Long-term Outcome of Patients Presenting With Acute Infectious Encephalitis of Various Causes in France

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Background. A prospective study of infectious encephalitis was conducted in France in 2007. In total, 253 patients were enrolled with a proven etiological diagnosis for 52%. The cohort of surviving patients with encephalitis was assessed for sequelae and impairment 3 years after enrollment.

Methods. Patients, their family, and general practitioners (GPs) were interviewed by phone to document persisting symptoms, return to work, and past and current leisure activities, with standardized questionnaires. The IQCODE (Informant Questionnaire on Cognitive Decline in the Elderly) was completed with relatives. The global outcome was determined in all patients with the Glasgow outcome scale.

Results. In 2010, 20 patients (10%) were unavailable for follow-up, 2 (1%) were excluded, and 18 (9%) had died since hospital discharge. Data were available for 167 survivors and 9 patients whose death was related to the encephalitis. The outcome was favorable in 108 of 176 patients (61%) (71 with complete resolution), 31 (18%) were mildly impaired, 25 (14%) were severely impaired, and 3 (1%) were in a vegetative state. The most frequent symptoms were difficulty concentrating (42%), behavioral disorders (27%), speech disorders (20%), and memory loss (19%). Fifteen of 63 patients (24%) previously employed were still unable to resume work. Long-term outcome was significantly associated with comorbid conditions, age, level of education, and the causative agent of encephalitis.

Conclusions. Most patients with encephalitis experienced a favorable outcome 3 years after hospital discharge. However, minor to severe disability persists in a high number of cases with consequences for everyday life. Physical and mental impairment should be evaluated in all patients with encephalitis, and neuropsychological rehabilitation implemented whenever needed.

Acute encephalitis has been described in large studies, giving an overview of acute clinical disease and improving knowledge about their etiology [1–3]. The existence of persisting symptoms and sequelae after acute encephalitis was first reported in 1923 [4]. However, most articles described short case-series, or focused on herpes simplex encephalitis (HSE) [5–8] despite the large number of possible causative agents [9]. Studies about the sequelae in patients with encephalitis of various causative agents are rare [10–13].

In 2007, we enrolled 253 patients with encephalitis in a prospective national multicenter study in France and demonstrated a specific causative agent for 52% of cases [2]. Initial clinical presentation and short-term outcome in the enrolled patients were described elsewhere [2]. The objective of this work is to assess long-term sequelae and quality of life 3 years after enrollment in the prospective cohort of patients with encephalitis who survived the acute episode in 2007.

METHODS

In 2007, 26 of 253 patients died during hospitalization, 10 refused to participate in the long-term follow-up, and
were transferred abroad (Figure 1). Two patients with diagnoses of Gougerot-Sjögren or opsoclonus-myoclonus syndrome after discharge were excluded a posteriori. Therefore, 205 patients were eligible for the follow-up study.

Data were collected by telephone 27–40 months after onset of encephalitis (median and mean, 31) using closed-question standardized questionnaires about general and neurological symptoms, current treatments, patients’ return to work or school, and the resumption of previous leisure activities. The cognitive decline was assessed with patients’ relatives using the short version of the IQCODE (Informant Questionnaire on Cognitive Decline in the Elderly) [14, 15]. Cognitive decline was defined as an IQCODE score >3, and major cognitive decline as a score at least equal to the mean score of all cases plus 2 standard deviations. Because the IQCODE compares the situation at the time of assessment with the situation 10 years before in adults, we used it in patients >26 years old. The quality of life was assessed using a structured questionnaire about emotional and physical state.

The Glasgow outcome scale (GOS) was used as the main outcome measure [16, 17]. A favorable outcome was defined as a GOS score of 5 (Table 1). The GOS scores of all eligible patients were assessed by the collegial review of the clinical data by the authors. If a patient had died since discharge, information about the cause of death was collected from the general practitioner (GP) and, if needed, from the relatives.

Patients whose encephalitis could not be considered as the immediate or contributory cause of death according to the international recommendations for death certification [18] were excluded from the analysis, as well as those for whom the cause of death was unknown.

All patients were described with regard to the different tests and clinical data. Patients with HSE were compared with other patients with encephalitis using the Pearson’s $\chi^2$ test for qualitative variables and Student $t$ test or Wilcoxon rank sum test for quantitative variables. All ages are those reported at the time of onset in 2007.

Factors associated with the long-term outcome (favorable vs poor outcome, as defined above) were identified by logistic regression. Children were excluded from this analysis because there were few of them and because the influence of their education level was not evaluable. Demographic features, causes of encephalitis, and clinical symptoms present at admission in 2007 were tested in univariate analysis (Pearson $\chi^2$ for indicative variables, Student $t$ test, or nonparametric test for continuous variables). Explicative variables associated with the outcome with $P \leq .25$ in univariate analysis were included in the logistic regression. The fit of the final model was assessed by the Hosmer and Lemeshow goodness-of-fit statistic.

