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Outcome and Sequelae of Autoimmune Encephalitis

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Autoimmune etiologies are a common cause for encephalitis. The clinical syndromes consistent with autoimmune encephalitis are both distinct and increasingly recognized, but less is known about persisting sequelae or outcomes. We searched PubMed for reports on outcomes after autoimmune encephalitis. Studies assessing validated, quantitative outcomes were included. We performed a narrative review of the published literature of outcomes after autoimmune encephalitis. We found 146 studies that produced outcomes data. The mortality rates were 6%–19% and the relapse risks were 10%–62%. Most patients achieved a good outcome based on a score on the modified Rankin Scale (mRS) of ≤2. Forty-nine studies evaluated outcomes beyond mRS; these studies investigated cognitive outcome, psychiatric sequelae, neurological deficits, global function, and quality-of-life/patient-reported outcomes using various tools at varying time points after the index hospital discharge. These more-detailed assessments revealed that most patients had persistent impairments, with frequent deficits in cognitive function, especially memory and attention. Depression and anxiety were also common. Many of these sequelae continued to improve over months or even years after the acute illness. While we found that lasting impairments were common among survivors of autoimmune encephalitis, additional research is needed to better understand the nature and impact of these sequelae. Standardized evaluation protocols are needed to improve the ability to compare outcomes across studies, guide rehabilitation strategies, and inform outcomes of interest in treatment trials as the field advances.

Keywords autoimmune encephalitis; outcomes; cognitive impairment; patient-reported outcome.

INTRODUCTION

Since the first series of patients with N-methyl D-aspartate receptor (NMDAR) encephalitis was reported in 2007,[1] there has been a rapid growth in the recognition of the associated syndromes, various described antibodies, and evolving treatment approaches. Diagnostic criteria were recently proposed.[2] Many patients develop severe symptoms and require critical-care services at some point during their illness.[3] Consensus treatment recommendations include treating an associated tumor, if present, and early aggressive immunotherapy typically with steroids, intravenous immunoglobulin (IVIG), and/or plasma exchange as first-line treatment.[4] Second-line treatments include rituximab and/or cyclophosphamide, and some case series have shown responses to bortezomib,[5] tocilizumab,[6] and interleukin-2 treatment.[7] Trials are underway to evaluate the effects of the anti-interleukin-6 receptor antibody satralizumab[8] and the anti-CD19 drug inebilizumab.[9]

Counseling patients and families about what to expect following a diagnosis of autoimmune encephalitis is challenging because few large, high-quality studies of outcomes have been performed. Previous reviews have focused on the modified Rankin Scale (mRS) score alone, often focusing on a binary choice between a "good outcome" and other outcomes,[10,11]

or cataloging the various outcome measures used without attempting to summarize findings.[12]

We aimed to address this gap by reviewing the literature on outcomes and sequelae of autoimmune encephalitis 1) to summarize existing knowledge about treatment outcomes comprehensively for use by clinicians and 2) to identify gaps in the understanding of outcomes and sequelae that might inform future research.

METHODS

Search criteria

We performed a comprehensive search of all published papers and Abstracts (in English, French, or German) reported on PubMed up to June 2023. Two search strategies were used: ((autoimmune AND encephalitis) AND (sequel* OR outcome OR persisting symptom)) and etiology-specific terms (NMDA, GABA-A, GABA-B, LGI1, Caspr2, AMPA, DPPX, Ma2, Hu, CRMP, GAD65, glycine, MOG, and seronegative), to produce searches such as ((NMDA AND encephalitis) AND (sequel* OR outcome OR persisting symptom)). Only studies evaluating posthospitalization sequelae using validated, quantitative outcome measures were included. Studies in which less than half of the cohort received any treatment were excluded. Studies were included if the functional status, neuropsychiatric sequelae, and patient-reported outcomes for at least five patients were reported. Studies focusing on mortality or seizure outcomes only were excluded, as were studies evaluating only pediatric patients (≤18 years old). When results for patients of different ages were presented separately, we focused on those for the adult patients. Studies of isolated cerebellitis, myelitis, neuropathy, or meningitis, and of infectious, toxic, metabolic, or neoplastic encephalopathy/encephalitis were excluded. Studies for which the outcomes of patients with autoimmune encephalitis could not be separated from those with isolated myelitis, cerebellitis, or neuropathy were also excluded, as were retrospective studies and case series of clinical or administrative databases (i.e., without clinical contact or evaluations or with questionable clinical documentation).

Data collection

Data were collected in five outcome domains: cognitive disorders (assessed using standardized neuropsychological tests), psychiatric deficits, neurological deficits (outside the normal ranges for standard neurological examinations), global functioning (e.g., mRS and activities of daily living), and quality-of-life/patient-reported outcomes (including the patient-reported outcomes measurement information system [PROMIS], validated fatigue and sleep scales, and quality-of-life measures). Data were collected on study period, number of patients enrolled, cause of encephalitis, patient ages, methods and timing of assessment, and assessment results.

RESULTS

Combining the 2 search strategies for autoimmune encephalitis and etiology-specific antibody terms yielded 1,614 results. Reviewing the Abstracts identified 239 unique studies, and their review revealed 146 publications that met the inclusion criteria. No studies of Hu-antibody-associated encephalitis were consistent with our study criteria (Fig. 1). The study methods, including the assessment tools, are summarized in Table 1 and Supplementary Table 1 in the online-only Data Supplement (the latter is for studies that included only mRS). mRS is a measure of global disability that was first developed for stroke (Supplementary Table 2 in online-only Data Supplement),[13] and it was the most frequently used assessment tool to evaluate outcomes.

Measured outcomes

Forty-nine studies produced outcomes that were outside the standard neurological examinations and mRS (33.5% of the included studies). The outcome domains and assessment tools used in these studies are summarized in Table 1. Major findings of these studies are detailed in Supplementary Table 3 (in the online-only Data Supplement). Most of these studies (n=37) applied cognitive assessments using various different scales, including the Montreal Cognitive Assessment (MoCA), MoCA-B (an improved version for accurate screening in the elderly regardless of literacy),[14] Wechsler Abbreviated Scale of Intelligence, and Rey Auditory Verbal Learning Test (RAVLT). Seventeen studies included psychiatric outcomes, the most common of which were the Hospital Anxiety and Depression Scale (HADS)-A (Anxiety) and HADS-D (Depression), Beck Depression Inventory (BDI), and Beck Anxiety Inventory (BAI). Three studies used the Adaptive Behavior Assessment System (ABAS)-3, a rating scale that assesses skills in performing the activities of daily living across numerous domains. Six studies measured quality of life or other validated patient-reported outcomes.

NMDAR encephalitis

NMDAR encephalitis most commonly presents with seizure, psychosis, and memory impairment, often following a viral-like prodrome. A characteristic movement disorder is also reported frequently that typically comprises a combination of orofacial-lingual dyskinesia and chorea, autonomic symptoms, and central hypoventilation.[11] Many patients develop severe symptoms, with up to half requiring an intensive care unit (ICU) admission. An associated tumor is found

