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Outcome and Sequelae of Infectious Encephalitis

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Acute infectious encephalitis is a widely studied clinical syndrome. Although identified almost 100 years ago, its immediate and delayed consequences are still neglected despite their high frequency and possible severity. We reviewed the available data on sequelae and persisting symptoms following infectious encephalitis with the aim of characterizing the clinical picture of these patients at months to years after hospitalization. We searched PubMed for case series involving sequelae after infectious encephalitis. We carried out a narrative review of the literature on encephalitis caused by members of the *Herpesviridae* family (herpes simplex virus, varicella zoster virus, and human herpesvirus-6), members of the *Flaviviridae* family (West Nile virus, tick-borne encephalitis virus, and Japanese encephalitis virus), alphaviruses, and Nipah virus. We retrieved 41 studies that yielded original data involving 3,072 adult patients evaluated after infectious encephalitis. At least one of the five domains of cognitive outcome, psychiatric disorders, neurological deficits, global functioning, and quality of life was investigated in the reviewed studies. Various tests were used in the 41 studies and the investigation took place at different times after hospital discharge. The results showed that most patients are discharged with impairments, with frequent deficits in cognitive function such as memory loss or attention disorders. Sequelae tend to improve within several years following flavivirus or Nipah virus infection, but long-term data are scarce for other pathogens. Further research is needed to better understand the extent of sequelae after infectious encephalitis, and to propose a standardized assessment method and assess the rehabilitation efficacy in these patients.

Keywords infectious encephalitis; viral encephalitis; herpesvirus infection; *Flaviviridae* infection; sequelae; outcome.

INTRODUCTION

Acute encephalitis is a severe neurological syndrome affecting physical, cognitive, and behavioral functions. It is associated with substantial mortality during the acute stage of the disease, particularly in low- and middle-income countries. Most survivors do not recover fully and often require extended posthospitalization rehabilitation and care to regain their functional abilities. A recent initiative of the World Health Organization targeted encephalitis as a public health priority due to its wide extent of neurological signs, the consequences on performing the activities of daily living, and the burden of sequelae both for patients and their caregivers.[1] The disability-adjusted life years related to encephalitis, regardless of the cause, was estimated to 4.8 million in 2019.[2] The mean case fatality rate (CFR) for infectious encephalitis in the USA has been estimated to be 6%.[3] The disease also exerts a high cost burden on the healthcare system due to long hospitalizations and frequent admissions to intensive care units.[3]

Many different infectious agents such as viruses, bacteria, parasites, and fungi can cause encephalitis, sometimes with indistinguishable clinical presentations. Although the patient's history, examination findings, and unique environmental or travel exposures can

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greatly facilitate differential diagnoses, laboratory testing is required to confirm the etiology.[4] Autoantibodies targeting neuronal cell-surface and intraneuronal antigens have recently been demonstrated as a frequent cause of encephalitis mimicking infectious processes.[5,6] Importantly, despite extensive laboratory testing, most patients with acute encephalitis do not receive a substantiated diagnosis.[7-9]

The outcomes and sequelae of encephalitis can vary significantly based on the etiological agent. The occurrence of cognitive, psychiatric, and neurological sequelae following infectious encephalitis has long been recognized.[10] We reviewed the literature on outcomes and sequelae of infectious encephalitis with the aim of summarizing the existing knowledge for clinicians and identifying gaps in the understanding of persisting symptoms and outcomes that might inform future research and clinical applications.

METHODS

Search criteria

We comprehensively searched PubMed from its inception (circa 1,800) up to March 2022 for all published papers and abstracts written in English, French, or German using the following keyword string: ((encephalitis OR meningoencephalitis) AND (infecti*) AND (sequel* OR persisting symptoms OR outcome) NOT (autoimmune) NOT (pediat*)). Only studies that evaluated posthospitalization sequelae and outcomes were included. Study reports describing mortality, functional status, neuropsychiatric sequelae, and patient-reported outcomes including quality of life (QOL) and including at least five patients were included.

Studies of patients with isolated cerebellitis, myelitis, or meningitis were excluded. Studies including only pediatric patients were also excluded since the sequelae for this condition have already been thoroughly reviewed.[11] Studies of encephalitis of unknown cause were included, while those involving outcomes of immune, toxic, metabolic, or neoplastic encephalopathy/encephalitis were excluded. Studies or case series of both adult and pediatric patients were included only if the results were presented separately so that the sequelae specifically in adults could be assessed. Studies or case series of patients with various clinical presentations of a given infection (e.g., West Nile neuroinvasive disease [WNND] and West Nile fever) were retained only if it was possible to distinguish between neurological and nonneurological presentations in the reported results. Retrospective studies or case series of clinical or administrative databases (i.e., without clinical contact with or evaluation of patients by investigating clinicians) were also excluded, as were reports with incomplete or questionable clinical documentation.

Data collection

Data were collected from the selected papers in five outcome domains: cognitive disorders (assessed using standardized cognitive tests including memory, attention, and intelligence scales), sleep disorders, objective neurological deficit examinations (motor, sensory, and cranial nerve dysfunctions), psychiatric assessments (assessed using standardized scales or tests), global functioning (e.g., modified Rankin Scale [mRS]), and patient-reported outcomes (QOL and self-reported symptoms). The data collected included the study period, number of patients enrolled in the study, causes of encephalitis, tests and other methods used to assess the patients, delays between hospital discharge and assessments, and the results of the assessments.