All collected data were computed and analyzed using Stata 11 (Stata Corporation). All patients or relatives in charge of legal matters gave written consent. The study was authorized by the ethics committee of Grenoble, France (Comité de Protection des Personnes Sud-Est V, Grenoble, No. 172003), according to French regulations.

Table 1. Glasgow Outcome Scale (GOS) Categories and Outcomes in Patients Included in Follow-up Study

<table>
<thead>
<tr>
<th>GOS Score</th>
<th>Clinical Meaning</th>
<th>Outcome</th>
<th>Patients, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Death</td>
<td>Poor</td>
<td>9 (5)</td>
</tr>
<tr>
<td>2</td>
<td>Neurovegetative state; patient unresponsive and speechless for weeks or months</td>
<td>Poor</td>
<td>3 (2)</td>
</tr>
<tr>
<td>3</td>
<td>Severe disability; patient dependent for daily support</td>
<td>Poor</td>
<td>25 (14)</td>
</tr>
<tr>
<td>4</td>
<td>Moderate disability; patients independent in daily life</td>
<td>Poor</td>
<td>31 (18)</td>
</tr>
<tr>
<td>5</td>
<td>Good recovery; resumption of normal life with minor neurological and psychological deficits</td>
<td>Favorable</td>
<td>108 (61)</td>
</tr>
</tbody>
</table>

Details in Jennett and Bond [16] and Fayol et al [17].

Figure 1. Follow-up and outcome in 2010 in patients with encephalitis enrolled in 2007. Of the 15 patients unavailable for follow-up, 12 had no causative agent identified, 1 had varicella-zoster virus encephalitis, and 2 had Mycobacterium tuberculosis encephalitis. Four of 5 patients who refused follow-up had no causative agent identified, and 1 had herpes simplex virus encephalitis. The 9 deaths that were unrelated to encephalitis or undocumented were caused by cancer (n = 3), accident (n = 2), age-related comorbid conditions (n = 1), death during cardiac surgery (n = 1), or unknown causes (n = 2).
RESULTS

Demography
In total, 176 of 205 eligible patients could be included in the study: 167 surviving patients (81%) and 9 patients (5%) whose death was related to encephalitis (Figure 1). Among 29 non-included patients, 9 had died and their death was not related to the encephalitis (n = 7) or the cause of their death could not be assessed (n = 2), 15 were unavailable for follow-up, and 5 refused to participate. The causative agents of encephalitis and the demographic features of the patients are described in Table 2. A causative agent had been identified in 91 of 176 patients during their initial hospitalization.

Among 167 living patients, data were collected from the triumvirate patient, family, and GP for 98 patients, from 2 sources for 63 patients (patient plus family, n = 21; patient plus GP, n = 11; family plus GP, n = 31), and from 1 source for 6 patients (family, n = 5; GP, n = 1). Thirty-seven patients (22%) were unable to answer the questionnaire by themselves because of deafness (n = 4), memory impairment (n = 3), vegetative state (n = 3), poor understanding of French (n = 5), refusal of the family (n = 10), and age <10 years (n = 12).

Long-term Outcome
In total, 108 of 176 patients (61%) had a favorable outcome, 71 (40%) of total having fully recovered (Table 1). Sixty-eight patients (38%) had a poor outcome: 25 (14%) experienced severe disabilities, 31 (18%) had moderate disabilities, 3 were in a vegetative state, and 9 (5%) died (Table 1). A favorable outcome was more frequent in children than in adults (81% vs 62%), but the difference was not significant (P = .09).

The 9 encephalitis-related deaths occurred 38–809 days after discharge (median, 505 days) in 6 women and 3 men. A 1-year-old child with influenza A encephalitis experienced recurrent neurological signs and later died while in a coma, 8 months after discharge. Another 1-year-old child presenting with encephalitis of unknown origin, who had been discharged to a long-term medical facility, died 4 months later. The last 7 deceased patients were 56–86 years old (mean age, 75 years) and had had encephalitis due to herpes simplex virus (n = 3), Mycobacterium tuberculosis (n = 1), varicella-zoster virus (VZV) (n = 1), or unknown origin (n = 3).

Among 176 included patients, 43 (24%) had had HSE. Only 18 patients with HSE (42%) experienced a favorable outcome, compared with 90 other patients (68%) (P = .03), and 6 patients with HSE (14%) had fully recovered at follow-up, compared with 65 other patients (49%) (P = 3.10^{-5}) (Table 2). No HSE relapse occurred after discharge. In sum, 7 of 10 patients with tuberculosis and 3 of 4 with listeriosis experienced a favorable outcome, and all 3 patients with tick-borne encephalitis (TBE) presented with a moderate disability.