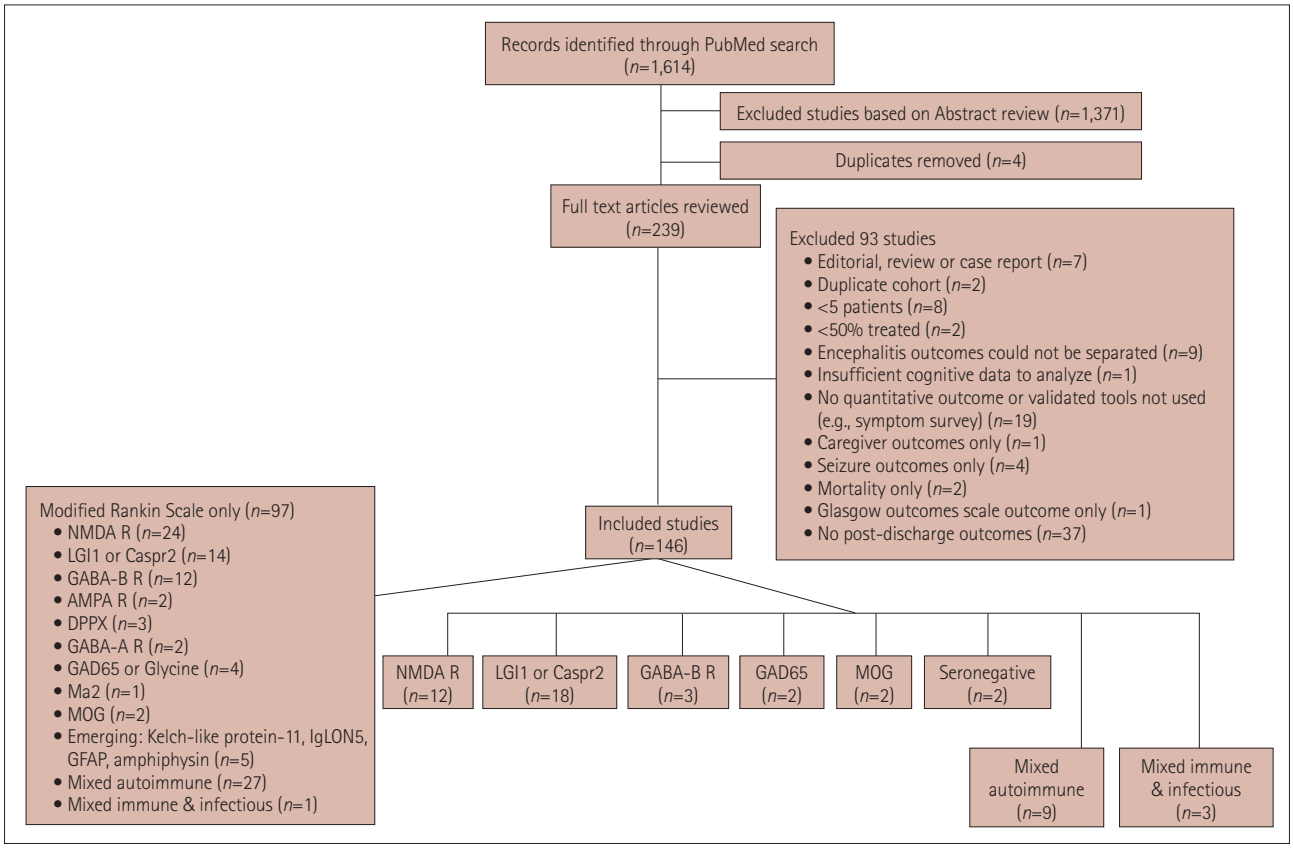

Fig. 1. Flow diagram of included studies. AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; Caspr2, contactin-associated protein-like 2; DPPX, dipeptidyl-peptidase-like-protein-6; GABA-A, gamma aminobutyric acid A; GABA-B, gamma aminobutyric acid B; GAD65, glutamic acid decarboxylase-65kD; GFAP, glial fibrillary acidic protein; IgLON5, immunoglobulin-like cell adhesion molecule 5; LGI1, Leucine-rich glioma-inactivated 1; MOG, myelin oligodendrocyte glycoprotein; NMDA, N-methyl D-aspartate; R, receptor.

in 25% of patients, most commonly ovarian. Treatment involves a combination of tumor resection (if applicable) and immunotherapy.[11] Relapses are typically milder and more likely to be monosymptomatic than the initial episode.[11] Treatment paradigms continue to evolve rapidly, with recent evidence that outcomes are better in patients treated with second-line therapies such as rituximab.[11]

A recent large meta-analysis of 1,059 patients with a median follow-up of 12 months found that 71.5% had a good outcome, defined as an mRS score of 0–2, with mortality and relapse rates of 6% and 13%, respectively.[11] Patients who received second-line treatment or maintenance IVIG were less likely to relapse. A recent prospective cohort study of 182 patients with at least 24 months of follow-up found that 86% attained a good outcome (mRS score=0–2).[15] Outcomes continued to improve over time and were still improving at 42 months after the onset. Favorable functional outcomes (mRS score=0–2) in most NMDAR-encephalitis survivors have been observed in other large retrospective series (Supplementary Table 1 in the online-only Data Supplement).

Longitudinal studies using high-quality neurocognitive assessments are increasingly being performed, although most are limited by their retrospective designs and small samples. Six studies used neuropsychological testing to measure cognitive sequelae of NMDAR encephalitis.[16-21] Most of those studies found persisting cognitive impairments despite patients improving to a good outcome according to mRS. In the studies including cognitive outcomes that could be dichotomized, 40%–88% of patients had cognitive impairment in at least one domain (defined as from 1.5 to 2 standard deviations [SDs] below the mean),[16,17,21] with specific impairments in attention (20%–44%),[16,17,21] working memory (20%–55%),[16,17,21] episodic memory (22%),[21] verbal memory (40%),[16] visual memory (20%),[16] and executive function (20%–60%).[17,21]

Only two of these studies had a prospective design.[16,17] Heine et al.[16] included 40 patients and 30 matched controls who underwent a broad neuropsychological battery along with clinical follow-up. While most patients had mild or no physical disability at the follow-up performed a median of 2.3 years after symptom onset for the first study visit, 93% of patients had cognitive impairment (defined as 1 SD below the mean) and 50% met the criteria for severe cognitive impair-

Table 1. Included studies of patient outcomes after encephalitis (excluding the mRS)

Study	Number of patients	Age (yrs)	Etiology	Delay to encephalitis assessment*	Domains assessed	Assessment tests used	Prevalence of sequelae†
NMDAR encephalitis							
Blum et al., 2020[26]	61	34±13 (range=15–77)	NMDAR	4.4±3.1 y, (range=0.6–13.3 y)	Q, F	Q: 8-item PROMIS positive PSII and 8-item PROMIS Negative PSII F: mRS	-
Finke et al., 2012[21]	9 patients+ 12 controls	Mean=28 (range=21–44)	NMDAR	Median=43 m (range=23–69 m)	C, Ps	C: digit span, block span, RAVLT, ROCF, BADS, Stroop, TOL, DMTS Ps: HAM-D (no control comparison)	C: Impaired ≤2 SDs below control-group mean 88% cognitive impairment (≥1 domain) 55% executive function 44% attention 44% working memory 22% episodic memory
Finke et al., 2016[18]	40 patients+ 25 controls	28±1.6	NMDAR	26.6±3.3 m (range=1–82 m)	C, F	C: RAVLT, ROCF F: mRS	-
Gordon-Lipkin et al., 2017[24]	6 adults+ 4 children	Median=26 (range=22–41)	NMDAR	Median 3.6 y from diagnosis (IQR=2.1–5.5 y)	F	F: ABAS-3	-
Guasp et al., 2022[17]	28 NMDAR encephalitis +27 schizophrenia +27 controls Prospective	Median=27 (range=13–57)	NMDAR	V1: Median=4 m (IQR=3–7 m) V3: Median=16 m (IQR=15–19 m)	C, Ps, N, F	C: WAIS-IV, MoCA Ps: PANSS, HAM-D, Young Mania Rating Scale, Stressful Life Events Questionnaire, Perceived Stress Scale N: CASE F: Global Assessment of Functioning Scale, mRS	C: Impaired ≤1.5 SDs below the mean V1: 89% cognitive impairment (≥1 domain) V3: 40% cognitive impairment 20% executive function 20% working memory 20% attention P: V1: 86% psychiatric or behavioral disturbance V3: 44% psychiatric or behavioral disturbance12% at least mild depression (HAM-D score >7) 8% at least mild psychosis (PANSS score >57)

Table 1. Included studies of patient outcomes after encephalitis (excluding the mRS) (continued)

Study	Number of patients	Age (yrs)	Etiology	Delay to encephalitis assessment*	Domains assessed	Assessment tests used	Prevalence of sequelae†
Heine et al., 2021[16]	40 patients+ 30 controls Prospective	29±7 (range=15–45)	NMDAR	V1: Median=2 y V2: Median=5 y	C, Ps, F	C: Go/No-Go, Stroop, semantic fluency, digit span forward & backward from WAIS-IV; word learning list similar to RAVLT; ROCF; attention-cued/noncued reaction time task, dual-task paradigm Ps: BDI-II, BAI (no control comparison) F: mRS	C: Impaired ≤1 SD below control-group mean V1: 100% cognitive impairment V2: 92.5% cognitive impairment 60% executive function 55% working memory 40% verbal memory 35% attention 20% visual memory 75% cognitive impairment (≤1.5 SDs) Ps: 60% at least mild anxiety 32% at least mild depression
Lee et al., 2022[27]	36	29±15	NMDAR	Median=28.5 m (range=12–63 m)	N, F	N: CASE F: mRS	-
McKeon et al., 2016[20]	7 patients+ 14 controls	Mean=26 (range=16–37)	NMDAR	Median=19 m from treatment start (range=7–41 m)	C, Ps, F	C: IQ, WAIS, WMS, ROCF, semantic memory, WAIS-IV, language (spontaneous speech, cookie-theft picture, graded naming test), digit span subtest, D-KEFS, TMT, verbal fluency, color word interference test, Sustained Attention to Response Task, social cognition assessments Ps: HADS-A, HADS-D F: mRS	-
Phillips et al., 2018[19]	46 patients+ 30 controls	26.6±7.4 recovered 26.7±1.8 non-recovered	NMDAR	23.9±5.2 m recovered 26.5±4.3 m non-recovered	C, F	C: Alertness and divided attention, digit span, block tapping, RAVLT, ROCF, computerized Go/No-Go F: mRS	-
Wang et al., 2016[22]	51	Median=21.6 (range=9–39)	NMDAR	Median=12 m after dc (range=5–41 m)	Ps, F	Ps: Zung Depression Scale, Zung Anxiety Scale F: mRS	Ps: 79% depression and/or anxiety
Wu et al., 2023[23]	58	Median=29 (IQR=21–43)	NMDAR	24 m	Ps, N, F	Ps: GAD-7, PHQ-9, NPI N: CASE F: mRS	Ps: 33% neuropsych symptoms (NPI score ≥1) 12% anxiety (GAD-7 score ≥5) 10% depression (PHQ-9 score ≥5)

