Intensive Care Med (2019) 45:1103–1111
https://doi.org/10.1007/s00134-019-05684-0

ORIGINAL

Functional outcomes in adult patients with herpes simplex encephalitis admitted to the ICU: a multicenter cohort study

P. Jaquet[1], E. de Montmollin[1,2], C. Dupuis[1,2], C. Sazio[3], M. Conrad[4], V. Susset[5], S. Demeret[6], J. M. Tadie[7], L. Argaud[8], F. Barbier[9], B. Sarton[10], R. Chabane[11], D. Daubin[12], N. Brulé[13], N. Lerolle[14], M. Alves[15], D. Da Silva[16], A. El Kalioubi[17], S. Silva[10], P. Bailly[18], M. Wolff[1], L. Bouadma[1,2], J. F. Timsit[1,2], R. Sonneville[1,19]* and ENCEPHALITICA study group

© 2019 Springer-Verlag GmbH Germany, part of Springer Nature

Abstract

Purpose: We aimed to study the association of body temperature and other admission factors with outcomes of herpes simplex encephalitis (HSE) adult patients requiring ICU admission.

Methods: We conducted a retrospective multicenter study on patients diagnosed with HSE in 47 ICUs in France, between 2007 and 2017. Fever was defined as a body temperature higher or equal to 38.3 °C. Multivariate logistic regression analysis was used to identify factors associated with poor outcome at 90 days, defined by a score of 3–6 (indicating moderate-to-severe disability or death) on the modified Rankin scale.

Results: Overall, 259 patients with a score on the Glasgow coma scale of 9 (6–12) and a body temperature of 38.7 (38.1–39.2) °C at admission were studied. At 90 days, 185 (71%) patients had a poor outcome, including 44 (17%) deaths. After adjusting for age, fever (OR = 2.21; 95% CI 1.18–4.16), mechanical ventilation (OR = 2.21; 95% CI 1.21–4.03), and MRI brain lesions > 3 lobes (OR = 3.04; 95% CI 1.35–6.81) were independently associated with poor outcome. By contrast, a direct ICU admission, as compared to initial admission to the hospital wards (i.e., indirect ICU admission), was protective (OR = 0.52; 95% CI 0.28–0.95). Sensitivity analyses performed after adjustment for functional status before admission and reason for ICU admission yielded similar results.

Conclusions: In HSE adult patients requiring ICU admission, several admission factors are associated with an increased risk of poor functional outcome. The identification of potentially modifiable factors, namely, elevated admission body temperature and indirect ICU admission, provides an opportunity for testing further intervention strategies.

Keywords: Encephalitis, Herpes simplex, Fever, Functional outcome, ICU

*Correspondence: romain.sonneville@aphp.fr
[1] Department of Intensive Care Medicine and Infectious Diseases, Bichat-Claude Bernard University Hospital, AP-HP, 46 Rue Henri Huchard, 75877 Paris Cedex, France
Full author information is available at the end of the article

ENCEPHALITICA study group members are listed in "Acknowledgements".

Springer

Introduction

Herpes simplex virus (HSV) remains the most frequent cause of sporadic acute encephalitis [1, 2]. When untreated, Herpes simplex encephalitis (HSE) carries extremely high mortality rates, with many survivors left with severe disability [3]. Use of high-dose intravenous acyclovir combined with early diagnosis allowed by HSV-1/2 polymerase chain reaction (PCR) and brain magnetic resonance imaging (MRI) have dramatically reduced mortality rates to 10% [4]. However, HSE remains a severe condition associated with significant disability in 29–43% of survivors [5, 6]. Recent studies suggest that up to 40–70% of HSE patients require admission to the intensive care unit (ICU) and close to 20% require mechanical ventilation [4–6]. However, predictors of functional outcome in patients requiring ICU admission have not been thoroughly investigated. Together with early initiation of intravenous acyclovir, ICU admission may be beneficial for detection and treatment of intracranial complications (i.e., raised intracranial pressure and seizures) and management of fever and other systemic complications [7]. Of note, the relationship between peak temperature at ICU admission and outcome of patients with meningitis or encephalitis remains controversial. In a recent study, increased temperature at admission was not associated with an increased risk of death [8].

The previous cohorts which aimed to investigate factors associated with outcome in HSE had limitations, including a single-center design, low sample size, and/or variability in inclusion criteria [5, 6, 9, 10]. In a recent population-based observational multicenter study, HSE patients were identified with positive cerebrospinal fluid (CSF) PCR [11], but not all patients fulfilled recently accepted standardized case definitions of the encephalitis consortium criteria [12]. Moreover, data on neurocritical care and outcomes of the most severe cases of HSE are limited. To date, only one single-center retrospective study focused on HSE cases admitted to the ICU [11].

In this large multicenter cohort study, we aimed to investigate the association of admission body temperature and other admission factors with outcomes of herpes simplex encephalitis (HSE) adult patients requiring ICU admission.

Take-home message

In HSE adult patients requiring ICU admission, several admission factors identify patients at risk for poor functional outcome. The identification of potentially modifiable factors, namely, elevated admission body temperature and indirect ICU admission, provides an opportunity for testing further intervention strategies.

Methods

Design

We conducted a multicenter retrospective study in 47 ICUs in France, between 2007 and 2017. Patients were screened through the PMSI database (Programme de Médicalisation des Systèmes d'Information) of each participating hospital, using the International Classification of Diseases (ICD)-9 code "054.3" and ICD-10 code "B00.4". All medical records were reviewed by investigators, including two neurointensivists (PJ, RS). The ethical committee of the French society of intensive care medicine (FICS) approved the study and waived the requirement for informed consent.

