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RESULTS OF A MULTINATIONAL STUDY SUGGESTS RAPID DIAGNOSIS AND EARLY ONSET OF ANTIVIRAL TREATMENT IN HERPETIC MENINGOENCEPHALITIS

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ABSTRACT

Data regarding factors predicting unfavorable outcomes in adult herpetic meningoencephalitis (HME) cases is scarce in the literature. We conducted a multicenter study to provide insights into the predictors of outcome with special emphasis to use and timing of antivirals. Overall, 501 patients with molecular confirmation from the cerebrospinal fluid were included from 35 referral centers in 10 countries. Overall, 438 patients were found to be eligible for the analysis. Finally, 232 (52.9%) patients experienced unfavorable outcomes; 44 died and 188 survived with sequlae. Age (OR 1.04, 95% CIs 1.02-1.05), Glasgow coma scale (OR 0.84, 95% CIs 0.77-0.93), symptomatic period of 2-7 days (OR 1.80, 95% CIs 1.16-2.79) and over seven days (OR 3.75, 95% CIs 1.72-8.15) until treatment commenced, 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 favorable outcome.

INTRODUCTION

Encephalitis due to Herpes Simplex Virus (HSV) is the most frequent form of sporadic fatal encephalitis in the world and accounts for 10-20% of all viral encephalitis worldwide (1-3). The annual incidence for herpetic meningoencephalitis (HME) per 100.000 isaround 0.2-0.4 in adults (4). In addition, HME cases experience exceedingly high unfavorable outcomes including death and long term sequelae despite treatment (5-8).

There were studies assessing the outcomes particularly by comparing the efficacies of herpetic antiviral drugs in the past (9, 10). To the best of our knowledge, data assessing thoroughly 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. Hence, in this multinational study we included HME patients solely with definite virological diagnosis. Consequently, our study makes use of the largest case series ever reported in the literature to provide data for the predictors of unfavorable outcome in HME.

METHODS AND MATERIALS

Study design

This retrospective multicenter study included hospitalized patients from referral centers in 10 countries (Croatia, Czech Republic, Denmark, Egypt, France, Iraq, Italy, Lebanon, Slovenia, and Turkey) between 2000 and 2013. Only the adult patients with HME over the age of 15 were included. No control groups were included for this study. Dr. Lütfi Kirdar Training and Research Hospital's Review Board in Istanbul approved the study and informed consent was exempt.

The inclusion criteria comprised the presence of all of the following:

1. Positive CSF-PCR result for HSV-1 or HSV-2 or both in a patient with meningoencephalitis.
2. The unlikely presence of any other infectious disease of the brain.

Definitions

Meningoencephalitis: The clinical and/or radiological and/or laboratory presentation compatible with encephalitis (3, 8, 14) and meningitis (1, 15). The clinical findings related to encephalitis mainly included alterations in conscious, language and behavioral abnormalities, memory impairment, and seizures. The magnetic resonance imaging and/or electrophysiological studies and/or CSF analysis were used to provide clues of the encephalitic component of the disease (3). Meningitis was identified by the presence of abnormal number of leucocytes in the CSF along with compatible clinical findings like fever, headache, meningism, cranial nerve palsies, or altered consciousness (16).

Unfavorable outcome: Patients who died of HME or survived with sequelae.

New onset convulsion: Convulsion observed between the onset of symptoms and the start of antiviral treatment for HME.

Immunosuppression: If the patient was under a long-term steroid treatment or had diseases causing immunosuppression such as malignity, autoimmune disease or diabetes, she or he was classified in this category.

Motor symptoms: Locomotor deficiency, paresis, tetraparesis, hemiparesis, quadriparesis, quadriplegia, spasticity, left foot drop or disrupted motoric skills.

Statistical analysis

Statistics were done on the software package, Stata 13.1 (StataCorp Texas, USA). In univariate analysis; categorical variables were compared by Pearson's chi-squared test and where applicable by Fisher's exact test. Continuous variables were compared by Student's t-

test or by Wilcoxon rank-sum test depending on the normality assumption for which Shapiro-Wilk and Shapiro-Francia tests were used.

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

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

RESULTS

In this study, 501 HME patients' data was 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), Czech Republic (n=23), Italy (n=12), Lebanon (n=8), Egypt (n=7)]. Sixty-three patients were excluded either due to missing critical data or for 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 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 53 (12.1%) cases oral valaciclovir was given sequential to intravenous aciclovir treatment. Nine cases were treated with valaciclovir. Finally, one case received intravenous ganciclovir sequential to intravenous aciclovir. The mean treatment duration of aciclovir alone arm was 21.6 ±12.3 days while

valaciclovir alone was given for a mean of 10.3±4.6 days. In intravenous aciclovir followed by oral valaciclovir group, the drugs were given 15.5±10.7 and 32.7±18.9 days respectively. The mean dose of intravenous aciclovir was 36.7± 5.7 mg/kg/day. In this study, 232 (52.9%) patients experienced unfavorable outcomes. Forty-four HME patients died and 188 survivors of the disease have 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 reasons of unfavorable outcome in descending order. Tinnitus, sleeping disorder, coma, autoimmune encephalitis, neurogenic bladder, and autonomy loss were seen in single cases.

