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ORIGINAL ARTICLE

Long-term neurological outcome in patients presenting with encephalitis

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Abstract

Background Advances in encephalitis research have improved the definition and management of encephalitis during the acute phase. Still, little is known about long-term outcomes in different subtypes of encephalitis.

Objectives To analyze the prevalence and predictors of long-term clinical outcomes in different subtypes of encephalitis.

Methods All patients discharged from a tertiary hub for acute neurology with a confirmed diagnosis of encephalitis were included. Encephalitis were classified into autoimmune (AE), infectious (IE) and of unknown origin (UE) according to guidelines. Long-term neurological sequelae were evaluated using a 16-item questionnaire assessing severity and frequency of neurological symptoms, disability was scored using the expanded Disability status scale (EDSS). Long-term symptoms distribution and predictors were evaluated using univariate and multivariate regression models.

Results Seventy out 105 survived patients were included (AE n = 30, IE n = 12, UE n = 28). Disability at discharge was worse in AE compared to UE (p = 0.018). Additionally, AE had a higher risk of relapse (n = 8 AE, n = 1 UE, p = 0.001). 36 patients (51,4%) showed significant disability according to EDSS; whereas 72,9% reported a significant neurological long-term sequela, including cognitive deficits (50,0%), depression (41,4%) and numbness (21,0%). Older age and abnormal MRI at onset were the strongest predictors of long-term severe sequelae. independently from the subtype of encephalitis.

Discussions Long-term sequelae are common in encephalitis, and are associated with MRI abnormalities, premorbid disability, and older age at onset. Further longitudinal studies are needed to focus on biological and clinical predictors, to identify patients who might benefit from cognitive and behavioral training after discharge.

Keywords Autoimmune encephalitis · Cognitive disorders in encephalitis · Neurological burden in encephalitis

Introduction

Encephalitis is an inflammatory condition of the brain which may recognize different etiologies. Despite the evidence pointing out a substantial similar prevalence of autoimmune and infectious encephalitis [5], viral forms still represent a major concern in this context (Venkatesan et al., 2013a). Although decreasing mortality rates have been recently reported for viral encephalitis, its 5–20% lethality still represent a major concern in acute setting. depending largely on the specific cause [9, 24]. Most of the available surveys and studies have evaluated short-term outcomes, especially in infectious and autoimmune disorders, whereas the long-term impact of encephalitis is still an important unexplored issue.

Feng and colleagues [6] described how low Glascow Coma Scale (GCS) scores, focal neurological deficits on admission, and a prolonged hospitalization are predictors

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of poor outcome at discharge in clinically diagnosed viral encephalitis, while Mailles and coauthors [16] highlighted that although according to Glasgow Outcome Scale most patients with encephalitis experienced a favorable outcome 3 years after hospital discharge, herpetic encephalitis continues to bear the most concerning and worrisome consequences. Since the definition by Graus [10], an emerging interest in autoimmune encephalitis has led to a better definition and management of encephalitis due to autoimmune abnormal response during the acute phases. Few works investigated the long-term outcomes of encephalitis, focusing on antiepileptic drugs [14, 22] or cognitive outcome [12], especially in anti-NMDAr and anti-LGI1 encephalitis.

However, little is known about long-term outcomes in survivors and whether biological markers may predict the degree of disability.

The aim of this study was to investigate the long-term outcome of different subtypes of encephalitis to define the neurological burden of the disease and the specific of sequelae associated with different encephalitis subtypes.

Methods

All patients discharged from the Neurology Unit of A.S.S.T Spedali Civili di Brescia between January 2011 and November 2022 with a diagnosis of encephalitis, were invited to participate in a follow-up study.

The case definition included any person aged > 18 admitted to hospital with altered mental status (defined as decreased or altered level of consciousness, lethargy or personality changes) lasting ≥ 24 h and the presence of two or more of the following criteria [26]: i) generalized or partial seizures not fully attributable to a pre-existing epilepsy ii) new-onset of focal neurologic findings iii) CSF white blood cell count ≥ 5/cubic mm3 iv) abnormality of brain parenchyma on neuroimaging suggestive of encephalitis that is either new to prior studies or appears acute in onset v) abnormality on electroencephalography consistent with encephalitis and not attributable to another cause.