Persisting Symptoms and Cognitive Decline in Surviving Patients
The most frequent symptoms reported by the GPs of survivors were difficulties concentrating (42%), behavioral disorders (26.8%), speech disorders (19.9%), and memory impairment (19.3%) (Table 3). Compared with other patients, patients with HSE more frequently experienced concentration (P = .007) and behavioral (P = .001) disorders, especially disinhibition (P = .01), but the frequencies of memory impairment and speech disorders did not differ significantly. At the time of follow-up, 37 patients (22.2%) were treated with anticonvulsant drugs (1 with intractable seizures), and 19 (11.3%) with antidepressive drugs.

Both patients with encephalitis due to Mycoplasma pneumo-niae experienced a poor outcome. In a 6-month-old infant, the development of motor, sensorial, and cognitive functions stopped after the acute episode, with irreversible brain damage. The child was 3 years and 2 months old at the time of discharge.

Table 2. Demographic Features of Patients Enrolled in Follow-up, by Causative Agent

<table>
<thead>
<tr>
<th>Causative Agent</th>
<th>Patients, No. (%)</th>
<th>Age, Median (Range)</th>
<th>Age &lt;16 y</th>
<th>Male-Female Ratio</th>
<th>Favorable Outcome: GOS Score, 5)</th>
<th>Full Recovery</th>
<th>Encephalitis-Related Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>176 (100)</td>
<td>53.5 y (1 mo to 89 y)</td>
<td>23 (13)</td>
<td>1.6</td>
<td>108 (61)</td>
<td>71 (40)</td>
<td>9 (5.1)</td>
</tr>
<tr>
<td>HSVa</td>
<td>43 (24)</td>
<td>58 y (1 mo to 85 y)</td>
<td>1 (2)</td>
<td>1.3</td>
<td>18 (42)</td>
<td>6 (14)</td>
<td>3 (7.0)</td>
</tr>
<tr>
<td>VZV</td>
<td>15 (9)</td>
<td>63 y (6 mo–to 86 y)</td>
<td>3 (20)</td>
<td>4</td>
<td>7 (47)</td>
<td>5 (33)</td>
<td>1 (6.7)</td>
</tr>
<tr>
<td>M. tuberculosis</td>
<td>10 (6)</td>
<td>64 y (17–75 y)</td>
<td>0</td>
<td>1</td>
<td>7 (70)</td>
<td>5 (50)</td>
<td>1 (10.0)</td>
</tr>
<tr>
<td>Other causeb</td>
<td>23 (13)</td>
<td>51 y (6 mo to 87 y)</td>
<td>8 (35)</td>
<td>2.8</td>
<td>16 (70)</td>
<td>12 (52)</td>
<td>1 (4.3)</td>
</tr>
<tr>
<td>Unknown</td>
<td>85 (48)</td>
<td>43 y (1–89 y)</td>
<td>11 (13)</td>
<td>1.4</td>
<td>60 (71%)</td>
<td>43 (51)</td>
<td>3 (3.5)</td>
</tr>
</tbody>
</table>

Data are No. (%) of patients unless otherwise indicated.

Abbreviations: GOS, Glasgow Outcome Scale; HSV, herpes simplex virus; M. tuberculosis, Mycobacterium tuberculosis; VZV, varicella-zoster virus.

a In 2007, all adult patients with HSV encephalitis were treated with acyclovir for 2 or 3 weeks at a dosage of 10–15 mg/kg/8 hours. The 1-month-old patient received 20 mg/kg/8 hours for 3 weeks. Acyclovir was started 0–10 days after onset (mean, 1 day) [19].

b Causative agents included Listeria monocytogenes (n = 4), tick-borne encephalitis (n = 3), Mycoplasma pneumoniae (n = 2), Epstein-Barr virus (n = 2), cytomegalovirus (n = 2), enterovirus (n = 2), Legionella pneumophila (n = 1), influenza A (n = 1), Borrelia burgdorferi (n = 1), Rickettsia coronii (n = 1), Francisella tularensis (n = 1), Cryptococcus neoformans (n = 1), and Toscana virus (n = 2).
Table 3. Persisting Symptoms in 164 Survivor Patients With a GOS Score >2, by Causative Agent