Table 1. Included studies of patient outcomes after encephalitis (excluding the mRS) (continued)

Study	Number of patients	Age (yrs)	Etiology	Delay to encephalitis assessment*	Domains assessed	Assessment tests used	Prevalence of sequelae†
Yeshokumar et al., 2022[25]	41	23±17	NMDAR	Mean=4 y	F	F: ABAS-3, mRS	-
LGI1 and Caspr2 encephalitis							
Alkabie and Budhram, 2023[31]	17	Median=65 (IQR=62–70)	LGI1	Median=21 m (IQR=11–31 m)	C, F	C: MoCA F: mRS	C: 35% cognitive impairment (MoCA score ≤25)
Benoit et al., 2022[46]	35	Median=64 (IQR=61–73)	Caspr2	Median=64 m (range=15–189 m)	C, Q, F	C: t-MMSE Q: SF-36 F: mRS	-
Bettcher et al., 2014[40]	12	Mean=64 (range=48–79)	VGKC, LGI1, and/or Caspr2	Median=296 days (range=152–1,205 days)	C	C: memory: CVLT, Benson D figure; executive function: total words, digit span backward, Stroop inhibition Modified Trails, design fluency; visuospatial function: Benson's figure copy; language: BNT, Peabody Picture Vocabulary Test, repetition	C: Impaired ≤1.5 SDs below the mean 100% cognitive impairment (≥1 domain) 83% verbal memory 83% executive function 42% language 33% visual memory 25% visuospatial function
Binks et al., 2021[32]	60	Median=70 (range=44–92)	LGI1	Median=41 m (range=4–179 m)	C, Ps, N, Q, F	C: ACE, MMSE, Frontal Assessment battery Ps: HADS-D, HADS-A N: CASE Q: FSMC, MFIS F: mRS	C: 32% cognitive impairment (ACE score <88/100) Any score below population mean: 16% memory 16% fluency 16% visuospatial function 9% attention 5% language Ps: 33% anxiety (HADS-A score >7) 19% depression (HADS-D score >7)
Butler et al., 2014[37]	19	60.0±14.6	9 LGI1 1 Caspr2	V1: Mean=111 days (range=16–377 days) V2: 3–44 m later	C	C: National adult reading test or Wechsler Adult Reading Test, WMS, immediate and delayed recall of AMIPB, ROCF, letter and category fluency, TMT B, WAIS-III	C: Impaired (z score <–1.67) V1: 67% verbal memory 5% executive function 5% processing speed 0% language V2: 33% verbal memory 0% executive function 5% processing speed 0% language

Table 1. Included studies of patient outcomes after encephalitis (excluding the mRS) (continued)

Study	Number of patients	Age (yrs)	Etiology	Delay to encephalitis assessment*	Domains assessed	Assessment tests used	Prevalence of sequelae†
Chen et al., 2021[45]	73	Median=60 (IQR=47–65)	LGI1	Median=33 m (range=6–78 m)	C, Ps, F	C: TICS-M Ps: NPI F: mRS, activities of daily living	C: 40% cognitive impairment (TICS-M score ≤34) Ps: 22% neuropsych symptoms (NPI score ≥1)
Finke et al., 2017[33]	30 patients +27 controls	66.0±12.3	LGI1	Median=23 m (IQR=6–35 m)	C, F	C: RAVLT, ROCF, TMT A&B, Go/No Go, word fluency, interference, MoCA, German national reading test, German RPM F: mRS	-
Frisch et al., 2013[36]	27	VGKC: Median=57 (range=38–73) GAD: Median=25 (range=12–46)	15 VGKC 12 GAD	VGKC: Median=25 m (range=1–68 m) GAD: Median=30 m (range=2–54 m)	C	C: Attention or executive function: Epitrack Battery (TMT, response inhibition, digit span, word fluency, maze test); verbal and nonverbal memory: VLMT, DCS-R	C: Impaired ≤1 SD below the mean VGKC V1: 86% cognitive impairment last follow-up: 57% cognitive impairment GAD V1: 64% cognitive impairment last follow-up: 64% cognitive impairment
Galioto et al., 2023[35]	10	Median=68	LGI1	Median=38.5 m	C, Ps	C: WAIS-IV, digit span forward, CPT-3, SDMT, TMT, D-KEFS, Wisconsin Card-Sorting Test, BNT, ROCF, BVMT, CVLT, RAVLT, WMS Ps: BDI-II, BAI	C: Impaired ≤1.5 SDs below the mean 90% cognitive impairment (≥1 domain) 71% attention 60% visuospatial function 50% verbal memory 50% visual memory 40% processing speed 40% executive function 20% language Ps: 40% depression (BDI score ≥13) 60% anxiety (BAI score ≥8)
Hang et al., 2020[29]	21	Mean=51 (range=20–72)	LGI1	1 y after dc	C	C: MoCA-B, MMSE	C: 5% moderate-to-severe cognitive impairment (MoCA-B score ≤20) 0% moderate-to-severe impairment (MMSE score ≤20)

Table 1. Included studies of patient outcomes after encephalitis (excluding the mRS) (continued)

Study	Number of patients	Age (yrs)	Etiology	Delay to encephalitis assessment*	Domains assessed	Assessment tests used	Prevalence of sequelae†
Loane et al., 2019[34]	24 patients+ 39 controls	64.0±11.3	VGKC	5±4 y	C, Ps	C: Numerous batteries: episodic memory, executive function, intelligence, semantic memory and language, visuospatial and motor function Ps: HADS	Ps: 4% severe anxiety (HADS score ≥15) 0% depression (HADS score ≥15)
Malter et al., 2014[39]	18	Median=55 (range=20–73)	VGKC	Median=26 m (range=5–84 m)	C	C: VLMT, DCS-R	C: Impaired ≤1 SD below the mean 64% verbal or visual memory
Rodriguez et al., 2022[38]	54 (32 completed neuropsych testing)	Median=66 (range=17–87)	LGI1	At least 24 m	C, F	C: Kokmen STMS, Mattis Dementia Rating Scale, RAVLT, delayed recall, CVLT-2-SF, WMS, BNT, Controlled Oral Word Association Test, Category Fluency; ROCF, digit span subtest from WAIS, TMT A&B, Stroop Color-Word Test F: mRS	C: Impaired ≤1.5 SDs below the mean 40% cognitive impairment (Dementia Rating Scale) 37% verbal memory 20% executive function 14% language 13% attention 11% visuospatial function 5% visual memory
Sola-Valls et al., 2019[43]	36 patients+ 23 controls	Median=74 (IQR=63–81)	LGI1	Median=87 m (IQR=63–136 m)	C, Ps, Q, F	C: t-MMSE, verbal memory (Free and Cued Selective Reminding Test), executive function (TMT A&B), verbal fluency, Cognitive Reserve Questionnaire Ps: HADS Q: EuroQol-5, PSQI F: Functional Activities Questionnaire	C: 47% cognitive impairment (t-MMSE score ≤21) 28% dementia 53% verbal fluency 50% verbal memory 31% executive function
Szots et al. 2017[30]	9 patients +9 controls	60.0±14.5	LGI1	Median=27 m (range=21–30 m)	C, F	C: MMSE, ACE F: mRS	-
Thieben et al., 2004[42]	7 patients	Median=65 (range=44–73)	VGKC	Median=24 m (range=7–36 m)	C	C: TICS	C: 85% cognitive impairment (TICS score ≤30)
van Sonderen et al., 2016[41]	38	Median=64 (range=31–84)	LGI1	Median=27 m ≥2 y in 21 patients	C	C: CANTAB, spatial recognition memory and intradimensional-extradimensional set shift test	-
Wagner et al., 2016[44]	16 VGKC+ 14 GAD	VGKC: Mean=58 (range=23–76) GAD: Mean=37 (range=20–61)	GAD and VGKC	VGKC: Mean=3.6 y (range=0.1–6.9 y) GAD: Mean=3.9 y (range=0.2–8.6 y)	C	C: VLMT, DCS-R	-

