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Results of a Multinational Study Suggest the Need for Rapid Diagnosis and Early Antiviral Treatment at the Onset of Herpetic Meningoencephalitis

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Data in the literature regarding the factors that predict unfavorable outcomes in adult herpetic meningoencephalitis (HME) cases are scarce. We conducted a multicenter study in order to provide insights into the predictors of HME outcomes, with special emphasis on the use and timing of antiviral treatment. Samples from 501 patients with molecular confirmation from cerebrospinal fluid were included from 35 referral centers in 10 countries. Four hundred thirty-eight patients were found to be eligible for the analysis. Overall, 232 (52.9%) patients experienced unfavorable outcomes, 44 died, and 188 survived, with sequelae. Age (odds ratio [OR], 1.04; 95% confidence interval [CI], 1.02 to 1.05), Glasgow Coma Scale score (OR, 0.84; 95% CI, 0.77 to 0.93), and symptomatic periods of 2 to 7 days (OR, 1.80; 95% CI, 1.16 to 2.79) and >7 days (OR, 3.75; 95% CI, 1.72 to 8.15) until the commencement of treatment predicted unfavorable outcomes. The outcome in HME patients is related to a combination of therapeutic and host factors. This study suggests that rapid diagnosis and early administration of antiviral treatment in HME patients are keys to a favorable outcome.

Encephalitis due to herpes simplex virus (HSV) is the most frequent form of sporadic fatal encephalitis in the world and accounts for 10 to 20% of all viral encephalitis cases worldwide (1–3). The annual incidence for herpetic meningoencephalitis (HME) is around 0.2 to 0.4 adults per 100,000 (4). In addition, patients with HME experience exceedingly high unfavorable outcomes, including death and long-term sequelae, despite treatment (5–8).

Previous studies (9, 10) have assessed outcomes, in particular by comparing the efficacies of herpetic antiviral drugs. To the best of our knowledge, data thoroughly assessing the predictors of unfavorable outcome in HME patients do not exist in the literature. One more potential limitation of the studies published was that they included cases without virological confirmation (11–13), thus blurring the inferences made. Hence, in this multinational study, we included only HME patients with a definite virological diagnosis. Consequently, our study makes use of data from the largest case series ever reported in the literature to determine the predictors of unfavorable outcome in HME.

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MATERIALS AND METHODS

Study design. This retrospective multicenter study included hospitalized patients from referral centers in 10 countries (Croatia, the Czech Republic, Denmark, Egypt, France, Iraq, Italy, Lebanon, Slovenia, and Turkey) between 2000 and 2013. Only adult patients (>15 years of age) with HME were included. No control groups were included for this study. The institutional review board of the Dr. Lütfi Kırdar Training and Research Hospital in Istanbul, Turkey, approved the study, which was exempt from the requirement for informed patient consent.

The inclusion criteria comprised both of the following: (i) positive cerebrospinal fluid (CSF)-PCR result for herpes simplex virus 1 (HSV-1), HSV-2, or both in a patient with meningoencephalitis and (ii) the unlikely presence of any other infectious disease of the brain.

Definitions. Meningoencephalitis was defined as a clinical, radiological, and/or laboratory presentation compatible with encephalitis (3, 8, 14) and meningitis (1, 15). The clinical findings related to encephalitis mainly included changes in consciousness and/or language, behavioral abnormalities, memory impairment, and seizures. The magnetic resonance imaging, electrophysiological studies, and/or CSF analysis data were used to provide clues regarding the encephalitic component of the disease (3). Meningitis was identified by the presence of an abnormal number of leukocytes in the CSF, along with compatible clinical findings, like fever, headache, meningism, cranial nerve palsies, or altered consciousness (16). Unfavorable outcome was defined as patients who died of HME or survived with sequelae. New-onset convulsion was defined as a convulsion observed between the onset of symptoms and the start of antiviral treatment for HME. Immunosuppression was defined as a patient who was under a long-term steroid treatment or had a disease(s) causing immunosuppression, such as malignancy, autoimmune disease, or diabetes. Motor symptoms were defined as locomotor deficiency, paresis, tetraparesis, hemiparesis, quadriparesis, quadriplegia, spasticity, left foot drop, or disrupted motoric skills.

Statistical analysis. Statistics were done using the software package Stata 13.1 (StataCorp, TX, USA). In the univariate analysis, categorical variables were compared by Pearson's chi-square test and where applicable by Fisher's exact test. Continuous variables were compared by Student's *t* test or by the Wilcoxon rank-sum test, depending on the normality assumption for which the Shapiro-Wilk and Shapiro-Francia tests were used.