<table>
<thead>
<tr>
<th>Signs</th>
<th>All Patients (n = 164)</th>
<th>HSE (n = 40)</th>
<th>Non-HSE (n = 124)</th>
<th>P for HSE vs Other</th>
<th>VZV (n = 14)</th>
<th>Tuberculosis (n = 9)</th>
<th>Other Determined Origin (n = 21)</th>
<th>Unknown Origin (n = 80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trouble concentrating</td>
<td>56/124 (45.2)</td>
<td>20/30 (66.6)</td>
<td>36/94 (38.3)</td>
<td>0.007</td>
<td>6/12 (50.0)</td>
<td>1/7 (14.3)</td>
<td>6/17 (35.3)</td>
<td>23/58 (39.7)</td>
</tr>
<tr>
<td>Behavioral troubles</td>
<td>38/133 (28.6)</td>
<td>17/34 (50)</td>
<td>21/99 (16.5)</td>
<td>0.001</td>
<td>4/13 (30.8)</td>
<td>0</td>
<td>1/17 (5.9)</td>
<td>16/61 (26.2)</td>
</tr>
<tr>
<td>Irritability</td>
<td>18/134 (13.4)</td>
<td>6/34 (17.7)</td>
<td>12/100 (12.0)</td>
<td>0.40</td>
<td>1/13 (7.7)</td>
<td>2/8 (25.0)</td>
<td>2/18 (11.1)</td>
<td>8/61 (11.1)</td>
</tr>
<tr>
<td>Aggressiveness</td>
<td>6/133 (4.5)</td>
<td>3/33 (9.1)</td>
<td>3/100 (3.0)</td>
<td>0.14</td>
<td>0</td>
<td>0</td>
<td>3/61 (4.9)</td>
<td>3/61 (4.9)</td>
</tr>
<tr>
<td>Disinhibition</td>
<td>6/132 (4.6)</td>
<td>4/33 (12.1)</td>
<td>1/99 (1.0)</td>
<td>0.001</td>
<td>0</td>
<td>0</td>
<td>1/60 (1.7)</td>
<td>1/60 (1.7)</td>
</tr>
<tr>
<td>Disorientation</td>
<td>17/135 (12.5)</td>
<td>7/34 (20.6)</td>
<td>10/101 (7.5)</td>
<td>0.1</td>
<td>2/13 (15.4)</td>
<td>0</td>
<td>7/61 (11.5)</td>
<td>7/61 (11.5)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>4/133 (3.0)</td>
<td>1/33 (3.0)</td>
<td>3/100 (0.02)</td>
<td>0.99</td>
<td>0</td>
<td>0</td>
<td>3/61 (4.9)</td>
<td>3/61 (4.9)</td>
</tr>
<tr>
<td>Depression</td>
<td>9/133 (6.8)</td>
<td>4/33 (12.1)</td>
<td>5/100 (0.04)</td>
<td>0.16</td>
<td>1/13 (7.7)</td>
<td>0</td>
<td>4/61 (6.6)</td>
<td>4/61 (6.6)</td>
</tr>
<tr>
<td>Speech disorders</td>
<td>27/136 (19.9)</td>
<td>10/34 (29.4)</td>
<td>17/102 (16.6)</td>
<td>0.10</td>
<td>4/13 (30.8)</td>
<td>0</td>
<td>1/18 (5.6)</td>
<td>12/63 (19.1)</td>
</tr>
<tr>
<td>Memory impairment</td>
<td>26/135 (19.3)</td>
<td>10/33 (30.3)</td>
<td>16/102 (16%)</td>
<td>0.06</td>
<td>2/13 (15.4)</td>
<td>0</td>
<td>1/19 (5.3)</td>
<td>13/62 (21.0)</td>
</tr>
<tr>
<td>Motor deficit</td>
<td>20/137 (14.6)</td>
<td>3/34 (8.8)</td>
<td>17/103 (16.5)</td>
<td>0.27</td>
<td>4/13 (30.8)</td>
<td>1/8 (12.5)</td>
<td>3/19 (15.8)</td>
<td>9/63 (14.3)</td>
</tr>
<tr>
<td>Limb paralysis</td>
<td>3/136 (2.2)</td>
<td>1/34 (2.9)</td>
<td>2/102 (2%)</td>
<td>0.73</td>
<td>1/13 (7.7)</td>
<td>1/8 (12.5)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Paresis</td>
<td>9/136 (6.6)</td>
<td>2/34 (5.9)</td>
<td>7/102 (6.9%)</td>
<td>0.84</td>
<td>1/13 (7.7)</td>
<td>0</td>
<td>3/19 (15.8)</td>
<td>3/62 (4.8)</td>
</tr>
<tr>
<td>Facial palsy</td>
<td>1/136 (0.7)</td>
<td>0</td>
<td>1/124 (0.8%)</td>
<td>0.56</td>
<td>0</td>
<td>0</td>
<td>1/19 (5.3)</td>
<td>0</td>
</tr>
<tr>
<td>Ataxia</td>
<td>1/138 (0.7)</td>
<td>0</td>
<td>2/104 (1.9)</td>
<td>0.41</td>
<td>0</td>
<td>0</td>
<td>1/19 (5.3)</td>
<td>1/63 (1.6)</td>
</tr>
<tr>
<td>Headache</td>
<td>20/125 (16.0)</td>
<td>6/30 (20)</td>
<td>14/95 (14.7)</td>
<td>0.49</td>
<td>3/12 (25.0)</td>
<td>0</td>
<td>1/19 (5.3)</td>
<td>10/58 (17.2)</td>
</tr>
<tr>
<td>Pain</td>
<td>8/135 (5.9)</td>
<td>2/23 (8.7)</td>
<td>6/112 (504)</td>
<td>0.95</td>
<td>0</td>
<td>0</td>
<td>2/19 (10.6)</td>
<td>4/61 (6.6)</td>
</tr>
<tr>
<td>Intractable seizures</td>
<td>2 (1.4)</td>
<td>1/34 (2.9)</td>
<td>1/104 (0.9)</td>
<td>0.40</td>
<td>0</td>
<td>0</td>
<td>1/63 (1.6)</td>
<td>0</td>
</tr>
<tr>
<td>Sensitive deficit</td>
<td>2/123 (1.5)</td>
<td>1/33 (3.0)</td>
<td>1/99 (1.0)</td>
<td>0.41</td>
<td>0</td>
<td>0</td>
<td>1/19 (5.3)</td>
<td>0</td>
</tr>
<tr>
<td>Spatial neglect</td>
<td>1/138 (0.6)</td>
<td>1/34 (2.9)</td>
<td>0</td>
<td>0.08</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Data are No. with sign/total No. (%) unless otherwise indicated.

