: AE, autoimmune encephalitis; NMDARE, anti-*N*-methyl-D-aspartate receptor encephalitis; QOL, quality of life. *$P < 0.05$

日本大学医学部内科学系神経内科学分野

横田 優樹

Long-term outcomes and health-related quality of life in patients with autoimmune encephalitis: An observational study（自己免疫性脳炎患者の長期転帰と健康関連 QOL についての観察研究）

和文要約

1. 研究概要

自己免疫性脳炎には様々な神経学的後遺症があり、時に生命に関わることもあることが知られている[1, 2]。一般的に多くの自己免疫性脳炎患者は急性期に重篤な症状を認めるものの、集中的な治療により改善し modified Rankin Scale（mRS）による評価では最終的な予後は良好とされている[2-5]。しかし近年、予後良好と判断される患者の中には発症から数年経過しているにも関わらず、精神症状の残存のために社会復帰に支障をきたす症例が少なくないことが明らかになり[6-8]、身体機能の指標である mRS のみでは自己免疫性脳炎患者の予後評価は不十分と考えられる[8, 9]。これまでのところ社会復帰や後遺症障害に関する長期のデータは限られており、我々は自施設の自己免疫性脳炎患者を対象に quality of life（QOL）を含めた社会的長期予後について検討した。今回の観察研究では mRS に加え、残存症状の有無と内容について対面や電話でのアンケート調査を行い、Neuro-QOL を用いて健康関連 QOL（health-related QOL, HRQOL）を調査した。

2. 方法

2.1. 対象患者

2011 年 1 月 1 日から 2020 年 10 月 31 日の期間、当院で治療した Venkatesan, A. 2013. [10] の脳炎および脳症の診断基準を満たす患者のうち、Graus AE criteria 2016 [11] で definite/probable AE と診断された者を対象とし、reconsider diagnosis に分類される患者は除外した。このうち連絡がとれ対面や電話でアンケート調査を行った患者を対象とした。21 人の患者から回答が得られ、得られた情報を解析した。

2.2. アンケート調査

現在の身体機能は mRS と Neuro-QOL（Physical ドメイン）で評価した。社会復帰の有無、家庭での自立、後遺症の有無や種類、脳炎以外の既往症はアンケート調査を通じて調査した。HRQOL は Neuro-QOL を用いて評価した。

2.3. Neuro-QOL について

Neuro-QOL は 2012 年に開発された、神経疾患患者の HRQOL を評価する指標である [12]。12 種類のドメインについて、1 つのドメインにつき 1 つの質問紙票がある。各質問紙票には 8 つ前後の質問が含まれており、回答者は各質問に対して 5 段階評価で回答する。Physical ドメインは Upper Extremity Function（上肢の機能）、Lower Extremity Function（下肢の機能）、Fatigue（疲労感）、Sleep Disturbance（睡眠障害）の 4 つで構成され、mental ドメインは Depression（気分の落ち込み）、Anxiety（不安）、Stigma（差別、偏見）、Positive Affect and Well-Being（前向きな気持ちと幸福感）、Emotional and Behavioral Dyscontrol（感情や行動のコントロール）、Cognition Function（認知機能）の 6 つ、social ドメインは Satisfaction with Social Roles and Activities（社会的役割や社会活動に対する満足感）と Ability to Participate in Social Roles and Activities（社会的役割や社会的活動に参加する能力）から構成される。すべての質問の回答集計により、各ドメインの素点（raw score）が得られる。この素点はさらに、Neuro-QOL 開発者の提供する得点変換表により T-score に変換でき、T-score は、健常者集団における平均値が 50、標準偏差が 10 になるように調整されており、患者集団と健常者集団の比較が