Demographic information, clinical manifestations, laboratory findings, EEG, neuroimaging, treatment and outcomes were extracted from medical records using a standardized anonymized data collection form by physicians [19]. First-line testing included all commonly recognized causes of encephalitis according to current guidelines [10],Venkatesan et al., 2013b).

CSF viral screening included herpes simplex virus (HSV-1, HSV-2, HSV-6, HSV-8, CMV, Epstein-Barr virus, varicella zoster virus), adenovirus and enterovirus. Autoimmune encephalitis panel included antibodies against NMDAR, LGI1, CASPR2, GABAbR, AMPAR, DPPX, Ri, Yo, Ma2, CV2, Hu, amphiphysin, titin (Euroline and Mosaic kit, Euroimmun, Luebeck), MOG (live cell-based assay) and GFAP (fixed cell-based assay).

Brain MRI, standard EEG and CSF analyses were performed in all patients unless contraindicated by general medical conditions, modified Ranking Scale (mRS) was used to set premorbid conditions. Only patients with full data available for MRI, EEG and CSF were included in the final analyses.

After at least one year of follow-up data were collected via telemedicine, using a structured questionnaire evaluating the presence of neurological symptoms related to central, peripheral, myopathic and cognitive manifestations [19]. In case of persistence of a symptom, patients were asked to point out whether it occurred rarely or frequently. Three subgroups of patients were created, according to the burden of neurological sequelae, as having "mild" (0–1 symptom), "moderate" (2–3 symptoms) or "severe" (> 3 symptoms) neurological burden. Patients were classified according to the median value of in "favourable disability (D –EDSS score from 0 to 1,5)" or an "unfavourable EDSS (D –EDSS score higher than > 2)".

The Institutional Ethical Standards Committee on human experimentation at Brescia University Hospital provided approval for the study (NP 4067, approved 8 May 2020).

Statistical analysis

Differences in demographic and clinical characteristics and neurological complaints between AE, UE, and IE, were evaluated using Fisher's exact test or ANOVA with Bonferroni correction for dichotomic and continuous variables, respectively.

Univariate and multivariate analyses adjusted for age, sex and encephalitis subtypes were performed to evaluate the predictors of long-term sequelae.

Using ANOVA with Bonferroni correction for dichotomic and continuous variables we investigated any possible predictors of a more important neurological complaint. An adjusted risk ratio was calculated for each clinical predictor resulted significantly associated with long-term outcomes in univariate analyses.

Results

Out of 117 patients diagnosed as encephalitis, 3 deceased during the hospitalization (2 IE, 1 AE). Nine patients died after discharge during follow-up (2 IE, 3 UE, 4 AE). Of these, one case of AE and one case of IE were attributed to complications of encephalitis, while the remaining deaths were due to unrelated events such as oncology complication, or cardiac events. Therefore, we assessed

a total mortality rate of 12 patients (10.2%). Seventy out 105 survived patients underwent a clinical follow-up (mean 3.6 years after discharge) to assess long-term neurological status and disability, including 30 AE, 12 IE and 28 UE.

LGI-1 encephalitis was the most common AE affecting eight patients (pt; 26.67%), followed by NMDA-R (6 pt; 20,0%), ADEM (3pt, 10,0%) and SREAT (2 pt; 6,67%). For the IE subgroup, HSV-1 accounted for the 41,67% of patients, followed by enterovirus (2pt; 16,67%) and VZV (2pt; 16,67%). No other pathogen accounted for more than one case.

Patients who underwent follow-up were comparable in terms of severity, diagnosis distribution and clinical findings compared to the patients who refused the follow-up All patients were treated with different lines of therapy, according to the clinical suspicion: 46 patients (65,7%) received acyclovir, 37 (52,9%) received corticosteroids, 35 (50,0%) antibiotics 23 (32,9%) IVIG, 4 (5,7%) plasma exchange and 4 (5,7%) rituximab (Supplementary Table 1).