A total of 3% (15/438) of the observations were missing. The pattern of missingness indicated this as "missing completely at random." Therefore, missing observations were not filled via a multiple imputation procedure.

A binary logistic regression model was constructed via a bootstrap resampling procedure described in detail elsewhere (17). Briefly, the data set was replaced by resampling 200 times during the logistic regression analysis of the full model, consisting of all potential variables. Eventually, variables with frequencies of >30% of the bootstrapped data sets with a 0.1 significance threshold were included in the final model. The final model was tested with logistic regression, including all possible interaction terms. Colinearity was also tested and eliminated.

RESULTS

In this study, data from 501 HME patients were submitted from 35 referral centers in 10 countries (Turkey [*n* = 144], Denmark [*n* = 127], France [*n* = 64], Slovenia [*n* = 54], Croatia [*n* = 32], Iraq [*n* = 30], the Czech Republic [*n* = 23], Italy [*n* = 12], Lebanon [*n* = 8], and Egypt [*n* = 7]). Sixty-three patients were excluded, due to either missing critical data or the absence of molecular confirmation, leaving 438 patients eligible for outcome analysis. HSV-1/2 PCR was found to be positive in 105 patients. HSV-1 DNA was positive in 300 cases, and HSV-2 DNA was positive in 79 cases. A brain biopsy was not performed in any of the patients. In this study, 375 (85.6%) patients received intravenous aciclovir, and in

TABLE 1 Baseline characteristics

Variable	Data ^a
Age (mean ± SD) (yr)	50.58 ± 18.27
Gender	
Women	226 (51.6)
Men	212 (48.4)
Elapsed time between OS & AVT (days) ^b	
≤2	195 (44.5)
>2 and ≤7	191 (43.6)
>7	47 (10.7)
Missing data	5 (1.1)
Glasgow Coma Scale score (median [IQR])	14 (13–15)
New-onset convulsion ^c	
No	343 (78.3)
Yes	91 (20.8)
Missing data	4 (0.9)
Immunosuppression ^d	
No	379 (86.5)
Yes	59 (13.5)
Outcome	
Favorable	206 (47.0)
Unfavorable	232 (53.0)
Died	44 (10.0)
Survived with severe sequela(e)	188 (42.9)

^a Values are no. (%) of patients, unless otherwise indicated. Total *n* = 438.

^b Elapsed time between onset of symptoms (OS) and the start of antiviral treatment (AVT).

^c Defined as a convulsion observed before therapy.

^d Defined as long-term steroid use or other immunosuppressive state.

53 (12.1%) cases, oral valaciclovir was given following intravenous aciclovir treatment. Nine cases were treated with valaciclovir. Finally, one case received intravenous ganciclovir following intravenous aciclovir. The mean ± standard deviation (SD) treatment duration of the aciclovir-only arm was 21.6 ± 12.3 days, while valaciclovir alone was given for a mean ± SD of 10.3 ± 4.6 days. In the group receiving intravenous aciclovir followed by oral valaciclovir, the drugs were given for 15.5 ± 10.7 and 32.7 ± 18.9 days, respectively. The mean ± SD dose of intravenous aciclovir was 36.7 ± 5.7 mg/kg of body weight/day. In this study, 232 (52.9%) patients experienced unfavorable outcomes. Forty-four HME patients died, and 188 survivors of the disease had experienced sequelae at the end of antiviral treatment. Overall, there were 313 disorders attributed to HME in 188 patients with sequelae. Memory disorder (*n* = 62), behavioral disorders (*n* = 55), speech impairment (*n* = 53), motor symptoms (*n* = 40), epilepsy (*n* = 34), cognitive impairment (*n* = 29), headache (*n* = 13), psychiatric disorders (*n* = 10), balance disorder (*n* = 6), and visual disturbances (*n* = 5) were the frequent unfavorable outcomes. Tinnitus, sleeping disorder, coma, autoimmune encephalitis, neurogenic bladder, and autonomy loss were seen in a single case each.