可能である。回答者一人につき、合計 12 個の T-score（1 ドメインに 1 つの T-score）が得られる。

2.4. Physical QOL, mental QOL, social QOL, global QOL の定義について

12 個あるドメインの評価を行うだけではなく、患者の physical, mental, social ドメインの包括的な評価と全体の QOL を評価するために、今回の研究では新たに「Physical QOL」「Mental QOL」「Social QOL」「Global QOL」を以下のように定義した。まず 12 個あるドメインを、T-score が高いほど QOL が良好となる「Positive category」と、反対に T-score が高いほど QOL が不良となる「Negative category」の 2 つの category に分類した。Fatigue（疲労感）、Sleep Disturbance（睡眠障害）、Depression（気分の落ち込み）、Anxiety（不安）、Stigma（差別、偏見）、Emotional and Behavioral Dyscontrol（感情や行動のコントロール）の 6 ドメインが negative category となり、他の 6 ドメインを positive category とした。次に negative category に含まれる 6 ドメインについて、数直線上で 50 を軸とする対称移動を行い inverted T-score を計算した。この変換の前後でもともとの T-score がもつ「健常人の平均値が 50 で標準偏差が 10」という性質は変わらずに保たれる（Figure 1）。この変換によって得られた T-score の physical ドメイン, mental ドメイン, social ドメインの平均をそれぞれ「Physical QOL」、「Mental QOL」、「Social QOL」とし、この得られた 3 つの包括ドメインの平均を「Global QOL」と定義した。新たに得られた 4 つの指標は健常人の平均値が 50 となるため、患者と健常人との比較が可能である。

2.5. 統計解析

患者の T-score と 50（健常人の平均値）との比較を Wilcoxon signed-rank test で検定した。ここでは健常人の平均値のみ参照しており、健常人の標準偏（10）は参照しなかった。患者の physical QOL, mental QOL, social QOL, global QOL と 50（健常人の平均値）との比較も同様に Wilcoxon signed-rank test で検定した。T-score 50 以上を within

normal limit, T-score 50 未満を under normal limit とした。21 人の患者を NMDA 受容体脳炎（NMDARE, n = 10）とその他の自己免疫性脳炎（other AEs, n = 11）にわけ、両者の年齢や後遺症頻度、社会復帰率などを比較した。連続値の比較は Mann–Whitney U test を用いて検定し、質的データ（Categorical data）の比較は Fisher's exact test を用いて検定した。

3. 結果

3.1. 患者背景、臨床的特徴および長期転帰

2011 年 1 月から 2020 年 10 月までの間に当院で治療を行った Venkatesan, A. 2013. の脳炎および脳症の診断基準を満たす患者は 111 人であった。このうち 40 人が Graus AE criteria 2016 で possible AE の診断基準を満たし、32 人が probable/definite AE の診断基準を満たした。このうち 23 人と連絡が取れ、21 人よりアンケート調査の回答を得た（回答率 91%）。21 人のうち autoimmune limbic encephalitis が 2 人、acute disseminated encephalomyelitis（ADEM）が 2 人、NMDARE が 10 人、Bickerstaff brainstem encephalitis が 1 人、definite AE が 3 人、Hashimoto encephalopathy が 1 人、autoantibody-negative but probable AE（Ab (-) probable AE）が 2 人であった。（Figure 2）。年齢の中央値は 26 歳（15–71 歳）であり、15 人（71%）が女性であった。発症からアンケート調査までの期間の中央値は 63 ヶ月（25–156 ヶ月）であり、入院期間の中央値は 66 日（19–210 日）であった。全ての患者が first-line の免疫治療を受け、5 人（24%）が second-line の免疫治療（シクロホスファミド）を受けた。急性期の mRS の中央値は 5（3–5）で、フォローアップの mRS の中央値は 0（0–2）であった。9 人（43%）に何らかの後遺症を認めた。19 人（90%）は家庭での生活が自立していたが、以前の職場・学校への復帰は 15 人（71%）であった（Figure 3）。