Table 1. Included studies of patient outcomes after encephalitis (excluding the mRS) (continued)

Study	Number of patients	Age (yrs)	Etiology	Delay to encephalitis assessment*	Domains assessed	Assessment tests used	Prevalence of sequelae†
GABA-B receptor encephalitis							
Chen et al., 2022[49]	22	55±10	GABA-B	Median=13 m (range=6–75 m)	C, Ps, F	C: TICS-M Ps: NPI F: mRS	C: 27% cognitive impairment (TICS-M score <34) Ps: 27% neuropsych sequelae (NPI score ≥1)
Ji et al., 2021[48]	5 patients+ 5 controls	Median=49 (range=35–61)	GABA-B	Range=6–36 m	C	C: Stroop, SDMT, digit span, Semantic Fluency Test: fruit and vegetables, animals, block design test, Chinese CVLT, AFLT	-
Lin et al., 2021[50]	20 patients underwent MoCA at 12 m 10 patients underwent neuropsych testing at 24 m	Median=52 (range=18–75)	GABA-B	Median=18 m (range=6–63 m)	C, Ps	C: MoCA, WMS, BVMT-R, TOL, Stroop, CPT, RPM Ps: NPI	C: 65% cognitive impairment (MoCA score <26) at 12 m, 50% (5/10) at 24 m At 24 m, impairments (≤75% of normative score): 50% memory WMS (5/10) 67% visuospatial function (6/9) 38% attention (3/8) 40% executive function (4/10), Ps: 75% neuropsych symptoms (NPI score ≥1) at 12 m, 50% (7/14) at 24 m
GAD65-antibody-associated encephalitis							
Frisch et al., 2013[36]	See above						
Wagner et al., 2016[44]	See above						
MOG encephalitis							
Lee et al., 2023[58]	18 cortical encephalitis 5 limbic encephalitis	Cortical: Median=26 Limbic: Median=70	MOG	Cortical: Median=29.5 m Limbic: Median=27 m	F	N: CASE F: mRS	-
Wang et al., 2021[57]	13	Median=33 (range=13–62)	MOG	Median=24 m (range=3–53 m)	C, F	C: MMSE F: mRS, EDSS	-
Seronegative encephalitis							
Lee et al., 2022[63]	147	Median=40	None	At least 24 m	F	F: CASE, mRS	-

Table 1. Included studies of patient outcomes after encephalitis (excluding the mRS) (continued)

Study	Number of patients	Age (yrs)	Etiology	Delay to encephalitis assessment*	Domains assessed	Assessment tests used	Prevalence of sequelae†
von Rhein et al., 2017[64]	28	45±16	Antibodynegative	Median=18 m (SD 17 m)	C, Ps	C: VLMT, DCS-R, word fluency, response inhibition Ps: BDI-I	C: Posttreatment cognitive data not dichotomized Ps: 36% depression (BDI-I score >10)
Mixed Autoimmune Encephalitis							
Abboud et al., 2022[68]	33	47±20	Mixed autoimmune	Mean=18 m (range=2–78 m)	N, F	N: CASE F: mRS	-
Diaz-Arias et al., 2021[71]	338 cohort 1+ 69 cohort 2	48±19 in cohort 2	Mixed autoimmune	Cohort 1: At least 6 m Cohort 2: Mean=3.7 y	Ps, N, Q, F	Ps: BDI Fast Screen N: CASE Q: MFIS, PSQI F: mRS	Ps: 34% (23/68) depression (BDI score ≥4)
Dogan Onugoren et al., 2016[67]	19	15–74	Mixed autoimmune	Median=3.9 m (range=3–8.7 m)	C, F	C: VLMT, DCS-R, ROCFT F: mRS	-
Du et al., 2022[72]	59	Mean=42 in rituximab cohort; 38 in control	Mixed autoimmune	NR	C, Ps, N, F	C: MMSE Ps: NPI N: CASE F: mRS	-
Griffith et al., 2023[69]	50 prospective	52±18	Mixed autoimmune	Mean=3.2 y	C	C: WAIS, WASI, WMI, WMS, CVLT	C: Impaired ≤1.5 SDs below the mean 41% cognitive impairment (≥1 domain) 19% visual memory 18% processing speed 16% verbal memory 16% delayed memory
Griffith et al., 2022[65]	59 retrospective	49.0±17.2	Mixed autoimmune	14.7±16.0 m	C	C: WAIS, WMS, digit span, TMT, D-KEFS, BNT, RBANS, ROCF, CVLT, RAVLT	C: Impaired ≤1.5 SDs below the mean 75% cognitive impairment (≥1 domain) 42% executive function 41% memory 33% attention

Table 1. Included studies of patient outcomes after encephalitis (excluding the mRS) (continued)

Study	Number of patients	Age (yrs)	Etiology	Delay to encephalitis assessment*	Domains assessed	Assessment tests used	Prevalence of sequelae†
Hébert et al., 2018[66]	21	Median=35 (range=14–73)	Mixed autoimmune	Median=20 m (range=13–182 m)	C	C: MoCA	-
Macher et al., 2023[73]	27 autoimmune	Median=58	Mixed autoimmune	Median=2 y (range=1–5.5 y)	N, F	N: CASE F: mRS	-
Yeshokumar et al., 2017[70]	44	43.0±22.8	Mixed autoimmune	Mean=4 y	F	F: ABAS-3	-
Mixed autoimmune and infectious encephalitis							
Chen et al., 2018[77]	72	Median=29 (IQR=20–41)	Immune and infectious	12–12.5 m after diagnosis	C, F	C: TICS-M F: mRS, PSMS	-
Harris et al., 2020[76]	45 patients+ 45 controls+ 81 in long-term cohort (≥1 y)	Mean=48–50 depending on etiology	Immune and infectious	4 m after dc; 9–12 m later (*n*=28) ≥1 y in 81 patients	C, Ps, Q	C: WAIS-II, Doors and People Battery, Autobiographical Memory Interview, FAS, TMT, Hayling test, Brixton test, Graded Naming Test, Pyramids and Palm Trees, Visual Object and Space Perception, Benton Facial Recognition Ps: BDI, BAI Q: ABNAS	-
Kim and Cheong, 2021[78]	18	43.0±19.6	Immune and infectious	Mean=211 days	C, F	C: MMSE F: BBS, FAC, K-MBI, BBT	-

Data are mean±SD or mean±SEM values except where otherwise indicated.
*Time from symptom onset except where otherwise indicated; †Results for studies whose cognitive and/or psychiatric outcomes could be dichotomized.
ABAS, Adaptive Behavior Assessment; ABNAS, A-B Neuropsychological Assessment (self-report) schedule; ACE, Addenbrooke's Cognitive Examination; AFLT, Aggie Figures Learning Test; AMIPB, Adult Memory and Information Processing Battery; AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; BADS, Behavioral Assessment of Dysexecutive Syndrome; BAI, Beck Anxiety Inventory; BBS, Berg Balance Scale; BBT, Box and Block Test; BDI, Beck Depression Inventory; BNT, Boston Naming Test; BVMT, Brief Visuospatial Memory Test; BVMT-R, BVMT–Revised; C, cognitive; CANTAB, Cambridge Neuropsychological Test Automated Battery; CASE, Clinical Assessment Scale in Autoimmune Encephalitis; Caspr2, contactin-associated protein-like 2; CPT, Continuous Performance Test; CVLT, California Verbal Learning Test; d, days; dc, discharge from index hospitalization; DCS-R, German adaptation of RAVLT; D-KEFS, Delis-Kaplan Executive Function System; DMTS, Digit Memory Test; DPPX, dipeptidyl-peptidase-like-protein-6; EDSS, Expanded Disability Status Scale; F, functioning; FAC, Functional Ambulation Category; FAS, F-A-S verbal fluency test; FSMC, Fatigue Scale for Motor and Cognitive Function; GABA-A, gamma aminobutyric acid A; GABA-B, gamma aminobutyric acid B; GAD, General Anxiety Disorder 7-item; GAD65, glutamic acid decarboxylase-65kD; GFAP, glial fibrillary acidic protein; HADS, Hospital Anxiety and Depression Scale; HADS-A, HADS–Anxiety; HADS-D, HADS–Depression; HAM-D, Hamilton Depression Rating Scale; IgLON5, immunoglobulin-like cell adhesion molecule 5; IQR, interquartile range; K-MBI, Korean version of the Modified Barthel Index; LGI1, Leucine-rich glioma-inactivated 1; m, months; MFIS, Modified Fatigue Impact Scale; MMSE, Mini Mental Status Examination; MoCA, Montreal Cognitive Assessment; MOG, myelin oligodendrocyte glycoprotein; mRS, modified Rankin Scale; N, neurological; neuropsych, neuropsychiatric; NMDA, N-methyl D-aspartate; NPI, Neuropsychiatric Inventory; NR, not reported; PANSS, Positive and Negative Syndrome Scale; PHQ, Patient Health Questionnaire; PROMIS, Patient Reported Outcomes Measurement Information System; Ps, psychological/psychiatric; PSII, Psychosocial Impact Illness; PSMS, Physical Self-Maintenance Scale; PSQI, Pittsburgh Sleep Quality Index; Q, quality of life; R, receptor; RAVLT, Rey Auditory Verbal Learning Test; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; ROCF, Rey-Osterrieth Complex Figure; RPM, Raven Progressive Matrices; SD, standard deviation; SDMT, Symbol-Digit Modalities Test; SF, Short Form; STMS, Short Test of Mental Status; TICS-M, Modified Telephone Interview for Cognitive Status; t-MMSE, telephone-based MMSE; TMT, Trail-Making Test; TOL, Tower of London; V, visit number; VGKC, voltage-gated potassium channel; VLMT, Verbal Learning & Memory Test; WAIS, Wechsler Adult Intelligence Scale; WASI, Wechsler Abbreviated Scale of Intelligence; WMI, Working Memory Index; WMS, Wechsler Memory Scale; y, year; yrs, years; z score, age standardized z score.