The baseline characteristics of the study group are presented in Table 1. Briefly, the study group consisted of patients with a mean

TABLE 2 Comparison of variables among patients with favorable and unfavorable outcomes

Variable	Data for outcome of ^a :		P value
	Favorable	Unfavorable	
Age (mean ± SD) (yr)	44.50 ± 16.80	55.97 ± 17.86	<0.001
Gender			0.005
Women	121 (58.7)	105 (45.3)	
Men	85 (41.3)	127 (54.7)	
Elapsed time between OS & AVT (days) ^b			<0.001
≤2	113 (55.7)	82 (35.7)	
>2 and ≤7	78 (38.4)	113 (49.1)	
>7	12 (5.9)	35 (15.2)	
Glasgow Coma Scale score (mean ± SD)	13.80 ± 2.15	12.57 ± 3.05	<0.001
New-onset convulsion ^c	31 (15.1)	60 (26.2)	0.005
Immunosuppression ^d	24 (11.7)	35 (15.1)	0.29

^a Values are no. (%) of patients, unless otherwise indicated.
^b Elapsed time between onset of symptoms (OS) and the start of antiviral treatment (AVT).
^c Defined as a convulsion observed before therapy.
^d Defined as long-term steroid use or other immunosuppressive state.

(± SD) age of 50.6 (± 18.3) years, and 48.4% (212/438) were of the male gender. Almost half of the patients (44.5% [195/438]) received antiviral treatment during the first 2 days after the onset of symptoms. The median elapsed time between the onset of symptoms and antiviral treatment was 3 days (interquartile range [IQR], 1 to 5 days). In this study, 10% (44/438) died, while 42.9% (188/438) survived with severe sequelae. A univariate comparison of the variables between the patients with favorable and unfavorable outcomes is presented in Table 2. Age, male gender, longer time gap between the onset of symptoms and antiviral treatment, lower Glasgow Coma Scale (GCS) scores, and convulsion were significantly different in the patients with unfavorable outcomes compared to those in the patients with favorable outcomes. Among these, however, only age, GCS score, and time to antiviral treatment were included in the final model (Table 3).

This multivariate model found that a delay in establishing an effective antiviral treatment significantly increases the risk of unfavorable outcome. Accordingly, a delay of >7 days causes a significant increase in unfavorable outcome among patients. This is documented by the multivariate model, in which the odds ratio for a delay in the onset of aciclovir treatment of >7 days being 3.75 (95% confidence interval [CI], 1.72 to 8.15) and that for 2 to 7 days being 1.80 (95% CI, 1.16 to 2.79) are significant, whereas the odds ratio for ≤2 days being 0.48 (95% CI, 0.32 to 0.74; P = 0.001) is protective (estimates made by univariate logistic regression).

The predicted percentages of unfavorable outcome versus elapsed time since the onset of symptoms are presented in Fig. 1, where unfavorable outcome increases from 0.44 to 0.71 depending on the delay in establishing an effective antiviral treatment. The observed outcomes against the predicted outcomes estimated by the logistic regression analysis were in perfect agreement (Fig. 2).

The multivariate model documented that age and GCS score

TABLE 3 Final model, including independent predictors of unfavorable outcome

Variable	OR ^a	95% CI		P
		Low	High	
Age (yr)	1.04	1.02	1.05	0.000
Glasgow Coma Scale score	0.84	0.77	0.93	0.000
Elapsed time (days) ^b				
>2 and ≤7	1.80	1.16	2.79	0.009
>7	3.75	1.72	8.15	0.001

^a OR, odds ratio.
^b Elapsed time between onset of symptoms and administration of antiviral treatment.

independently predict unfavorable outcome. The relationship between these and outcome is shown in Fig. 3. Briefly, unfavorable outcome was more frequent with increasing age, at >80% among the geriatric patients. An interaction between age and male gender was also found, indicating that elderly males experienced more unfavorable outcomes. Lower GCS scores were found to be associated with more unfavorable outcome, at >80% in patients with scores lower than five.

DISCUSSION

There are a number of published reports with relatively small case series assessing unfavorable outcome in HME. Advanced age (10, 18, 19), lower GCS score (10), greater extent of brain involvement (20, 21), low serum albumin level (18), longer duration of disease (20), delayed aciclovir use (18, 19, 21–24), the presence of red blood cells in the CSF (19), and immunosuppression (24) have been found to be associated with poorer outcomes in HME. In this study, we detected that a combination of therapeutic and host factors contributed to the outcomes in HME patients. Advancing age, delayed start of antivirals, and worsening of consciousness determined by the GCS contributed to the development of unfavorable outcomes in these patients. In a relatively large study by Raschilas (22), higher Simplified Acute Physiology Score II and a delay in the initiation of antiviral therapy were associated with

