Journal of Infection (2017) 74, 42—49

BIA
British Infection Association

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Incidence and mortality of herpes simplex encephalitis in Denmark: A nationwide registry-based cohort study

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Accepted 14 September 2016
Available online 4 October 2016

KEYWORDS
Herpes simplex virus;
Herpes simplex encephalitis;
Viral encephalitis;
Epidemiology;
Incidence;
Mortality;
Comorbidity;
Prognosis

Summary *Objectives:* We aimed to investigate the incidence and mortality of herpes simplex encephalitis (HSE) in a nationwide cohort.
Methods: From the Danish National Patient Registry, we identified all adults hospitalised with a first-time diagnosis of HSE in Denmark during 2004—2014. The HSE diagnoses were verified using medical records and microbiological data. Patients were followed for mortality through the Danish Civil Registry System. We estimated age-standardised incidence rates of HSE and 30-day, 60-day, and 1-year cumulative mortality. Furthermore, we assessed whether calendar year, age, gender, level of comorbidity, virus type, and department type was associated with HSE mortality.
Results: We identified a total of 230 cases of HSE. Median age was 60.7 years (interquartile range: 49.3—71.6). The overall incidence rate was 4.64 cases per million population per year (95% confidence interval: 4.06—5.28). The cumulative mortality within 30 days, 60 days, and 1 year of the HSE admission was 8.3%, 11.3%, and 18.6%, respectively. Advanced age and presence of comorbidity were associated with increased 60-day and 1-year mortality.
Conclusions: This nationwide study of verified HSE found a higher incidence than reported in previous nationwide studies. Presence of comorbidity was identified as a novel adverse prognostic factor. Mortality rates following HSE remain high.

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http://dx.doi.org/10.1016/j.jinf.2016.09.004

Introduction

Herpes simplex encephalitis (HSE) is a potentially lethal viral infection of the brain parenchyma caused by herpes simplex virus (HSV). Despite being a rare disease, HSE is the most common form of sporadic encephalitis worldwide.[1,2]

The 1-year mortality rates following HSE is in latest studies reported to be 10—14% and in-hospital mortality between 6 and 9%.[3—6] Advanced patient age, extent of brain involvement, and delay of acyclovir treatment have been identified by several studies as key determinants of poor prognosis.[7—10] HSE survivors, frequently have severe neurological sequelae.[8,11] Thus, HSE still causes devastation and better knowledge of the short-term mortality as well as prognostic factors is needed.

Previous studies on HSE incidence have reported conflicting estimates. Most studies reported incidence rates (IR) ranging from 2.2 to 4.3 cases per million population per year.[3—5,7,12—16] A Swedish nationwide registry-based study from 1990 to 2001 found an IR of HSE of 2.2 cases per million population per year.[3] However, a regional French population-based study recently reported a HSE incidence of 12 cases per million suggesting that the incidence of HSE vary.[4] The methodological approaches vary widely among these studies. In particular, the studies have different degrees and methods of case verification. Moreover, continuous development of novel diagnostic techniques is reflected in the methods chosen by the studies with the earliest of the studies being from 1984.[12,14] Finally, only few nationwide studies have been conducted and none in Denmark.

Based on the diverging reports on HSE incidence and the continuous need for large population-based cohorts, we aimed to utilise the advantages of the Danish health registries to describe incidence and prognosis of HSE in a national cohort in Denmark during 2004—2014. We believe, that findings from this study will contribute with important knowledge on HSE epidemiology, which is a prerequisite for improving awareness, rapid diagnosis, and early treatment of patients with this rare and serious disease.

Methods

Setting and study design

This is a nationwide historical cohort study of adult patients (≥15 years) with HSE in Denmark. In 2014, Denmark had a population of ~4.7 million aged 15 and above.[17] The Danish population has unrestricted access to tax-financed medical care.

Data sources

Since 1968, a unique 10-digit personal identification number (CPR number) has been assigned to all Danish residents at birth or upon immigration. The CPR number enables highly valid and cost-effective individual-level record linkage of data between Danish registries.[18] From the Danish National Patient Registry (DNPR) we identified incident cases of HSE during the study period. The DNPR was established in 1977 and contains data from all admissions to Danish medical hospitals. Since 1995 the DNPR also include outpatient hospital visits. The DNPR contains administrative information such as dates of admission and discharge, primary and secondary diagnoses codes, and place of admission. Diagnoses are coded according to the Danish version of the *International Classification of Diseases*, 8th revision (ICD-8) (1977—1993) and 10th revision (ICD-10) (since 1994). DNPR data are continuously updated with complete nationwide coverage.[19]

The nationwide Danish Civil Registration System (CRS) provided data on gender, age, and dates of emigration and deaths of study participants. This registry was established in 1968 and is continuously updated permitting long-term follow-up with accurate censoring at migration or death.[20]

The Danish Microbiology Database (MiBa) was used to access microbiological test results from 2010 to 2014. MiBa is a nationwide, automatically updated database of microbiological test results from all the Departments of Clinical Microbiology since January 2010.[21] Furthermore, microbiological test results of a limited number of patients diagnosed before 2010 were obtained from two of the seven microbiological departments in Denmark.

For validation purposes we accessed the patient medical records and assessed the record notes, radiology descriptions, and results from microbiological tests. The medical records were assessed for all the remaining patients identified in the DNPR (including those diagnosed before 2010 and patients whose diagnosis could neither be confirmed nor disproved by microbiological findings obtained from MiBa or the two microbiological departments).

Identification of herpes simplex encephalitis patients

We identified hospitalised patients with putative HSE in the DNPR using the following inclusion criteria: 1) A primary or secondary ICD-10 diagnosis code indicating HSE (B00.4 "Encephalitis caused by herpes simplex virus", B00.4A "Meningoencephalitis caused by herpes simplex virus", or G05.1E "Herpesvirus encephalitis") from a Danish hospital during January 1st 2004 to December 31st 2014; 2) Danish resident ≥15 years at time of the HSE diagnosis; and 3) No previous HSE diagnoses recorded (ICD-10 codes: B00.4, B00.4A, G05.1 and ICD-8 code: 054.03).

Case definition and validation of diagnoses

To verify the HSE diagnoses in the DNPR we used data from MiBa, Departments of Clinical Microbiology, and patient medical records as described previously.[22] In brief, the following criteria for confirmed and probable HSE, respectively, were applied based on previously established criteria.[23,24]

Confirmed HSE

- PCR verified presence of HSV-1 DNA in the cerebrospinal fluid (CSF) or intrathecal HSV-1 antibody production