慢性耗损性疾病（CWD），一种可传染的慢性疾病，影响鹿和驯鹿，带来了新的挑战动物和人类健康。虽然CWD的传染给人类尚未得到证实，这仍然有其可能性。如果真是这样，它的重要特点是知道“获得”疾病的特征是否与Scrapie病原蛋白（PrPSc）特征不同，这些特征与人类慢病有关。在本研究中，我们比较了慢性耗损性疾病和CJD-受影响的鹿和鹿在多个受慢性Creutzfeldt-Jakob病（CJD）影响的物种中，以及CJD-受影响的个体，谁可能已被传染CWD，使用了图谱学、免疫组织化学、免疫沉淀和耐蛋白酶K蛋白序列。Spongiforma form changes and intense PrPSc staining were present in several subjects potentially exposed to CWD and non-exposed subjects.

Moreover, PrPSc of CWD exhibited a distinct constellation of glycoforms distinguishable from that of sCJDMM1 in two-dimensional glycoprofiling. N-terminal sequencing showed that the PK cleavage site of PrPSc in CWD affected elk and deer with those in subjects homozygous for methionine at codon 129 (sCJDMM1). Conformation stability assay also showed no significant difference between elk CWD PrPSc and the PrPSc species associated with sCJDMM1. However, there was a major difference in glycosylation of PrPSc between CWD and sCJDMM1 affecting both subjects potentially exposed to CWD and non-exposed subjects. Moreover, PrPSc of CWD exhibited a distinct constellation of glycoforms distinguishable from that of sCJDMM1 in two-dimensional immunoblotting. These findings underline the importance of detailed PrPSc characterization in trying to detect novel forms of acquired prion disease.

Chronic wasting disease (CWD),2 first described in 1967, was identified in 1977 as a transmissible spongiform encephalopathy or prion disease that affects both captive and free-ranging cervids (1, 2). Three species are known to be affected, mule deer (Odocoileus hemionus), white-tailed deer (O. virginianus), and Rocky Mountain elk (Cervus elaphus nelsoni) (3).

In addition to progressive loss of body weight, CWD is clinically characterized by abnormal behavior, polydipsia, hypersalivation, and occasionally ataxia and tremor (2, 4). The major histopathological features include spongiform degeneration, astroglisis, and neuronal loss, as in most other forms of prion disease (2, 4). However, in CWD these lesions are reported to have a distinct distribution (5, 6). In the central nervous system, the spongiform degeneration is apparently more prominent in subcortical regions, including the thalamus and hypothalamus, lower brain stem, cerebellum, and spinal cord, whereas the cerebral cortex is less affected or unaffected (5, 6). Kuru plaques, often surrounded by vacuoles as in the “florid” plaques of variant Creutzfeldt-Jakob disease (vCJD), the human prion disease acquired from the consumption of prion-containing beef, have been convincingly shown only in captive mule deer (7, 8). The disease-associated prion protein isoform (PrPSc) is detected by immunohistochemistry with a topography similar to, but wider than, that of the histological lesions (5–7). The immunostained PrPSc deposits have been reported to be dispersed in the parenchyma with a punctate or “synaptic” pattern, in addition to the loose clusters forming the so-called plaque-like pattern as well as packed clusters in the kuru plaques (7–11). The PrPSc deposits may line along the surface of neuronal cell bodies and processes as well as in the parenchyma immediately surrounding small vessels (7). Consistent PrPSc immunostaining has also been reported in the peripheral nervous system, especially the vagus and sympathetic nerves, lymphoreticular system, and visceral organs (5, 10).

