Clinical Microbiology and Infection 23 (2017) 421–422

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Letter to the Editor

Managing atypical and typical herpetic central nervous system infections: results of a multinational study – Authors' reply

We have read the letter by S. Keske and O. Ergonul and welcome this opportunity to further detail the methodologies in our two herpetic meningoencephalitis (HME) articles, which used the same database established by the data of participating centres from 10 countries. The first article [1], published in *Antimicrobial Agents and Chemotherapy* (AAC), provided an outcome analysis, and by its nature, it focused on parameters that could affect HME patients' outcomes. Although it did not principally target therapeutic approaches, early initiation of antiviral therapy was one of the parameters that affected outcome. The second article [2], published in *Clinical Microbiology and Infection* (CMI), was not a diagnosis article. By means of clinical and laboratory analysis of HME cases, we provided a management algorithm as a flowchart; the analysis was descriptive.

Although herpes simplex virus PCR positivity was a must in this study, data of five cases without molecular confirmation were erroneously submitted by the participating centres. In both analyses [1,2], we excluded these five cases. Added to that, we excluded 58 more cases with missing critical data for our outcome analysis [1]. As an example, although the absence of Glasgow Coma Scale data is one of the parameters leading to exclusion in these 58 cases in the AAC article [1], we used their clinical and laboratory data in the CMI article [2]. In short, the numbers in both articles are reliable.

We did not divide patients as 'encephalitis' or 'nonencephalitis' patients in the CMI article. Rather, we divided them as patients with 'encephalitis presentation' or 'nonencephalitis presentation' on the basis of admission to hospital findings. We believe that this point was the most critical one in our study. That is, when the magnetic resonance imaging (MRI) and EEG findings were taken into consideration for patients classified into the 'nonencephalitis presentation' category, they were most likely to be true encephalitis cases, but without overt symptoms of encephalitis. Similarly, the timing of laboratory data in the article such as C-reactive protein belonged to hospital admission data.

To address the concerns of our colleagues regarding our molecular methodology, we have detailed the PCR methodology in Table 1. However, we did specify the PCR methodology in the 'Molecular Analysis' subsection of the CMI article [2]. The major reason for the unknown PCR methodology in 129 patients (26%) was that the participants in this study underwent PCR long ago, and they did not recall the PCR methodology. However, the PCR data were recorded as positive in hospital records. As the organizers of the study, we tended to accept these cases previously diagnosed on a molecular basis, and who were treated as HME at the participant centres. This was our preference, and this was disclosed in the articles. In addition, only 56 cases (11.3%) were cured in the year 2005 or before. Hence, most of our cases were diagnosed after the year 2005, as they indicated as the time point for diagnostic improvement.

The use of antiviral therapy in our HME patients was detailed in both articles. The principal aim of the CMI article with a management algorithm [2] was to inform the examining clinician that a HME patient may present to hospital with pure meningitis and without overt encephalitis findings. Thus, we recommended that both EEG and MRI should be applied to all probable central nervous system (CNS) infection patients to exclude encephalitis. Hence, our algorithm recommending the concordant use of MRI and EEG provides insight into when to stop or continue antiviral therapy in probable HME cases. All these comments and their reasons were detailed in depth in the article [2].

The use of radiologic tests, computed tomography (CT; 79%) and MRI (67%) were criticized by Keske and Ergonul, who indicated the lesser use of MRI. In fact, these patients are evaluated as a having a CNS infection of an undetermined type at hospital admission in routine medical practice; the examining clinician may prefer CT if MRI was not feasible. This was likely related to the capacities of the participating hospitals during the long (13 years) study period. Although MRI resulted in more positive findings than CT in our article [2], the aim of our study was not to compare CT and MRI in HME cases. This was beyond the scope of our article, and there is much information regarding this topic in the literature.

Table 1
PCR methodologies used in patients according to clinical presentation

PCR method	Encephalitis presentation	Nonencephalitis presentation
Real time PCR	261 (68.86%)	104 (88.9%)
Nested PCR	2 (0.52)	—
Methodology unknown	116 (30.6%)	13 (11.1%)
Total	379	117

DOIs of original article: http://dx.doi.org/10.1016/j.cmi.2016.12.012, http://dx.doi.org/10.1016/j.cmi.2016.03.027.

http://dx.doi.org/10.1016/j.cmi.2017.01.016

HME is rare, and finding an affected cohort to study is difficult. As Keske and Ergonul indicate, only a few proven HME cases occur annually in hospitalized patients, even in large institutions. We thus took advantage of the large HME database provided by participating centres from 10 countries when we drew our conclusions.

Transparency Declaration

Both authors report no conflicts of interest relevant to this article.

References

[1] Erdem H, Cag Y, Ozturk-Engin D, Defres S, Kaya S, Larsen L, et al. Results of a multinational study suggest the need for rapid diagnosis and early antiviral treatment at the onset of herpetic meningoencephalitis. Antimicrob Agents Chemother 2015;59:3084–9.

[2] Cag Y, Erdem H, Leib S, Defres S, Kaya S, Larsen L, et al. Managing atypical and typical herpetic central nervous system infections: results of a multinational study. Clin Microbiol Infect 2016;22:568e9–568e17.

H. Erdem*
Infectious Diseases International Research Initiative (ID-IRI), Ankara, Turkey

Y. Cag
Department of Infectious Diseases and Clinical Microbiology, Istanbul Medeniyet University, Goztepe Training and Research Hospital, Istanbul, Turkey

* Corresponding author. H. Erdem.

16 December 2016
Available online 29 January 2017

Editor: M. Paul