ORIGINAL ARTICLE

Managing atypical and typical herpetic central nervous system infections: results of a multinational study

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Abstract

There have been many studies pertaining to the management of herpetic meningoencephalitis (HME), but the majority of them have focussed on virologically unconfirmed cases or included only small sample sizes. We have conducted a multicentre study aimed at providing

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management strategies for HME. Overall, 501 adult patients with PCR-proven HME were included retrospectively from 35 referral centres in 10 countries; 496 patients were found to be eligible for the analysis. Cerebrospinal fluid (CSF) analysis using a PCR assay yielded herpes simplex virus (HSV)-1 DNA in 351 patients (70.8%), HSV-2 DNA in 83 patients (16.7%) and undefined HSV DNA type in 62 patients (12.5%). A total of 379 patients (76.4%) had at least one of the specified characteristics of encephalitis, and we placed these patients into the encephalitis presentation group. The remaining 117 patients (23.6%) had none of these findings, and these patients were placed in the nonencephalitis presentation group. Abnormalities suggestive of encephalitis were detected in magnetic resonance imaging (MRI) in 83.9% of the patients and in electroencephalography (EEG) in 91.0% of patients in the encephalitis presentation group. In the nonencephalitis presentation group, MRI and EEG data were suggestive of encephalitis in 33.3 and 61.9% of patients, respectively. However, the concomitant use of MRI and EEG indicated encephalitis in 96.3 and 87.5% of the cases with and without encephalitic clinical presentation, respectively. Considering the subtle nature of HME, CSF HSV PCR, EEG and MRI data should be collected for all patients with a central nervous system infection.

Keywords: Atypical presentation, encephalitis, herpes simplex virus, managing, meningitis
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Introduction

Herpetic meningoencephalitis (HME) is a rare but devastating infectious disease with a mortality rate of up to 70% in the absence of appropriate treatment [1]. Despite rapid diagnostic tests and antiviral therapies, HME is still associated with high rates of mortality and serious sequelae [2–6]. The most important parameters influencing a favourable clinical course are rapid diagnosis and early antiviral therapy initiated within 2 days of the onset of symptoms [6]. Current guidelines recommend the use of acyclovir in proven or suspected cases of encephalitis [7]. However, the question of what constitutes suspected encephalitis is unclear for the majority of cases in routine practice because the symptoms of meningitis and encephalitis generally overlap at the initial stages of both diseases [8,9]. As a result, a significant fraction of cases cannot be classified as suspected meningitis or suspected encephalitis by the examining clinician. Accordingly, the clinician may not predict a herpetic central nervous system (CNS) infection and may delay antiviral therapy. There are a large number of studies devoted to the management of HME, but most of them involve virologically unconfirmed cases, have small sample sizes or are literature reviews [4,10–17].

The goals of this retrospective, multicentre, multinational study included identifying the characteristic features of HME, determining the performance of diagnostic tests for the disease and developing an algorithm for an optimal clinical approach to reach the diagnosis of HME.

Materials and methods

Study design

This retrospective multicentre study was approved by the review board of the Dr Lütfi Kirdar Training and Research Hospital, Istanbul, Turkey.

The predictors of unfavourable outcome in HME cases have been previously published elsewhere [6].

Setting

Patients were drawn from 35 referral centres in ten countries, including Croatia, the Czech Republic, Denmark, Egypt, France, Iraq, Italy, Lebanon, Slovenia and Turkey.

Participants

This study included all consecutive hospitalized patients with HME between 2000 and 2013. The inclusion criteria comprised the presence of all of the following: only adult patients (>15 years of age); patients with positive cerebrospinal fluid (CSF) PCR results for herpes simplex virus (HSV)-1, HSV-2 or both in a patient with a CNS infection; and the unlikely presence of any other infectious disease of the brain or any neurologic disorder other than HSV infection.

The exclusion criteria comprised the presence of all of the following: paediatric patients and the presence of any other infectious or noninfectious disease of the brain.