RESULTS

The initial search for infectious encephalitis identified 4,424 papers. After reading their abstracts, 185 relevant studies were selected for full text reviews. Forty of these studies met the inclusion criteria. The included studies along with the assessment tools used and results are summarized in Table 1 and Supplementary Table 1 (in the online-only Data Supplement).

The mRS was the most frequently used tool in any domain to evaluate the outcome of the patients. The mRS was first developed for stroke and measures the degree of disability or dependence in performing the activities of daily living (Table 2).[12,13]

Measured outcomes

Twenty-two of the 40 studies investigated the cognitive outcomes of patients using the following classical tests or batteries: Mini Mental State Examination (MMSE), full Wechsler Adult Intelligence Scale, Wechsler Memory Scale, Montreal Cognitive Assessment Scale, Trail-Making Test, and Rey Complex Figure Test. The different studies used different combinations of tests. Sixteen studies included a neurological examination and 12 included self-reported symptoms. Six of the 12 studies investigating psychiatric outcomes focused on depression and anxiety. The five studies assessing the QOL comprised three using 36-item short-form medical outcome survey (SF-36), one using 12-item shortened version of SF-36 (SF-12), and one using a questionnaire derived from SF-12. Global functioning was reported for 15 studies, using the mRS, Glasgow Outcome Scale (GOS), Liverpool Outcome Scale (LOS), or in-house questionnaires. Eleven studies investigated a single domain, mainly the cognitive outcome or global functioning. Only self-reported symptoms or global functioning were investigated in seven studies.

Table 1. Summary of patients and methods in the 40 papers included in the review

Study	Etiologies	Domains assessed	Assessment methods used
Raschilas et al.[15]	HSV	F	F: 5-grade scale derived from the GOS
McGrath et al.[17]	HSV	F	F: GOS, graded following telephone interviews with the patients, their relatives, and GPs
Utley et al.[18]	HSV	C	C: Portland aAdaptability Interview, National Adult Reading Test, WAIS, Wechsler Memory Scale–Revised, RCFT, California Verbal Learning Test, Warrington Word and Face Recognition Memory Test, Autobiographical Memory Interview, Otago Remote Memory Questionnaire, Wisconsin Card-Sorting Test, Controlled Oral Word Association Test, Minnesota Test for the Differential Diagnosis of Aphasia, Short Token Test, Funnel Test, Sheridan Test
Harris et al.[20]	HSV, other, unknown, control group	C/P	C: Wechsler Test of Adult Reading, Wechsler Abbreviated Scale of Intelligence, Door and People Battery, Autobiographical Memory Interview, F-A-S Test, Trail-Making Test, Hayling Test, Brixton Test, Graded Naming Test, Pyramid and Palm Trees, Visual Object and Space Perception Battery, Benton Focal Recognition P: Beck Depression Inventory, Beck Anxiety Inventory
Berlit[21]	HSV, VZV, rubella, adenovirus, unknown	P/N/S	P: Psychiatric examinations N: Neurological examinations S: Self-reported symptoms
Wetzel et al.[22]	VZV	C	C: MMSE, RCFT , Clock-Drawing Test, Rey Auditory Verbal Learning Test, Rey Visual Design Learning Test, Digit Span, Stroop test, d2 test
Hokkanen et al.[24]	VZV	C/P	C: WAIS, Wechsler Memory Scale, Benton Visual Retention Test, Stroop Test, basic calculation, imitation of movements P: Behavioral observations
Grahn et al.[25]	VZV	C/P	C: MMSE, Montreal Cognitive Assessment, Cognitive Assessment Battery, Trail-Making Test Part A, PaSMO, RCFT (copying) N: NIHSS P: Hospital Anxiety and Depression Scale
Persson et al.[26]	VZV	N	N: Neurological examinations
Eckerström et al.[27]	VZV	C	C: Symbol Digit Modalities Test, Trail-Making Test Parts A and B, Continuous Performance Test (reaction time, and errors of omissions and commissions), California Verbal Learning Test, Brief Visuospatial Memory Test–Revised, Block Tapping Test, Visual Objects and Space Perception Battery (silhouettes subtest), Boston Naming Test, Category Fluency Animal Naming, Letter-Number Sequencing Comparison of results with norm values in the same age group
Ogata et al.[28]	HHV-6	F/S	F/S: Retrospective questionnaire
Carson et al.[34]	WNV (not limited to encephalitis)	C/P/N/Q/F	C: Complete cognitive battery, including Wechsler Memory Scale, Wisconsin Card-Sorting Test, Modified Fatigue Impact Scale, Brief Test of Attention, Purdue Pegboard P: Beck Depression Inventory N: Neurological examinations Q: SF-12 version 2 F: mRS, Barthel Index
Sejvar et al.[35]	WNV (not limited to encephalitis)	N/F/S	N: Neurological examinations F: Functional status, ability to perform the activities of daily living S: Standardized questionnaire on symptoms

Table 1. Summary of patients and methods in the 40 papers included in the review (continued)

