CSF analysis in patients with sporadic CJD and other transmissible spongiform encephalopathies


Keywords: cerebrospinal fluid, Creutzfeldt-Jakob disease, transmissible spongiform encephalopathies

Introduction

The analysis of cerebrospinal fluid (CSF) in patients with suspected sporadic Creutzfeldt–Jakob disease (CJD) is an important investigation for the differential diagnosis. The detection of CSF 14-3-3 protein is a useful diagnostic test for this condition provided it is used in the appropriate clinical circumstances [1,2]. The major differential diagnosis of sporadic CJD is other neurodegenerative diseases such as Alzheimer’s disease; however, a small proportion of patients with suspected sporadic CJD may have inflammatory conditions that are potentially treatable [3]. Standard CSF examination has an important utility in identifying these conditions in patients with suspected transmissible spongiform encephalopathies (TSEs). There have been a number of studies showing that there are no substantial inflammatory changes within the CSF of patients with CJD, but most of these reports have only included small numbers of cases, single case reports or brief descriptions of results [4–9]. In this study, we describe the results of the white cell count, total protein and the detection of oligoclonal IgG found in neuropathologically confirmed cases of sporadic, genetic and variant CJD.

Methods

The study was conducted in the framework of an EC-supported multinational study. The countries involved were Greece, Germany, Italy, Poland, Spain, Slovakia, Switzerland and the UK. CSF lumbar punctures were performed as part of the routine diagnostic investigation of the patient by each of the requesting hospitals. As a part of this examination CSF white cell count, total protein and the detection of oligoclonal IgG were performed. All CSF samples investigated for oligoclonal IgG in this study were accompanied by a serum sample, and as such reflect true intrathecal IgG.

Patients with suspected Creutzfeldt-Jakob disease (CJD) often have routine cerebrospinal fluid (CSF) analysis performed to exclude treatable inflammatory conditions; however, little information is available about the range of results obtained for CSF tests in patients with sporadic CJD and other transmissible spongiform encephalopathies (TSE). Data from 450 patients with sporadic CJD and 47 patients with other TSEs were collected as part of an EC-supported multinational study. Raised white cell counts of >5 cells/μl were found in three of 298 patients with sporadic CJD, with two cell counts of 7 cells/μl and one of 20 cells/μl. Total protein concentrations of >0.9 g/l were found in five of 438 patients with sporadic CJD, although none had a concentration of >1 g/l. CSF oligoclonal IgG was detected in eight of 182 sporadic CJD patients. Of the patients with other TSEs, six had elevated cell counts ranging from 6 to 14 cells/μl but none had total protein concentrations of >0.9 g/l and one patient had detectable oligoclonal IgG. None of the patients with sporadic CJD or other TSEs had abnormalities in all three tests.
production. CSF samples were also sent to national laboratories for 14-3-3 analysis and the results of the white cell count, total protein and oligoclonal IgG were obtained by the centres from the notifying hospitals. The diagnoses of sporadic CJD and the other forms of TSE were made according to recognized neuropathological criteria and genetic analysis [10,11].

CSF analysis

CSF results were available from 450 patients with sporadic CJD, 40 patients with genetic CJD and seven patients with variant CJD (Table 1). All CSF samples included in the study were clear and colourless; six blood-stained CSF samples were excluded. The patient demographics are shown in Table 1. A white cell count >5 cells/μl was considered to be raised [12] and a total protein of >0.6 g/l was considered to be abnormal [13].

Statistics

All statistical analyses were performed using SPSS 11.0 for Windows 2000 (SPSS Inc., Chicago, IL, USA). Mann–Whitney tests were used to assess differences between quantitative variables. All statistical analyses were performed by P S-J.

Results

Raised white cell counts were detected in three of 298 patients with sporadic CJD, five of 26 patients with genetic CJD and one out of six patients with variant CJD. Of the three patients with sporadic CJD with raised white cell counts, two patients had cell counts of 7 cells/μl and the remaining case had a cell count of 20 cells/μl. In the genetic CJD cases, the cell counts were 6 cells/μl (one patient), 8 cells/μl (one patient), 10 cells/μl (two patients) and 14 cells/μl (one patient). In none of these cases was there a history of epileptic fits, infection or preceding lumbar puncture to account for the presence of a raised white cell count. The single patient with variant CJD who had an elevated white cell count, had a cell count of 8 cells/μl. All of these cases had microscopic examination of the CSF and none had an elevated red cell count. Detailed information on the differential cell count was available in only three of the genetic CJD cases but not in any of the sporadic CJD cases or in the variant CJD case. The differential white cells counts in the three genetic CJD cases were 88% monocytes, 9% lymphocytes and 3% monocytes (case with 6 cells/μl); leukocytes (case with 10 cells/μl) and lymphocytes (case with 14 cells/μl).