CWD appears to be freely transmitted among the three susceptible species of cervids by direct or indirect horizontal contact (2, 4, 11). The oral port of infection through forage contaminated by feces or saliva from infected animals is considered the most likely mode of transmission (2–4, 11). Intra-species transmissibility and increased surveillance have contributed to the discovery that geographic distribution and

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2 The abbreviations used are: CWD, chronic wasting disease; CJD, Creutzfeldt-Jakob disease; vCJD, variant CJD; PrPSc, the disease-associated, scrapie isoform of prion protein; BSE, bovine spongiform encephalopathy; PK, proteinase K; GdnHCl, guanidine hydrochloride; mAb, monoclonal antibody; CHAPS, 3-[3-cholamidopropyl]dimethylammonio]-1-propanesulfonic acid.
prevalence of CWD are greater than previously suspected (2–4). In free-ranging and captive animals, CWD has now been detected in fourteen states in the United States and in two Canadian provinces, with a prevalence of up to 20% (2, 4, 12). Furthermore, CWD has been transmitted to a number of experimental animals, including laboratory mice, ferrets, mink, goats, and cattle (13, 14). The expanded geographic distribution and increased prevalence as well as the infectivity of CWD have raised questions concerning CWD transmissibility to humans. These questions are particularly alarming in North America where almost all the CWD-affected animals have been observed and a large number of hunters and their families regularly consume cervid meat. Although prion disease has been demonstrated in at least 27 hunters or their family members, as a group these cases were heterogeneous in terms of the clinical and pathological phenotypes, the PrP genotype, and the PrPSc subtype (15). Furthermore, the “hunter” cases appeared to fit rather well in the known subtypes of human prion disease (16). However, the phenotype of the human prion disease that might be acquired from CWD is not known; it might mimic any of the subtypes of sporadic CJD, making the detection of this hypothetical “CWD-acquired CJD” difficult. Thus far, the findings with the CJD in the hunter cases (15) contrast with the reports on vCJD, where affected cases have highly homogeneous features (17, 18). The homogeneity of vCJD has been contrast with the reports on vCJD, where affected cases have highly homogeneous features (17, 18). The homogeneity of vCJD has been attributed to the exposure of the affected individuals to the same type of PrPSc or prion strain associated with bovine spongiform encephalopa-thy (BSE) (19). Indeed, features of the BSE-associated PrPSc are reproduced in vCJD (20). By analogy, it is likely that the possible CWD-acquired CJD may reproduce the features of the PrPSc associated with CWD. To gain insights into important pathological features and molecular characteristics of PrPSc in CWD-affected elk and deer, we have carried out a comparative study of the histopathological, immunohistochemical, and PrPSc characteristics of CWD and sporadic CJD subjects as well as CJD-affected subjects who might have been exposed to CWD.

MATERIALS AND METHODS

Reagents and Antibodies—All chemicals were purchased from Sigma unless specified otherwise. Immobilized pH gradient strips (pH 3–10, 11 cm long), ampholine pH 3–10, and reagents for enhanced chemiluminescence were from Amersham Biosciences. Mouse monoclonal antibodies (mAb) against PrP 8H4 (21) and 3F4 (Signet Laboratories, Dedham, MA) were used in this study.

Brain Tissues—Tissue samples from free-ranging animals were collected from the wild, including seven mule deer (O. hemionus), one white-tailed deer (O. virginianus), and six Rocky Mountain elk (C. elaphus nelsoni). Brain tissues were stored at –80 °C until use. Brains from animals affected by CWD were diagnosed and characterized by histopathology, immunohistochemistry, and immunoblotting. Human brain tissue was processed and characterized as previously reported (16, 22). Brain tissue was obtained from five cases of elk and deer hunters who also had a history of regularly consuming elk and deer meat; one of these cases was also known to hunt in an area where CWD has been proven to be endemic. They were all homozygous methionine at codon 129, had PrPSc type 1 and a phenotype consistent with CJD, with an average age of onset of 71 years (range 61–84 years) and an average duration of 5 months (range 2–5 months). Sporadic cases of human CJD having either PrPSc type 1 or 2 were also used.

Molecular Genetics—Genomic DNA was extracted from frozen brain tissues. The open reading frame of cervid PrP gene was sequenced from both alleles as described previously (16).