Study	Etiologies	Domains assessed	Assessment methods used
Hawkes et al.[36]	WNV (not limited to encephalitis)	C/F	C: TICS F: mRS
Klee et al.[37]	WNV	F/S	F: Instrumental Activities of Daily Living Scale S: Standardized questionnaire on persisting symptoms
Sejvar et al.[38]	WNV (not limited to encephalitis)	C/N/Q/S	C: Cambridge Neuropsychological Testing Automated Battery N: Neurological examinations Q: SF-36 S: CDC Symptom Inventory
Haaland et al.[39]	WNV (not limited to encephalitis)	C	C: TICS
Loeb et al.[40]	WNV (not limited to encephalitis)	C/P/Q	C: Fatigue Severity Scale P: Depression Anxiety Stress Scale Q: SF-36
Berg et al.[41]	WNV (meningitis, encephalitis, and fever only)	C/P	C: Brief Fatigue Inventory, Modified Fatigue Impact Scale P: CES-D
Murray et al.[42]	WNV (not limited to encephalitis)	P/S	P: CES-D F: Barthel Index S: Self-reported symptoms of depression
Sadek et al.[43]	WNV	C	C: Wide-Range Achievement Test-3 Reading (premorbid abilities), Finger Tapping, Symbol Digit Modalities, Hopkins Verbal Learning Test–Revised (total trials 1–3), Hopkins Verbal Learning Test–Revised Delayed Recall, Animal Fluency, Trail-Making Test, Digit Span, RCFT, Wechsler Memory Scale III
Anastasiadou et al.[44]	WNV (encephalitis/ meningo-encephalitis)	C/P/N	Evaluation carried out during a follow-up examination; no mention about whether the deficits were self-reported by the patients or assessed using standardized tests
Karelis et al.[46]	TBE	F/S	F/S: Standardized questionnaire with 29 items on persisting symptoms, employment status, and social restrictions
Czupryna et al.[47]	TBE	C/N	C: No details N: Neurological examinations
Lämmli et al.[48]	TBE	F/S	F/S: Standardized questionnaire on residual symptoms
Kaiser[49]	TBE	C/N	C: Neuropsychological tests (no details) N: Physical examinations
Laursen and Knudsen[50]	TBE	F/S	F/S: Standardized questionnaire on residual symptoms
Mickiene et al.[51]	TBE (not limited to encephalitis)	N/F	In-house classification (mild, moderate, or severe sequelae) of the remaining symptoms
Lenhard et al.[52]	TBE	N/F	N: Neurological examinations F: mRS

Table 1. Summary of patients and methods in the 40 papers included in the review (continued)

Study	Etiologies	Domains assessed	Assessment methods used
Veje et al.[53]	TBE	N/F/S	N: Clinical examinations on follow-up visits F/S: ESGQ (self-reported symptoms in phone interviews), FOSQ (quality of life related to sleep in phone interviews)
Bogovič et al.[56]	TBE (not limited to encephalitis)	N/Q/S	N: Neurological examinations Q: SF-36 version 2 S: Self-reported symptoms Unfavorable outcome defined as ≥2 new or exacerbated self-reported symptoms, or ≥1 objective symptoms. Mild PES defined as ≥2 new or exacerbated self-reported symptoms, moderate PES as ≥3 new or exacerbated self-reported symptoms, severe PES as ≥1 objective symptom
Kalita et al.[57]	JE, HSV, unknown	C/N	C: MMSE, cognitive evoked potentials N: MRI
Sarkari et al.[58]	JE	C/P/N	C: Past and recent memory assessed using a standardized questionnaire, tests derived from Binett Intelligence Scale guidelines, tests for agnosia and apraxia in those patients able to complete the tests P: Assessment of mood, behavior, personality, hallucinations, and delusions reported by relatives N: Neurological examinations, seizures reported by relatives
Wang et al.[30]	JE	C/N/F	C: WAISRC (verbal, and performance IQ), Wechsler Memory Scale, Mental Handicap Rating Scale N: Neurological examinations F: LOS
Deresiewicz et al.[59]	EEEV	F	F: Clinical sequelae classified according to functional status on discharge: normal (no deficits), mild sequelae (self-care possible away from an institutional setting), moderate sequelae (institutional care required for performing the activities of daily living), severe sequelae (permanent vegetative state), death
Sejvar et al.[60]	Nipah virus	N/S	N: Neurological examinations S: Self-assessment scale of overall health and well-being, standardized questionnaire on persisting symptoms
Goh et al.[61]	Nipah virus	F	No details
Ng et al.[62]	Nipah virus	C/P	C: WAIS–Revised, Standard Progressive Matrices, Rey Auditory Verbal Learning Test, Wechsler Memory Scale P: Psychiatric interview using the Schedules for Clinical Assessment in Neuropsychiatry
Hokkanen and Launes[63]	HSV, VZV, other, unknown	C	C: Blessed Dementia Scale, WAIS, Wechsler Memory Scale, Word Fluency, Stroop Test, Benton Visual Retention Test, comprehension of sentences with complex semantic structures, copying of figures, clock-hand tasks
Mailles et al.[16]	Various causative agents and unknown etiology	C/Q/F/S	C: Informant questionnaire on cognitive decline in the elderly, F-TICS Q: Questionnaire derived from SF-12 F: GOS, questionnaire on the resumption of work/school and leisure S: Standardized questionnaire on persisting symptoms

C, cognitive; CDC, US Centers for Disease Control and Prevention; CES-D, Center for Epidemiologic Studies Depression Scale; EEEV, Eastern equine encephalitis virus; ESGQ, Encephalitis Support Group Questionnaire; F, functioning; FOSQ, Functional Outcome of Sleep Questionnaire; F-TICS, French version of the Telephone Interview for Cognitive Status; GOS, Glasgow Outcome Scale; HHV-6, human herpesvirus-6; HSV, herpes simplex virus; IQ, intelligence quotient; JE, Japanese encephalitis; LOS, Liverpool Outcome Scale; MMSE, Mini Mental State Examination; mRS, modified Rankin Scale; N, neurological; NIHSS, National Institutes of Health Stroke Scale; P, psychological/psychiatric; PaSMO, Parallel Serial Mental Operations; PES, postencephalitis syndrome; Q, quality of life; RCFT, Rey Complex Figure Test; S, self-reported outcome; SF-12, 12-item shortened version of SF-36; SF-36, 36-item Short-Form Medical Outcome Survey; TBE, tick-borne encephalitis; TICS, Telephone Interview for Cognitive Status; VZV, varicella zoster virus; WAIS, Wechsler Adult Intelligence Scale; WAISRC, WAIS revised in China; WNV, West Nile virus.