The encephalitis subgroups did not differ in terms of age, gender, and premorbid disability status, as defined by mRS. MRI alterations were more common in AE and IE encephalitis (Table 1). Nine patients showed a clinical relapse throughout the follow-up period, which were more frequent in the autoimmune subgroup (8 AE, 1 UE, p = 0.011).

At follow-up, 72,9% of patients reported at least one symptom, the most common being memory complaints (50%), depressive symptoms/anxiety (41,4%), numbness/tingling (30,0%) and sleep disorders (27,1%), followed by headache, vertigo, gait and balance disturbances and myalgia (Fig. 1). No significant differences were observed between the subgroups of encephalitis, concerning both cognitive and non-cognitive disturbances, except for sleep disturbances, more common in infectious disease (58% vs 20% of AE e 21% of UE) (Supplementary Table 2).

Thereafter, we compared the AE subgroup with IE and UE combined. Concerning symptoms persistence at long-term follow-up, headache and vertigo were more frequent in UE/IE than in AE (Supplementary Table 3).

The persistence of symptoms was compared according to MRI alterations and standard CSF biomarkers, using the median value of each of the investigated markers as point of separation (CSF-cell count, CSF-proteins, IgG count and Link index).

In T-Test for unpaired samples, no differences emerged comparing groups according to CSF proteins or cell counts.

In our analyses, the subgroup of encephalitis presenting with an altered MRI during hospitalization was significantly related to a higher risk of persistent gait disturbances (20,6% vs 0%: p = 0.003), myalgia (26,5% vs 8,3% p = 0.041) and balance disturbance (22,9% vs 5%; p = 0.030), when compared to the subgroup with a normal MRI (Supplementary Table 4).

As previously stated, we subdivided our patients according to the burden of neurological symptoms (Supplementary Table 5). The subgroup presenting with a more severe neurological involvement was significantly older (58,3 years ± 18,5; p = 0.002; Hazard Ratio (HR) 1,043) presented a worse premorbid mRS (HR 2,324) and more frequently associated with an altered MRI performed during hospitalization (68,2%; p = 0.020; HR 4,358) (Table 2).

The same analyses were performed for the most common symptoms presented, namely memory complaints. Patients who reported the persistence of these symptoms were older (55,46 years ± 19,84; p < 0.001) and exhibited a worse premorbid disability (mRS 0,50 ± 0,90; p = 0.038). Furthermore, this subgroup was more likely to report brain fog (10%, p = 0.003), depressive symptoms/anxiety (57,1%; p = 0.005), loss of independence (28,6%: p = 0.011), vertigo/dizziness (31,4%; p = 0.035), hyposmia/hypogeusia (17,1%; p = 0.042), urinary dysfunction (28,6%, p = 0.032), myalgia (28,6%; p = 0.027) (Supplementary Table 6). No significant correlation between memory complaints and any demographic variable was observed (Supplementary Table 7).

Table 1 Demographic and biochemical characteristics of patients according to encephalitis subtypes with follow-up. Abbreviations: UE: encephalitis of unknown origin; mRS: modified Rankin Scale

	Autoimmune (*n* = 30)	Infective (*n* = 12)	UE (*n* = 28)	*p**
Age at onset	45,99 ± 20,40	58,65 ± 19,97	43,41 ± 19,95	0,090
Sex, fem	17 (56,7%)	7 (58,3%)	17 (60,7%)	0,954
CSF proteins	657,11 ± 405,07	867,91 ± 597,71	614,18 ± 331,64	0,227
CSF cells	48,74 ± 68,12	86,27 ± 92,59	71,68 ± 103,07	0,431
CSF glucose	63,28 ± 14,84	60,45 ± 9,96	85,26 ± 102,27	0,422
Abnormal MRI	18 (60,0%)	7 (58,3%)	7 (25,0%)	**0,031**
Abnormal EEG	28 (93,3%)	11 (91,7%)	25 (89,3%)	0,617
Follow-up				
EDSS, mean	2,15 ± 2,11	2,38 ± 2,55	1,91 ± 1,73	0,790
Unfavourable EDSS	16 (53,3%)	5 (41,7%)	15 (53,6%)	0,699
Number of symptoms	3,17 ± 2,94	4,17 ± 2,69	3,54 ± 2,89	0,595

p values were calculated using ANOVA with Bonferroni correction. Bold indicates $p < 0.05$