Baseline characteristics of the study group are presented in table 1. Briefly study group consisted of patients with a mean age of 50.6 (± 18.3) years and 48.4% (212/438) was male gender. Almost half of the patients (44.5%; 195/438) received anti-viral treatment during the first two days after the onset of symptoms. The median of elapsed time between the onset of symptoms and antiviral treatment was 3 days (IQR 1, 5). In this study, 10% (44/438) died while 42.9% (188/438) survived with severe sequelae. Univariate comparison of variables between patients with favorable and unfavorable outcomes is presented in table 2. Age, male gender, longer time gap between onset of symptoms and anti-viral treatment, lower Glasgow coma scale (GCS) scores and convulsion were significantly different in patients with unfavorable 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 delay in establishing an effective anti-viral treatment significantly increases unfavorable outcome. Accordingly, delay of more than seven days causes a significant increase of unfavorable outcome among patients.

This is documented by the multivariate model, where odds ratio for delay in onset of aciclovir of more than seven days is 3.75 (95% CIs 1.72-8.15) and two to seven days is 1.80(95% CIs 1.16-2.79) are significant whereas odds ratio of less than or equal to two days is 0.48 (95% Cl, 0.32-0.74; p-value, 0.001) is protective (estimates by univariate logistic regression).

Predicted percentages of unfavorable outcome versus elapsed time since the onset of symptoms are presented in figure 1, where unfavorable outcome increases from 0.44 to 0.71 depending on the delay in establishing an effective anti-viral treatment. Observed outcomes against predicted outcomes estimated by the logistic were in perfect agreement (Figure 2).

The multivariate model documented that age and GCS independently predicts unfavorable outcome. The relation between these and the outcome is shown in Figure 3. Briefly unfavorable outcome is more frequent among older patients exceeding 80% among geriatric patients. On the other hand an interaction between age and male gender was found indicating that elderly males experience more unfavorable outcomes. Lower GCS scores were found with more unfavorable outcome exceeding 80% in patients with scores lower than five.

DISCUSSION

There are a number of published reports with relatively small case series in the literature assessing unfavorable outcome in HME. Advanced age (10, 18, 19), lower GCS (10), extent of brain involvement (20, 21), low serum albumin level (18), duration of disease (20), delayed aciclovir use (18, 19, 21-24), presence of red blood cells in 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 outcomes in HME patients. Advancing age, delayed start of antivirals, and worsening of conscious determined with GCS contributed to the development of unfavorable outcomes in

these patients. In a relatively large study by Raschilas, higher Simplified Acute Physiology Score II and delay in initiation of antiviral therapy were associated with poor prognosis. These results are quite in accordance with this study. On the other hand, the data related to the efficacy of treatment in HSV-2 meningitis is rather unclear in the literature (25, 26).The host parameters directly affect the course of central nervous system (CNS) infections. In different types of CNS infections, age and lower GCS scores have long been known to have poor outcomes (27-29). Our HME data were also in accordance with the other infectious CNS disorders and with the initial reports of adult HME series (10, 18, 19). According to our results, patients with GCS score of less than five experienced unfavorable outcome more frequently. Added to that, older males were more likely to have unfavorable outcomes from HME. On the other hand, convulsions are believed to occur in patients with poor outcomes (30). In this study, we could not disclose a significant relation between new onset convulsions and poor outcome in HME patients.

In daily medical practice the use of aciclovir in standard dosages has been reported to be of paramount importance in HME patients (1, 3, 8). But, the optimum timing of aciclovir administration has been unclear in improving outcomes. Added to that, the benefit of empirical use of aciclovir in patients with a likely diagnosis of encephalitis, rather than those with confirmed HSV encephalitis, has not been proven yet in a randomized controlled clinical trial (1). In a study 17 out of 24 (71 %) of patients with suspected encephalitis did not receive empirical aciclovir in the emergency department, but after inpatient admission (median time 16 hours; 95% CI, 7.5 to 44 hours). In this study, three of five confirmed HSV encephalitis were not given aciclovir in the emergency department (31). On the other hand, in a large study a mean delay of 5.5 ± 2.9 days elapsed between the onset of symptoms and initiation of antiviral treatment (22). These data indicate that the early start of antiviral treatment is not likely in HME patients. This study suggests that aciclovir administered within the first two

days after the onset of symptoms significantly contributed to better outcomes. The goal of empirical antiviral treatment is to improve prognosis in patients who are ultimately proven to have HME. Thus, suspected encephalitis patients should be urgently given antiviral treatment when the results of diagnostic studies are pending.