Table 2. Categories of the modified Rankin Scale[12,13]

Score	Definition
0	No symptoms
1	No significant disability. Able to carry out usual activities, despite some symptoms
2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities
3	Moderate disability. Unable to attend to own bodily needs without assistance, but able to walk unassisted
4	Moderate severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted
5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent

The *Herpesviridae* family

Herpes simplex virus

Herpes simplex virus (HSV) is the most frequently identified and most-studied cause of encephalitis worldwide. Acyclovir (ACV) was discovered in the 1970s, but its benefit over vidarabin in treating herpes simplex encephalitis (HSE) was demonstrated in 1984.[14] Prior to the use of high-dose intravenous ACV for treating HSE, the in-hospital CFR of HSE was around 70%, but this has decreased to less than 20% in recent studies.[15,16] The prevalence of sequelae in HSE survivors is high, with case series showing that 30%–70% of HSE survivors have persisting symptoms and sequelae with significant consequences.[17,18] A recent study found full recovery in only 14% of 43 patients at 3 years after HSE.[16] Although HSE sequelae may be permanent, some improvement in signs at the time of discharge has been observed in most patients in the ACV era. Rehabilitation interventions usually implemented after head trauma injury might be effective for HSE patients.[19]

Cognitive decline in several domains have been reported in most patients and has a major impact on functional outcomes. Anterograde or retrograde episodic memory and semantic memory can both be negatively affected.[16,17,20] Executive dysfunction occurs frequently and is responsible for the inability for some patients to return to work or even perform the usual activities of daily living, with proportions as high as 41% of patients being reported.[18] Attention disorders have been reported in as many as 67% of patients.[16] A study found the 23% of 24 post-HSE patients had mild intellectual impairment based upon intelligence quotient (IQ) estimates,[18] although pre-encephalitis IQ scores were not available for comparison. Language and/or speech impairments also occur frequently after acute HSE and can persist for years.[16-18] While some degree of cognitive injury observed in HSE may be permanent, there have been reports of gradual improvement over time, often taking from months to years. A recent study found improvements in executive function and IQ in an unspecified number of patients with HSE after 1 year.[20]

Behavioral sequelae may be observed in 40%–50% of survivors, including affective/mood disorders, personality changes, aggressiveness, anxiety, depression, sleep disorders, and emotional instability.[16,17] A case-control study of 30 patients and 70 healthy controls found that HSE patients had higher levels of depression and anxiety than did healthy controls after 1 year.[20] These sequelae can be responsible for inappropriate behavior and reactions, and may result in interpersonal challenges, including strained interactions with family members and friends.

Persisting motor or coordination deficits are less common than cognitive and behavioral symptoms after HSE.[16,21] Seizures were found in 14% of 34 patients in a case series.[17]

Varicella zoster virus

Central nervous system varicella zoster virus (VZV) infection can result in meningitis, myelitis, encephalitis, vasculitis, and stroke. Here we discuss only sequelae following VZV encephalitis. Sequelae are frequently reported in patients with VZV encephalitis.[22,23] During follow-up, attention deficits may be present in 30%–50% of patients,[16,24] with mild memory disorders and mental slowing in 15%–45%,[16,24,25] and speech disorders in 30%.[24] VZV encephalitis patients have been found to score poorly on IQ scales, and exhibit mild behavioral disorders including disinhibition and euphoria.[24] Data available on the long-term outcome of VZV encephalitis suggest that improvements occur over time in at least half of patients.[22]

Objective neurological sequelae are variably reported. In a French cohort, 30% of patients had mild motor deficits at 3 years after discharge,[16] while there were none in a Swedish cohort using the National Institutes of Health Stroke Scale.[25] In another study from Sweden, 10 of 13 patients with VZV encephalitis had neurological sequelae at 1 month after their hospital discharge, and 6 of 7 had them at a 3-month follow-up.[26]

A recent study evaluated 10 Swedish patients aged 24 to 85 years using 11 cognitive tests.[27] Compared with normative values adjusted for age, these patients had lower scores for executive function, speed and attention cognitive domains, learning and memory, and language. Moreover, the scores were lower for older patients than younger ones.

Human herpesvirus-6

A single study investigated the sequelae following human

herpesvirus-6 (HHV-6) encephalitis in adult patients.[28] That cohort of 145 hematopoietic stem cell transplant (HSCT) recipients was retrospectively assessed using a questionnaire administered at a median of 4.5 years after acute encephalitis. The most-frequent sequela was subjective memory impairment (33% of survivors), and only one in five patients had been able to return to their previous state of activities of daily living at the time of the study. However, it was not possible to distinguish the consequences of the encephalitis vs the underlying disease associated with HHV-6 encephalitis (immunosuppression, hematological malignancy, and any other indication for receiving an HSCT).

