Accumulation of Prion Protein in the Peripheral Nervous System in Human Prion Diseases

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Abstract

After the finding that anti-prion antibodies stain sensory and sympathetic ganglia in variant Creutzfeldt-Jakob disease (vCJD), it was suggested that this localization supported the oral route of entry. However, prion accumulation subsequently also appeared in the peripheral nervous system (PNS) in sporadic cases. This study aims at evaluating the extent of prion protein accumulation in the PNS in all clinicopathologic subgroups of the disorder, with the exception of the familial and sporadic forms of fatal insomnia. Patients included 2 vCJD cases, 2 Gerstmann-Sträussler-Scheinker (GSS), 2 iatrogenic (iCJD), and 16 sporadic CJD (sCJD) cases. Gasserian (17) and spinal (9), celiac (2) and thoracic sympathetic (one) ganglia, spinal cord and medulla of one vCJD, 2 GSS, one iCJD, and 5 sCJD cases were examined. Immunostained sensory ganglia were seen in both vCJD, both iCJD, one GSS, and 10 sCJD cases; the celiac ganglion was positive in one of two sCJD cases, and the spinal dorsal horn and the medullary sensory nuclei were positive in one patient with vCJD, one with iCJD, and 3 with sCJD. Western blot demonstrated presence of PrPSc in the gasserian ganglion of one patient with sCJD. Accumulation of prion in ganglia (including autonomic) of the PNS, shared by all subgroups of spongiform encephalopathy, and in the dorsal horns and medullary sensory nuclei, shows that the sensory route is involved in the trafficking of this protein.

Key Words: Creutzfeldt-Jakob disease (CJD), Ganglia, Peripheral nervous system, Prion protein, Variant Creutzfeldt-Jakob disease (vCJD).

INTRODUCTION

Prion disease (Creutzfeldt-Jakob disease [CJD]) is a unique disorder that can occur in sporadic, acquired, and familial forms (1). It is characterized by accumulation in the central nervous system (CNS) of a protease-resistant 27- to 30-kDa protein, which most contain the infectious agent (2).

The pathogenesis of the sporadic form of CJD (sCJD) is still poorly understood; instead, in the variant form (vCJD), transmission from bovine spongiform encephalopathy (BSE) has been proven on biochemical (3) and epidemiologic grounds (4–6), as well as through transmission to inbred mice (7, 8) and primates (9). In addition, unlike sporadic CJD, the new variant is characterized by accumulation of abnormal prion protein in the tonsils (10) and other lymphatic structures (11).

The peripheral nervous system (PNS) is known to be involved in the spread of the disease to the CNS in spontaneous (12) and experimental (13–15) scrapie, experimental CJD (16), and BSE (17). However, evidence of accumulation of the protein in the PNS in the human forms of the disease is limited. Guirroy et al reported immunostaining of both sensory neurons and satellite cells in the gasserian ganglia of two patients with sCJD (18). More recently, Head et al described accumulation of the prion protein by immunohistochemistry in 5 of 7 thoracic and 3 of 6 gasserian ganglia in sCJD (19). On the other hand, no accumulation of abnormal prion protein was reported by others in the dorsal root ganglia in sCJD and Gerstmann-Sträussler-Scheinker (GSS) (20) or in sympathetic ganglia in sCJD (21). The accumulation in sympathetic (21) and sensory (22) ganglia in vCJD was interpreted by the authors as supporting the oral route of entry of the agent.

We undertook the study of a relatively large series of ganglia and of a smaller number of spinal cords of patients from a large number of clinicopathologic subgroups of CJD to extend the evidence of protein accumulation in the PNS to all the forms of the disease and to ascertain whether localization in selected subtypes could lend support to conclusions reached by some groups regarding the route of entry and the spreading of the prion protein.