Histology and Immunohistochemistry—Cervid brains removed at autopsy were fixed in formalin and sampled. Tissue blocks were kept in 98% formic acid for 1 h, followed by a second formalin fixation and paraffin embedding. They were then sectioned and prepared for histological examination according to standard techniques. For PrPSc immunohistochemistry, sections were immersed in 1.5 mM hydrochloric acid and microwaved for 15 min at 20% power. Sections were then rinsed and incubated for 2 h in a 4 mM guanidine thiocyanate solution at 4 °C. The endogenous peroxidase was blocked by incubation with 8% hydrogen peroxide in distilled water for 10 min. After rinsing, sections were incubated with mAb 8H4 at 1:600, washed, and incubated with Dako Cyto-\n
One- and Two-dimensional Immunoblot—Cervid and human brain homogenates (10%, w/v) were made in ice-cold lysis buffer (100 mM NaCl, 10 mM EDTA, 0.5% Nonidet P 40, 0.5% sodium deoxycholate, 10 mM Tris-HCl, pH 7.5), followed by centrifugation at 1,000 × g for 10 min at 4 °C to remove debris. An aliquot of the brain homogenate was digested with protease K (PK) at 50 µg/ml for 1 h at 37 °C. The digestion was terminated by the addition of 3 mM phenylmethylsulfonyl fluoride and an equal volume of 2× gel loading buffer (6% sodium dodecyl sulfate (SDS), 5% β-mercaptoethanol, 4 mM EDTA, 20% glycerol, 125 mM Tris-HCl, pH 6.8), followed by boiling for 10 min. In some cases, deglycosylated proteins were performed following precipitation with 5 volumes of methanol. The methanol-precipitated proteins were denatured and incubated with recombinant peptide N-glycosidase F according to the manufacturer’s protocol (Roche Applied Science). Deglyco-

S. G. Chen and P. Gambetti, unpublished data.
RESULTS

Histopathology of CWD—The cerebral cortex and basal ganglia of the elk with CWD show minimal fine spongiform degeneration and astrogliosis with focal distribution. The spongiform degeneration with astrogliosis is more prominent in the thalamus where it forms clusters of coarse vacuoles. Fine spongiosis, often in small clusters, is present in the molecular layer of the cerebellum, dorsal nuclei of the pons, and in the substantia gelatinosa of the spinal cord (Fig. 1A). Occasional large neurons in various nuclei of the pons show a vacuole (Fig. 1A). No kuru or multicore plaques are detected. Neuronal loss and astrogliosis are minimal except for the molecular layer of the cerebellum, which shows rarefaction of granule cells with no indication of apoptosis.

Immunohistochemistry—PrPSc immunostaining of the elk brain tissue affected by CWD shows rounded granular aggregates of various sizes and densities corresponding to the so-called plaque-like pattern (Fig. 1B). Occasionally small plaque-like formations are arranged in short rows or the immunostain is linear, consistent with staining of cell processes. When the plaque-like deposits are confluent and loose, the immunostaining is linear over gray structures, whereas in the spinal cord it is generally confined to the dorsal part of the dorsal horns.

Detection and Typing of PrPSc in CWD—Brain samples from a total of seven mule deer, one white tail deer, and six elk affected by CWD tested positive for PK-resistant PrPSc on immunoblots. PrPSc characteristics of CWD-affected animals were compared with those of sporadic CJD cases associated with either PrPSc type 1 or type 2 (using nomenclature of Parchi et al. (28)). Representative results from three mule deer, one white tail deer, and three elk samples are shown in Fig. 2. The bands of the unglycosylated form of PK-resistant PrPSc species from mule deer, white tail deer, and elk all migrated to ~21 kDa and match the gel mobility of human PrPSc type 1, but not type 2 (Fig. 2, A and B). However, the PrPSc associated with all three species of cervids differs significantly in the ratio of the three glycoforms from the human PrPSc type 1 associated with sCJD affecting subjects who were homozygous for methionine at codon 129 (sCJDMM1, Ref. 16) (Fig. 2C). In the PrPSc type 1 associated with sCJDMM1, the monoglycosylated form is predominant, accounting for 44–45% of all the glycoforms, whereas the diglycosylated and unglycosylated account for 21–24 and 31–35%, respectively (16). In contrast, both elk and mule deer PrPSc species show the prevalence of the diglycosylated, representing 47–50% of the total, whereas the monoglycosylated and unglycosylated forms represent ~30–33 and 20%,
respectively (Fig. 2C). This PrP\textsuperscript{Sc} glycoform ratio of CWD is similar to that of BSE and variant CJD (20).