The *Flaviviridae* family

West Nile virus (WNV), Japanese encephalitis (JE) virus (JEV), and tick-borne encephalitis (TBE) virus are the most common flaviviruses responsible for encephalitis. Their incidence and prevalence vary with the presence of competent vectors as well as temporal factors including season and rainfall. Most flavivirus infections are asymptomatic, and only a minority of symptomatic patients will present with neurological signs. The CFR may be significant among these infections, such as 18% for WNV encephalitis[29] and 20% for JE.[30] The CFR following TBE depends on the viral subtype: the Far East subtype is known to be more pathogenic than the Siberian and European subtypes, with the CFR following TBE due to the European subtype reportedly being less than 1%.[31]

Flaviviruses share a common neurotropism for the thalamus, basal ganglia, brainstem, and anterior horn cells of the spinal cord.[32,33] Their clinical presentation and outcomes consequently share common features and sequelae, although there also are some differences. Flaviviruses are responsible for neuroinvasive illness with a wide range of clinical presentations and severities: meningitis, encephalitis, myelitis, and acute flaccid paralysis (AFP). Many studies of sequelae following flavivirus neuroinvasive infections have detected cohorts of patients presenting with the full spectrum of neuroinvasive diseases, not restricted to encephalitis. It may therefore be difficult to distinguish sequelae specific to encephalitis in some of these cases.

West Nile virus

Neurological sequelae are frequent following WNND, including tremor and parkinsonism being observed in about 20% of patients.[34] A case series evaluating motor function found that 34 patients (69%) had abnormalities in motor speed.[34] These signs and symptoms may last for months to years.[35,36] Severe and persistent neurological deficits are seen in patients presenting with myelitis or AFP, which are often challenging to distinguish from encephalitis sequelae in cohort studies.[35,36]

Up to 75% of patients report persistent cognitive and physical symptoms following WNND, the most common being extreme fatigue, generalized weakness associated with joint pain, and depressive mood.[34,37,38] One case series found that 42% of patients complained of memory loss and concentration disorders.[39] These symptoms may be responsible for decreased QOL: in WNND patients evaluated 18 months after acute infection, low scores were obtained in the physical domain as well as in the social functioning and emotional components of the mental health domain of the SF-36.[38] However, QOL improves during the first year after hospital discharge.[40]

Depression is a common long-term consequence of WNV infections, and is more frequent following WNV encephalitis than other clinical presentations.[41] Moderate-to-severe depression was found in 24% of 49 adult patients with WNND[34] and in 34% of 38 patients with WNV encephalitis.[42] Another study applying a complete neuropsychological battery found that patients with WNND performed slightly worse than a normative population in psychomotor speed, executive function, and attention.[38] Comparable results were obtained in a further study.[43]

Assessments of 116 patients with WNND or West Nile fever in New Mexico in 2006 performed 9 months after symptom onset revealed that cognitive impairment was more prevalent in patients who had WNND.[39] In that case series, among 52 WNND patients, 42% experienced concentration difficulties and subjective memory deficits, 27% had impaired comprehension, 25% were confused, and 25% experienced difficulties in decision-making. Another case series from New Mexico found that 56% of 41 WNND patients had cognitive impairment, mainly affecting verbal memory and psychomotor speed.[43]

A recent study assessed functional outcomes using the mRS in 30 patients at from 1 month to 12 years after WNND, and found that 24 patients (80%) had mRS scores of 0−2 (from no symptoms to slight disability), suggesting a favorable outcome in most patients.[36] However, seven patients in that cohort still experienced cognitive impairment as assessed using the French version of the Telephone Interview for Cognitive Status.

After WNV emerged in Greece, a case series found sequelae following WNND in 22 patients at 16 months after discharge.[44] That study found a high prevalence and wide range of sequelae, including anorexia (77%), muscle weakness (72%), memory disorders (37%), and depression (22%).

Tick-borne encephalitis

TBE is the most common type of arboviral encephalitis in Eu-

rope, and both its incidence and geographic range are increasing.[31] Sequelae following TBE have been well documented, which some authors consider to be a compelling argument for widespread vaccination.[45] The morbidity and mortality are higher for the Far Eastern subtype of the virus than for the other two subtypes present in Europe (European and Siberian).

Neurological sequelae are seen primarily in patients with encephalomyelitis or encephaloradiculitis, with focal deficits in nearly one-quarter of patients.[46,47] Shoulder girdle paralysis can occur in up to 14%, with hearing impairment and facial palsy being less common (6%).[48] In a German study, 47 of 230 patients (20%) presented with motor deficits of the extremities at a 3-month follow-up.[49] Persistent dizziness, tremors, and other symptoms of parkinsonism are reported in 5%−10% of patients at discharge, but these improve significantly during the first year.[48,50,51] Not surprisingly, motor sequelae are more severe in patients with meningoencephaloradiculitis than in those with encephalitis or meningitis alone.[52]

In Latvia, 29 patients with TBE or tick-borne encephalomyelitis diagnosed between 1994 and 2006 were assessed at a median of 7 years after acute neurological illness.[46] At the time of follow-up, 41% presented with moderate sequelae and 31% with severe sequelae (the criteria were not defined in the report). These patients were part of a larger cohort of 100 TBE patients presenting with various clinical presentations: fever, AFP, meningitis, or encephalitis. The main persisting symptoms among these 100 patients were fatigue (61%), headache (58%), mood disorders (47%), sleep disorders (42%) and dizziness (40%).[46]

Memory disorders and concentration difficulties were found in 42% of patients at the time of hospital discharge in a Swiss case series of 132 patients diagnosed between 1976 and 1996.[48] Evaluations of 32 of these patients performed at 5 years after symptom onset revealed that 31% were still disabled.

