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Background. Herpes simplex encephalitis (HSE) is a devastating disease.

Methods. In Sweden, a nationwide retrospective study of the incidence, morbidity, and mortality associated with HSE during the 12-year period 1990–2001 was conducted. The national inpatient register data were used, and diagnostic data from the virus laboratories were validated.

Results. In the study period, 638 patients hospitalized in Sweden received a primary diagnosis of HSE. Of these, 236 patients had a confirmed infection of the central nervous system due to herpes simplex virus type 1. This corresponds to an incidence of confirmed HSE due to herpes simplex virus type 1 of 2.2 cases per million population per year. Of the survivors, 87% were readmitted to the hospital. The most frequent diagnosis at readmission was epilepsy, which was found in 49 patients (21% of the 236 total patients; 24% of 203 survivors), with a median onset 9.3 months after the diagnosis of HSE. This corresponds to a 60- to 90-fold increase in risk, compared with that for the general population. Neuropsychiatric sequelae were evident in 45 (22%) of 203 surviving patients. The incidence of venous thromboembolism, including pulmonary embolism, was 5–14 times higher than that in the general population. Among patients with HSE due to herpes simplex virus type 1, the 1-year mortality was 14% (33 of 236 patients died), which was 8 times higher than expected.

Conclusions. This is, to our knowledge, the first study to report long-term, nationwide follow-up data for patients with virologically confirmed HSE. There is considerable morbidity after HSE, with epilepsy being the most common diagnosis. This demonstrates the need for expanding our knowledge of the pathogenesis of HSE to direct more effective antiviral and antiinflammatory treatments.

Herpes simplex encephalitis (HSE) remains the most common form of sporadic fatal encephalitis worldwide [1, 2]. HSE is a rare disease that is estimated to occur in 2–4 individuals per million population per year [1]. More than 90% of the cases are caused by herpes simplex virus type 1 (HSV-1), and 7% are caused by herpes simplex virus type 2 (HSV-2) [3]. HSE is a devastating disease, and during its natural course, up to 70% of patients die [4]. During the 1980s, 2 independent trials showed that aciclovir was superior to vidarabine in the treatment of HSE and resulted in reduced mortality and morbidity [1, 2]. Despite treatment, the associated mortality rate is still high (~20%), and permanent disability, particularly cognitive and memory impairment, is common [5].

The current knowledge of HSE is mainly based on 2 clinical trials from the 1980s [1, 2]. The Swedish study [1] included all cases diagnosed in Sweden during a period of 34 months. Nevertheless, these studies [1, 2] reported only 53 and 69 patients with HSE, respectively. The study with the largest number of patients so far (113 patients) was published in 1982 [6]. Since then, there have been considerable changes in diagnostic methods, and antiviral treatment has been introduced. The studies made during the past 10 years are based on <100 patients each [7, 8]. To our knowledge, no nationwide long-term study has been published previously. The aim of this study was to investigate incidence, morbidity, case fatality rate, and virological diagnoses of HSE in patients first admitted to the hospital with this disease in Sweden during the period 1990–2001.
METHODS

Setting. Sweden, with a population of 8.8 million in 1996 [9], has a national health care system that is based on administratively independent county councils. The private hospital sector is small and provides mainly elective care.

Since 1964, the Swedish National Board of Health and Welfare has compiled data on individual hospital discharges in the National Inpatient Register, and since 1987, the register has covered all Swedish hospitals [10]. Approximately 1.3 million hospital admissions are recorded annually. In addition to a national registration number that uniquely identifies every resident of Sweden, information on sex, age, place of residence, hospital and department, and dates of hospital admission and discharge is collected. Each record also contains medical data, including diagnoses at hospital discharge (coded according to the Swedish version of the International Classification of Diseases, Ninth Revision and International Classification of Diseases, Tenth Revision).