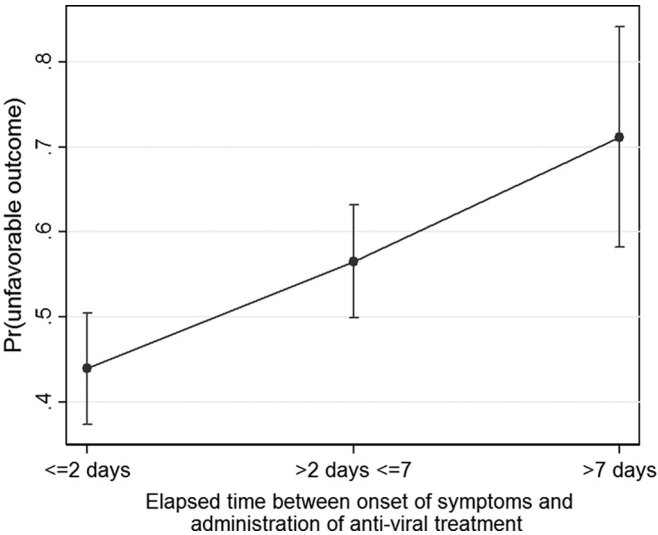


FIG 1 Predictions (Pr, probability) of antiviral treatment timing for unfavorable outcome. The data are presented as the mean values with the 95% CI.

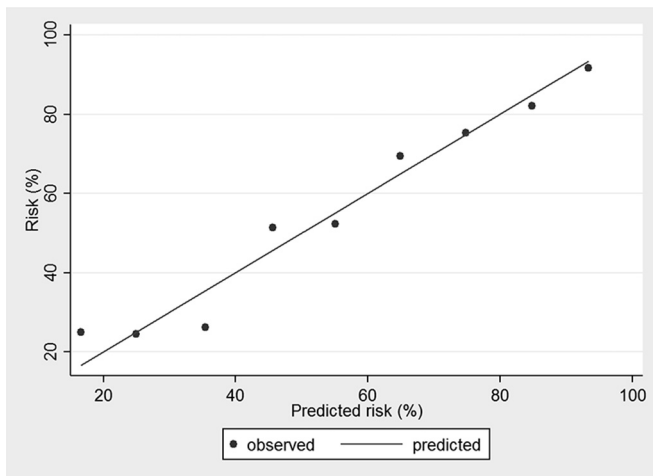


FIG 2 Observed outcomes against predicted outcomes estimated by the model.

poor prognosis. These results are quite in accordance with those of this study. On the other hand, the data in the literature related to the efficacy of treatment in HSV-2 meningitis are rather unclear (25, 26). The host parameters directly affect the course of central nervous system (CNS) infections. In different types of CNS infections, increasing age and lower GCS scores have long been known to be associated with poor outcomes (27–29). Our HME data were also in accordance with those regarding other infectious CNS disorders and with the initial reports of adult HME series (10, 18, 19).

According to our results, patients with a GCS score of less than five experienced unfavorable outcome more frequently. Added to that, older males were more likely than were others to have unfavorable outcomes from HME. Convulsions are also believed to occur in patients with poor outcomes (30). In this study, we did not determine a significant relationship between new-onset convulsions and poor outcome in HME patients.

In daily medical practice, the use of aciclovir at standard dosages has been reported to be of paramount importance in HME patients (1, 3, 8). However, the importance of the optimal timing of aciclovir administration in the improvement of outcomes has been unclear. Added to that, the benefit of the empirical use of aciclovir in patients with a likely diagnosis of encephalitis, rather than in those with confirmed HSV encephalitis, has not yet been proven in a randomized controlled clinical trial (1). In a previous study (31), 17 out of 24 (71%) of patients with suspected encephalitis did not receive empirical aciclovir in the emergency department but rather after inpatient admission (median time, 16 h; 95% CI, 7.5 to 44 h). In this study, three of five confirmed HSV encephalitis cases were not given aciclovir in the emergency department (31). In a large previous study (22), a mean \pm SD delay of 5.5 ± 2.9 days elapsed between the onset of symptoms and the initiation of antiviral treatment. These data indicate that an early start to antiviral treatment in HME patients is not likely. This study suggests that aciclovir administered within the first 2 days after the onset of symptoms significantly contributed to better outcomes. The goal of empirical antiviral treatment is to improve the prognoses in patients who are ultimately proven to have HME. Thus, suspected encephalitis patients should urgently be given