Patients

Patients were included if they fulfilled the two following criteria: (1) admission to the ICU with possible acute encephalitis and (2) a positive CSF PCR for HSV DNA during hospitalization. Possible acute encephalitis was defined as an acute change in mental status or behavior ≥ 24 h, with at least 2 of the following manifestations: fever within 72 h before or after presentation, generalized or partial seizures, new onset of focal neurological findings, lumbar puncture (LP) with CSF white blood cell count $\geq 5/mm^3$, neuroimaging, or EEG abnormalities suggestive of encephalitis [12]. Exclusion criteria were: (1) missing data on functional outcome at 90 days; (2) ICU length of stay less than 24 h; (3) multiple pathogen detection in the CSF; and (4) initial admission to the ICU in a foreign country.

Collected data

Patients' history, along with clinical, laboratory, neuroimaging, and brain electrophysiologic data were retrieved from medical records. Data on major initial events were collected, including date of first neurological symptoms, date of hospital admission, date of ICU admission, the start date of intravenous acyclovir, and reason for admission to the ICU. Type of ICU admission was defined as "direct" (from the Emergency Room or Emergency Medical Services) or "indirect" (after initial admission to the hospital wards). Functional status prior to ICU admission was graded by the modified Rankin scale (mRS) and the Knaus score (i.e., a scale used to describe baseline health status) [13, 14]. The Simplified Acute Physiology Score (SAPS II) [15] and the SOFA scores [16] were calculated within the first 24 h of admission. Mental status at baseline was graded using the Glasgow coma scale (GCS). Coma was defined as a GCS < 8 [17]. Immunodepression was defined as the use of long term (> 3 months) steroids, use of other immunosuppressant drugs, solid organ transplantation, solid tumor requiring chemotherapy in the last 5 years, hematologic malignancy

(regardless of time since diagnosis and received treatments) or AIDS. Body temperature measured at ICU admission was collected and fever was defined as a body temperature higher or equal to 38.3 °C [18]. Fever treatment was left at the discretion of treating physicians in each center, according to local practice protocols. Aspiration pneumonia was defined on the day of ICU admission in patients with greater risk of oropharyngeal aspiration (e.g., witnessed aspiration event, marked depressed level of consciousness and/or swallowing disorders) by the following criteria: (1) the presence of symptoms or signs suggestive of lower respiratory tract infection; (2) a new radiographic infiltrate compatible with pneumonia, predominating in the right lower lobe; and (3) the use of antibiotics. LP was defined as normal if leucocyte count was < 5/mm^3, and protein level < 0.5 g/L. For each patient, brain MRI reports were reviewed, and the number of cerebral lobes affected in both hemispheres was calculated.

Outcome

Two neurointensivists (PJ, RS) assessed functional outcomes by reviewing the medical charts and or by contacting the physician in charge of the patient. The outcome was graded at ICU discharge and 90 days after ICU admission using the modified Rankin scale (mRS) [14]. A systematic evaluation with key criteria was made, based on available follow-up consultation records and/or information given by physicians [19, 20]. A poor functional outcome at 90 days was defined by a score on the mRS of 3–6 (indicating moderate to severe disability or death) [6]. Patients who were discharged home with functional independence before day 90 were considered to have a good functional outcome at 90 days. Data on persistent cognitive changes (i.e., cognitive impairment, aphasia, or behavioral changes) mentioned in the medical records after ICU discharge were collected.

Statistical analysis

Patients' characteristics were described as counts and frequencies for categorical variables and median (interquartile range) for quantitative variables. Univariate comparisons between subgroups were performed using Fisher exact test for categorical variables and Wilcoxon rank sum test for continuous variables. Univariate and multivariate analyses were used to identify predictors of poor outcome at day 90. Log linearity of continuous variables was tested and, if necessary, variables were categorized according to clinically relevant cutoffs or at median values. Then, variables associated with the outcome in univariate analysis ($p < 0.1$) were entered into the multivariate model. Collinearity between variables and 2-by-2 interactions was tested. The final model was determined after a backward selection procedure. The magnitude of association with outcome was expressed as Odds ratio (OR) and 95% confidence intervals (95% CI). We performed internal validation by using a bootstrapping procedure, which was done by taking a large number of samples of the original one. This technique provides nearly unbiased estimates of the confidence intervals of the odds ratio (OR) of the independent covariates. An additional exploratory analysis according to body temperature quartiles was performed. Two sensitivity analyses were conducted with the reason for ICU admission and mRS before ICU admission added to the multivariate model. Missing data were imputed with the median and the mode for quantitative and qualitative variables, respectively. All tests were two-sided, and $p < 0.05$ was considered statistically significant. All analyses were performed using the SAS software, version 9.4 (SAS Institute Inc., Cary, North Carolina) and R, Version 3.5.2 (R Project for Statistical Computing, https://www.r-project.org).

Results

A total of 314 patients were identified in 47 centers through the PMSI database with a diagnosis of HSE. Among them, 20 did not fulfill at least one inclusion criterion, and 35 patients had to be excluded because of missing outcome data or another exclusion criterion. (Electronic supplemental material, Figure S1). The final cohort consisted of 259 patients [age 64 (54–73) years], of whom 132 (51%) were males. Encephalitis was caused by HSV type 1 in 205/215 (95%) patients. Overall, 49/256 (19%) patients were immunocompromised, 33/256 (13%) had chronic alcohol abuse and 245/257 (95%) had a good functional status before admission.