Abbreviations: GOS, Glasgow Outcome Scale; HSE, herpes simplex encephalitis; HSV, herpes simplex virus; VZV, varicella-zoster virus.

a Three surviving patients in a vegetative state are not included in this table because the persisting symptoms are not relevant for them.

b Causative agents included Listeria monocytogenes (n = 4), tick-borne encephalitis (TBE) (n = 3), Epstein-Barr virus (n = 2), cytomegalovirus (n = 2), enterovirus (n = 2), Mycoplasma pneumoniae (n = 1), Legionella pneumophila (n = 1), influenza A (n = 1), Borrelia burgdorferi (n = 1), Rickettsia coronii (n = 1), Francisella tularensis (n = 1), Cryptococcus neoformans (n = 1), and Toscana virus (n = 1).

c This patient had encephalitis due to TBE virus.

d This patient had encephalitis due to M. pneumoniae.

Follow up and was unable to stand, stay sitting, talk or eat; was incontinent; and had no reaction to external stimuli. A 15-year-old girl presented with a major ataxia and limbs shaking at follow-up. She was unable to walk, stand, or write; needed a wheelchair; and had difficulties maintaining a social life and relationships with friends, especially at school.

Three patients were in a vegetative state at the time of follow-up: the 6-month-old boy with Mycoplasma encephalitis (see above), a 6-year-old boy, and a 60-year-old man with encephalitis of unknown origin. The IQCODE demonstrated a cognitive decline in 97 of 125 adult patients (77.6%), with a major decline in 10 (8%); IQCODE scores was positively correlated with age (ρ = 0.39; P = 10⁻⁶) but not with the causative agent of encephalitis.

Resumption of Previous Life Activities in 167 Surviving Patients

At follow-up, 20 (12%) were legally disabled according to the national health insurance (defined in France as a decrease of ≥66% in the ability to work): 8 presenting with HSE, 2 with VZV encephalitis, 1 with TBE, and 9 with encephalitis of unknown cause. Of 26 who were students or pupils, 3 (12%) did not resume their education due to lack of commitment (n = 2) or major disability (n = 1; vegetative state). Twenty (77%) had their education adjusted to fit their medical condition or impairment.

Before encephalitis, 75 adult patients (45%) had no occupation: 65 (87%) were retired, and 10 (13%) unemployed for various reasons. At follow-up, 21 of 75 (28%) had resumed their previous leisure activities, 31 (41%) had abandoned ≥1 activity, and 23 (31%) had resumed none of their activities. Fourteen (20%) had new leisure activities, most being physically or mentally less challenging than their previous activities.

Sixty-three adult patients (36%) were employed at the onset of encephalitis. At follow-up, 46 (73%) had returned to work, 49% in the 3 months after discharge and 87% in the year after discharge. Sixteen (34%) had first resumed their occupation part time or with less responsibility. At follow-up, 7 (15%) had easier occupational tasks than before the encephalitis.
17 patients (27%) with no return to work, 2 retired shortly after hospital discharge, for a total of 15 formerly working patients (24%) unemployed at the time of follow-up. Eight (45%) of the previously working patients with HSE were unemployed at the time of follow-up. A return to work was significantly associated with the level of education; it was achieved in 74% of patients with college degree or higher vs 29% in others (P < .001). Among patients employed before encephalitis, a return to work was significantly associated with the resumption of leisure activities (P = .024).