Although it would be very difficult to provide such a large cohort prospectively, the major limitation of this study is its' retrospective design. The discrimination of pure meningitis and pure encephalitis was very difficult in a retrospective study since they have been known to be two interrelated syndromes with quite a similar clinical presentation and thus, we cautiously favored not to discriminate these two entities. 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 more than 95% in 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 were in perfect agreement in this study.

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, and coexistent immunosuppressive conditions may not be preventable for the treating clinician. However, the major concerns should be the both rapid diagnosis and the early start of antiviral treatment either in suspected or proven HME cases.

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388 **FIGURE LEGENDS**

389 **Figure 1.** Predictions of anti-viral treatment timing for unfavorable outcome (mean, 95% CIs)

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391 **Figure 2.** Observed outcomes against predicted outcomes estimated by the model

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393 **Figure 3.** Predictive margins of "Age" and "Glasgow coma scale (mean, 95% CIs)

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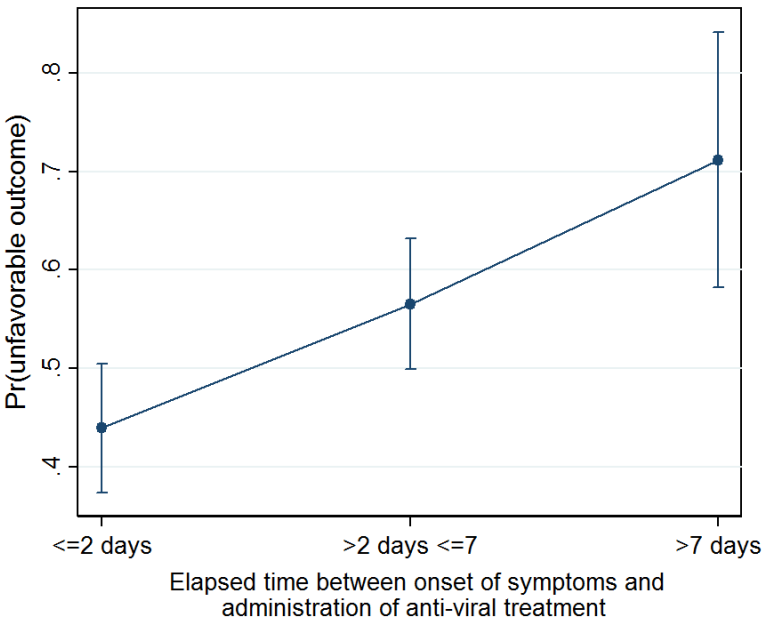

Figure 1. Predictive margins with 95% confidence intervals of "elapsed time between onset of symptoms and the start of anti-viral treatment" to unfavorable outcome