The principal method of diagnosing HSE is through the detection of the viral genome by PCR of CSF samples [11, 12]. This method has been available for routine clinical use since 1991. Previously, the diagnosis of HSE was verified by detection of intrathecal antibody production against HSV or by brain biopsy [1, 6]. During the study period, specialized virological diagnostics were performed at 6 laboratories in Sweden, all of which were located at university hospitals. The virological laboratories have kept computer-registered data of all results since 1990.

Patients. To assess the incidence of HSE, we used data from the National Inpatient Register from January 1990 through December 2001 inclusive. The data set consisted of all hospital admissions involving a primary diagnosis of HSE (International Classification of Diseases, Ninth Revision: 054D; International Classification of Diseases, Tenth Revision: B00.4). For all patients, data on hospital admissions that occurred before and after the first HSE-related admission were also collected. The data set was linked to the National Register of Death and Causes of Death [13].

Permission from the Research Ethics Committee of the Karolinska Institutet (Stockholm, Sweden) was obtained (Dnr: 03–297) to gain access to the national registration numbers of the patients. This enabled each clinical diagnosis of HSE to be validated, because this registration number is used by the virological laboratories in their local registries for patient identification. Verified HSE was defined as a positive finding of HSV-1 by DNA PCR of CSF samples or as detection of intrathecal HSV-1 antibody production. It was not possible to decide from available data whether a verified HSV-2 infection in the CNS actually was HSE and not aseptic meningitis, which is the most common CNS manifestation of infection due to HSV-2 [14]. The patients with verified HSV-2 infection in our series of cases were probably mainly patients with viral meningoencephalitis. There were no deaths in this group, and the age and sex distributions were similar to those in earlier studies; 71% of the patients were female, and >50% of the patients were 20–50 years old [3].

To calculate the incidence of HSE, all data were also related to the Swedish population for 1996 (8.8 million). All hospital admissions prior to the first HSE-related admission were evaluated. Obstetric admissions were excluded, as were admissions immediately preceding the first HSE-related admission with a primary diagnoses suggestive of probable HSE (i.e., admissions with symptoms involving seizures or confusion). Also excluded were hospital admissions that occurred >5 years before the HSE diagnosis. A check of the register coverage verified the 5-year pre-HSE observation time in all patients. The primary diagnoses before the diagnosis of HSE were categorized into 13 groups, most of them according to International Classification of Diseases chapters. The category gastrointestinal disease included appendicitis, cholelithiasis, cholecystitis, inflammatory bowel disease, gastric ulcer, and pancreatitis and excluded symptomatic diagnoses, such as constipation and abdominal pain. Infectious diseases included septicemia, erysipelas, pneumonia, urinary tract infection, gastroenteritis, and viral diseases. The number of previous hospital admissions and the length of stay associated with these admissions were analyzed.

The admissions after the first hospital admission with a diagnosis of HSE were assessed with regard to primary and secondary diagnoses and length of stay. Also, the number of in-hospital days in the first year after the first HSE-associated hospital admission was calculated as an indicator of the severity of the disease. This was done because the initial hospital admission often is followed by transfer to a rehabilitation or psychiatric clinic, from which the patients may be readmitted to the initial clinic if complications develop. The characteristics of patients readmitted because of epilepsy are described in detail below. The diagnoses classified as epilepsy range from unclassified seizures to status epilepticus. Also, the diagnoses at hospital admissions subsequent to the first HSE-related admission were grouped in the same way as those at the admissions that occurred before HSE, but in this group, we also considered secondary diagnoses, because a diagnosis of HSE is often retained as the primary diagnosis at subsequent admissions. Added to the previous 13 groups was the category "neuropsychiatry," defined as hospital admission because of cognitive dysfunction, undefined dementia, hospitalization for social reasons, nutritional difficulties, aphasia, and other neurological symptoms indicating severe neuropsychiatric or neurological handicap. Because of the low incidence of hospital admissions in each diagnostic category, it was not feasible to analyze pre-HSE and post-HSE admissions formally by use of standardized incidence ratios. Instead, we compared the patients’ previous
and subsequent hospital admissions by year at risk with the mean national annual rates of hospital admission during the period 1998–2001, which were provided by the Centre for Epidemiology at the National Board of Health and Welfare (Stockholm, Sweden). To estimate the accuracy of this data, we also compared the data with the national incidence of hospital admissions in the age group 65–69 years, because this was the age group closest to the median age of the patients in our series. Mortality was analyzed by comparing the number of observed deaths with the number of expected deaths in an age-, sex-, and calendar year–matched group (the standardized mortality ratio).