The time between first neurological symptoms and ICU admission was 2 (1–4) days. At ICU admission, the score on the GCS was 9 (6–12) and 89/243 (34%) were comatose. Ninety-two (36%) patients had convulsive seizures. Admission body temperature was 38.7 (38.1–39.2) °C and a body temperature higher or equal to 38.3 °C was observed in 165/241 (69%) cases. Overall, 72/258 (29%) patients had aspiration pneumonia and 166 (62%) required invasive mechanical ventilation (Table 1).

The time between first neurological symptoms and LP was 1 (0–3) days. Patients presented with moderately elevated CSF leucocyte counts [50 (12–140) cells/mm^3] with predominance of lymphocytes [86 (61–96) %] and mildly elevated protein levels [0.7 (0.5–1.1) g/L]. The initial LP was normal in 16 (6%) patients.

CT-scan studies performed at ICU admission showed abnormalities in 73/214 (34%) cases. Two hundred and twenty-five (87%) patients underwent brain MRI, with parenchymal lesions noted in 221/223 (98%) cases. The time between hospital admission and the first MRI

Table 1 Patients' characteristics at ICU admission

Variables	Total *n* = 259	mRS 0–2 *n* = 74	mRS 3–6 *n* = 185	*P* value
Demographics				
Age (years)	64 (54–73)	60 (44–69)	65 (57–75)	< 0.01
Male sex	132 (51)	38 (51)	94 (51)	0.94
Coexisting conditions				
Diabetes	36/256 (14)	7 (9)	29/182 (16)	0.18
Alcohol abuse	33/256 (13)	5 (7)	28/182 (15)	0.06
Epilepsy	9/257 (4)	3 (4)	6/183 (3)	0.76
Immunocompromised	49/256 (19)	10 (14)	39 (21)	0.16
Functional status before admission				
Knaus score A or B[a]	245/257 (95)	74 (100)	171/183 (93)	0.02
mRS > 2	13/257 (5)	1/74 (1)	12/183 (7)	0.08
Reason for ICU admission				
Altered mental status	128 (49.4)	36 (48.6)	92 (49.7)	0.06
Seizure	65 (25.1)	25 (33.8)	40 (21.6)	
Other[b]	66 (25.5)	13 (17.6)	53 (28.6)	
Clinical characteristics				
Glasgow coma scale				
Score[c]	9 (6–12)	10 (6–13)	8 (6–12)	0.11
< 8, indicating coma	89/243 (34)	22/72 (31)	67/171 (39)	0.11
Temperature				
Degrees (°C)[d]	38.7 (38.1–39.2)	38.4 (38–39)	38.9 (38.2–39.2)	0.02
≥ 38.3 °C, indicating fever	165/241 (69)	41/69 (60)	124/172 (72)	0.06
Convulsive seizures	92 (36)	28 (38)	64 (35)	0.62
Uncomplicated seizure(s)	66 (26)	20 (27)	46 (25)	
Status epilepticus	26 (10)	8 (11)	18 (10)	
Focal signs	68/258 (15)	11 (15)	57/184 (31)	< 0.01
Aspiration pneumonia	72/258 (29)	16 (22)	56/184 (30)	0.16
Invasive mechanical ventilation	166 (62)	35 (47)	131 (71)	< 0.01
CSF				
HSV 1 genotype	205/215 (95)	55/59 (93)	149/155 (96)	0.37
Leucocytes (/mm^3)[e]	50 (12–140)	83 (15–200)	42 (10–120)	0.08
Lymphocytes (%)[f]	86 (61–96)	80 (55–97)	87.8 (63.8–95)	0.65
Protein level (g/l)[g]	0.7 (0.5–1.1)	0.7 (0.5–1)	0.7 (0.5–1.3)	0.98
EEG				
Abnormal EEG	218/226 (96)	52/62 (92)	161/164 (98)	0.024
Brain imaging				
CT-scan performed	215/250 (83)	58/72 (78)	157/178 (85)	0.21
Abnormal CT-scan	73/214 (34)	21/58 (36)	52/156 (33)	0.69
MRI performed	225 (87)	67 (91)	158 (85)	0.27
Abnormal MRI	221/223 (98)	64/67 (96)	155/156 (99)	0.04
MRI brain lesions > 3 lobes[h]	60/214 (33)	9/64 (14)	51/150 (34)	<0.01
Initial management				
Time between onset of symptoms and ICU admission (days)[i]	2 (1–4)	2 (0–4)	2 (1–4)	0.45
Time between ICU admission and initiation of acyclovir (days)[j]	0 (0–1)	0 (0–1)	0 (0–1)	0.17
Direct ICU admission[k]	136/257 (53)	49 (66)	87/183 (48)	<0.01

Table 1 (continued)

Results expressed as median (quartiles) or numbers (%)

mRS modified Rankin Scale, *ICU* intensive care unit, *GCS* Glasgow Coma Scale, *SAPS* simplified acute physiology score, *CSF* cerebrospinal fluid, *HSV* herpes simplex virus, *EEG* electroencephalogram, *CT* computed tomography, *MRI* magnetic resonance imaging

[a] A good functional status prior admission was defined by a KNAUS score of A or B

[b] Mainly respiratory failure

[c] GCS was determined in 243 patients

[d] Temperature was determined in 241 patients

[e] Leukocyte count was determined in 245 patients

[f] Lymphocyte count was determined in 228 patients

[g] Protein level was determined in 219 patients

[h] The number of lobes involved on MRI was determined in 180 patients

[i] Time between onset of symptoms and ICU admission was determined in 253 patients

[j] Time between ICU admission and initiation of acyclovir was determined in 256 patients

[k] vs. initial admission to hospital wards

study and the time between ICU admission and the first MRI study were 3 (1–9) and 1 (0–7) days, respectively. Extensive lesions in more than three cerebral lobes were documented on MRI reports in 60/214 (33%) patients.