3.2. 急性期、フォローアップの WAIS-III スコア

包括的な精神神経学的検査である WAIS-IIIスコアの変化を調査した。急性期およびフォローアップ両方の WAIS-III のデータが得られた患者は全て NMDARE 患者であった。急性期とフォローアップの比較では、全検査 IQ（中央値、急性期 vs フォローアップ：78 vs 98, P = 0.047）、作業記憶（中央値、急性期 vs フォローアップ：72 vs 98, P = 0. 016）、動作性 IQ（中央値、急性期 vs フォローアップ：71 vs 103, P = 0.031）、知覚統合（中央値、急性期 vs フォローアップ：75 vs 101, P = 0.031）、処理速度（中央値、急性期 vs フォローアップ：92 vs 110, P = 0.016）であった。言語性 IQ（中央値、急性期 vs フォローアップ：85 vs 93, P = 0.156）、言語理解（中央値、急性期 vs フォローアップ：86 vs 104, P = 0.219）では有意な改善はみられなかった（Figure 4）。

3.3. HRQOL, social QOL が within normal group と under normal group との比較

Neuro-QOL の 12 個の各ドメインの raw score は T-score に変換され、T-score から各患者における physical QOL, mental QOL, social QOL, global QOL を評価した。Global QOL が within normal limit の患者は 15 人（71%）であった。Physical QOL は 18 人（86%）が within normal limit であり、mental QOL は 15 人（71%）が within normal limit であった。一方，social QOL において within normal limit の患者は 11 人（52%）、under normal limit は 10 人（48%）であり（Figure 5）、他の包括ドメインと比較して social QOL の within normal limit に該当患者は他の QOL と比較して少なかった。そのため患者群を within normal group と under normal group に分けて解析を行った。その結果、social QOL under normal group は within normal group と比べ、後遺症が有意に多く（90.0 % vs 0%, $p = < 0.001$）、社会復帰率も有意に低かった（40.0 % vs 100 %, $p = 0.004$）（Table 1）。

3.4. 後遺症がある患者とない患者の比較

後遺症の有無に基づいて患者 21 人を 2 群にわけて比較解析したことろ（後遺症あり 9 人 vs 後遺症なし 12 人)、後遺症がある群はない群と比べ、社会復帰率が有意に低かった（33.3 % vs. 100 %, $p = 0.002$）（Table 2）。また global QOL と social QOL の T-

score も後遺症のある群はない群と比べ有意に低かった（global QOL 中央値 49.8 [range 40.2–56.1] vs 57.7 [range 44.7–61.7], $p = 0.002$, social QOL 中央値 44.8 [range 26.3–50.0] vs 56.1 [range 40.4–60.4], $p = < 0.001$）（Table 3）。

3.5. NMDARE と other AEs の比較

自己免疫性脳炎において比較的予後が良好とされる NMDAR 脳炎（NMDARE）の患者（10 人）と、その他の自己免疫性脳炎（other AEs）の患者（11 人）の臨床的特徴、長期予後や QOL を比較した。NMDARE 群は other AEs 群と比べ後遺症が有意に少なく（10 % vs 72.3 %, $p = 0.008$）、発症年齢が若く（中央値 20 [range 15–34] vs 40 [range 15–71], $p = 0.021$）、調査時の mRS は良好であった（中央値 0 [range 0–0] vs 1 [range 0–2]）（Table 4）。Other AEs 群は NMDARE 群と比較し social QOL が有意に低かった（中央値 45.8 [range 26.3–56.1] vs 55.8 [range 40.4–60.4], $p = 0.018$）（Table 5）。

4. 考察・結論

自己免疫性脳炎の全ての患者は、発症後 5 年（中央値）の時点での mRS による評価において神経学的に良好な転帰（mRS ≦2）を得ていた。しかし、43%の患者は何らかの後遺症を有し、以前の職場や学校生活に復帰できたのは 71%以下であり、48%の患者は social QOL が平均以下（T-score＜50）であった。特に後遺症のある患者は以前の職場や学校生活への復帰が困難であり、HRQOL の悪化が顕著であった。自己免疫性脳炎の長期予後評価には神経学的・身体的評価だけではなく HRQOL を含めた社会的予後の評価も重要であることがわかった。患者の社会復帰と長期的な HRQOL を改善のためには後遺症を少なくすることが重要であり、後遺症予防のための早期診断と早期治療に力を注ぐ必要があると考えられた。本研究は加齢の影響や他の併存疾患の影響を厳密に排除できなかった。さらに、自施設単独での少数例による検討であり、また約半数が NMDARE 患者であるため自己免疫性脳炎患者のプロファイルは均一ではない。これら