Quality of Life
Seven patients divorced after hospital discharge and reported that their divorce was related to their encephalitis. Four others had to move to a new place more adapted to their medical condition. Of 125 patients who answered the quality of life questionnaire: 71 (56.8%) reported emotional troubles, 59 (46.8%) felt depressed, and 21 (16.8%) acknowledged difficulties in maintaining normal relationships. None of the items was associated with age, level of education, or the causative agent of encephalitis. Bradypsychia and chronic fatigue were spontaneously reported by 6 and 3 patients, respectively.

Factors Associated With the Long-term Outcome
Some variables were significantly associated with the outcome in univariate analysis and therefore included in the logistic regression: age, sex, presence of comorbid conditions, level of education, living in a house (vs an apartment), causative agent of the encephalitis, digestive symptoms before encephalitis, normal computed tomographic and magnetic resonance imaging findings, length of hospitalization, need for mechanical ventilation, and some symptoms at admission (disorientation, incoherent speech, cerebellar signs, meningeal signs). Imaging results were excluded from the multivariate analysis to limit missing data. In the final multivariate model, factors independently associated with a favorable outcome were causative agent of the encephalitis other than herpes simplex virus and VZV (P < .05) and high levels of education (P < .02), whereas the presence of comorbid conditions (P = .01) and increasing age at the time of onset (P = .01) were negatively associated with a favorable outcome (Table 4). The P value for the Hosmer and Lemeshow goodness of fit test was .98.

DISCUSSION
We assessed the outcome in patients with encephalitis 3 years after hospital discharge. To our knowledge, this is the largest published cohort studying sequelae after encephalitis of various causes. The mean 31-month delay between onset and follow-up may allowed a good overview of sequelae, because recovery happens more rapidly initially and then slows down. In our study, 61% of patients experienced a favorable outcome, which was comparable to the neuropsychological outcome in 45 Finnish patients presenting with encephalitis.
of various causes [10]. The comparison with other studies is difficult owing to different methods (especially length of follow-up, assessment) and study periods (Table 5). The oldest studies found higher frequency of sequelae, but most were monocentric case patient series with possible selection bias [4, 7, 13]. More recently, 198 patients with encephalitis (including those with noninfectious causes) had less favorable GOS results, but they were assessed 6 months after discharge; their medical condition may have improved after the assessment. The long-term outcome of HSE has been studied, demonstrating a full recovery in 14% [6], in 17% [8], and 48% of patients [5]. Our results are comparable to those of the first 2 studies. The results of the third study are difficult to interpret because patients were enrolled during a 12-year period and evaluated 6 months to 11 years after onset [5].

A large number of patients in our study, altogether 61.2%, presented with persisting symptoms or impaired quality of life. Some authors have described a complete neuropsychological assessment of great value but did not describe the persisting symptoms or only those after HSE (Table 5). We demonstrated that symptoms can persist in encephalitis of all origins 3 years after discharge. The most frequent persisting symptoms were concentration and behavioral disorders, and 57% of patients with emotional disorders and 47% of patients felt depressed. These symptoms have been described as usual sequelae of traumatic brain injuries, suggesting common patterns in the evolution of both syndromes [21].

Patients with HSE had a low case fatality rate during hospitalization in 2007 [2]. All surviving patients with HSE were started on treatment with acyclovir a mean of 1 day after onset (0–10 days) and treated according to recommendations [19]. A major improvement in the short-term outcome has been achieved, thanks to acyclovir, but our data emphasize their poor functional outcome and the need for further research to improve the long-term medical condition and quality of life in surviving patients. In contrast, we observed that patients surviving acute encephalitis due to tuberculosis or listeriosis had a favorable long-term outcome, although these bacteria accounted for the highest case-fatality rate in the early stage of the disease [2]. However, these results should be carefully interpreted considering the low number of patients. Unexpectedly, both enrolled patients with Mycoplasma encephalitis had major disability at follow-up. The diagnosis in these 2 patients was achieved by demonstrating seroconversion during the acute episode. No large series have been published, but a meta-analysis demonstrated that more than half of the patients with Mycoplasma encephalitis fully recover [22, 23]. We enrolled few patients with Mycoplasma encephalitis because of a stringent case definition for confirmed cases; therefore, these 2 patients might not be representative of the previously reported clinical case patients.

The association of initial clinical presentation with short-term prognosis has been reported in the literature [1, 2, 8]. By contrast, no clinical features of the acute episode were associated with the long-term outcome in our patients. This might be explained by the death during initial hospitalization of those patients with the more severe acute clinical presentation. It could also be hypothesized that the acute presentation is related to specific neurological lesions and nonspecific infectious pathophysiological process, the second being absent at the time of follow-up. As for the long-term outcome, the negative independent association of favorable outcome with comorbid conditions and age was expected. All groups of infectious agents, except VZV, displayed a better outcome than HSE. Finally, the main finding was the association of the level of education with the outcome. Such association has been known for years for stroke and traumatic brain injury but, to our knowledge, had never been described for encephalitis [24–28]. It might be explained by a better ability for relearning in these patients or by a higher income in the household, allowing better long-term management of impairment. These first results need further confirmation before one can conclude that patients with low levels of education require specific care after discharge.