ment (defined as an impairment score of at least 1.5 SDs worse than for controls in four of five cognitive domains) at the first visit.[16] The proportion with severe impairment had decreased significantly by the second study visit after a median of 2.1 years (50% at visit 1 vs. 30% at visit 2, p=0.021). At the second visit, deficits of at least 1 SD below the mean were seen in executive function (60%), working memory (55%), verbal memory (40%), visuospatial memory (20%), and attention (35%). Guasp et al.[17] prospectively enrolled 28 patients with NMDAR encephalitis, 27 with schizophrenia, and 27 healthy controls to compare cognitive and psychiatric impairments over time. Although the median mRS score had improved to 2 by the first follow-up after a median of 4 months, 89% had deficits in at least one cognitive domain (1.5 SDs below the mean). By the third visit after a median of 12 months, the median mRS score was 1 but 40% of the patients still had cognitive impairment, including in executive function (20%), working memory (20%), and attention (20%).[17]

There have also been several other retrospective studies. Finke et al.[18] found that patients with NMDAR encephalitis (n=40) had significantly more impairments in verbal memory (RAVLT sum score: 57.0±1.9 [mean±standard error of the mean {SEM}] in patients vs. 65.5±1.4 in controls, p=0.001) and visual memory (Rey-Osterrieth Complex Figure [ROCF] delayed recall: 24.9±1.4 in patients vs. 28.3±1.1 in controls, p=0.035).[18] Impairment (defined as 2 SDs below the mean) was seen in at least one domain in 88% of patients, with deficits in executive function (55%), attention (44%), working memory (44%), and episodic memory (22%). In 36 nonrecovered patients (mRS score ≥1 at a median of 27.6 months from symptom onset), Phillips et al.[19] demonstrated ongoing significant impairment in verbal memory (RAVLT sum score: 53.0±11.7 [mean±SD] in patients vs. 65.3±7.9 in controls, p<0.001), visual memory (ROCF delayed recall: 24.18±8.00 vs. 27.8±5.12, p=0.041), working memory (Wechsler memory scale [WMS] composite score: -0.174±0.864 vs. 0.472±0.776, p=0.007), attention (alertness score: 0.362±1.22 vs. 0.371±0.565, p=0.006), and executive function (Go/No-Go score: 525.9±77.5 vs. 442.3±66.5, p<0.001). The 10 recovered patients (mRS score=0) also had significantly worse working memory than controls (WMS composite score: 0.119±0.507 vs. 0.472±0.776, p=0.036).[19] McKeon et al.[20] studied seven patients at a median of 19 months after treatment initiation and found similar deficits in visual memory and executive function compared with age- and gender-matched healthy controls. IQ, semantic memory, and language were relatively unaffected.[20] Finke et al.[21] investigated 9 patients at a median of 43 months after diagnosis and 12 controls, and found that 8 of the patients had persistent cognitive impairments (≤2 SDs from the control-group mean) including in executive function (n=5), working memory (n=4), attention (n=4), and episodic memory (n=2). Early immunotherapy (within 3 months of symptom onset) was found to have a significant effect on cognitive outcomes, with mean percentile rank performances of 60% vs. 30% (Mann-Whitney test: p=0.032).[21]

We found six studies that assessed psychiatric outcomes. Many of the included patients had psychiatric sequelae at their last follow-up, with studies finding at least some type of psychiatric or behavioral disturbance in 33%–79%,[17,22,23] at least mild depression (10%–32%),[16,17,23] and at least mild anxiety (11.5%–60%)[16,17,23] when applying various assessment tools at various intervals. A prospective study of 40 patients by Heine et al.[16] found that at a median of 2.3 years after symptom onset, moderate, mild, and minimal depressive symptoms persisted in 12%, 20%, and 12%, respectively, with no symptoms in 56%. Clinically relevant, moderate, and mild anxiety was seen in 8%, 20%, and 32%, respectively, and no or minimal anxiety in 40%.[16] Guasp et al.[17] prospectively analyzed 28 patients using the combination of the Positive and Negative Symptom Scale, Hamilton Depression Rating Scale (HAM-D), Young Mania Rating Scale, Stressful Life Events Questionnaire, and Perceived Stress Scale, and found that 86% and 44% of patients had psychiatric or behavior impairments at medians of 4 and 12 months after symptom onset, respectively. At the last follow-up, 8%, 12%, and 40% had at least mild psychosis, depression, and anxiety, respectively.[17] Wu et al.[23] evaluated 52 patients after a median of 46 months and found that 33% had at least 1 neuropsychiatric symptom (Neuropsychiatric Inventory [NPI] score ≥1), 12% had anxiety (General Anxiety Scale [GAD-7] score ≥5), and 10% had depression (Patient Health Questionnaire-9 score ≥5). Wang et al.[22] evaluated 39 patients and found that 79% had depression and/or anxiety according to the Zung Depression Scale and the Zung Anxiety Scale. McKeon et al.[20] found significantly higher anxiety in seven patients than in controls (HADS-A score: 8.71±2.13 vs. 5.35±3.87, $t(19)$=2.119, p<0.048) but no significant difference in depression (HADS-D score: 3.85±4.01 vs. 1.78±1.47, U=36, p=0.303). Finke et al.[21] found no evidence of significant depression in nine patients (HAM-D score: median=4, range=0–6).

Two studies applied the ABAS-3, and both found that younger patients tended to do score worse.[24,25] Gordon-Lipkin et al.[24] found that overall adaptive function was intact in the six included adults, which differed from the four included children having below-average function. Yeshokumar et al.[25] found that ABAS-3 mean scores were within the average range at a mean of 4 years after symptom onset, but that a lower age of onset predicted worse scores.

Our search identified only one study that evaluated validated patient-reported outcomes in NMDAR encephalitis.[26]

In that study, 61 patients completed the Patient-Reported Outcomes Measurement Information System (PROMIS) II Short Forms at a mean of 4.2 years after symptom onset. The PROMIS Negative Psychosocial Impact Illness (PSII) score was significantly higher (60.7±7.9 in patients vs. 50±10 in controls, $p<0.001$) and the PROMIS Positive PSII score was significantly lower (43.7±8.9 vs. 50±10, $p<0.001$) than for the calibrated population for this instrument, both suggesting a significant negative impact of illness on psychosocial function.

Scores on the Clinical Assessment Scale in Autoimmune Encephalitis (CASE) were evaluated in two other studies.[23,27] Wu et al.[23] found that 82% of patients had a good outcome according to that scale (score=0–3) compared with 85% according to mRS (score=0–2), and Lee et al.[27] found that 61% had what they reported as an excellent outcome (CASE score=0–4).

LGI1 and Caspr2 encephalitis

Patients previously classified as having voltage-gated potassium channel (VGKC) autoimmune encephalitis can be divided into those with antibodies targeting Leucine-rich glioma-inactivated 1 (LGI1), contactin-associated protein-like 2 (Caspr2), or both. Caspr2 antibodies are most strongly associated with limbic encephalitis, but Morvan syndrome or hyperkinetic movement disorders can also occur. A good outcome (mRS score ≤2) has been reported in 35%–88% of patients with Caspr2 encephalitis (Supplementary Table 1 in the online-only Data Supplement).