は本研究の結果に影響し得るバイアスになるため、本研究における limitation と考えられた。これらバイアスを最小限にするため、多施設での症例集積による更なる検討が必要と考えた。

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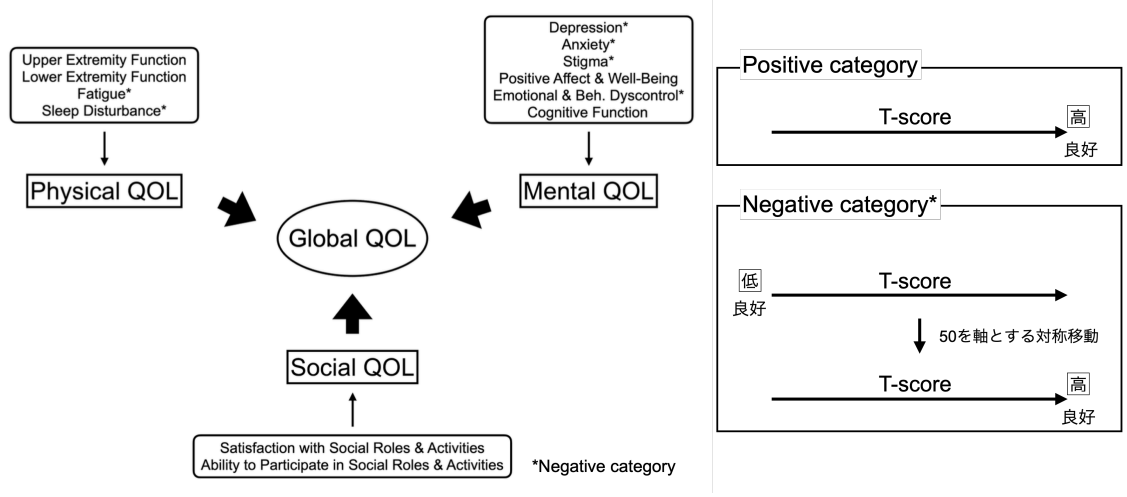
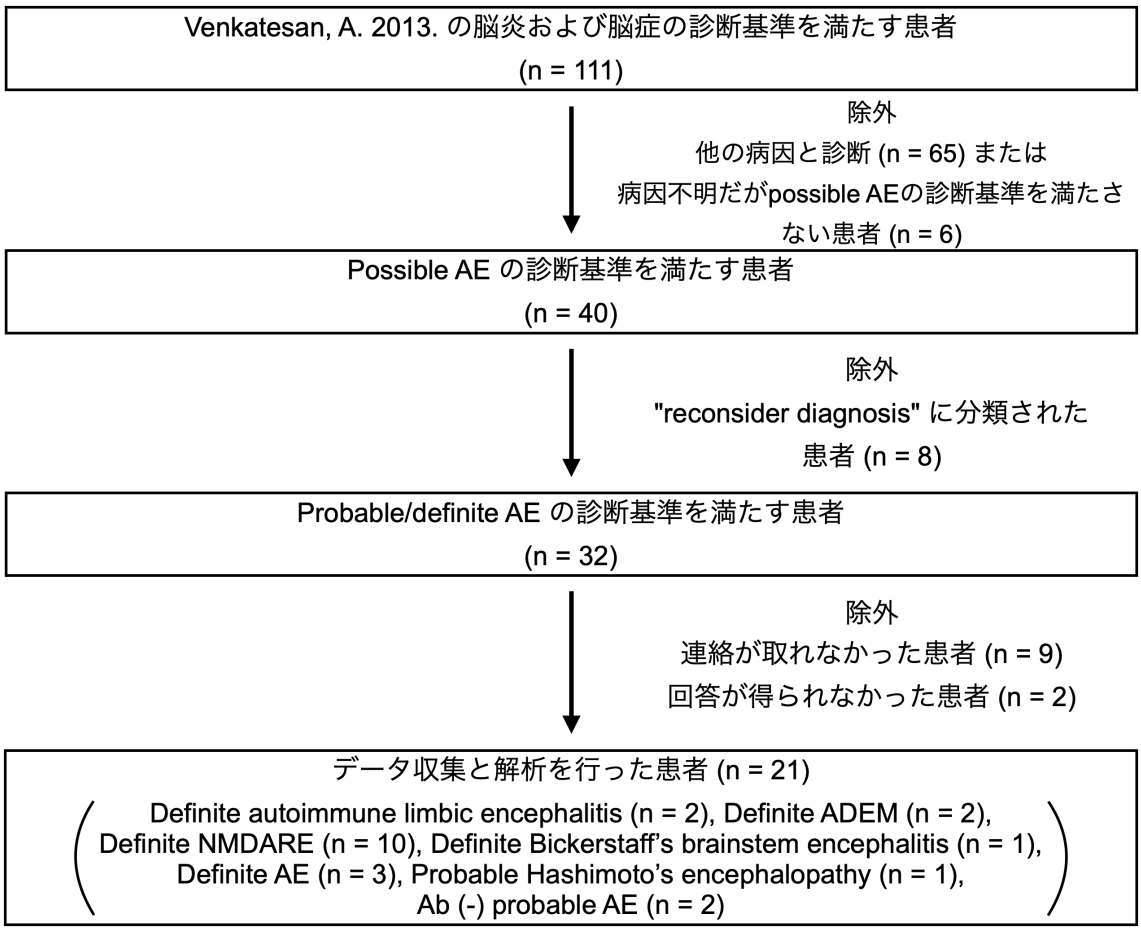
Figure 1.　Physical QOL, mental QOL, social QOL, global QOL の定義