RESULTS

Incidence. During the 12-year period from 1990 through 2001, a total of 638 patients were admitted to Swedish hospitals with HSE as a primary diagnosis (6.3 cases per million population per year). Of these, 236 (37%) had laboratory-verified HSV-1 infection of the CNS, which corresponds to an incidence of 2.2 cases of encephalitis due to HSV-1 infection per million population per year (95% CI, 1.7–2.8 cases per million population per year). In addition, 11 patients had verified untyped HSV infection of the CNS.

Virological diagnosis. A total of 223 patients received a virological diagnosis of HSE based on the detection of HSV-1 DNA by PCR in CSF samples; 13 patients received a diagnosis only on the basis of intrathecal production of antibody to HSV-1. Of the 638 patients with a primary diagnosis of HSE, 11 had a confirmed CNS infection due to HSV but had no type-specific diagnosis, 1 patient had PCR verification, and 10 had intrathecal antibody production. Seventy-five patients had a confirmed CNS infection due to HSV-2, 125 had PCR results that were negative for HSV DNA in CSF, 27 had negative results of intrathecal antibody analysis, and 164 had no HSV diagnostic tests performed on CSF samples.

Unverified HSE. Data on the 327 patients with negative test results or no virological diagnosis of HSE who had been discharged from the hospital with a diagnosis of HSE were further analyzed. The annual number of cases of unverified HSE decreased from 60 cases in 1990 to 21 cases in 2001. Of these patients, 52% had a change of diagnosis after transfer to a specialist clinic. In ~50% of the cases, the diagnosis was changed to unspecified encephalitis or encephalopathy. Malignant diseases, particularly brain tumor with temporal location and cerebrovascular disease, were the second most common diagnoses. In 30% of the remaining patients, the diagnosis was considered to be unlikely because of the sequence of admissions and corresponding diagnostic coding (e.g., patients who were only admitted to gynecology departments and patients with a length of stay <1 day). Excluding these patients, 110 patients with possible but unverified HSE remained. If these patients were considered to have confirmed cases of HSE, this would give an incidence of 3.2 cases per million population per year.

Demographic data. Data from 236 cases of verified HSE due to HSV-1 indicated no significant variation in incidence between the years. A tendency to a higher incidence during the summer months was noted. The sex distribution of the patients was approximately equal, with 116 female and 120 male pa-

Figure 1. Cases of herpes simplex encephalitis due to herpes simplex virus type 1 in Sweden, 1990–2001, by patient age at hospital admission
patients, and the median age was 62 years in male patients (interquartile range, 40–74 years) and 66 years in female patients (interquartile range, 46–74 years). Figure 1 shows the age distribution of the patients.

**Morbidity prior to HSE.** The patients were monitored for 1180 person-years (5 years per patient) before the onset of HSE. The incidence of morbidity before the HSE diagnosis in this group was not significantly higher than the incidence of morbidity in the general population, despite the fact that 47% of the patients had been hospitalized before the onset of HSE. These patients had a median of 2 hospital admissions, with a median length of stay of 4 days. The most common diagnoses were ischemic heart diseases, gastrointestinal diseases, and infections (table 1).

**Morbidity after HSE.** The patients were followed up for a total of 1008 person-years (median duration of follow-up, 4.3 years per person), and 87% of the patients were readmitted to the hospital. The patients spent a mean of 55 days (95% CI, 48.5–61.8 days) in a hospital during the year following the onset of HSE. The patients had a median of 4 hospital admissions (interquartile range, 3–7 admissions) with a median length of stay of 6 days.