In a Swedish study comparing patients with TBE or tick-borne meningitis with controls, only 14% of the TBE patients were considered asymptomatic without sequelae or persisting symptoms at the first follow-up visit conducted from a few weeks to 2 months after the acute illness, while this increased to 19% at the second follow-up visit (up to 6 months after discharge).[53] The patients and controls in that study were also interviewed by phone using a standardized questionnaire at 2 to 15 years after the patients had been discharged, which revealed that the scores for memory, executive symptoms, physical disorders, concentration, learning abilities, fatigue, and coordination were worse for the patients than for the controls.

A postencephalitic syndrome (PES) has been reported in 10%−58% of patients during 1 year following hospital discharge.[54] This is described as a constellation of persistent psychiatric, cognitive, and neurological symptoms, which include emotional lability, low tolerance of stressful situations, concentration difficulties, anterograde memory deficit, aphasia, visual and hearing deficits, tinnitus, ataxia, tremors, and pain in the limbs.[55] This syndrome resulted in 44% of patients requiring psychiatric follow-up and treatment after discharge in a large Polish case series.[47] That study also found mild cognitive impairment in 31% of patients.

The PES was recently studied in Slovenia with a more stringent definition: at least two new or exacerbated symptoms at follow-up, or at least one objective neurological symptom.[56] Among 304 patients with TBE, tick-borne meningitis, or tick-borne meningoencephalitis, 127 (42%) had PES at 6 months after discharge while 68 of 207 patients (32%) had PES after 12 months. The global picture of sequelae improved after 12 months, with fewer cases with severe PES and more of those with mild PES. During the final follow-up visit (performed after various intervals), 58% of patients reported at least one subjective symptom, most frequently headaches (31%), memory/concentration disorders (21%), and emotional lability (14%). The following objective symptoms were less frequent (6% of all patients): 3% with paresis/paralysis, and 1% with tremors, 1% with hearing loss, and 1% with visual deficits. The patients had a decreased QOL compared with a control group.[56]

The sequelae following TBE are more severe in cases of encephalomyelitis. In a German case series of 57 patients, 19% had fully recovered at 10 years after TBE while 51% still reported sequelae on follow-up.[54]

Japanese encephalitis

JE is the most frequent epidemic encephalitis worldwide, and it has the highest burden, especially in low- and middle-income countries with less access to healthcare. JE most frequently affects children, but elderly persons can also present with acute neuroinvasive infections. The disease can also be seen in adults who recently settled in areas where the virus is present or among unvaccinated travelers to endemic areas. A study found that 81% of 16 patients with JE had a decreased score on the MMSE at 3 months after discharge.[57]

Sequelae following JE can affect the cognitive, behavioral, and neurological domains. Most studies of the sequelae following JE have focused on children. However, late sequelae in adult patients were found in a study enrolling patients at 14 years after JE in India.[58] Among 453 of 651 patients with psychiatric disorders at discharge, including hallucinations and delusions, 78% had improved during the first year and 98% had by 5 years, but 2% still reported restlessness after 14 years. Depression was observed in 34% of these 453 pa-

tients with psychiatric disorders at discharge, but 99% of them had fully recovered from depression after 5 years. In the same cohort, 514 of 651 patients presented with speech disorders at discharge, and 95% of 203 who were followed up over 14 years recovered. Among the 174 patients who initially presented with a parkinsonian syndrome encompassing dysarthria and monotonous speech, only 56% had returned to their premorbid speech ability at the end of the follow-up.[58] Hyperkinetic movements (71 of 338 patients, 21%) including tremors (98 of 174 patients, 56%) were frequent at discharge, but had improved in 95% of patients after 14 years. Comparable proportions and evolution trends were seen for limb paralysis (151 of 485 patients, 31%) and corticospinal signs (334 of 485 patients, 69%).[58] Although most patients improved significantly over time, 14 (3%) showed no improvement after 14 years, with 4 being bedridden, 9 having coarse tremors, and 1 suffering from other movement disorders. In that study, 381 of 651 patients (59%) had initial cognitive impairment, including concentration disorders, memory disorders, impaired capacity for reasoning and judgement, decreased scores on IQ scales, and inability to count or use cash.[58] The deficits on IQ scales had improved in 98% of patients by 5 years, except for memory remaining impaired in 16 of 370 patients (4%) at the end of follow-up.

A recent Chinese cohort study including 35 adults among 85 JE patients found that neurological and cognitive sequelae were more frequent in adult patients than children at follow-ups performed 1 to 8 years after discharge.[30] Sensory disorders were seen in 60% of 35 adults, motor disorders in 41%, aphasia in 14%, and epilepsy in 6%. General, verbal, and performance IQ scores were lower than 70 in 37% of adult patients, and 72% had memory disorders. The global functioning was impaired in 70% of adult patients, with 32% exhibiting severe impairment as measured using the LOS.