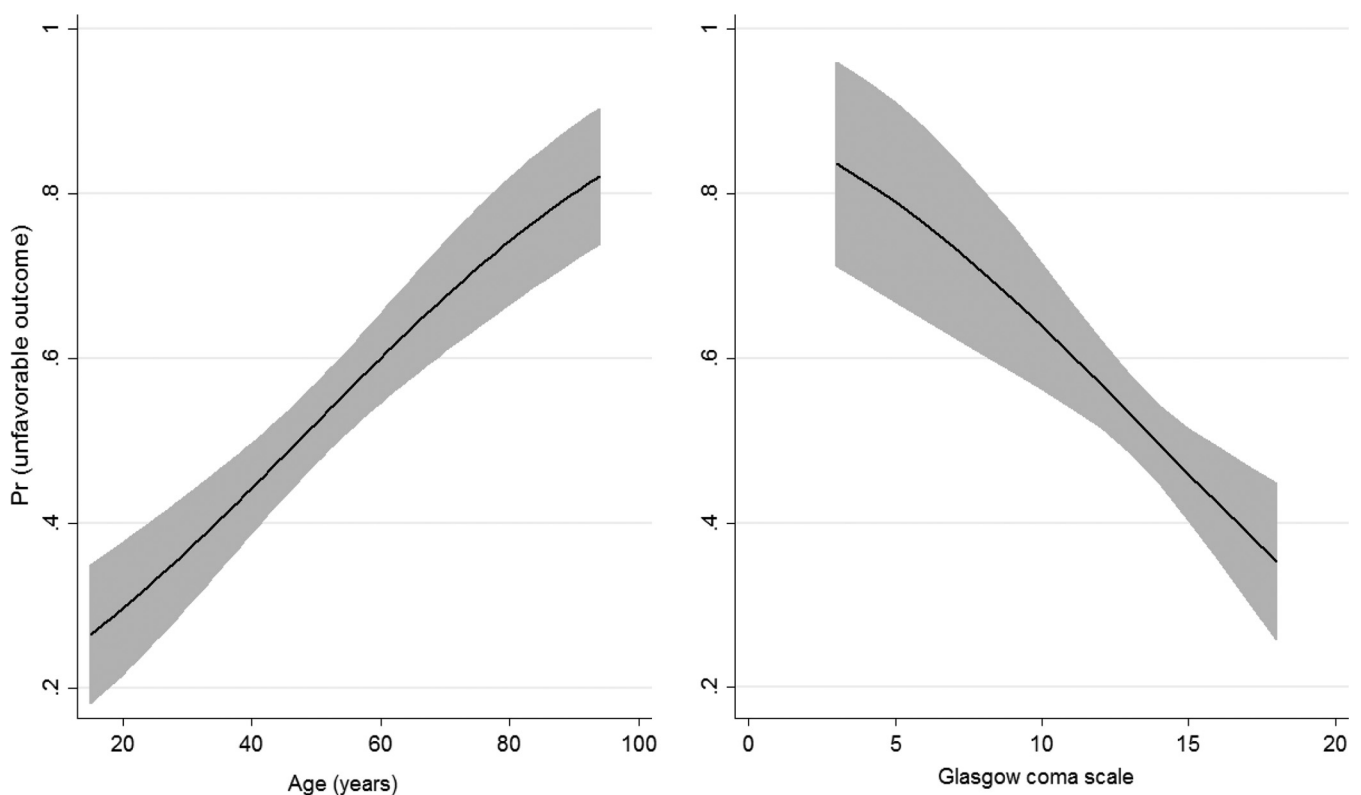


FIG 3 Predictive margins of age and Glasgow Coma Scale score on unfavorable outcome. The data are presented as the mean values with the 95% CI.

antiviral treatment when the results of diagnostic studies are pending.

Although it would be very difficult to prospectively provide such a large cohort, the major limitation of this study is its retrospective design. The discrimination between pure meningitis and pure encephalitis is very difficult in a retrospective study, since they have been known to be two interrelated syndromes with quite similar clinical presentations; thus, we cautiously erred in favor of not discriminating between these two diseases. On the other hand, the major problem was the microbiological confirmation of HSV cases due to diagnostic difficulties in previous studies (32, 33). Since PCR testing in the CSF has an overall sensitivity and specificity of >95% with HME (8), we view the inclusion of only CSF-PCR-positive cases to be a strength of the study. Added to that, the predicted and observed probabilities of the final model in this study were in perfect agreement.

In conclusion, the outcome in HME patients is directly related to both therapeutic and host factors. Host factors, like age, gender, unconsciousness, and seizures, detected during initial evaluation, as well as coexistent immunosuppressive conditions, may not be preventable for the treating clinician. However, the major concerns should be both the rapid diagnosis and early start to antiviral treatment in either suspected or proven HME cases.

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