MATERIALS AND METHODS

Specimens

Tissue for this study was removed at postmortem from the following 20 patients with neuropathologically confirmed diagnoses of CJD and two with GSS disease: 2 with vCJD, both male, one aged 21 years with a duration of 3 months and the other aged 26 years with 1-year-long illness; 2 with iCJD, one female aged 45 (dural graft 8 years before death) and one male aged 34 (administration of human growth hormone for 4 years beginning 20 years before death) and with duration of the disease 4 and 8 months, respectively; 16 with sCJD, 6 males and 10 females aged from 50 to 79 (mean 66.6 ± 8.9
years) and duration from one month to 4 years (9.3 ± 12.9 months). The 2 female patients with GSS (from the same family, see Discussion) were aged 51 and 46 with disease duration 3 and 5 years, respectively. Ganglia from 4 patients of similar age and with various diseases unrelated to CJD were also included in this study. In all 22 patients, the diagnosis was reached applying well-defined criteria for the disease (22–24). The following specimens of the PNS were studied: formalin-fixed gasserian ganglion (GG) from 17 patients, dorsal root ganglion (DRG) from 9 patients, and autonomic ganglia from 2 of the 22 patients; the spinal cord and medulla of nine of these patients (one vCJD, 2 GSS, one iCJD, and 5 sCJD); and frozen GG of one patient (case 22) with sCJD. The salient data regarding the patients, type of disease, and the ganglia studied are shown in the Table.

### Immunohistochemistry

Tissues were fixed in 10% buffered formalin for periods of time varying from 3 weeks (most cases) to several months or years for a small group of them. After inactivation of the prion protein for 1 hour with 98% formic acid, the tissue was embedded in paraffin. Five-μm-thick sections were immersed in alcohol-saturated picric acid for 15 minutes to remove formalin precipitates before being further processed for routine and immunohistochemical staining. For the latter, after blocking endogenous peroxidase with hydrogen peroxide in methanol solution for 15 minutes, sections were re-exposed to 98% formic acid for 15 minutes, autoclaved for 10 minutes in citric buffer at 121°C in a pressure cooker, and immersed in proteinase K (50 μg in 1 mL phosphate-buffered saline) for 5 minutes. The following anti-prion protein antibodies were used: KG9 (CJD Surveillance Unit, Edinburgh, U.K., 1/150), 6H4 (Prionics, Zurich, Switzerland, 1/2,000), and ICSM18 (Prion Unit, IoN, London, U.K., 1/50), and streptavidin peroxidase, according to the Labeled Streptavidin Biotin System (Dako, Cambridgeshire, U.K.). The number of immunostained ganglion cells and the intensity of the staining (peripheral, diffuse cytoplasmic) were assessed semiquantitatively and assigned an overall score as 1+, 2+, or 3+ (Table). The pattern of the immunostaining and the number of positive cells were virtually the same with the three antibodies; however, because the staining obtained with 6H4 was the sharpest and most intense, the features described in Results and

### Table. Subtype and Duration of Disease, Age, and Sex of Patients, Type of Ganglia, and Scores of Positive Staining in Ganglia and Spinal Cord