The most frequent cause of rehospitalization was epilepsy; 49 of the patients (21% to the total patients; 24% of survivors) had subsequent hospital admissions associated with this diagnosis (table 1). The second and third most common causes of rehospitalization were infection other than HSE (46 patients) and admission for a neuropsychiatric condition (45 patients).

Venous thromboembolic diseases were common; 14 patients were rehospitalized for this condition, 8 of whom had had a pulmonary embolism within 1 year after receiving a diagnosis of HSE. This risk was elevated 5–15-fold, compared with the risk in the general population. Seventeen patients had subsequent hospital admissions for diabetes mellitus, corresponding to an estimated risk 5–11 times higher than that among the general population.

Patients who were readmitted to the hospital because of epilepsy after receiving a diagnosis of HSE had a median age of 58 years (interquartile range, 40–70 years); 43% were female. The first readmission for epilepsy occurred late, a median of 280 days (interquartile range, 71–630 days) after the diagnosis of HSE. Only 1 of the 3 patients who had received a diagnosis of epilepsy before receiving a diagnosis of HSE survived to have hospital admissions after receipt of the HSE diagnosis that were associated with an epilepsy diagnosis. The risk of being admitted to the hospital because of epilepsy was 60–90-fold greater than the risk in the general population.

**Mortality.** The 1-year mortality rate was 14.0%, and the overall mortality rate was 25.4% (table 2 and figure 2). The mortality rate was significantly increased in the first year after diagnosis but not later. There was no difference in mortality between the sexes, and there was no significant increase in mortality in age groups <70 years old. The most common cause of death was HSE, followed by cardiovascular diseases (table 3).

**DISCUSSION**

The incidence of HSE due to verified HSV-1 infection in Sweden was 2.2 cases per million population per year. Inclusion of cases of untyped HSV infection and the expected 7% of HSE cases due to HSV-2 infection increased the estimated incidence of HSE to 2.5 cases per million population per year. This is the same incidence as that found in Sweden at the beginning of the study period.
of the 1980s [1]. In other regions, the incidence varies up to 4 cases per million population per year [15]. The finding that the incidence of premorbidity among patients with HSE was similar to that in the general population has not, to our knowledge, been reported previously. Morbidity after HSE has not previously been described in relation to diagnostic groups, and in previous studies, the duration of follow-up has been limited to 1 year [2, 7, 8, 16]. The incidence of morbidity after HSE in the latter studies was categorized into groups by degree of sequelae. A comparison is difficult to make, because the registered inpatient data do not give a full description of patient status. In previous studies [2, 7, 16], the incidence of seizures referred to the acute phase of the disease, and the incidence of seizures during follow-up was usually not analyzed.

The considerable number of patients in the initial selection from the inpatient register raises the question of whether HSE is overdiagnosed clinically or underdiagnosed virologically. When the unconfirmed cases were evaluated, more than one-half of them had a change of diagnosis in an adjacent hospitalization at a specialist clinic. Among these patients, unspecified encephalitis was the most common diagnosis, indicating the lack of virological confirmation, but there were also a variety of other diagnoses, such as cerebrovascular disease and cerebral malignancy, as well as several cases of viral and bacterial meningitis. The annual number of cases of unverified HSE decreased during the study period, reflecting the adoption of diagnostic PCR.

The incidence of morbidity after HSE was found to be considerable. Most apparent was the increased risk of postencephalitic epilepsy. The median interval between HSE diagnosis and onset of epilepsy was also long (9 months). Three factors might contribute to the high incidence of epilepsy after HSE. First, seizures during the acute phase of HSE are common [1, 6]. Second, temporal and hippocampal regions are frequently involved in HSE, and change in hippocampal excitability has been demonstrated in experimental HSV infection [17]. Third, data indicate chronic HSV infection or immunoreactivity in the CNS during HSE [18].