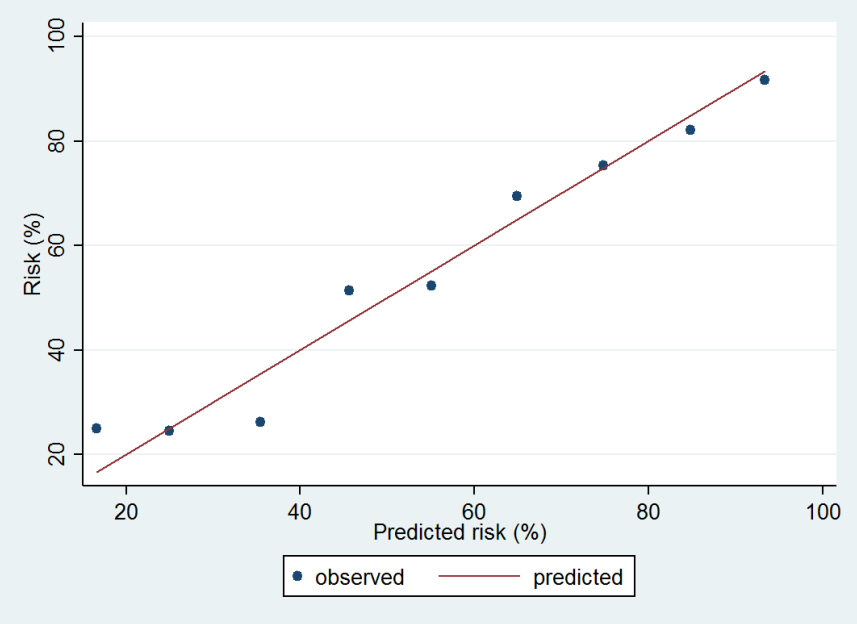

Figure 2. Observed outcomes against predicted outcomes estimated by the model

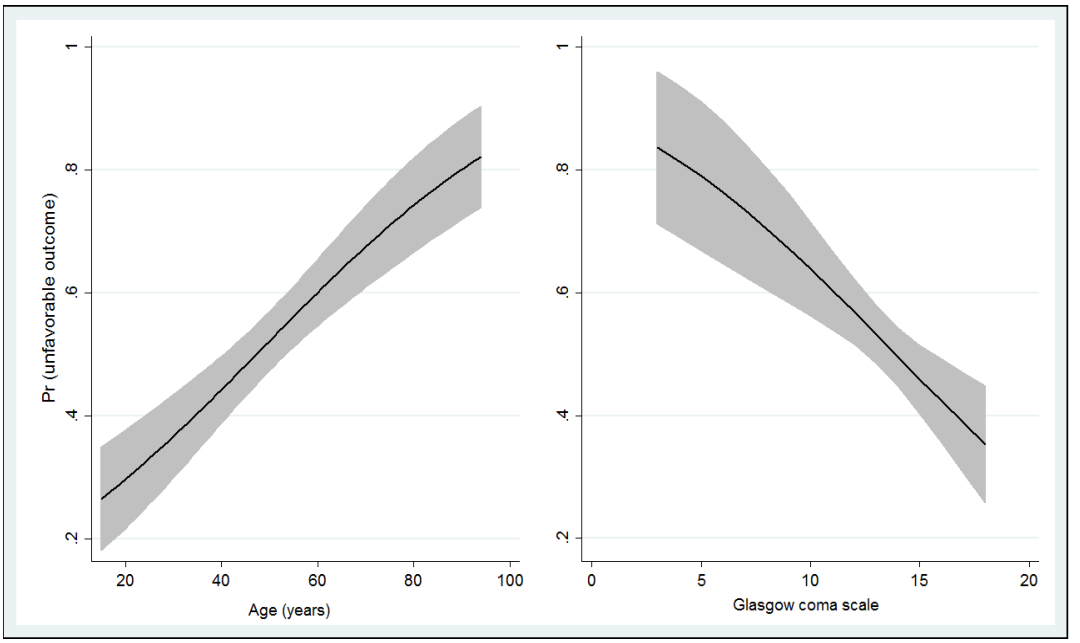

Figure 3. Predictive margins of "Age" and "Glasgow coma scale (mean, 95% CIs)

Table 1. Baseline characteristics

Variables	Value (n=438)
Age (years), mean +/- SD	50.58+/-18.27[a]
Gender	
Women	226 (51.6%)
Man	212 (48.4%)
Elapsed time between OS & AVT [b]	
<=2 days	195 (44.5%)
2>days<=7	191 (43.6%)
>7 days	47 (10.7%)
Missing data	5 (1.1%)
Glasgow coma scale, 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 sequel	188 (42.9%)

[a] n=438
[b] Elapsed time between onset of symptoms and the start of anti-viral treatment
[c] Convulsion observed before therapy
[d] Long term steroid use or other immunosuppressive state

Table 2. Comparison of variables among patients with favorable and unfavorable outcomes

	Outcome		
	Favorable (n=206)	Unfavorable (n=232)	*p*-value
Age (years), mean +/- SD	44.50+/-16.80[a]	55.97+/-17.86	<0.001
Gender			0.005
Women	121 (58.7%)	105 (45.3%)	
Man	85 (41.3%)	127 (54.7%)	
Elapsed time between OS & AVT [b]			<0.001
<=2 days	113 (55.7%)	82 (35.7%)	
>2 days <=7	78 (38.4%)	113 (49.1%)	
>7 days	12 (5.9%)	35 (15.2%)	
Glasgow coma scale, mean+/-SD	13.80+/-2.15[e]	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] n=206 vs n=232 for favorable and unfavorable outcome patients respectively
[b] Elapsed time between onset of symptoms and administration of anti-viral treatment
[c] Convulsion observed before hospital admission
[d] Long term steroid use or other immunosuppressive state

Table 3. Final model including independent predictors of unfavorable outcome

		95% CIs		
	OR [a]	Low	High	*p*
Age (years)	1.04	1.02	1.05	0.000
Glasgow coma scale	0.84	0.77	0.93	0.000
Elapsed time [b]				
>2 days ≤7 days	1.80	1.16	2.79	0.009
>7 days	3.75	1.72	8.15	0.001

[a] OR, odds ratio
[b] Elapsed time between onset of symptoms and administration of anti-viral treatment