Two-dimensional Immunoblot—We further compared the PK-resistant PrP\textsuperscript{Sc} species associated with CWD of mule deer, white tail deer, and elk with that of sCJDMM1 using two-dimensional gel electrophoresis. All gel profiles show three rows of well resolved spots. However, the molecular mass, representation, and number of these spots vary between the cervid and sCJDMM1 samples (Fig. 3). In CWD preparations not treated with N-glycosidase, the upper row migrates between ~29–30 kDa as compared with the upper row in sCJD preparations that is detectable between ~27 and 29.5 kDa. Furthermore, the upper row includes at least 8 spots, which migrate between pH 8.3 and 5.3 of the gradient in the CWD preparations, whereas there are 9 spots in sCJDMM1 that migrate between pH 6.7 and 5.0. The middle row includes at least 9 spots between pH 9.0 and 5.7 in CWD and at least 8 spots between pH 7.0 and 5.0 in sCJDMM1. The molecular mass range of the middle row also is different, being ~27.5–25.0 kDa in CWD and ~26.5–24 kDa in sCJDMM1. The third row also differs as it includes at least three spots of 21.5–22.5 kDa distributed between pH 9.0 and 7.0 in CWD, whereas at least four spots of ~22 kDa are seen in sCJDMM1 that migrate between pH 8.0 and 6.7. The two-dimensional gel also confirms that, although in sCJDMM1 the middle and lower rows are much more prominent than the upper row, the opposite happens in CWD, where the upper row is much better represented than the other two. The profiles of the PK-resistant PrP\textsuperscript{Sc} core proteins obtained following deglycosylation by N-glycosidase confirm that the PrP\textsuperscript{Sc} unglycosylated core proteins of sCJDMM1 and CWD have similar molecular weights (Fig. 3, B, D, F, H). However, in CWD, deglycosylated PrP\textsuperscript{Sc} species are more basic than that in sCJDMM1. This difference is especially noticeable between sCJDMM1 and mule deer and white tail deer PrP\textsuperscript{Sc} preparations. Whereas in sCJDMM1 PrP\textsuperscript{Sc} distributes over the ~5.8–8.5 pH gradient with the major spots located between pH 5.9 and 6.8, in CWD PrP\textsuperscript{Sc} migrates between pH 6.5 and 9.5 with conspicuous spots located at pH 8.5–9.5 (Fig. 3, B, D, F). The number of the spots is also different with six detectable spots in sCJDMM1 and 5 and 7 in the mule and white tail deer. The PK-resistant PrP\textsuperscript{Sc} core of elk CWD displays a pH gradient distribution between 5.8 and 8.5, similar to that of sCJDMM1, but the spots appear to form a quite different pattern (Fig. 3, B and H).

Conformational Stability Assay of PrP\textsuperscript{Sc}—Conformational stability assay has been used to distinguish different prion strains based on the concentration of GdnHCl needed to denature the PK-resistant PrP\textsuperscript{Sc} present in the individual strains. GdnHCl-dependent PrP\textsuperscript{Sc} denaturation is determined by the fraction of PrP\textsuperscript{Sc} that is rendered PK sensitive following GdnHCl treatment (24, 25, 29). The GdnHCl concentration required to make half of the total PrP\textsuperscript{Sc} sensitive to PK digestion (GdnHCl \(0.12\)) is used as a measurement of the relative conformational stability of PrP\textsuperscript{Sc}. The GdnHCl \(0.12\) was ~1.62 ± 0.01 M (n = 3) for PrP\textsuperscript{Sc} from CWD-affected elk and ~1.84 ± 0.17 M (n = 4) for PrP\textsuperscript{Sc} from sCJDMM1 (Fig. 4), but the difference was not statistically significant (p = 0.12, two-tail t-test). Our data indicate that there is no significant difference in the conformational stability between the two PrP\textsuperscript{Sc} species.