Other infectious causes of encephalitis

Alphaviruses

Eastern equine encephalitis is a rarely reported but probably underrecognized arboviral disease, with 36 cases reported in North America from 1988 to 1994.[59] Eight of the 23 survivors had permanent moderate-to-severe sequelae, consisting of spastic paralysis, intellectual impairment, and personality changes. Among the cases reported to the US Centers for Disease Control and Prevention, the CFR was 36%, with only 1 of 36 patients fully recovering and 8 presenting with moderate-to-severe sequelae.[59]

Nipah virus

Nipah virus emerged in the late 1990s in Malaysia and Singapore during a major outbreak, and has more recently been recognized as an important cause of encephalitis in Bangladesh.[60] During the 1999 outbreak in Malaysia, 30 of 94 patients (32%) hospitalized with Nipah virus encephalitis died during hospitalization, while 50 (53%) fully recovered and 14 (15%) were discharged with sequelae or persistent symptoms.[61] Five patients were in a vegetative state, while two were discharged with cognitive impairment requiring permanent assistance, three with mild cognitive impairment, three with cerebellar disorders, and two with encephalitis relapses with persistent deficits.

Only one of eight patients infected during the 1999 outbreak in Singapore who were evaluated at 2 years after encephalitis onset had no sequelae, while five experienced major depression, two had personality changes, and two reported chronic fatigue syndrome.[62] All seven patients with sequelae had impaired memory, which was mostly visual memory but some also had impairment of verbal memory. Two of the seven patients who had worked before contracting encephalitis were unable to resume work: one due to leg weakness and the other due to major memory impairment and fatigue.

In Bangladesh, 17 patients with a history of Nipah virus encephalitis between 2001 to 2004 were assessed for sequelae in 2005 and 2006.[60] Follow-up examinations of these 17 patients revealed that 7 (32%) had moderate-to-severe sequelae, while 4 had cognitive dysfunction, 2 had ataxia, 2 had focal weakness, 1 had cervical dystonia, and 1 had facial weakness and dysarthria. Four patients experienced symptoms after discharge: oculomotor impairment in three and cervical dystonia in one. In self-assessments, about 70% reported chronic fatigue, 60% mood disorders, and 40% behavioral disorders.

Sequelae in cohort studies of encephalitis cases of various infectious causes

Very few studies have found persistent symptoms and sequelae after encephalitis of mixed infectious cause and encephalitis of unknown cause but presumed to be infectious etiology. Only two studies were consistent with the criteria that we applied for our search, and they had enrolled patients with encephalitis of proven or suspected infectious cause. It should be noted that both studies were conducted before immune encephalitis was recognized as a major differential diagnosis of infectious encephalitis and before the appropriate diagnostic tools were widely available. Some patients enrolled in these studies without a cause identified for their encephalitis may have had undiagnosed immune encephalitis.

A Finnish study enrolled 45 adult patients hospitalized for encephalitis between 1990 and 1994 caused by HSV (n=8), VZV (n=7), other identified infectious agent (n=9), or un-

known cause (n=21).[63] Patients were assessed twice, at means of 45 months and 81 months postdischarge. At the first follow-up evaluation, 30% of patients had an unfavorable outcome (defined as a score of ≥4 out of 28 on the Blessed Dementia Scale), including six of the eight patients with HSE. The persistent symptoms included epilepsy in four patients and hemiplegia in one; only one-third of patients had been able to resume work. Only 12 patients were evaluated at the second follow-up, at which time the medical condition had deteriorated in 2 and was unchanged in 1. The remaining nine patients performed better in neuropsychological testing, but eight of them still had neuropsychiatric symptoms, including depression (n=4), aggression (n=2), anxiety (n=1), and bipolar disorder (n=1).

A prospective study carried out in France used the GOS to assess the outcome of 176 patients (including 158 adults) at 3 years after encephalitis.[16] The most-frequent causes of encephalitis were HSV, tuberculosis, and VZV. A poor outcome, defined as a GOS score of <5, was identified in 45% of the adult patients. Overall, 75% of previously employed adults had returned to work, but the proportion was only 55% for those with HSE (p<0.01). In adult patients, a poor outcome was significantly associated with age, a low level of education, HSV or VZV encephalitis, and medical comorbidities such as cancer or systemic disease requiring immunosuppressive drugs.

DISCUSSION

We aimed to review studies that have investigated the sequelae and persistent symptoms following infectious encephalitis. Our main findings are summarized in Table 3. Sequelae following encephalitis of proven or suspected infectious origin have long been known, but only a small number of rigorous, comprehensive studies evaluating outcomes have been reported. We found that the sequelae of infectious encephalitis are diverse and can be quite substantial. Despite achieving a good functional recovery (most commonly defined using the mRS in the neurology literature), most studies that incorporated more-comprehensive neuropsychiatric evaluations and/or patient-reported symptoms found persistent deficits in most patients.

Our review of the literature revealed some patterns related to etiology-specific outcomes. Sequelae following *Herpesviridae* encephalitis are more likely to affect cognitive and psychiatric domains, whereas flavivirus encephalitis are more likely to impact neurological and psychiatric domains.

Our review also demonstrated that sequelae continue to improve over time for most causes of encephalitis in studies with longer follow-ups. This improvement might be seen over years for certain specific infectious agents such as JEV, Nipah virus, and HSV. Such findings can be an important source of hope for patients and caregivers. The substantial burden of disease and protracted recovery also underscore the need for sufficient resources to optimally care for this population, not only during the acute period but also over the long term with comprehensive rehabilitation services.