The increase in hospital admissions for infectious diseases, mainly pneumonia and urinary tract infection, may have been attributable to immobilization. The incidence of venous throm-

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<table>
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<th>Variable</th>
<th>Observed deaths</th>
<th>Expected deaths</th>
<th>SMR (95% CI)</th>
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<td>Age at diagnosis, years</td>
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<tr>
<td>≤39</td>
<td>1</td>
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<td>40–49</td>
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<td>0.2</td>
<td>12.51 (2.58–36.56)</td>
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<tr>
<td>50–59</td>
<td>3</td>
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<td>60–69</td>
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<td>0.91 (0.25–2.32)</td>
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<td>70–79</td>
<td>36</td>
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<td>&gt;80</td>
<td>13</td>
<td>3.9</td>
<td>3.36 (1.79–5.74)</td>
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<tr>
<td>Sex</td>
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<td></td>
</tr>
<tr>
<td>Male</td>
<td>32</td>
<td>10.4</td>
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<tr>
<td>Female</td>
<td>28</td>
<td>10.8</td>
<td>2.59 (1.72–3.75)</td>
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<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>33</td>
<td>4.1</td>
<td>8.11 (5.59–11.4)</td>
</tr>
<tr>
<td>≥1 but &lt;5</td>
<td>17</td>
<td>11.2</td>
<td>1.51 (0.88–2.42)</td>
</tr>
<tr>
<td>≥5</td>
<td>10</td>
<td>5.9</td>
<td>1.7 (0.82–3.13)</td>
</tr>
<tr>
<td>All patients</td>
<td>60</td>
<td>21.2</td>
<td>2.83 (2.16–3.65)</td>
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**NOTE.** SMR, standardized mortality ratio analysis.

<table>
<thead>
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<th>Cause of death</th>
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<td></td>
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<tr>
<td>Herpes simplex encephalitis</td>
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<tr>
<td>Cardiovascular disease</td>
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<td>Neurological disease</td>
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<td>Pulmonary disease</td>
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<tr>
<td>Miscellaneous</td>
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<tr>
<td>Total</td>
<td>32</td>
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</table>

boembolic diseases, including pulmonary embolism, was 5–14 times higher than that in the general population, and venous thromboembolism is a complication that is also well known to be related to immobilization. The incidence of diabetes mellitus among patients with HSE was normal during the period before HSE diagnosis but increased 5- to 10-fold after HSE, compared with the incidence among the general population. One reason for this may be that severe HSE disease and the frequent use of steroid treatment during the acute phase of HSE can trigger latent diabetes. This finding may also be attributable to detection bias, which could be induced by frequent medical contacts after receiving a diagnosis of HSE. The high frequency of psychiatric admissions is not surprising, because personality changes are common in patients with HSE [4]. The finding that 87% of surviving patients were readmitted to the hospital during the study period illustrates the high incidence of morbidity after HSE.

A limitation of our study is that we did not have access to individual medical records. This would have allowed a more precise evaluation of the severity of the disease and quantification of complications following HSE. The computer–registered data provide a blunt tool that, nevertheless, enabled us to analyze all patients nationwide, with complete follow-up of all in-hospital care and mortality.

The incidence of HSE has neither increased nor decreased in recent years. According to our data, there was no specific pattern of hospital admissions before HSE diagnosis. The incidence of morbidity after HSE diagnosis presented in this study is also a conservative estimate, because a large proportion of patients with complications (including epilepsy) can be treated in ambulatory care. More frequent monitoring for epilepsy following HSE may be indicated. The main conclusion of our study is that, despite the development of highly effective antiviral therapy in the past 2 decades, the level of morbidity following HSE is still high, and the mortality associated with HSE remains considerable, underscoring the need to expand our knowledge of the pathogenesis of HSE to direct more effective antiviral and antiinflammatory treatments.

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