Total protein concentrations of >0.6 g/l were found in 44 of 438 patients with sporadic CJD, although only five of these patients had levels of >0.9 g/l and none had a value of >1 g/l. These five patients had a relatively late onset of disease (median 75 years; range: 66–82) and a median disease duration of 9 months (range: 2–15). Age at disease onset was significantly higher than that found in the sporadic CJD group with total protein concentrations of <0.9 g/l (median 66 years; range 19–88), \( P < 0.05 \). Two of these patients were homozygous for MM at codon 129 and the remaining three were heterozygous for methionine and valine. Only one patient with genetic CJD and one patient with FFI had total protein concentrations of >0.6 g/l but in neither of these cases did the protein concentration exceed 0.9 g/l. Oligoclonal IgG was detected in 4.4% of patients with sporadic CJD and in one patient with genetic CJD.

When the patients were considered together as a TSE group and the results of the tests combined, only 0.6% of patients had a raised total protein concentration and an elevated white cell count. Only 1% of patients had a raised total protein concentration plus detectable oligoclonal IgG. None of the patients had abnormalities in all three CSF parameters.

Discussion

A raised CSF total protein concentration was the most common abnormality found in this study, with 10% of sporadic CJD patients having concentrations of >0.6 g/l, and only 1.1% of patients had a total protein concentration of >0.9 g/l. Interestingly the median age at onset of disease of these latter patients was significantly higher than that of the rest of the sporadic CJD group. There is evidence that the concentrations of both

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Table 1 Patient demographics and number of patients investigated for each of the cerebrospinal fluid parameters, for each TSE group

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number</th>
<th>Females (%)</th>
<th>Median age at onset in years (range)</th>
<th>Median disease duration in months (range)</th>
<th>Number tested for WCC</th>
<th>Number tested for TP</th>
<th>Number tested for OCB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sporadic CJD</td>
<td>450</td>
<td>245 (54.4)</td>
<td>66 (19–88)</td>
<td>5 (1–48)</td>
<td>298</td>
<td>438</td>
<td>182</td>
</tr>
<tr>
<td>Genetic CJD</td>
<td>40</td>
<td>19 (59.4)</td>
<td>60 (41–77)</td>
<td>6 (2–34)</td>
<td>26</td>
<td>40</td>
<td>15</td>
</tr>
<tr>
<td>Variant CJD</td>
<td>7</td>
<td>2 (28.6)</td>
<td>33 (25–43)</td>
<td>14 (10–27)</td>
<td>6</td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>

WCC: white cell count; TP: total protein; OCB: oligoclonal IgG

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albumin and IgG within the CSF increase with age [14,15] and as both of these are the major proteins in CSF it suggests that the concentration of total protein will also increase with age. It has also been proposed that reduced CSF flow rate may increase total protein concentrations [16,17]. As body movement aids the CSF flow rate being bed-bound may reduce the CSF flow rate and, as a result increase CSF total protein concentrations. In this study, we found that the median disease duration in sporadic CJD patients with a CSF total protein concentration of > 0.9 g/l, was longer than those with total protein concentrations of < 0.9 g/l. Therefore, it is possible that the raised total protein concentrations found in these patients reflect the age and immobility of the patient rather than any underlying pathology.

The prevalence of CSF oligoclonal IgG in sporadic CJD was found to be 4.4%, which is less than that found in a previous study that reported a prevalence of oligoclonal IgG of 8% [9]. Interestingly, a study investigating patients with primary neurodegenerative dementia also found oligoclonal IgG in 7% of their patients, although only a few of these patients had neuropathological examination [18]. All of the patients in our study had neuropathological examination and none had evidence of an inflammatory disorder that would have accounted for the presence of oligoclonal IgG.

In the other sub-types of TSE investigated patients with genetic CJD had a higher frequency of raised white cell counts when compared with those with sporadic CJD. It is unclear at present whether this finding is due to the small numbers of genetic CJD cases examined or whether it is a genuine phenomenon.

This study has shown that whilst a small percentage of patients with CJD may have isolated increases in CSF white cell count or total protein the magnitude of these changes are small and that the presence of CSF oligoclonal IgG is also rare. None of the patients investigated had abnormalities in all three of these parameters which suggests that the isolated changes seen are not due to a classical inflammatory response. Raised white cell count and total protein in the CSF is unusual in TSE. The presence of > 20 cells/μl and/or 1 g/l of proteins in the CSF suggests an alternative diagnosis.

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Disclosure

The authors have reported no conflicts of interest.

References