N-terminal Sequencing—Additional experiments have been carried out to further characterize the protein core of the PK-resistant PrP\textsuperscript{Sc} fragment associated with CWD and compare it with those of human PrP\textsuperscript{Sc} type 1. In two elk affected by CWD, we detected two major co-existing N-terminal sequences of PrP\textsuperscript{Sc} following treatment with PK (Fig. 5A), as previously observed in PrP\textsuperscript{Sc} type 1 associated with CJD (22). The N termini of the two fragments are at residues Gly-86 and Gly-82 (ref 22). These findings confirm that the main PK cleavage sites of PrP\textsuperscript{Sc} are the same in CWD and sCJDMM1 but different from those of prion associated with CJD. PrP\textsuperscript{Sc} from the Hunter Cases—Immunoblots of brain homogenates from five hunter cases who had a genotype of MM and carried PrP\textsuperscript{Sc} type 1 show gel migration of the PK-resistant PrP\textsuperscript{Sc} fragment at 21 kDa, indistinguishable from that of sCJDMM1 and CWD (Fig. 5A). However, the glycoform ratio of each of these cases matches that of sCJDMM1 (Fig. 6B), but not CWD (Fig. 2C).

DISCUSSION

Consistent with previous studies, we observed that spongiform degeneration involving the neuropil as well as the cell body of neurons is the histopathological hallmark of CWD in free-ranging elk, whereas argyrophilia and neuronal loss are generally minimal. These lesions preferentially affect subcortical regions, especially the thalamus and the lower brain stem where some anatomical structures are preferentially
affected. The immunostaining shows a PrPSc distribution in loose clusters of granules of different sizes, a pattern commonly defined as plaque like. Other patterns such as perivascular and perineuronal arrangements are occasionally seen. PrPSc has a wider distribution than the spongiform degeneration, so cerebral cortex and cerebellum that show minimal spongiform degeneration are relatively well immunostained for PrPSc.

The type and distribution of the histological lesions and of the PrPSc immunostaining in the cervid samples are different from those observed in human prion diseases. However, the lack of similarity between CWD and the human disease may be possible even if a subtype of CJD believed to be sporadic is actually acquired from CWD. Overwhelming evidence indicates that vCJD is caused by the transmission of BSE to humans (30, 31). Therefore, comparing BSE with vCJD may provide guidance on how to approach the issue of possible transmission of CWD to humans. The histopathology and the PrPSc immunohistochemistry of BSE are different from those of vCJD in the type and topography of the lesions as well as the pattern of the PrPSc immunostaining (32, 33). In BSE the lesions are most prominent in subcortical structures of the brain, especially basal ganglia, thalamus, hypothalamus, and selected regions of brain stem and spinal cord, whereas the cerebral and cerebellar cortices are minimally affected (33). Vacuole formation in the neuronal cell body is a prominent lesion in BSE, whereas kuru plaques are lacking (33). In contrast, vCJD is characterized by severe involvement of cerebral and cerebellar cortices and the presence of kuru plaques surrounded by vacuoles called florid plaques (32). Consistent with the different histopathology, PrPSc immunostaining in BSE is distributed as thick granules widespread in the neuropil but often with a perineuronal and perivascular distribution (33), whereas in vCJD the PrPSc immunohistochemistry is dominated by the intense staining of the kuru plaques. Contrary to the histopathology and immunohistochemistry, the characteristics of the PrPSc are fairly similar in BSE and vCJD (34): both PrPSc species are type 2 and have similar glycoform ratios (32). Assuming that if CWD is transmitted to humans it would follow the BSE-to-vCJD pattern of disease conversion in which histopathology and PrPSc immunostaining change but the basic characteristics of PrPSc are conserved, we have compared in detail the characteristics of the PrPSc associated with CWD with those of the PrPSc species associated with sCJD as well as with CJD in individuals who may have been exposed to CWD.