LGI1 antibodies are most strongly associated with limbic encephalitis, and affected patients present acutely with seizures (typically of the faciobrachial dystonic subtype [FBDS]), amnesia, and executive dysfunction. An associated tumor was found in only 8% of cases.[28] The time to the cessation of seizures and long-term outcomes are predicted by the time to immunotherapy. Early treatment of FBDS may prevent the development of cognitive impairment, but the relapse risk is up to 31%,[28] and the mortality rates have been reported to be 6%–19%. Functional outcomes are generally good, with most patients achieving functional independence (79%–97% with mRS score ≤2, see Supplementary Table 1 in the online-only Data Supplement).

We found 18 studies using a wide variety of neurocognitive assessments to characterize cognitive impairments in survivors of LGI1 and Caspr2-antibody encephalitis.[29-46] The studies that included cognitive outcomes that could be dichotomized produced a range of outcomes, with 32%–90% of patients having cognitive impairment (defined in most studies as 1–1.5 SDs below the mean) in at least one domain at the last follow-up.[31,32,35,36,38,42,43,45] Binks et al.[32] evaluated 60 patients over a median follow-up of 41 months, and found that 32% had impaired cognition based on Addenbrooke's Cognitive Examination, with impairments in memory in 16%, fluency in 16%, visuospatial function in 16%, attention in 9%, and language in 5%. Alkabie and Budhram[31] evaluated 17 patients over a median follow-up of 21 months, and found that 35% had ongoing cognitive impairment based on MoCA scores of ≤25. Hang et al.[29] applied the Mini Mental Status Examination (MMSE) and MoCA-B to 21 patients within 1 week of their index hospital admission and at a 1-year follow-up; the MMSE scores were significantly higher at 1 year than at the initial assessment (21.3±3.5 vs. 26.1±3.0, $p<0.001$).[29] Szots et al.[30] found similar results in nine patients, with a median MMSE score of 22 (range=10–28) after a median of 27 months.

We found two controlled studies examining cognitive sequelae. The largest controlled study with detailed neurocognitive testing applied to 30 LGI1 encephalitis patients by Finke et al.[33] found significant impairments in multiple cognitive domains, including verbal memory and visual memory (RAVLT delayed recall: 6.52±1.05 in patients vs. 11.78±0.56 in controls, t50=-4.51, $p<0.001$; ROCF delayed recall: 16.00±1.96 vs. 25.86±1.24, t48=-4.17, $p<0.001$), working memory (digit span forward: 6.92±0.47 vs. 8.12±0.35, t50=-2.04, $p=0.047$), executive function, attention, and semantic and phonemic fluency at a median of 23 months after disease onset. Loane et al.[34] investigated the relationship between the focal amnesia of LGI1 encephalitis and hippocampal connectivity in 24 patients, and found continued verbal and visual recall impairment that spared visual recognition memory at a mean of 5 years from disease onset. However, neither of these two studies included outcomes that could be dichotomized.

The studies that performed detailed cognitive assessments that could be dichotomized revealed specific impairments in attention (9%–71%),[32,35,38] verbal memory (37%–83%),[35,37,38,40,43] visual memory (5%–50%),[32,35,38,40] executive function (20%–83%),[35,38,40,43] language (5%–42%),[32,35,38,40] and visuospatial function (16%–60%).[32,35,40] These studies used various assessment tools, intervals, and cutoffs to define impairment. Rodriguez et al.[38] followed 31 patients for at least 24 months, and found persistent impairments in delayed verbal recall (37%), executive function (20%), language (14%), and attention (13%). Butler et al.[37] evaluated 19 patients using a more-comprehensive neurocognitive test battery, and found that verbal memory was most durably affected (affecting 33% at the last follow-up). Malter et al.[39] found that 65% of their 18 patients with LGI1 had deficits in verbal memory, visual memory, or both after a median of 26 months. Frisch et al.[36] found that 57% of their 15 patients had impairment in at least 1 domain (verbal memory, nonverbal memory, attention-executive function) after a median of 25 months. Bettcher et al.[40] found that all 12 investigated patients had cognitive impairment

when tested at a median of 296 days (9.7 months) since onset, with specific impairments in verbal memory (83%), executive function (83%), language (42%), visual memory (33%), and visuospatial function (25%). Galioto et al.[35] found that 90% of patients had impairments (n=10, defined as ≤1.5 SDs below the normative mean) in at least 1 of the 15 batteries applied, and that 80% had impairment in more than 1 measure. Another study found impairments in verbal and visual memory in 16 patients, but did not perform comparisons with normative values or controls.[44] It was particularly interesting that van Sonderen et al.[41] saw a different pattern of findings in 21 patients, with significant persistent deficits in spatial recognition (Z score: mean=-1.06, 95% CI=-1.89 to -0.23), p=0.018) and attention (matching the sample Z score: mean=-0.67, 95% CI=1.31 to -0.03), p=0.041) but not in verbal memory or executive function.[41]

Four studies assessed neurocognitive outcomes using telemedicine approaches.[42,43,45,46] One study of seven patients with VGKC encephalitis found that 85% had at least mild cognitive impairment at a median of 24 months after disease onset (based on the Telephone Interview for Cognitive Status [TICS]).[42] Broad cognitive impairment compared with controls was seen in a series of 36 patients assessed using telemedicine approaches, with verbal fluency (53%), verbal memory (50%), and executive function (31%) being the most-prevalent impairments.[43] Chen et al.[45] applied cognitive evaluations via telephone after a median of 33 months to an uncontrolled series of 73 patients with LGI1 encephalitis, and found that cognitive impairment (defined as a TICS-modified [TICS-M] score of ≤34, 39.7%) and neuropsychiatric symptoms (22%) were persistent. Benoit et al.[46] found a median telephone-based MMSE score of 25 (range=18–26) in 35 survivors after a median of 64 months.

We found five studies of patients with LGI1 encephalitis that assessed psychiatric sequelae.[32,34,35,43,45] Psychiatric sequelae were found to be common, with at least some type of psychiatric or behavioral disturbance in 22%,[45] at least mild depression in 19%–40%,[32,35] and at least mild anxiety in 33%–60%.[32,35] Sola-Valls et al.[43] found that HADS-D scores were significantly higher in 36 patients (median=5.5, interquartile range [IQR]=3–9) than in controls (median=2, IQR=0–5, p=0.01). Loane et al.[34] similarly found significantly higher scores on the HADS-D in 24 patients (median=3, IQR=4.5) than in controls (median=1, IQR=1, U=182, p=0.008), but none were in the severe range. Binks et al.[32] evaluated 60 patients and found that 19% had depression (HADS-D score >7) and 33% had anxiety (HADS-A score >7). Chen et al.[45] found that 22% of their patients had at least one neuropsychiatric symptom on the NPI.[45] Galioto et al.[35] found that 40% of 10 patients had depression (BDI score ≥13) and that 60% had anxiety (BAI score ≥8).

We found two studies that investigated quality-of-life measures.[43,46] Sola-Valls et al.[43] used the European Quality of Life (EuroQoL)-5 dimensions instrument and found no difference in quality of life between 36 patients and controls at a median follow-up of 87 months.[43] Benoit et al.[46] found that Short Form-36 quality-of-life scores were similar to those in the normative population except for a moderate reduction in the vitality subscore (mean 50 vs. 58, p=0.037). Binks et al.[32] evaluated 31 patients for residual fatigue using the Fatigue Scale for Motor and Cognitive Function, and found that 52% reported fatigue, with 29% rating this as severe fatigue.

GABA-B receptor, AMPA receptor, and GABA-A receptor encephalitis

Patients with autoimmune encephalitis associated with gamma aminobutyric acid B (GABA-B) receptor antibodies commonly have limbic encephalitis (often with refractory status epilepticus), but progressive ataxia and opsoclonus-myoclonus syndromes have also been described.[47] In the largest series of 20 patients, 50% had an associated tumor, most commonly small-cell lung cancer, and 75% of them responded to immunotherapy and/or tumor treatments.[47] A good outcome (defined as an mRS score of ≤2) occurred in 43%–73% of patients, with poor outcomes associated with tumor progression (Supplementary Table 1 in the online-only Data Supplement).