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Diagnosis</th>
<th>Sex/Age</th>
<th>Duration</th>
<th>Ganglia</th>
<th>Type</th>
<th>Score (IHC)</th>
<th>Cell Loss</th>
<th>Spinal Cord and Medulla</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>vCJD</td>
<td>M, 26</td>
<td>1 year</td>
<td>GG</td>
<td>GG</td>
<td>3+</td>
<td>2+</td>
<td>N/A</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>M, 21</td>
<td>3 months</td>
<td>GG</td>
<td>GG</td>
<td>3+</td>
<td>3+</td>
<td>N/A</td>
</tr>
<tr>
<td>3</td>
<td>GSS</td>
<td>F, 51</td>
<td>3 years</td>
<td>DRG</td>
<td>DRG</td>
<td>N</td>
<td>2+</td>
<td>N/N</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>F, 46</td>
<td>5½</td>
<td>DRG</td>
<td>DRG</td>
<td>2+</td>
<td>3+</td>
<td>N/N</td>
</tr>
<tr>
<td>5</td>
<td>iCJD</td>
<td>F, 45</td>
<td>4 months</td>
<td>GG</td>
<td>GG</td>
<td>1+</td>
<td>3+</td>
<td>N/A</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>M, 34</td>
<td>8 months</td>
<td>GG</td>
<td>GG</td>
<td>2+</td>
<td>2+</td>
<td>+/+</td>
</tr>
<tr>
<td>7</td>
<td>sCJD</td>
<td>F, 62</td>
<td>1 year</td>
<td>GG</td>
<td>GG</td>
<td>2+</td>
<td>3+</td>
<td>+/+</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>M, 79</td>
<td>1 month</td>
<td>GG</td>
<td>GG</td>
<td>2+</td>
<td>3+</td>
<td>N/A</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>M, 50</td>
<td>N/A</td>
<td>GG</td>
<td>GG</td>
<td>3+</td>
<td>3+</td>
<td>+/+</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>F, 79</td>
<td>1 month</td>
<td>GG</td>
<td>GG</td>
<td>N</td>
<td>3+</td>
<td>N/A</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>F, 67</td>
<td>1 month</td>
<td>GG</td>
<td>GG</td>
<td>N</td>
<td>3+</td>
<td>N/A</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>M, 55</td>
<td>6 months</td>
<td>GG</td>
<td>GG</td>
<td>2+</td>
<td>3+</td>
<td>N/A</td>
</tr>
<tr>
<td>13</td>
<td></td>
<td>F, 63</td>
<td>5 months</td>
<td>GG, DRG</td>
<td>GG, DRG</td>
<td>1+</td>
<td>3+ 3+</td>
<td>++/</td>
</tr>
<tr>
<td>14</td>
<td></td>
<td>F, 66</td>
<td>2 years, 4 months</td>
<td>GG</td>
<td>GG</td>
<td>1+</td>
<td>3+</td>
<td>N/A</td>
</tr>
<tr>
<td>15</td>
<td></td>
<td>F, 78</td>
<td>4 months</td>
<td>GG</td>
<td>GG</td>
<td>1+</td>
<td>3+</td>
<td>N/A</td>
</tr>
<tr>
<td>16</td>
<td></td>
<td>M, 58</td>
<td>7 months</td>
<td>DRG</td>
<td>DRG</td>
<td>N</td>
<td>3+</td>
<td>N/A</td>
</tr>
<tr>
<td>17</td>
<td></td>
<td>F, 61</td>
<td>4 years</td>
<td>GG, DRG</td>
<td>GG, DRG</td>
<td>N N</td>
<td>3+</td>
<td>N/N</td>
</tr>
<tr>
<td>18</td>
<td></td>
<td>M, 78</td>
<td>4 months</td>
<td>DRG</td>
<td>DRG</td>
<td>N</td>
<td>3+</td>
<td>N/N</td>
</tr>
<tr>
<td>19</td>
<td></td>
<td>F, 68</td>
<td>4 months</td>
<td>DRG</td>
<td>DRG</td>
<td>N</td>
<td>2+</td>
<td>N/A</td>
</tr>
<tr>
<td>20</td>
<td></td>
<td>M, 72</td>
<td>3 months</td>
<td>GG, DRG, CG</td>
<td>GG, DRG, CG</td>
<td>2+ 2+</td>
<td>3+ 3+</td>
<td>N/A</td>
</tr>
<tr>
<td>21</td>
<td></td>
<td>F, 68</td>
<td>7 months</td>
<td>GG, DRG, ThG, CG</td>
<td>GG, DRG, ThG, CG</td>
<td>2+ 2+</td>
<td>3+ 3+</td>
<td>N/A</td>
</tr>
<tr>
<td>22</td>
<td></td>
<td>F, 61</td>
<td>3 months</td>
<td>GG</td>
<td>GG</td>
<td>2+</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>1C</td>
<td>Abdominal tumor, MS</td>
<td>M, 73</td>
<td></td>
<td>GG, DRG</td>
<td>GG, DRG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2C</td>
<td>Cord compression</td>
<td>F, 89</td>
<td></td>
<td>GG, DRG</td>
<td>GG, DRG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3C</td>
<td>Ewing’s</td>
<td>M, 19</td>
<td></td>
<td>DRG</td>
<td>DRG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4C</td>
<td>Sjögren’s disease</td>
<td>F, 71</td>
<td></td>
<td>GG</td>
<td>GG</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GG, gasserian ganglion; DRG, dorsal root ganglion; CG, celiac ganglion; C, spinal cord; M, medulla; N, negative; PSP, progressive supranuclear palsy; N/A, not available.
Quantified in the Table, as well as the micrographs result from this staining.