All patients received intravenous acyclovir for 21 (21–21) days, at an initial dose of 10 mg/kg/8 h for the first 24 h, secondarily adjusted to renal function. The time between hospital admission and acyclovir initiation and the time between ICU admission and acyclovir initiation were 1 (0–2) days and 0 (0–1) days, respectively. The time between the onset of neurological symptoms and acyclovir therapy was 2 (0–3) days.

EEG abnormalities (i.e., diffuse or focal slowing) were noted in 214/226 (96%) cases. Lateralized periodic discharges were noted in 66/223 (30%) patients, electrographic seizures in 29/225 (13%) patients, and triphasic waves in 23/223 (10%) patients.

Treatments during ICU stay are reported in Table 2. Overall, 177/258 (69%) patients required invasive mechanical ventilation, for a duration 10 (6–21) days and 40/258 (16%) patients required a tracheostomy. Forty-five/258 (17%) patients required vasopressors and 8/258 (3%) required renal replacement therapy. Intracranial pressure (ICP) monitoring and ICP-targeted therapies were used in less than 5% of cases.

Table 2 Treatments during ICU stay

Variables	Total *n* = 259	mRS 0–2 *n* = 74	mRS 3–6 *n* = 185	*P* value
Organ failure management				
Invasive mechanical ventilation	177/258 (69)	37 (50)	140/184 (76)	< 0.01
Tracheostomy	40/258 (16)	6 (8)	34/184 (18)	0.04
Renal replacement therapy	8/258 (3)	2 (3)	6/184 (3)	0.82
Vasopressors	45/258 (17)	12 (16)	33/184 (18)	0.76
Neurocritical care				
Anticonvulsant therapy	187/257 (73)	48/73 (66)	139/184 (75)	0.10
ICP monitoring	8/258 (3)	3 (4)	5/184 (3)	0.57
Antioedematous treatment	13/255 (5.3)	3/73 (4)	10/182 (5)	0.13
Osmotherapy[a]	7/255 (3)	0/73 (1)	7/182 (4)	
Steroids[b]	6/255 (2)	3/73 (4)	3/182 (2)	
Neurosurgery				
External ventricular drainage	1/258 (0.5)	0 (0)	1/184 (1)	0.53
Decompressive craniectomy	4/258 (2)	1 (1)	3/184 (2)	0.87

Results expressed as numbers (%)

mRS Simplified modified Rankin Scale, *ICU* intensive care unit, *ICP* intracranial pressure

[a] Mannitol or hypertonic saline solution

[b] Adjunctive steroids for management of raised intracranial pressure

At 90 days, 185 (71%) patients had a poor functional outcome, including 44 (17%) deaths.

Univariate analysis of factors associated with poor functional outcome is presented in the electronic supplemental material (Table S1). Variables associated with outcome in univariate analysis entered in the multivariate model were age, the reason for ICU admission, alcoholism, admission body temperature, invasive mechanical ventilation, MRI brain lesions >3 lobes, and direct ICU admission.

Multivariate analysis of factors associated with poor functional outcome is presented in Table 3.

After adjusting for age, admission body temperature ≥38.3 °C (OR = 2.21; 95% CI 1.18–4.16), invasive mechanical ventilation (OR = 2.21; 95% CI 1.21–4.03), and MRI brain lesions >3 lobes (OR = 3.04; 95% CI 1.35–6.81) were independently associated with poor outcome. By contrast, a direct ICU admission, as compared to initial admission to the hospital wards, was protective (OR = 0.52; 95% CI 0.28–0.95). Bootstrap confidence intervals are presented in the electronic supplemental material, Table S2. Distribution of the mRS scores according to independent predictors of poor outcome identified in the model is presented in Fig. 1. Among survivors, persistent cognitive impairment, aphasia, or behavioral changes were reported in 159/215 (84%) patients and persistent motor deficits in 53/215 (25%) patients.

When an exploratory analysis was performed according to temperature quartiles, only the third (OR = 2.95; 95% CI 1.29–6.76) and the fourth quartiles (OR = 3.07 95%CI 1.25–7.56) were independently associated with outcome (electronic supplemental material, Figure S1). Sensitivity analyses conducted with the reason for ICU admission and mRS before ICU admission added as covariables are described in the electronic supplemental material, Table S3 and Table S4, respectively. An alluvial diagram of mRS scores at ICU discharge and at 90 days is presented in the electronic supplemental material, Figure S3.

A table comparing directly vs. indirectly admitted patients is provided in the electronic supplemental material, Table S5. Indirectly admitted patients had more respiratory complications at admission, i.e., aspiration pneumonia and need for mechanical ventilation, than their counterparts.