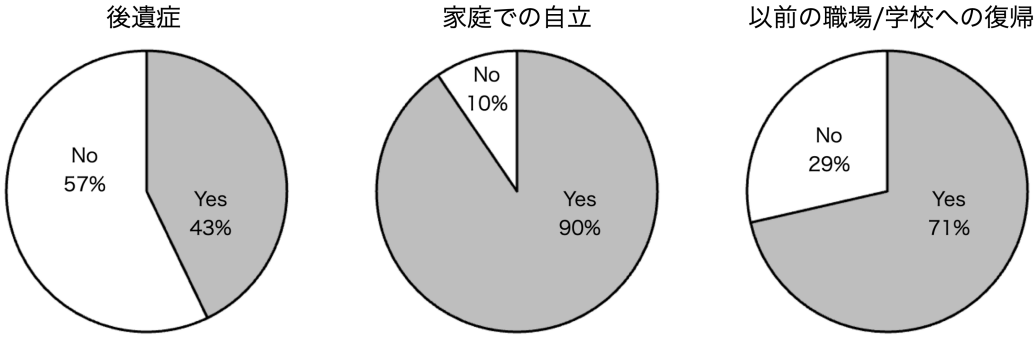
Neuro-QOL の 12 ドメインを positive category, negative category に分類し、negative category に含まれる 6 ドメインについて、数直線上で 50 を軸とする対称移動を行い T-score を変換した。この変換の前後でもともとの T-score がもつ「健常人の平均値が 50 で標準偏差が 10」という性質は変わらずに保たれ、得られた T-score の physical ドメイン、mental ドメイン、social ドメインの平均をそれぞれ「Physical QOL」、「Mental QOL」、「Social QOL」とし、この得られた 3 つの包括ドメインの平均を「Global QOL」と定義した。