**Morphometry**
Slides stained with hematoxylin and eosin were used to assess the extent of ganglion cell loss both in patients and four age-matched control subjects through a semiquantitative approach; all the nerve cells showing the nucleus and the total number of nodules of Nageotte and aggregates of satellite cells not surrounding any obvious nerve cell were counted. The severity of the loss was established as the ratio between the combined number of nodules of Nageotte and aggregates of satellite cells and the total number of these cells and of the viable neurones and defined as severe (> 15%, 3+), moderate (> 5%, 2+), or mild (< 5%, 1+).

**Western Blotting**
Homogenates of the GG of case 22 (10% w/v) were prepared in Dulbecco’s phosphate-buffered saline (PBS; lacking Ca2+ or Mg2+) by serial passage through needles of decreasing diameter. The homogenates were cleared of particulate matter by centrifugation at 1000 × rpm (80 × g) for 1 minute in a microfuge (Eppendorf). Samples of supernatant (10 μL) were removed and proteinase K added from a 10 mg/mL stock solution (prepared in water) to give a final concentration in the sample of 100 g/mL. After incubation at 37°C for 60 minutes, samples were centrifuged at 14,000 × rpm (15,800 × g) for 1 minute in a microfuge before terminating the digestion by the addition of an equal volume of 2 × SDS sample buffer (125 mM tris-HCl, pH 6.8, 20% v/v glycerol, 4% w/v sodium dodecyl sulphate, 4% v/v 2-mercaptoethanol, 0.02% [w/v] bromophenol blue) containing 8 mM 4-(2-aminoethyl)-benzene sulfonyl fluoride (AEBSF; Pefabloc SC, Roche, East Sussex, U.K.) and immediately transferred to a 100°C heating block for 10 minutes. Samples were centrifuged at 14,000 × rpm (15,800 × g) for 1 minute in a microfuge before electrophoresis in 16% tris-glycine gels (Novex; Life Technologies, Paisley, U.K.) according to the manufacturer’s instructions. Gels were electroblotted onto PVDF membrane (Immobilon-P; Millipore, Hertfordshire, U.K.) and subsequently blocked in phosphate-buffered saline containing 0.05% v/v Tween-20 (PBST) and 5% nonfat milk powder for 60 minutes. Blots were probed with a biotinylated anti-PrP monoclonal antibody (3F4 biotinylated-ICSM 35; 0.25 μg/mL in PBST containing 0.1% [w/v] sodium azide) for at least 60 minutes. After washing for 45 minutes with PBST, blots were incubated for 45 minutes with an avidin–biotin–alkaline phosphatase conjugate (Dako K0376) prepared in PBST, followed after washing for 60 minutes with PBST and 2 × 5 minutes with 20 mM Tris pH 9.8 containing 1 mM MgCl2 (1X assay buffer; Tropix, Inc., Bedford, MA) by development in chemiluminescent substrate (CDP-Star; Tropix, Inc.) and visualization on Biomax MR Film (Kodak, Harrow, U.K.). The relative sensitivity of detection of PrPSc by western blotting using CDP-star is approximately 20-fold higher than compared with conventional luminol based chemiluminescent substrates.

**RESULTS**

**Immunohistochemistry**
Immunostaining was detected in the ganglia of 15 of 22 patients. Because the intensity of the staining and the number of positive neurons in each ganglion varied among and within patients, a detailed description of each set of ganglia follows.

GG from 17 patients were examined: 2 vCJD, 2 iCJD, and 13 sCJD. In the first subgroup, immunostaining appeared as dark membrane-associated deposits as well as diffuse cytoplasmic staining (Fig. 1a). A small number of satellite cells were also stained (Fig. 1b). In the two patients with iCJD, the number of neurons showing immunoreaction was smaller than in the first subgroup; in addition, cytoplasmic and membranous staining was seen only in one patient whereas, in the other, only the latter was seen (Fig. 1c) and no satellite cells contained the deposit. In the ganglia of 10 of 13 patients with sCJD, only few cells per ganglion showed diffuse and membranous staining (Fig. 1d), most of them having only the peripheral pattern, with few positive satellite cells. Only one GG showed an intensity of the staining comparable to those described in vCJD (case 9).