Table 3 Multivariate analysis of factors associated with poor functional outcome (mRS > 2)

Variables	Odds ratio	95% CI	*P* value
Age, years			
< 50	1	–	0.03
≥ 50 and < 65	2.00	[0.92; 4.36]	–
≥ 65 and < 75	2.06	[0.89; 4.78]	–
≥ 75	4.81	[1.72; 13.5]	–
Body temperature ≥ 38.3 °C	2.21	[1.18; 4.16]	0.01
Invasive mechanical ventilation	2.21	[1.21; 4.03]	0.01
MRI brain lesions > 3 lobes	3.04	[1.35; 6.81]	<0.01
Direct ICU admission (versus initial admission to the hospital wards)	0.52	[0.28; 0.95]	0.03

The variables tested in multivariate analysis were: age, a direct ICU admission, the reason for ICU admission, Alcohol abuse, a body temperature ≥ 38.3 °C, more than 3 lobes on brain MRI, Invasive mechanical ventilation. The final model was obtained after a backward selection of the covariates. AUC for the model was 0.74

mRS modified Rankin Scale, *CI* confidence Interval; *ICU* Intensive Care Unit

Discussion

In this large multicenter study of 259 HSE adult patients requiring ICU admission, we found that a poor functional outcome (i.e., moderate-to-severe disability or death) at 90 days was observed in more than two-thirds of cases. We identified several demographic factors and medical characteristics associated with poor outcome, including potentially modifiable factors, namely, elevated admission body temperature and indirect ICU admission. Non-modifiable factors included older age, need for mechanical ventilation, and extensive lesions to more than three lobes on MRI.

In our study, we observed a high disability burden, with almost three out of four patients not reaching functional independence at 90 days, and persistent cognitive changes (i.e., cognitive impairment, aphasia, or behavioral changes) being noted in most survivors. Because we focused on the most severe cases of HSE admitted to the ICU, we observed a higher mortality rate (17%) than that reported in the previous studies conducted mainly in non-ICU settings, ranging from 5 to 16% [4–6, 11, 21–23].

We identified elevated admission body temperature as an independent predictor of poor functional outcome, with our exploratory analysis performed according to body temperature quartiles suggesting a "threshold" effect. Although fever is known to be a hallmark of acute encephalitis [12], this independent association has never been reported in HSE [24]. Recent French guidelines on acute encephalitis recommend fever control to achieve normothermia, irrespective of etiology or severity [25]. Unfortunately, data on fever time course and data on potential interventions to control fever during the ICU stay were not collected. Therefore, it remains unclear from our study whether fever control to achieve normothermia as part of the initial management of severe HSE is beneficial for patients.