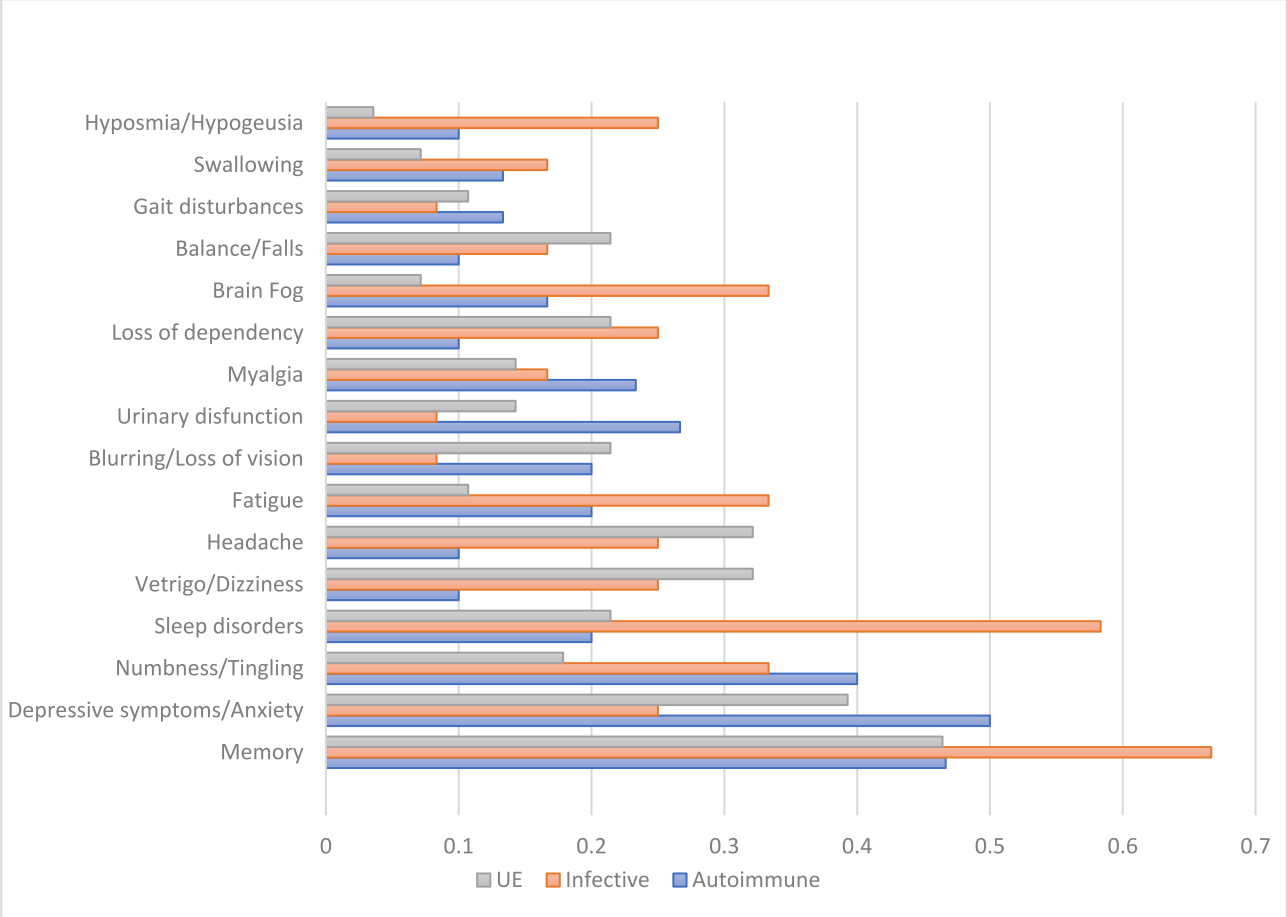

Fig. 1 Prevalence of symptoms per subtype of encephalitis. Abbreviations: UE: encephalitis of unknown origin

Table 2 Relation between demographic characteristics and risk of severe neurological sequelae (at least 4 symptoms). Abbreviations: HR: Hazard Ratio; MRI, magnetic Resonance Imaging; mRS, modified Ranking Scale