Three studies assessed cognitive sequelae in GABA-B receptor encephalitis.[48-50] Ji et al.[48] found no significant differences in performance on a neurocognitive battery at 6–36 months after diagnosis between five patients and controls. Chen et al.[49] evaluated 22 patients and found ongoing cognitive impairment (TICS-M score <34) in 27% and neuropsychiatric sequelae (NPI score ≥1) in 27% after a median of 13 months. A prospective study by Lin et al.[50] of 20 patients found cognitive impairment in 65% (MoCA score <26) at 12 months and in 50% (5/10) after 24 months. More-detailed neurocognitive testing applied to ten patients revealed cognitive impairments in 80% of them, including in working memory, visual memory, attention, executive function, and nonverbal reasoning. That study also included psychiatric outcomes, and found ongoing impairments in 50% of the patients after 24 months, most commonly sleep disorders and irritability, followed by anxiety and depression.[50]

Alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor encephalitis presents as a limbic encephalitis with prominent seizures. An associated tumor is found in up to 64% of cases. Höftberger et al.[51] found a good outcome (mRS score ≤2) in 57% of patients after a median of 72 weeks. Relapse occurred in 16%, and this was significantly less common in those who received more-aggressive thera-

py (chemotherapy for tumor or rituximab).

In gamma aminobutyric acid A (GABA-A) receptor encephalitis, patients present with seizures and often refractory status epilepticus requiring prolonged ICU stays.[52] Cognitive impairment is seen in most affected patients. In the largest series of 26 cases with a median follow-up of 9 months, 18 of 21 (86%) patients treated with immunotherapy showed partial (n=13, 72%) or complete (n=5, 28%) recovery.[52] There have been no detailed reports of other dimensions of functional or cognitive outcomes in GABA-A receptor encephalitis.

DPPX-antibody-associated encephalitis

In dipeptidyl-peptidase-like-protein-6 (DPPX) antibody-associated encephalitis, most patients present with prodromal weight loss, diarrhea, or other gastrointestinal symptoms. Cognitive or memory symptoms may be seen in as many as 92% of patients, with cortical hyperexcitability (most commonly myoclonus) in 77%. Hara et al.[53] followed nine patients for a median of 19 months, and 78% achieved a good outcome (mRS score ≤2) while 1 died. The literature review performed by those authors revealed mortality and relapse rates of 6% and 23%, respectively.

GAD65-antibody-associated encephalitis and glycine-associated diseases

Glutamic acid decarboxylase 65 (GAD65) antibodies are associated with various neurological phenotypes, most commonly stiff-person syndrome, cerebellar ataxia, and epilepsy with or without limbic encephalitis.[54] One investigation of cognitive outcomes that included 12 patients with GAD65-antibody-associated encephalitis found that 55% had impairments in 1 or 2 domains (attention, executive function, or verbal and nonverbal memory), and 9% had impairments in all 3 domains after a median of 30 months.[36] In another neuroimaging-focused study, Wagner et al.[44] obtained verbal and visual memory outcomes for 14 GAD-positive patients after a mean of 3.9 years, but provided little context for the reported scores.

Glycine antibodies have been found to be frequently associated with progressive encephalomyelitis with rigidity and myoclonus (PERM). In the largest series by Carvajal-González et al.[55] of 45 glycine-antibody-positive patients, including 33 classified as PERM, most cases had stiffness or spasms in addition to cranial nerve dysfunction (eye movement abnormalities and dysarthria), excessive startle, and cognitive impairment during the acute illness. In that series, 77% of patients had a good outcome (mRS score ≤2), while relapse occurred in five patients.

Ma2-associated encephalitis

Ma2-associated encephalitis is a rare but distinct type of encephalitis that may present with isolated or combined limbic, diencephalic, or brainstem dysfunction. In the largest series by Dalmau et al.[56] of 38 patients, in addition to limbic features, patients presented with oculomotor findings (37%) and/or ataxia (29%), excessive daytime sleepiness, and occasionally parkinsonism. Most (89%) had an associated tumor, most commonly testicular. In the 33 patients with outcome data, 63% had a good outcome (mRS score ≤2) over a median follow-up of 2.5 years.[56]

MOG encephalitis

Anti myelin oligodendrocyte glycoprotein (MOG)-antibody-associated disease has a wide spectrum of clinical presentations, dominated by optic neuritis, transverse myelitis, and white-matter lesions. A phenotype of encephalitis with prominent cortical lesions has recently been described.[57] Wang et al.[57] found that most of 13 patients presented with psychiatric symptoms (62%), cognitive impairment (69%), and/or seizures (54%). Most presented acutely or subacutely, but 30% had a more-insidious course, with symptom onset occurring over 2 years. Three had coexisting NMDAR antibodies, and most patients responded to treatment, with median mRS and MMSE scores of 0 and 28, respectively, after a median of 24 months.[57] Lee et al.[58] found that the median CASE score was still 5 (IQR=3–6) for the 5 patients with MOG limbic encephalitis after a median of 27 months, whereas the median CASE score was 0 (IQR=0–1) for 26 patients with cortical encephalitis. Notably, 39% of these patients were also positive for NMDAR antibodies.[58] Good outcomes based on mRS were found in other recent series (Supplementary Table 1 in the online-only Data Supplement).

IgLON5, GFAP, and other emerging antibodies

Neurological disease associated with anti-immunoglobulin-like cell adhesion molecule 5 (IgLON5) antibodies was first reported in 2014, and is characterized by a distinct sleep disorder (REM and non-REM parasomnia, often accompanied by stridor and sleep apnea), but may also present with a prodromal bulbar syndrome, cognitive impairment with or without chorea, and gait difficulty. There is some controversy about whether this is primarily degenerative with a secondary immune response or primarily antibody-mediated, but there is some evidence that patients respond to immunotherapy. There is a paucity of literature regarding outcomes, but Gaig et al.[59] found that 13 of 20 patients who were treated with immunotherapy died, often suddenly. Notably, the median time from symptom onset to diagnosis among all of the 22 included patients was 30 months.

A novel type of meningoencephalitis associated with antibodies to glial fibrillary acidic protein (GFAP) has recently been described. Some combination of meningoencephalomyelitis is the most-frequent presentation, and several cases have been found to be associated with neoplasm.

The largest series by Flanagan et al.[60] included 102 patients, 34% of whom had an associated tumor. Among the 22 with treatment data, 82% responded to immunotherapy, with a median mRS score at the last follow-up of 2 (range=0–6) after a median of 22 months. Iorio et al.[61] (Supplementary Table 1 in the online-only Data Supplement) found that 81% of 16 patients achieved a good outcome (mRS score ≤2) after a median of 10 months.

Dubey et al.[62] investigated 39 patients with paraneoplastic Kelch-like protein-11 encephalitis, which is primarily a brainstem encephalitis. Most patients in that series presented with gait difficulty (82%), diplopia (56%), and vertigo (54%), with hearing loss (39%) and tinnitus (36%) also being reasonably common, while seizures and encephalopathy were present in 23%. Cancer was found in 69% of those screened, mostly testicular. Nearly all of the patients were treated with immunotherapy and tumor removal, with most (58%) stabilizing or improving over time. However, the median mRS score at a median follow-up of 30 months was 4 (range=2–6).[62]

Seronegative autoimmune encephalitis

Seronegative autoimmune encephalitis encompasses patients who meet the criteria for probable autoimmune encephalitis but without a definite antibody. We found only two studies describing outcomes for this entity.[63,64] Lee et al.[63] included 147 patients followed for at least 2 years, and found a median CASE score of 3, with 56.5% achieving a good outcome based on mRS. von Rhein et al.[64] found that 86% of 28 patients with antibody-negative encephalitis had cognitive impairment at the first pretreatment visit (≥1 SD below the normative mean in any of 4 cognitive tests). At a median of 18 months, 57% improved while 32% worsened, but the absolute number and percentage of patients with impairment were not reported. In that series, 36% (9/25) had persistent depression at follow-up (BDI-I score >10).[64]

Studies with mixed populations of autoimmune encephalitis

Several studies involving mixed populations of antibody-associated autoimmune encephalitis have produced outcomes based on mRS alone (Supplementary Table 1 in the online-only Data Supplement). Five studies performed more-detailed assessments of neurocognitive outcomes and sequelae in patients with autoimmune encephalitis due to mixed etiologies,[65-68] but only one of those studies had a prospective design. Griffith et al.[69] evaluated 50 patients at a mean of 3.2 years after diagnosis. They found that 41% had impairment in at least one domain (1.5 SDs below the normative mean), with impairments being most common in visual memory (19%), processing speed (18%), auditory (16%), and delayed memory (16%). That group also investigated a large retrospective series of 59 patients,[65] and found that 75% of patients had impairment in at least 1 domain at a mean of 14.7 months after symptom onset, with executive function (42%), memory (41%), and attention (31%) being most commonly affected. Hébert et al.[66] retrospectively investigated 21 patients with autoimmune encephalitis and applied MoCA during follow-up, which revealed persistent cognitive impairment in 52% at the last follow-up at a median of 20 months. Delayed recall, executive function, language, attention, and visuospatial function were affected. Dogan Onugoren et al.[67] found that 8 of 19 patients who received immunoadsorption therapy had impaired memory (z score ≤-1.5) after a median of 3.9 months. Yeshokumar et al.[70] retrospectively investigated 44 patients including adults and children, and found that 40% scored below average on the composite ABAS-3, indicating ongoing impaired adaptive behavior.