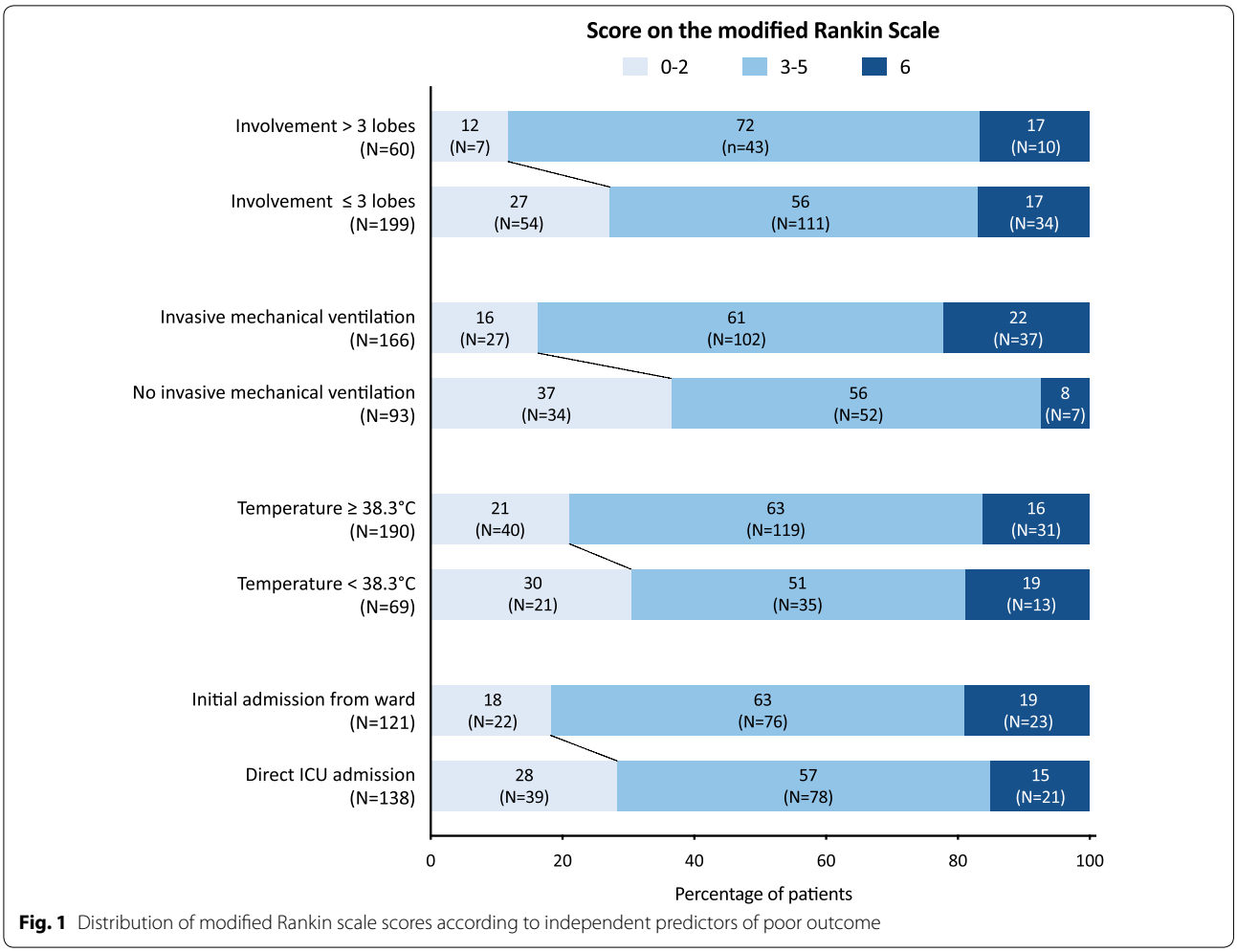

Fig. 1 Distribution of modified Rankin scale scores according to independent predictors of poor outcome

The association between direct ICU admission and outcome is consistent with previously published data on patients with all-cause encephalitis admitted to the ICU [26]. Of note, recent guidelines recommend early ICU admission for patients with all-cause encephalitis presenting with a score on the GCS inferior or equal to 13, seizure(s) and/or non-neurological organ failure [25]. We hypothesize that direct ICU admission, as compared to initial admission to the hospital wards, enables for faster diagnosis (i.e., CSF analysis, EEG, and brain MRI), early initiation of intravenous acyclovir, and management of major intracranial complications that are associated with outcome, i.e., cerebral edema, hydrocephalus, and refractory seizures [27, 28]. Moreover, ICU admission may facilitate the use of non-invasive neuromonitoring (e.g., continuous EEG) for detection of seizures. Interestingly, the use of invasive monitoring and ICP-targeted therapies was infrequent in our study, reflecting the current practice that most patients with encephalitis are managed in general ICUs [11].

Brain MRI is recommended for the management of patients with suspected encephalitis, irrespective of severity [12, 25]. It enables for faster diagnosis in atypical cases and may have a prognostic value. In line with a previous smaller study conducted in non-ICU patients with probable or confirmed HSE [29], our study shows that extensive brain lesions to more than three cerebral lobes on initial MRI were associated with a worse outcome. Another study reported that restricted diffusion on brain MRI portends poor outcome in HSE [6], but unfortunately, this information was not collected for the present study. Finally, mechanical ventilation at admission was also associated with outcome, likely simply reflecting the severity of patients included in our cohort [5].

Atypical clinical and biological findings were not infrequent in our study. Overall, 6% of patients presented with strictly normal CSF analysis (i.e., leucocyte count $<5/mm^3$ and proteins levels <0.5 g/L) at admission, suggesting that normal CSF analysis on the first LP does not rule out HSE diagnosis. Hence, acyclovir treatment

should not be discontinued until the results of a second CSF PCR for HSV. We also found in our study a higher prevalence of immunocompromised patients (19%) than that reported in other studies [1], suggesting that those patients have more severe presentation than their counterparts. It has been shown that these patients have atypical clinical presentation leading to a delay in diagnosis, and more extensive brain lesions that could explain higher morbidity and mortality [30].

Our study has limitations, including those inherent to its retrospective design. We collected functional outcome at 90 days with the use of the mRS based on the review of the medical charts and follow-up consultations, as a direct interview with patients or their relatives was not feasible. Moreover, the present study did not accurately evaluate patients for other important outcomes, including cognitive changes and post-encephalitic epilepsy. Finally, the primary outcome measure was performed at 90 days, which might be a too short timeframe for such a severe disease. Indeed, many patients may continue to improve after this period and an evaluation of longer term outcomes is warranted.

Conclusion

In HSE adult patients requiring ICU admission, several admission factors are associated with an increased risk of poor functional outcome. The identification of potentially modifiable factors, namely, elevated admission body temperature and indirect ICU admission, provides an opportunity for testing further intervention strategies.

Electronic supplementary material

The online version of this article (https://doi.org/10.1007/s00134-019-05684-0) contains supplementary material, which is available to authorized users.

Author details

[1] Department of Intensive Care Medicine and Infectious Diseases, Bichat-Claude Bernard University Hospital, AP-HP, 46 Rue Henri Huchard, 75877 Paris Cedex, France. [2] UMR 1137, IAME, Paris Diderot University, Paris, France. [3] Medical Intensive Care Unit, Bordeaux University Hospital, Bordeaux, France. [4] Medical Intensive Care Unit, Central Hospital, Nancy University Hospitals, Nancy, France. [5] Polyvalent Intensive Care Unit, Chambery Hospital, Chambery, France. [6] Neurologic Intensive Care Unit, Pitié–Salpêtrière University Hospital, AP-HP, Paris, France. [7] Medical Intensive Care Unit, Pontchaillou University Hospital, Rennes, France. [8] Medical Intensive Care Unit, Edouard Herriot University Hospital, Lyon, France. [9] Medical Intensive Care Unit, La Source Hospital, Orléans, France. [10] Intensive Care Unit, Purpan University Hospital, Toulouse, France. [11] Department of Perioperative Medicine, Clermont-Ferrand University Hospital, Clermont-Ferrand, France. [12] Medical Intensive Care Unit, Montpellier University Hospital, Montpellier, France. [13] Medical Intensive Care Unit, Nantes University Hospital, Nantes, France. [14] Medical Intensive Care Unit, CHU Angers, Angers University Hospital, Angers, France. [15] Polyvalent Intensive Care Unit, Poissy–Saint-Germain-en-Laye Hospital, Poissy, France. [16] Intensive Care Unit, Delafontaine Hospital, Saint-Denis, France. [17] Medical Intensive Care Unit, Roger Salengro University Hospital, Lille, France. [18] Medical Intensive Care Unit, La Cavale Blanche University Hospital, Brest, France. [19] UMR1148, LVTS, Sorbonne Paris Cité, Inserm/Paris Diderot University, Paris, France.