We found an important proportion 25% of patients previously employed were unable to return to work and 34% of those who resumed work required an adaptation of their tasks. This emphasizes the heavy burden of encephalitis sequelae. As the outcome, return to work was associated with high levels of education. One explanation could be that decreasing the level of responsibilities is easier for persons with managerial occupations encompassing various tasks than for those with manual or unskilled jobs, for whom a comparable impairment might become a major disability, resulting in complete inability to work.

The strengths of our study are its prospective design, the number of patients, and their various etiological diagnoses. Their enrollment during a 1-year period makes it unlikely that their outcome was influenced by the evolution of patients’ management. The crossed interviews of the patients, their relatives, and GPs probably limited the risk of underestimating or overstating of persisting symptoms.

Our study does have some limitations. First, because of a lack of funding, patients underwent neither clinical nor neuropsychological examinations. However, previous studies have demonstrated that encephalitis sequelae could be valuably evaluated by telephone interview [20, 29]. Furthermore, clinical features were reported by the GP following up the patients. The GOS has been proved valuable to assess the outcome after severe head injury [30] and encephalitis [1, 5, 8]. Despite clear guidelines avoiding misclassification, patients sharing the same score can present with very different levels of impairment [16, 17].
Table 5. Results of the Main Studies of Long-term Outcome of Encephalitis

<table>
<thead>
<tr>
<th>Year</th>
<th>Cases, No.</th>
<th>Study Design</th>
<th>Causative Agents</th>
<th>Length of Follow-up</th>
<th>Assessment</th>
<th>GOS</th>
<th>Frequency of Sequelae or Persisting Symptoms</th>
<th>Most Frequent Sequelae or Persisting Symptoms</th>
<th>Comment</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1923</td>
<td>12</td>
<td>Case patients series, monocentric study</td>
<td>Undetermined</td>
<td>1–3 years</td>
<td>Specific neurological and psychiatric examination</td>
<td>No</td>
<td>10/12 (83%)</td>
<td>Personality change, insomnia, mental deficiency, motor deficiency</td>
<td>Before infectious diseases diagnosis, treatment, or imaging; all pediatric patients</td>
<td>Ebaugh [4]</td>
</tr>
<tr>
<td>1978–1987</td>
<td>23</td>
<td>Cohort study, monocentric study</td>
<td>7 HSV, 2 VZV, 2 rubella, 1 adenovirus, 11 undetermined</td>
<td>1–8 years</td>
<td>Specific neurological and psychiatric examination</td>
<td>No</td>
<td>15/23 (65%)</td>
<td>Depressed mood in 35%, depression in 26%, decreased exercise tolerance in 22%, labile mood in 17%</td>
<td>All adult patients</td>
<td>Berlit [13]</td>
</tr>
<tr>
<td>Before 1990</td>
<td>4</td>
<td>Case patient series, monocentric study</td>
<td>All HSV</td>
<td>1–3 years</td>
<td>Mini-Mental State Examination, intelligence scales</td>
<td>No</td>
<td>4/4</td>
<td>Dysnomia, decreased intelligence, amnesia, and learning difficulties in all patients; 1 patient suicidal, depressed, and violent; 2 unable to return to work; 2 returned to work with decreased level of responsibility</td>
<td>Acyclovir available, PCR not available</td>
<td>Gordon [7]</td>
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<tr>
<td>1983–1995</td>
<td>42</td>
<td>Case patient series, multicenter study</td>
<td>All HSV</td>
<td>6 months to 11 years</td>
<td>Mini-Mental State Examination, short-term memory assessment, and GOS</td>
<td>Yes</td>
<td>1st part: 30% with poor outcome; 2nd part: 1/12 unchanged, 2 deteriorated</td>
<td>Amnesia in 69%, behavioral disorders in 45%, trouble concentrating in 20%, irritability in 35%, disorientation in 7%, speech disorders in 18%</td>
<td>PCR not available during early period of study</td>
<td>McGrath [5]</td>
</tr>
<tr>
<td>1990–1994</td>
<td>45</td>
<td>Cohort study, monocentric study</td>
<td>8 HSV, 7 VZV, 9 with other causative agents, 21 undetermined</td>
<td>1st part: 45 months (SD, 16); 2nd part: 36 months after 1st evaluation</td>
<td>Complete neuropsychological assessment</td>
<td>No</td>
<td>1st part: 60% cured, 15% dead</td>
<td>Personality changes, amnesia, cognitive decline</td>
<td>All adult patients</td>
<td>Hokkanen [10]</td>
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<td>1991–1998</td>
<td>91</td>
<td>Cohort study, multicenter study</td>
<td>All HSV</td>
<td>6 and 12 months after discharge</td>
<td>Questionnaire with patients, family and GP</td>
<td>Modified At 6 mo, GOS scale</td>
<td>No data available</td>
<td>All patients enrolled in ICU; all adult patients</td>
<td>Raschilas [8]</td>
<td></td>
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<tr>
<td>Year</td>
<td>Cases, No.</td>
<td>Study Design</td>
<td>Causative Agents</td>
<td>Length of Follow-up</td>
<td>Assessment</td>
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<td>2000–2004</td>
<td>71</td>
<td>Case-patients series, monocentric study</td>
<td>TBE, 5 VZV, 5 enterovirus, 2 HSV, 4 RSV, 3 rotavirus, 11 others, 34 undetermined</td>
<td>3–8 years after encephalitis (mean, 5)</td>
<td>Questionnaire with parents</td>
<td>No</td>
<td>60% in children ≥5 y old, 48% in children &lt;5 y old</td>
<td>Personality change, amnesia, trouble concentrating, speech disorders</td>
<td>All patients &lt;17 y old, no difference according to causative agent</td>
<td>Fowler [11]</td>
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<tr>
<td>1992–2004</td>
<td>32</td>
<td>Case patient series, monocentric study</td>
<td>All undetermined</td>
<td>2–15 years after hospitalization</td>
<td>Questionnaire with patients</td>
<td>No</td>
<td>17/32 (53%)</td>
<td>Attention disorders, sensory deficit, abnormal cognition, depression, headache</td>
<td>All adult patients</td>
<td>Schmidt [20]</td>
</tr>
<tr>
<td>2005–2006</td>
<td>198</td>
<td>Cohort study, multicenter study</td>
<td>HSV, 19%; M. tuberculosis, 5%; VZV, 5%; noninfectious, 21%</td>
<td>6 months after discharge</td>
<td>No data available</td>
<td>Yes</td>
<td>By GOS score: 1, 12%; 2, 0%; 3, 23%; 4, 42%; 5, 43%</td>
<td>No data available</td>
<td>Measure of outcome encompassed death during hospitalization; study enrolled patients with infectious or noninfectious encephalitis</td>
<td>Granerod [1]</td>
</tr>
<tr>
<td>2010</td>
<td>176</td>
<td>Cohort study, multicenter study</td>
<td>HSV, 24%; VZV, 9%; M. tuberculosis, 6%; other causes, 13%; undetermined, 48%</td>
<td>27–40 months after onset (mean, 31)</td>
<td>Questionnaire with patients, family, and GP</td>
<td>Yes</td>
<td>By GOS score: 1, 5%; 2, 2%; 3, 14%; 4, 18%; 5, 61%</td>
<td>Trouble concentrating in 45.2%, behavioral troubles in 28.6%, speech disorders in 19.9%, amnesia in 19.3%</td>
<td>Measure of outcome encompassed only death occurring after discharge</td>
<td>Our study</td>
</tr>
</tbody>
</table>