DRG of 9 patients were available: 2 GSS and 7 sporadic Creutzfeldt-Jakob disease. Immunostaining was visualized in one ganglion of the former subgroup (Fig. 1e) and in 3 of 7 of the latter. In both subgroups, the deposits were exclusively or predominantly peripheral and did not involve satellite cells. In all four patients in whom both GG and DRG were available, results were similar in the 2 sets of ganglia (positive in 3 patients and negative in one).

The autonomic ganglia of 2 patients with sCJD (cases 20 and 21) were examined. The celiac ganglion (but not the thoracic sympathetic chain) was positive in the latter (Fig. 1f) and negative in the former.

**Morphometric Studies**
Results showed that the highest proportion of immunoreactive ganglion cells (score 3+) was reached by both patients with vCJD and one patient with sCJD (Table).

The severity of ganglion cell degeneration was calculated in the ganglia of all patients; results (Table) show that degenerating ganglion cells are seen in patients of all subtypes, although the severity of the loss varies from score 3 to 2. All controls showed a smaller degree (1) of degeneration (< 5%).

Of the 9 spinal cords examined, 5 resulted positive (one vCJD, one iCJD, 3 sCJD). Both patients with GSS, 2 with sCJD, and all 4 controls did not show any staining. Immune reactivity was particularly intense in laminae I-III (Fig. 1g).

Immunoreaction was seen in the medulla of the same 5 patients, but not seen in the 4 with negative spinal cord or in control subjects. The staining was moderate in the gracile and cuneate nuclei and invariably strong in the inferior olives.

**Western Blot Analysis**
Western blot analysis in the single gasserian ganglion available for this study revealed presence of PrPSc. Because a phosphotungstate precipitation had been used to increase sensitivity, the glycoform ratio could not be determined as
FIGURE 1. Immunolabelling of pathological PrP in the PNS of patients with the 4 subtypes of prion disease and in the spinal cord of a patient with sCJD. (a) Gasserian ganglion of a patient (n 1 in Table.) with vCJD. Note that the immunostaining appears both at the level of the cell membrane and within the cytoplasm. Magnification: 658X. (b) In the same ganglion, a small cluster of satellite cells appears diffusely immunostained. Magnification: 438X. (c) Gasserian ganglion of a patient (n 6) with iCJD. The immunolabelling is visible only at the periphery of the cell. Magnification: 658X. (d) In the gasserian ganglion of a patient with sCJD (n 12) the peripheral deposit of the immune reaction is associated with a diffuse and moderately strong cytoplasmic staining. Magnification: 658X. (e) Dorsal root ganglion cell of a patient (n 4) with GSS, showing strong peripheral immunostaining. Magnification: 438X. (f) Coeliac ganglion of a patient with iCJD (n 6). The strong peripheral staining is associated with a weaker cytoplasmic deposit. Magnification: 658X. (g) The dorsal horn of the thoracic cord of a patient (n 13) with sCJD shows intense immunostaining. Note the absence of reaction in both posterior and lateral columns. Magnification: 75X. Gasserian ganglion of a patient (case 1 in the Table.) with variant Creutzfeldt-Jakob disease. Note that the immunostaining appears both at the level of the cell membrane and within the cytoplasm. Magnification: 658X.
DISCUSSION

Our study examined sensory ganglia and a smaller number of autonomic ganglia of 22 patients with the sporadic, iatrogenic, and new variant forms of prion disease as well as with GSS disease. Results revealed the presence of proteinase-resistant prion protein in GG and DRG of 15 of 22 patients, belonging to all subtypes investigated, and in the celiac ganglion of one of 2 patients with the sporadic form. Immunoreactivity was diffuse and quite strong in the 2 patients with vCJD and in only one patient with sCJD; it was moderate with vCJD and in only one patient with sCJD; it was moderate with vCJD and in only one patient with sCJD and weak in the remainder, as well as in the ganglia of patients of the other subgroups. In addition, Western blot confirmed the presence of PrPres in one GG positive with anti-prion protein antibodies. The protein was of intermediate type between 2 and 3. These findings and the lack of evidence of iatrogenic prion disease are consistent with a sporadic form of prion disease in an individual with prion gene codon 129MV polymorphism.