Acknowledgements

ENCEPHALITICA study group: Julien Marechal, M.D. (Medical Intensive Care Unit, Centre Hospitalier Universitaire de Poitiers, Poitiers, France). Bruno Mourvillier, M.D., (Medical Intensive Care Unit, CHU de Reims, Reims, France). Frederic Dailler, M.D., (Department of Anesthesiology and Intensive Care Medicine, Hôpital Pierre Wertheimer, Lyon, France). Fabrice Bruneel, M.D. (Medical Intensive Care Unit, André Mignot Hospital, Versailles, France). Alexandre Lautrette, M.D., Ph.D. (Medical Intensive Care Unit, Gabriel-Montpied University Hospital, Clermont-Ferrand, France). Emmanuel Novy, M.D. (Polyvalent Intensive Care Unit, Mercy Hospital CHR Metz-Thionville, Ars-Laquenexy, France). Bertrand Guidet, M.D. PhD. (Medical Intensive Care Unit, Hôpital Saint-Antoine, Paris, France). François Mateos, M.D. (Intensive care Unit, Centre hospitalier Saint-Brieuc, Saint-Brieuc, France). Clément Brault, M.D. (Department of Intensive Care Medicine, Amiens-Picardie University Hospital, Amiens, France). Quentin Maestraggi, M.D. (Medical Intensive Care Unit and UMR 1121, Hautepierre Hospital Strasbourg, France). Keyvan Razazi, M.D. (Medical Intensive Care Unit, hopitaux Universitaires Henri Mondor, Créteil, France). Jean-Pierre Quenot, M.D. (Medical Intensive Care Unit, Centre Hospitalo-Universitaire de Dijon, Dijon, France). Aurélie Joret, M.D. (Medical Intensive Care Unit, CHU de Caen, Caen, France). Albrice Levrat, M.D. (Intensive care unit, Centre Hospitalier Annecy-Genevois, Annecy, France). Alexandre Massri, M.D. (Intensive Care Unit, Centre Hospitalier Francois Mitterand Pau, France). Alexandre Robert, M.D. (Medical Intensive Care Unit, Hôpital de l'Archet 1, CHU de Nice, Nice, France). Damien Contou, M.D. (Polyvalent Intensive Care Unit, Centre Hospitalier Victor Dupouy, Argenteuil, France). Jean-Paul Mira, M.D. Ph.D. (Medical Intensive Care Unit, Cochin University Hospital, Paris, France). Gaudry Stephane, M.D., Ph.D. (Polyvalent Intensive Care Unit, Louis Mourier University Hospital, Colombes, France). Guillaume Voiriot, M.D., Ph.D. (Polyvalent Intensive Care Unit, Centre Hospitalier Universitaire Tenon, Paris, France). Asael Berger, M.D. (Intensive Care Unit, Centre Hospitalier de Haguenau, Haguenau, France). Vincent Das, M.D., Ph.D. (Medical-Surgical Intensive Care Unit, Centre Hospitalier Intercommunal André Grégoire, Montreuil, France). Nicolas Engrand, M.D. (Neurosurgical Intensive Care Unit, Fondation ophtalmologique Adolphe Rotschild, Paris, France. Martin Murgier, M.D. (Intensive care unit, Saint-Etienne University Hospital, Saint-Etienne, France). Shidasp Siami, M.D. (Polyvalent ICU, Centre Hospitalier Sud Essone Dourdan-Etampes-Siège, Etampes, France). Sami Hraiech, M.D., Ph.D. (Medical Intensive Care Unit, Aix-Marseille Universite, Hopital Nord, Marseille, France). Eric Mariotte, M.D. (Medical ICU, Saint-Louis Hospital, Paris, France). Claire Ragot, M.D. (Medical-Surgical ICU, Robert Boulin Hospital, Libourne, France). Annabelle Stoclin, M.D. (Intensive Care Unit, Institut Gustave Roussy, Villejuif, France). Pierre Trouiller, M.D. (Intensive Care Unit, Antoine Béclère Hospital, Clarmart, France). Mathieu Schmidt, M.D., Ph.D. (Medical Intensive Care Unit, Hôpital Pitié–Salpêtrière, AP-HP, Paris, France).