We found one study that evaluated psychiatric outcomes,[71] and that study also was the only one to investigate quality-of-life/patient-centered outcomes. It evaluated 69 autoimmune-encephalitis survivors and found that 65%, 79%, and 78% reported overall fatigue, physical fatigue, and cognitive fatigue, respectively, based on the Modified Fatigue Impact Scale. On the BDI Fast Screen, 57% reported depression, while 74% (211/285) reported poor sleep quality on the Pittsburgh Sleep Quality Index. That study also found that the impact of fatigue on quality of life was significantly lower for patients with NMDAR encephalitis than for those with other types of autoimmune encephalitis, although this may have been confounded by their lower age at diagnosis, shorter time from symptom onset to diagnosis and treatment, and high probability of receiving second-line immunotherapy.[71]

Three studies analyzed CASE scores.[68,72,73] Macher et al.[73] attempted to validate CASE scores based on their correlations with mRS scores in 34 patients with autoimmune encephalitis. The CASE score at 1 year varied with the antibody, being lowest for LGI1 (median=2, range=0–4), followed by NMDA (median=2.5, range=0–17) and GAD65/-67 (median=3, range=2–5). However, the cohorts were relatively small for each antibody in that study. Du et al.[72] retrospectively evaluated 59 patients to compare outcomes between those who did and did not receive rituximab. The median CASE score was significantly higher in the rituximab cohort (1.25 vs. 1, p=0.037), but there were no significant differences in the median scores on the MMSE (29 vs. 27), NPI (0 vs. 1.5), or mRS

(0.5 vs. 1), and insufficient granularity data were reported to understand the total percentage of patients with persistent impairment as indicated using MMSE or NPI. Abboud et al.[68] analyzed 33 patients, and found that the mean CASE score was 2.7 after a mean of 18 months.

Studies with mixed populations of autoimmune and infectious encephalitis

The natural history of autoimmune encephalitis differs from that of infectious encephalitis, especially regarding the relapse risk. However, it is not certain whether sequelae and outcomes differ between infectious and autoimmune encephalitis. One single-institution series by Thakur et al.[74] of 103 patients, which included 16 patients with autoimmune encephalitis, found that a poor outcome (mRS score=4 or 5) was more likely in patients with autoimmune than infectious encephalitis at hospital discharge. However, there was no significant difference either at discharge or a 1-year follow-up in a different series of 198 patients, including 44 with autoimmune etiology.[75] Harris et al.[76] found that the mean cognitive and psychiatric outcomes were worse in 45 patients with HSV encephalitis than in 45 controls or those designated as "other encephalitis" or unknown etiology, although a direct comparison between HSV and "other encephalitis" was not performed. Chen et al.[77] prospective analyzed the outcomes of 72 patients with status epilepticus due to encephalitis, and found that the memory outcome was worse for patients with autoimmune encephalitis than for those with infectious encephalitis (TICS-M memory score: median=8.5 [IQR=5–14.8] vs. 15 [IQR=9.5–17], p=0.017). Kim and Cheong[78] assessed MMSE scores, strength, and functional outcomes during the rehabilitation of 18 encephalitis survivors (9 viral, 8 autoimmune, and 1 unknown etiology), and found significant improvements in function and strength but not in MMSE scores.

DISCUSSION

We have performed a narrative review of studies investigating outcomes, sequelae, and persistent symptoms following autoimmune encephalitis. The mortality rate ranged from 6% to 19%, while the reported relapse risk was 10%–38% with the exception of two series, one on LGI-1 encephalitis that reported a relapse rate of 52% and one of MOG encephalitis patients in which it was 62%. Most studies focused on global outcomes, with functional assessments restricted to mRS scores.

Based on mRS, most autoimmune encephalitis patients had good outcomes. However, studies measuring in-depth cognitive, psychiatric, or patient-reported outcomes found that ongoing impairments were common, particularly in memory, attention, executive function, and processing speed. In terms of psychiatric assessments, three out of five controlled studies found that scores on depression scales were significantly worse for survivors of encephalitis than for controls. Five studies evaluated quality-of-life/patient-reported outcomes, and produced mixed results. The results of our review also suggest that sequelae of autoimmune encephalitis continue to improve over months and or years. Notably, for NMDAR encephalitis, good recoveries after months of severe disability have been reported.

We previous reviewed outcomes following infectious encephalitis.[79] Although autoimmune encephalitis due to cell surface or intracellular antibody targets was recognized only recently, we found more investigations of outcomes that met our criteria for autoimmune encephalitis. Using the same search period and search terms (apart from etiology), 146 studies met the inclusion criteria for autoimmune encephalitis, whereas only 41 met similar inclusion criteria for our review of infectious encephalitis outcomes. This discrepancy in the number of publications may partially be explained by the importance of documenting a new functional baseline for a relapsing disorder such as autoimmune encephalitis.

Previous studies of postencephalitis sequelae have used various tools and time points to define and assess outcomes, which makes it challenging to combine results from different studies and compare between etiologies. MMSE and MoCA were the main cognitive tests. These have the advantage of short administration times, particularly given the breadth of cognitive functions captured, but their sensitivities are rather low. Further research is therefore needed to identify the best tools for identifying persisting impairments. One study group proposed developing the novel CASE measure for better documenting encephalitis severity compared with the existing default mRS outcome measure.[80] That scale incorporates the following diverse array of clinical features that is each rated on a three-point scale: seizures, memory dysfunction, psychiatric symptoms, consciousness, language difficulty, dyskinesia/dystonia, brainstem dysfunction, gait instability, and breathing difficulty. When applied to a cohort of 50 patients with autoimmune encephalitis, the scale showed excellent interobserver and intraobserver reliabilities and was able to distinguish different severities among patients with the same mRS score.[80] A subsequent study of 33 patients at a different institution found that this scale achieved better granularity than mRS alone, but concluded that since the score lacks a rank for death, it is more suitable for symptom monitoring than as an outcome measure.[68]

A confounder in all studies of autoimmune encephalitis is the wide diversity in the times to treatment and the choices of immunotherapy types and doses. The increasing recognition, more-cohesive understanding of natural history, and

earlier initiation of immunotherapy may lead to substantial improvements in evaluations and treatments of these disorders. This is particularly notable with LGI1 encephalitis, where early immunotherapy after the onset of seizures leads to better outcomes, with a shorter time to seizure remission and fewer cognitive sequelae.[28] Shorter times to diagnosis and immunotherapy were significantly correlated with improvement in another study involving a mixed population.[81] The use of second-line therapies such as rituximab has also been shown to significantly impact functional outcomes,[82] and the first randomized controlled treatment trials are now underway. In addition, the outcomes of autoimmune encephalitis can be substantially affected by tumor identification and variations in screening and surveillance practices.

A comprehensive and more-uniform approach to assessing patients recovering from encephalitis using validated instruments at routine intervals to capture the dimensions of potential ongoing symptoms and sequelae is critical to understanding postencephalitis outcomes. Several of the studies described here performed outcome assessments using telemedicine approaches, which could increase the feasibility of larger cohort studies. At the patient level, routinely evaluating and screening for sequelae can facilitate 1) referrals to appropriate rehabilitation services (e.g., physical therapy, occupational therapy, and speech/language), 2) monitoring for signs of relapse, and 3) patient and family education on managing ongoing deficits. At the population level, systematically collecting data on outcomes and sequelae can facilitate 1) understanding the natural history of the disease, 2) estimating the disease burden, including persistent disability, 3) guidance for rehabilitation needs, and 4) outcomes that might form a basis for measuring treatment responses.

CONCLUSIONS

Autoimmune encephalitis can cause significant neuropsychiatric symptoms, with frequent and disabling sequelae that can persist for months or even years. Patients should be closely monitored after discharge, since cognitive and psychosocial sequelae may persist and relapses may occur.

The overlap in clinical presentations and sequelae between infectious and immune encephalitis makes it essential to study these conditions together. However, our review revealed the diversity of the applied neuropsychological tools, which makes it difficult to obtain a comprehensive picture of encephalitis sequelae. Therefore, a consensus should be sought on how and when to assess sequelae, including patient-reported outcomes such as quality of life.

Finally, some postencephalitis sequelae might be similar to those observed in acquired neurological conditions such as traumatic brain injury. Priority should be given to evaluating the benefit of brain injury rehabilitation programs adapted for survivors of encephalitis, but with the flexibility to be personalized for individual patients.

Supplementary Materials

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Availability of Data and Material

All data generated or analyzed during the study are included in this published article (and its supplementary information files).

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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