Figure 2.　患者の選択および分類のフローチャート



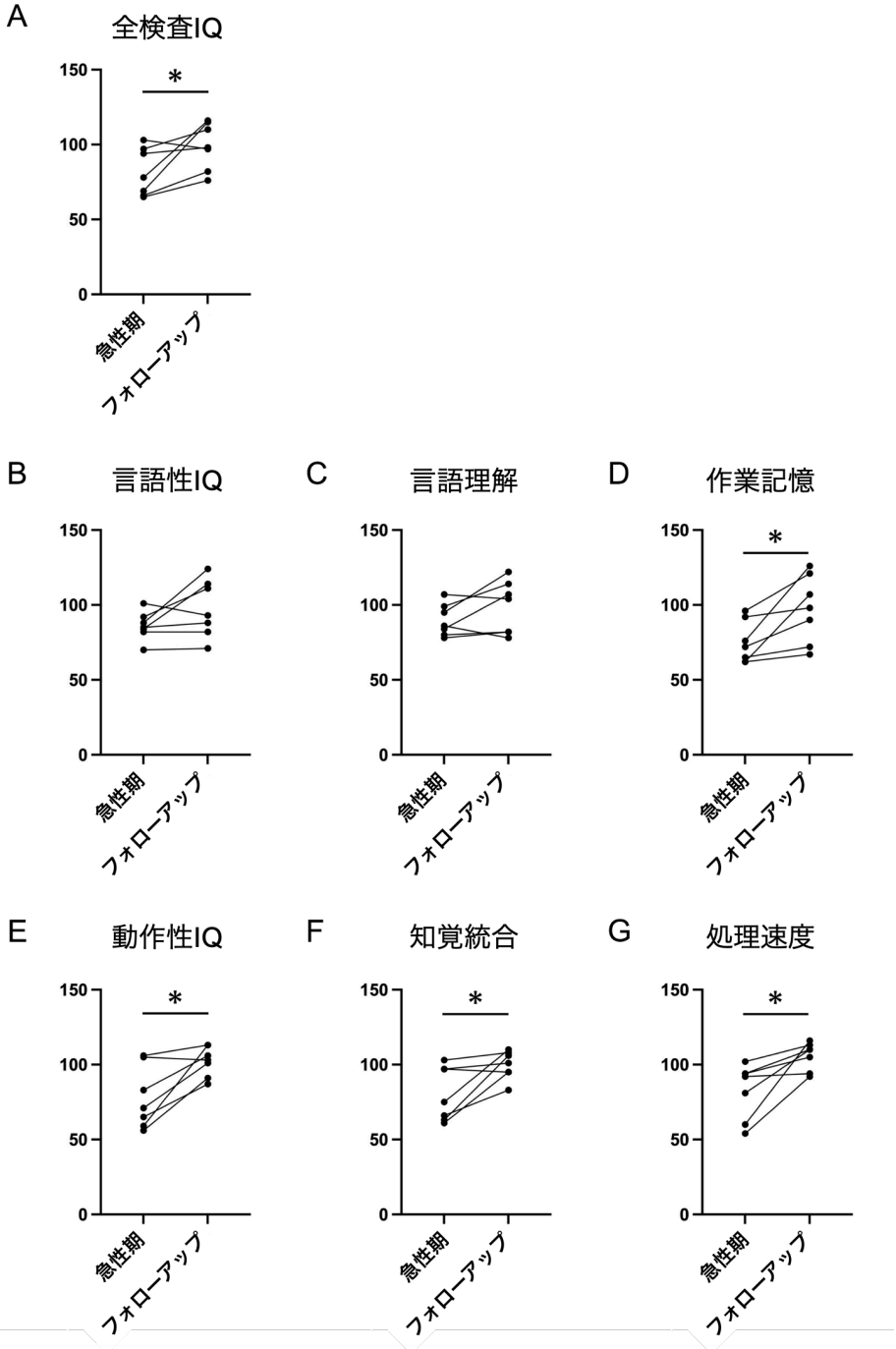
2011 年 1 月 1 日から 2020 年 10 月 31 日までに当院で治療を受けた患者のうち 111 人が Venkatesan, A. 2013. の脳炎および脳症の診断基準を満たしていた。このうち 65 人は感染、血管炎、膠原病など他の病因と診断された。6 人の患者の病因は特定できなかった。40 人は Graus AE criteria 2016 で possible AE の診断基準を満たした。8 人が reconsider diagnosis に分類され、32 人が probable/definite AE の診断基準を満たした。このうち 9 人とは連絡が取れず、2 人からアンケートの回答が得られなかった。21 人の患者が本研究に参加し、autoimmune limbic encephalitis が 2 人、ADEM が 2 人、NMDARE が 10 人、Bickerstaff brainstem encephalitis が 1 人、definite AE が 3 人、Hashimoto encephalopathy が 1 人、autoantibody-negative but probable AE が 2 人であった。