Compliance with ethical standards

Conflicts of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 16 April 2019 Accepted: 27 June 2019
Published online: 10 July 2019

References

1. Granerod J, Ambrose HE, Davies NW et al (2010) Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. Lancet Infect Dis 10:835–844
2. Mailles A, De Broucker T, Costanzo P et al (2012) Long-term outcome of patients presenting with acute infectious encephalitis of various causes in France. Clin Infect Dis 54:1455–1464
3. Whitley RJ, Soong SJ, Dolin R et al (1977) Adenine arabinoside therapy of biopsy-proved herpes simplex encephalitis. National Institute of Allergy and Infectious Diseases collaborative antiviral study. N Engl J Med 297:289–294

4. Modi S, Mahajan A, Dharaiya D et al (2017) Burden of herpes simplex virus encephalitis in the United States. J Neurol 264(6):1204–1208
5. Raschilas F, Wolff M, Delatour F et al (2002) Outcome of and prognostic factors for herpes simplex encephalitis in adult patients: results of a multicenter study. Clin Infect Dis 35:254–260
6. Singh TD, Fugate JE, Hocker S et al (2016) Predictors of outcome in HSV encephalitis. J Neurol 263:277–289
7. Wijdicks EFM, Menon DK, Smith M (2015) Ten things you need to know to practice neurological critical care. Intensive Care Med 41:318–321
8. Saxena M, Young P, Pilcher D et al (2015) Early temperature and mortality in critically ill patients with acute neurological diseases: trauma and stroke differ from infection. Intensive Care Med 41:823–832
9. Poissy J, Wolff M, Dewilde A et al (2009) Factors associated with delay to acyclovir administration in 184 patients with herpes simplex virus encephalitis. Clin Microbiol Infect 15:560–564
10. Poissy J, Champenois K, Dewilde A et al (2012) Impact of Herpes simplex virus load and red blood cells in cerebrospinal fluid upon herpes simplex meningo-encephalitis outcome. BMC Infect Dis 12:356
11. Jouan Y, Grammatico-Guillon L, Espitalier F et al (2015) Long-term outcome of severe herpes simplex encephalitis: a population-based observational study. Crit Care 19:345
12. Venkatesan A, Tunkel AR, Bloch KC et al (2013) Case definitions, diagnostic algorithms, and priorities in encephalitis: consensus statement of the international encephalitis consortium. Clin Infect Dis 57:1114–1128
13. Knaus WA, Zimmerman JE, Wagner DP et al (1981) APACHE-acute physiology and chronic health evaluation: a physiologically based classification system. Crit Care Med 9:591–597
14. Van Swieten JC, Koudstaal PJ, Visser MC et al (1988) Interobserver agreement for the assessment of handicap in stroke patients. Stroke 19:604–607
15. Le Gall JR, Lemeshow S, Saulnier F (1993) A new simplified acute physiology score (SAPS II) based on a European/North American multicenter study. JAMA 270:2957–2963
16. Vincent JL, Moreno R, Takala J et al (1996) The SOFA (sepsis-related organ failure assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on sepsis-related problems of the European society of intensive care medicine. Intensive Care Med 22:707–710
17. van de Beek D, de Gans J, Spanjaard L et al (2004) Clinical features and prognostic factors in adults with bacterial meningitis. N Engl J Med 351:1849–1859
18. O'Grady NP, Barie PS, Bartlett JG et al (2008) Guidelines for evaluation of new fever in critically ill adult patients: 2008 update from the American College of Critical Care Medicine and the Infectious Diseases Society of America. Crit Care Med 36:1330–1349
19. Bruno A, Shah N, Lin C et al (2010) Improving modified Rankin Scale assessment with a simplified questionnaire. Stroke 41:1048–1050
20. Bruno A, Akinwuntan AE, Lin C et al (2011) Simplified modified rankin scale questionnaire: reproducibility over the telephone and validation with quality of life. Stroke 42:2276–2279
21. Stahl JP, Mailles A, De Broucker T, Steering Committee and Investigators Group (2012) Herpes simplex encephalitis and management of acyclovir in encephalitis patients in France. Epidemiol Infect 140:372–381
22. Riancho J, Delgado-Alvarado M, Sedano MJ et al (2013) Herpes simplex encephalitis: clinical presentation, neurological sequelae and new prognostic factors. Ten years of experience. Neurol Sci 34:1879–1881
23. Cag Y, Erdem H, Leib S et al (2016) Managing atypical and typical herpetic central nervous system infections: results of a multinational study. Clin Microbiol Infect 22:568.e9–568.e17
24. Chow FC, Glaser CA, Sheriff H et al (2015) Use of clinical and neuroimaging characteristics to distinguish temporal lobe herpes simplex encephalitis from its mimics. Clin Infect Dis 60:1377–1383
25. Stahl JP, Azouvi P, Bruneel F et al (2017) Guidelines on the management of infectious encephalitis in adults. Med Mal Infect 47:179–194
26. Sonneville R, Gault N, de Montmollin E et al (2015) Clinical spectrum and outcomes of patients with encephalitis requiring intensive care. Eur J Neurol 22(1):6–16
27. Thakur KT, Motta M, Asemota AO et al (2013) Predictors of outcome in acute encephalitis. Neurology 81:793–800
28. Sonneville R, Mariotte E, Neuville M et al (2016) Early-onset status epilepticus in patients with acute encephalitis. Medicine (Baltimore) 95:e4092
29. Sili U, Kaya A, Mert A, HSV Encephalitis Study Group (2014) Herpes simplex virus encephalitis: clinical manifestations, diagnosis and outcome in 106 adult patients. J Clin Virol 60:112–118
30. Tan IL, McArthur JC, Venkatesan A, Nath A (2012) Atypical manifestations and poor outcome of herpes simplex encephalitis in the immunocompromised. Neurology 79:2125–2132