	HR	p
Age at Onset	1,043 (1,011–1,077)	0,008
Gender	1,068 (0,326–3,497)	0,914
mRS premorbid	2,324 (1,022–5,280)	0,044
Altered MRI	4,358 (1,174–16,129)	0,028
Undetermined encephalitis	0,424 (0,088–11,690)	0,364
Autoimmune encephalitis	1,556 (0,569–4,249)	0,389
Infectious encephalitis	0,487 (0,139–1,713)	0,262

Patients who presented an unfavorable EDSS at follow-up showed a worse premorbid mRS (0,79 ± 1,11; p = 0.008-Supplementary Table 8) and exhibited an altered MRI at the onset of disease (54,1% vs 32,4%; p = 0.020; HR 4,926, 95%-CI 1,362–17,857—Supplementary Table 9). This subgroup was more likely to report cognitive and non-cognitive complaints, such as memory disturbances (69,4% vs 29,4%; p = 0,004), depressive symptoms/anxiety (57,1% vs 26,5%; p = 0.014), sleep disorders (44,4% vs 8,8%; p = 0.011) and urinary disfunction (36,1% vs 0%; p = 0.001).

Discussion

The study findings underline the relevance of long-term neurological burden of encephalitis, regardless their etiology and resolution of acute phases. In addition to those twelve patients who did not survive the acute/post-acute phase (resulting in 10% of cumulative mortality rates), about two-third of the subjects included in the survey show the persistence of at least one neurological symptom, with about a third complaining about multiple symptoms with an evident burden in daily life after a mean follow-up duration of three and a half years.

Despite worse EDSS at discharge in AE, no evidence of a major symptomatic burden on a long-term follow-up emerged, exception made for a relevant higher risk of recurrent episodes in AE, as expected by the etiology [10].

Indeed, most recent studies were focused on neurological burden after specific subtypes of autoimmune encephalitis [21]. Halliday and coauthors found no association between treatment with second-line immunotherapy and lower disability levels in patients with AE, suggesting that the findings may also reflect the insensitivity of the EDSS to cognitive impairment at follow-up in patients with AE [11]. Misdiagnosis and diagnostic delay are relevant concerns in AE as they delay the start of suitable therapy which could account for the poorer outcome at discharge [7, 8]. However, the absence of a difference of disability burden in AE as compared to other encephalitis indicates that even after the complete resolution of the acute phase most AE patients did present symptoms with relevant impact on their activity and life.

The persistence of neurological sequelae in NMDAr encephalitis after discharge was previously assessed by Titulaer et al. [23], whose work provides evidence of how earlier treatment, increased use of second-line immunotherapy and tumor removal were associated with a lower rate of relapses and a minor neurological burden at follow up.

NMDAr encephalitis might occasionally represents a consequence of a previous herpetic encephalitis. In this specific subgroup the outcome at discharge is known to be worse, probably reflecting the persistency of clinical or subclinical neurological disturbances after the viral encephalitis. [3].

HSV encephalitis is associated with high mortality and long-term sequelae despite available therapy. Indeed, less than half of patients exhibit complete remission at 3 years follow-up [1].

A limited number of studies have evaluated outcomes in different functional neurological domains. However, there have been reports of cognitive decline in episodic and semantic memory, executive dysfunction and attention disorders. [15]. Furthermore, the subjective impact on activities of daily life remains an unexplored issue. Moreover, no predictive score for long-term clinical outcome has been developed.

Our study indicates a potential correlation between an unfavorable outcome and older age, premorbid disability, as well as altered MRI scan during hospitalization. The impact of older age and premorbid conditions and a wider number of short and long-term symptom is in line with the higher brain vulnerability at this age, impacting resilience in different ways and acute conditions, as recently demonstrated for Long-Covid syndrome [18].

The importance of MRI evidence is corroborated by earlier works, which indicate that a significant neuroradiological alteration may have a prognostic role in both viral [1] and autoimmune encephalitis [13], whereas some authors indicated atrophy in specific regions to be associated with higher risk of long-term burden (lizuka et al. 2016).