Figure 3.　後遺症の有無、家庭での自立、以前の職場/学校への復帰の有無の割合



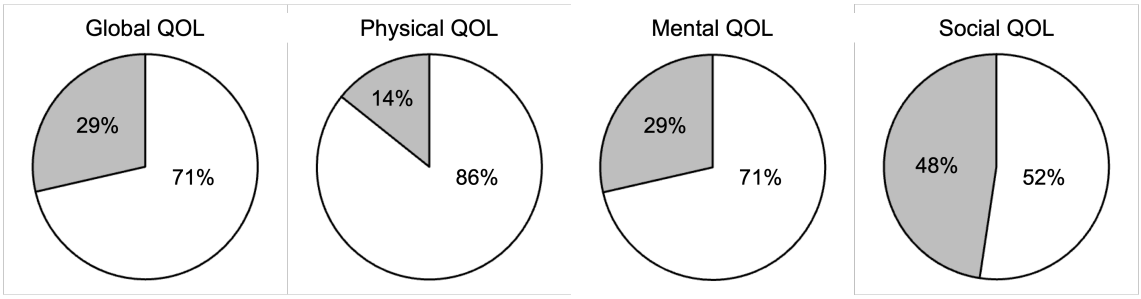
中央値は 63 ヶ月経過時点における患者報告による調査において、43%の患者に何らかの後遺症を認めた。家庭での自立は 90%で、以前の職場/学校への復帰は 71%であった。

Figure 4.　急性期とフォローアップの WAIS-IIIスコアの変化



急性期およびフォローアップの両方で WAIS-IIIが施行できた患者は全て NMDARE 患者であった。全検査 IQ、作業記憶、動作性 IQ、知覚統合、および処理速度（A, D, E, F, G）で有意な改善が得られ、言語性 IQ と言語理解では有意な改善を認めなかった（B および C）。*$P < 0.05$

Figure 5.　自己免疫性脳炎患者の長期経過における HRQOL



患者の global QOL, physical QOL, mental QOL, social QOL を 50（健常人の平均値）と比較した。T-score 50 以上を within normal limit, T-score 50 未満を under normal limit とした。Global QOL が within normal limit の患者は 15 人（71%）であった。Physical QOL は 18 人（86%）が within normal limit であり、mental QOL は 15 人（71%）が within normal limit であった。Social QOL が within normal limit の患者は 11 人（52%）であった。