Accumulation of abnormal PrP in the PNS is not an unusual finding in animals. It was detected by Groschup et al in peripheral nerves of one sheep with scrapie (12) and by the same group in sensory and autonomic ganglia of sheep and hamsters experimentally infected with scrapie (25). In addition, McBride and Beekes described accumulation of abnormal prion protein in dorsal root, nodose, and celiac ganglia of hamsters fed with scrapie (26).

In humans, Guiroy et al reported deposition of prion protein in trigeminal ganglia of 2 patients with sCJD (18), and more recently, Hań et al detected immunostaining in celiac ganglia of patients with vCJD, but not in the same ganglia of those with sCJD (21). In addition, Head et al found evidence of PrPres in peripheral ganglia in vCJD and sCJD, but not in similar ganglia in iCJD (19).

The localization of the immune reaction in somatic and autonomic ganglia in some subgroups of CJD has been used to discuss the port of entry of the infectious agent. On the basis of their findings in the autonomic ganglia, Hań et al suggested that in patients with vCJD, the infection followed the oral route (21). In support of this hypothesis, they quote the following data: detection of immunoreactive cells in autonomic ganglia of sheep and hamsters infected intraperitoneally with scrapie (25); comparable results in sympathetic ganglia of sheep and hamsters experimentally infected with scrapie (25). In addition, Head et al found evidence of PrPres in peripheral ganglia in vCJD and sCJD, but not in similar ganglia in iCJD (19).

The speculation of the route of spreading through the peripheral route is the pattern shown by Nailon and Ironside (22) and ourselves in one patient each with vCJD. In these, the accumulation appears particularly intense in laminae I–III of the cord. The strong staining of the sensory pathway, seen in the ganglia and spinal dorsal horns of our patients with vCJD, extends also to the gracile and cuneate nuclei. However, although there appears to be convincing evidence to support the idea that prion protein administered through the peritoneal or oral route follows the sensory pathway to reach the central nervous system, the immunohistochemical similarities between the findings in vCJD and those in the other subtypes of prion disease are not sufficient evidence to prove that the mechanism of spread is necessarily the same in all prion disorders. In particular, it is not possible (at the present state of our knowledge) to be certain about whether the spreading is centrifugal or centripetal. Although new findings may shed light on this issue, we suggest a more cautious approach such as that expressed by Guiroy et al (18). This is also supported by Zanusso et al, who examined the olfactory epithelium of patients with sCJD and could not conclude in favor of either the centripetal or centrifugal spread (29).

Studies of the PNS in familial forms of prion disease are too few in number and their sampling too small to draw any meaningful pathogenic speculations. Yamada et al examined the spinal cord and DRG of one patient with the P102L mutation (30). PrP protein immunoreactivity was seen in the grey matter, particularly in the substantia gelatinosa. The other hand, the absence of staining in the ganglia of the same patient, as well as in the ganglia of patients studied by Hainfeller and Budka (20), represents such a small sample that it cannot be taken as absolute proof of the sparing of these regions in GSS. Indeed, their conclusion is contradicted by the result in one of our patients with the same mutation (case 5 in...
Adam et al (31) and in one described by Yamada et al in whose ganglia there was evidence of prion protein deposition (30).

One of the main features of prion disease in the central nervous system is nerve cell loss. In tackling this issue in the PNS, we were aware that most of the patients with this disease, in particular those with sCJD, are above the seventh decade of life, a period in which cell loss in the DRG is a feature of aging (32). The severity of nerve cell death in ganglia was established by the number of nodules of Nageotte and by the presence of numbers of satellite cells surrounding degenerating ganglion cells. Our observation shows a variable but considerably high degree of loss in the ganglia of all patients, even among the younger and in those without evidence of prion protein in the surviving neurons. They are in keeping with those by Guiroy et al (18) but in sharp contrast with those by Yamada et al (30), who reported no obvious loss of ganglion cells.

In conclusion, our study has revealed immunostaining for prion protein in sensory ganglia of all subtypes of prion disease included in our investigation and shown that involvement of the autonomic nervous system is not exclusive to vCJD. The strong immunostaining in regions of the central nervous system representing the second-order sensory neurons as well as the strong correlation between the staining in these regions and that in the sensory ganglia suggest that the sensory pathway is involved in the trafficking of the prion protein, although, at present, there is no agreement regarding the direction of the flow.

REFERENCES


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