It is challenging to draw additional conclusions from previous studies of postencephalitis sequelae due to the diverse methodologies used to define and assess outcomes. We found that previous studies are not easily comparable due to differing case definitions of encephalitis, nonuniform assessment intervals, and variability in outcome measures, oftentimes using poorly validated or unvalidated measures. For example, understanding the outcome of an arbovirus encephalitis such as that caused by WNV is complicated by most studies including patients presenting with WNND rather than strictly encephalitis. Although encephalitis, meningitis, and myelitis/encephalomyelitis are different pathophysiological and anatomic entities, they often overlap clinically, and we opted to include studies with such overlap in our review since they represent the clinical reality and spectrum of neuroinvasive diseases encountered in clinical practice, in which phenotypes can be overlapping.

Our review suggests that most patients who are considered to have recovered at discharge should be evaluated both early and late after hospitalization so that both persistent and new symptoms (e.g., epilepsy) can be assessed. However, the assessment intervals were heterogeneous in most studies. Significant differences in the time interval between the acute episode and follow-up between patients (from several months to several years) among some of the retrospective studies make it difficult to interpret the results obtained in the entire cohort.

Another difficulty is the wide range of tests used to evaluate patients, including author-designed questionnaires, results from medical examinations, screening cognitive measures, and extensive neuropsychological testing. This lack of uniformity in evaluations makes it difficult to compare outcomes and draw more-generalized conclusions regarding postencephalitis recovery. Studies have examined different aspects of postencephalitis sequelae, with some focusing on cognitive disorders, some on neurological (motor and sensory) disorders, and others on functional and patient-reported outcomes, such as QOL.

Additional research is needed to better understand the sequelae of encephalitis and identify the most-robust tools for capturing ongoing impairments as well as documenting improvement. The mRS is a global disability rating scale that assesses overall functional independence, but interobserver

Table 3. Summary of affected domains and main sequelae following the most-frequent causes of viral encephalitis

Virus	Cognitive sequelae	Psychiatric/ behavioral sequelae	Neurological sequelae	Quality of life	Functioning	References
Herpes simplex virus	Memory disorders, executive dysfunction, decreased attention, intellectual impairment (reduced IQ), aphasia, speech disorders, emotional instability	Mood impairments (e.g., anxiety, depression), personality changes, inappropriate behaviors and reactions (e.g., aggressiveness)	Rarely: Coma, motor deficit, seizures			15–21
Varicella zoster virus	Attention deficit, memory disorders, mental slowing, speech disorders, executive dysfunction	Mild behavioral disorders (euphoria, disinhibition)	Mild motor deficits			16, 22–27
West Nile virus	Memory loss, impaired concentration, decreased psychomotor speed, executive dysfunction, confusion	Severe fatigue, depression, anorexia	Motor deficit (major if encephalomyelitis), tremors, parkinsonism, decreased motor speed, general weakness, joint pain	Severe fatigue, decreased physical and mental quality of life	Good functioning over time	34–44
Tick-borne encephalitis	Memory disorders, decreased concentration, executive dysfunction,impaired learning abilities	Fatigue, depression, sleep disorders	Dizziness, motor deficit, tremors, hearing loss, shoulder girdle paralysis, headaches, coordination impairment	Decreased quality of life, especially in PES	PES (new or exacerbated symptoms): emotional lability, limb pain, tinnitus, headaches	46–56
Japanese encephalitis virus	Decreased MMSE score, speech disorders, dysarthria, memory disorders, decreased intelligence and reasoning (reduced IQ), inability to count	Psychosis-like syndrome (hallucinations, delusions), restlessness, depression	Limb paralysis, hyperkinetic movements (frequent tremors), corticospinal deficits, sensitivity deficits, epilepsy		Globally impaired	30, 57, 58

IQ, intelligence quotient, MMSE, Mini Mental State Examination, PES, postencephalitic syndrome.

variability is possible[64] and so it might not adequately capture severity or the recovery patterns with regards to cognitive disabilities. The main criticism of the mRS is that the different levels are poorly defined, which leads to high interrater variability. Another challenge with the mRS is its lack of granularity, resulting in difficulty measuring or documenting more-subtle aspects of recovery and disability.

Severe sequelae can have consequences not only for the patients but also for their families and caregivers. Some patients may be dependent on formal or informal caregiver support for performing the activities of daily living. The inability to return to work may also have economic consequences for the household. Neuropsychiatric sequelae can result in substantial sociodynamic strain on family units. Finally, family members may experience challenges coping with the patient's impairment, which can lead to stress, conflict, and mood disorders in these family members.

This review of >3,000 adult patients followed up after infectious encephalitis highlights several unmet needs in the field of postencephalitis recovery. First, we propose that all encephalitis patients should undergo a comprehensive assessment of their neurological, cognitive, and psychiatric functions after hospital discharge, and should be referred to rehabilitation services and psychiatric support when necessary. Even for patients exhibiting significant recovery, evaluating more-subtle sequelae including cognitive and psychiatric dysfunction and referring for additional management and support if indicated can help improve the QOL of both the patient and their caregivers. Second, patients and families should be informed about the nature and persistence of symptoms that can last for months to years. Third, there is a need for a standardized assessment method for these patients to make it possible to cross-compare their conditions, progress, and outcomes. A standardized assessment method would also enable more-robust outcome measures for use in treatment trials.

CONCLUSIONS

Infectious encephalitis can have severe neuropsychiatric manifestations during the acute stage of the disease. Although various study methods have been used, the data available on long-term outcomes of infectious encephalitis demonstrate consistently that severe impairment is common at months or even years after the acute illness. Patients should therefore be closely monitored even after the infection has resolved, since the acute neurological infection may progress to a chronic neuropsychological disease.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2023.0240.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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