Abbreviations: GOS, Glasgow Outcome Scale; GP, general practitioner; HSV, herpes simplex virus; ICU, intensive care unit; M. tuberculosis, Mycobacterium tuberculosis; PCR, polymerase chain reaction; RSV, respiratory syncytial virus; SD, standard deviation; TBE, tick-borne encephalitis; VZV, varicella-zoster virus.

* The modified scale in this article makes it impossible to compare all categories with other studies.
The IQCODE test was primarily designed for aged patients. However, we used it to assess cognitive decline in our study because it can be used in patients unable to undergo evaluation; the results are independent of premorbid intelligence and level of education; and the results correlate with those of the mini mental state examination [14]. The IQCODE has also been used in younger patients after stroke [31]. Cognitive decline and dementia have been described after HSE [10, 32] but have not been assessed in a population of patients with encephalitis of various origins. In our study, cognitive decline was found to be logically associated with age but not with any causative agent. Finally, 20 eligible patients could not be evaluated. We have no evidence as to whether or not they were unavailable for follow-up because of their sequelae. If we assume such a link, the long-term burden of encephalitis might be underestimated in our study.

CONCLUSIONS

We carried out what was to our knowledge the first long-term follow-up study in a population of patients with encephalitis of various infectious causes. Our results demonstrate the frequent evolution of acute infectious encephalitis toward a chronic neurological disease requiring long-term management. Although the prognosis of HSE has been dramatically improved by acyclovir, these patients still carry the heaviest burden of sequelae. Long-term evaluation and neuropsychological rehabilitation should be included in guidelines for the management of all patients with encephalitis, even those whose acute symptoms are apparently resolved at hospital discharge.

Notes

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Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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