The lack of biological markers able to predict the neurological long-term burden is also of interest, whereas ongoing studies evaluating cerebrospinal fluid or even plasma markers of damage might help clinicians in selecting those people at higher risk of recurrent events but also long-term sequelae.

As expected, cognitive impairment, with particular attention to memory complaints, emerged as the most common symptom, consistent with prior research especially focused on specific subset of patients including anti-NMDAR [2, 12]. However, less is known about the whole spectrum of encephalitis. In our study, findings showed that patients presenting with memory complaints were older, highlighting again the importance of ageing and premorbid conditions as drivers of vulnerability and long-term deficits. An interesting difference we found was the increased sleep alterations in infectious encephalitis, although there is not currently evidence of persistence of these symptoms in viral encephalitis patients. Recent Covid outbreaks and the definition of SARS-CoV2 encephalitis and long-covid sequelae put on emphasis on sleep impairment [4]. Sleep impairment is a well-documented symptom of certain AE, such as anti IgLON-5 and anti-NMDAr, which is known to persist beyond the acute phase [17]. Nonetheless, the absence of anti IgLON5 patients in our cohort and the lack of altered sleep sequelae in our anti NMDAr patients potentially underestimated the impact of these in symptoms in the AE group. As such, it reasonable to assume that our findings may reflect a significant neurologic consequence in individual affected by viral encephalitis but further studies evaluating the potential confounders such as depressive conditions or cognitive impairment are necessary.

Although previous studies stated the insensitivity measures of disability such as EDSS to cognitive impairment at follow-up in patients with AE (Morrow et al., 2021), our work has found a higher prevalence of cognitive complaints in patients with worse disability. This may reflect, again, the heterogeneous alterations possibly related to encephalitis, including cognitive, motor, sensor and even other domains, which should be carefully screened and evaluated in clinical settings.

The study entails several limitations, including the single-center and observational design and the lack of in person re-evaluation of patients. The extensive assessment at baseline, including for all patients EEG, MRI and CSF, as well as the long-term follow-up and the inclusion of different subtypes of encephalitis are the major strength of the study, still needing further on-going validation.

In conclusion, findings highlighted that encephalitis is a life-threatening condition which is associated still with high mortality rates and with long-term poor outcome and support the view that a more extensive evaluation and follow-up for subjects with cognitive impairment is definitively

needed, as this subset of patients often claimed about different neurological symptoms, probably reflecting a more severe neurological burden. These findings provide further evidence for the need of long-term support and follow-up of subjects with encephalitis, regardless the etiology and the medical need of re-evaluation.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10072-024-07857-2.

Author contribution Davide Arici conceptualization, data curation, formal analysis, methodology, writing – original draft, Andrea Pilotto conceptualization, formal analysis, writing – review & editing, Giula Pedersoli data curation, Irene Volonghi data curation, writing – review & editing, Viviana Cristillo data curation, writing – review & editing, Enis Guso data curation, Francesco Castelli supervision, writing – review & editing, Alessandro Padovani conceptualization, supervision, writing – review & editing.

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Declarations

Ethical approval This study received approval from the ethical standards committee on human experimentation (local ethics committee of the ASST Spedali Civili Hospital, Brescia: NP 4067). All methods were carried out in accordance with relevant guidelines and regulations (Declaration of Helsinki).

Consent for publication Non Applicable.

Conflict of interests Davide Arici none, Andrea Pilotto served on the advisory board of Z-cube (technology division of Zambon pharmaceuticals); he received honoraria from Z-cube s.r.l., Biomarin, Zambon, Abbvie, Nutricia and Chiesi pharmaceuticals. He received research support from Vitaflo Germany and Zambon Italy, Giula Pedersoli none, Irene Volonghi none, Viviana Cristillo none, Enis Guso none, Francesco Castelli none, Alessandro Padovani is consultant and served on the scientific advi-sory board of GE Healthcare, Eli-Lilly and Actelion Ltd. Pharmaceuticals and received speaker honoraria from Nutricia, PIAM, Langstone Technology, GE Healthcare, Lilly, UCB Pharma and Chiesi Pharmaceuticals. He is funded by grant of the Ministry of University (MURST).

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