Table 1.　Social QOL が within normal group と under normal group の臨床的特徴と転帰の比較

Social QOL	within normal group (n = 11)	under normal group (n = 10)	P 値
発症時の年齢, 歳, 中央値 (範囲)	28 (15–49)	31 (15–71)	0.500
女性, n (%)	8 (72.7)	7 (70.0)	0.99
発症から調査までの期間 (月), 中央値, (範囲)	69 (28–156)	57 (25–116)	0.426
急性期			
入院期間, 日, 中央値 (範囲)	66 (37–210)	60 (19–186)	0.794
人工呼吸器の使用, n, (%)	6 (54.5)	6 (60.0)	0.99
ピーク時の mRS, 中央値 (範囲)	5 (3–5)	5 (3–5)	0.653
発症からファーストライン免疫治療までの期間, 日, 中央値 (範囲)	7 (3–29)	9 (3–22)	0.904
セカンドライン免疫治療の施行, n, (%)	3 (27.3)	2 (20.0)	0.99
フォローアップ			
再発, n (%)	1 (9.1)	1 (10.0)	0.99
調査時の mRS, 中央値 (範囲)	0 (0–0)	1 (0–2)	0.004*
後遺症, n (%)	0 (0)	9 (90.0)	< 0.001*
家庭での自立, n (%)	11 (100)	8 (80.0)	0.214
以前の職場/学校への復帰, n (%)	11 (100)	4 (40.0)	0.004*

*$P < 0.05$

Table 2.　後遺症がある患者とない患者の臨床的特徴と長期転帰の比較

	後遺症なし (n = 12)	後遺症あり (n = 9)	P 値
発症時の年齢, 歳, 中央値 (範囲)	23 (15–49)	36 (15–71)	0.212
女性, n (%)	9 (75.0)	6 (66.7)	0.99
調査時の年齢, 歳, 中央値 (範囲)	29 (18–56)	39 (21–76)	0.318
発症から調査までの期間 (月), 中央値, (範囲)	60 (28–156)	63 (25–116)	0.808
家庭での自立, n (%)	12 (100)	7 (77.8)	0.171
以前の職場/学校への復帰, n (%)	12 (100)	3 (33.3)	0.002*

*$P < 0.05$

Table 3.　後遺症がある患者とない患者の Neuro-QOL 包括ドメインの T スコアの比較

Neuro-QOL ドメイン	後遺症なし (n = 12)	後遺症あり (n = 9)	P 値
global QOL, 中央値 (範囲)	57.7 (44.7–61.7)	49.8 (40.2–56.1)	0.002*
physical QOL, 中央値 (範囲)	58.8 (51.5–62.7)	55.3 (45.2–62.7)	0.114
mental QOL, 中央値 (範囲)	56.9 (42.3–64.6)	48.8 (37.8–59.3)	0.096
social QOL, 中央値 (範囲)	56.1 (40.4–60.4)	44.8 (26.3–50.0)	< 0.001*

*$P < 0.05$

Table 4.　NMDARE と other AEs の臨床的特徴と長期転帰の比較

	NMDARE (n = 10)	other AEs (n = 11)	P 値
発症時の年齢, 歳, 中央値 (範囲)	20 (15–34)	40 (15–71)	0.021*
調査時の年齢, 歳, 中央値 (範囲)	25 (18–47)	46 (21–76)	0.041*
発症から調査までの期間 (月), 中央値, (範囲)	60 (25–156)	63 (28–116)	0.918
ピーク時の mRS, 中央値 (範囲)	5 (3–5)	5 (3–5)	0.580
調査時の mRS, 中央値 (範囲)	0 (0–0)	1 (0–2)	0.012*
後遺症, n (%)	1 (10.0)	8 (72.3)	0.008*
家庭での自立, n (%)	10 (100)	9 (81.8)	0.476
以前の職場/学校への復帰, n (%)	9 (90.0)	6 (54.5)	0.149

*$P < 0.05$

Table 5.　NMDARE と other AEs の Neuro-QOL 包括ドメインの T スコアの比較

Neuro-QOL ドメイン	NMDARE (n = 10)	other AEs (n = 11)	P 値
global QOL, 中央値 (範囲)	57.0 (44.7–61.7)	52.3 (40.2–59.7)	0.115
physical QOL, 中央値 (範囲)	58.8 (50.0–62.7)	56.5 (45.2–62.7)	0.544
mental QOL, 中央値 (範囲)	55.5 (42.3–62.4)	56.0 (37.8–64.6)	0.756
social QOL, 中央値 (範囲)	55.8 (40.4–60.4)	45.8 (26.3–56.1)	0.018*

*$P < 0.05$