Sporadic prion disease can be classified into five distinct subtypes of sCJD and sporadic fatal insomnia, based on the methionine/valine polymorphic genotype at codon 129 of the PrP gene and the two conformers (types 1 and 2) of the brain PrPSc (16, 28). PrPSc types 1 and 2 are distinguished because, following treatment with PK, their protease-resistant and unglycosylated fragments migrate to ~21 and ~19 kDa on SDS-PAGE gels, respectively (28, 35). The distinct gel mobility is the result of the different size of the PrPSc fragments generated by the PK treatment, which cleaves the two PrPSc types at different sites, likely because the two PrPSc types have distinct conformations (22). Of the five subtypes of sCJD, two are associated with PrPSc type 1 (16). The first subtype includes patients who are homozygous for methionine (MM) or heterozygous methionine/valine (MV) at codon 129, identified as sCJDMM1 and sCJDVM1, respectively; the patients of the second subtype, identified as sCJDVV1, are homozygous valine at codon 129 (16). We have compared in detail deer and elk PrPSc only with the human PrPSc type 1 associated with sCJDMM1 because the gel mobility and N terminus following PK cleavage of the PrPSc associated with CWD are indistinguishable in elk, mule deer, and white tail deer and match most

**FIGURE 3.** Two-dimensional maps of PK-resistant PrPSc in brains of CWD-affected cervids and sCJDMM1. A and B, sCJDMM1; C and D, mule deer; E and F, white tail deer; G and H, elk. A, C, E, and G, N-glycosidase F untreated; B, D, F and H, N-glycosidase treated. Three sets of spots are seen in the two-dimensional blots of all the PrPSc species from both sCJD and CWD (A, C, E, and G). The spots formed by the cervid PrPSc extend more toward the basic part of the pH gradient (3.0–10.0) than those of sCJDMM1 PrPSc (compare panel A with C, E, and G). Note the relative overrepresentation of the diglycosylated and the underrepresentation of the unglycosylated form in cervid PrPSc as compared with sCJDMM1 PrPSc (A, C, E, and G). The deglycosylated PrPSc from the mule and white tail deer migrates toward the more basic part of the pH gradient (D and F), whereas the pH mobility of the deglycosylated elk PrPSc is more similar to that of the sCJDMM1 PrPSc (B and H). The position of molecular mass markers (in kDa) is indicated by dotted lines.
PrPSc in CWD and CJD

The glycoform pattern and ratio of CWD-associated PrPSc is in basic agreement with an earlier report by Race et al. (36) although they observed much greater variability among individual animals. This glycoform ratio is also similar to that of BSE and vCJD (20, 34, 36–38). We have recently demonstrated that the type, glycoform pattern, and ratio of elk PrPSc as reported here are reproducible upon transmission to cervidized transgenic mice (39). In contrast, the glycoform ratios observed in all forms of sCJD show an overrepresentation of the monoglycosylated form that accounts for ~50%, whereas between 20 and 30% each is accounted for by the other two forms. We found a similar ratio of the PrPSc glycoforms in several CJD-affected big game hunters who might have been exposed to CWD. These cases had the genotype, PrPSc type, and disease phenotype of sCJD, strongly suggesting that in these cases the CJD is likely sporadic and not acquired from the consumption of CWD-contaminated cervid meat.

Two-dimensional immunobLOTS of PK-resistant PrPSc from CWD and sCJDMM1 also demonstrate heterogeneity between the two profiles. The heterogeneity is likely to be in large part due to the difference in the type and amount of glycans in the two glycosylated isoforms present in PrPSc of sCJDMM1 and CWD. Although most of the heterogeneity between the glycosylated forms can be attributed to the different glycoform ratios, some is likely to be because of differences in electrical charges that probably reflect distinct characteristics of the glycans associated with PrPSc. However, heterogeneity persists even after deglycosylation, indicating that there is additional diversity between PrPSc from CWD and sCJDMM1, most likely related to the variations in amino acid sequence.

There are thirteen variant amino acids between human PrP residues 78–231 and corresponding sequences of deer and elk. The differences between elk and deer PrP sequences include one variant amino acid and three polymorphic amino acids. The effect of these variations in the PrP sequences is a change in the predicted pI values. It is predicted that in the region corresponding to human PrP-(78–231), deer and elk PrP will exhibit an increase in pI by 0.88 and 0.56, respectively, as compared with human PrP. Therefore, deer PrP is most basic, followed by elk PrP and human PrP. This is consistent with the result of two-dimensional...
immunoblots showing that deglycosylated PrPSc of deer migrated toward most basic pl, followed by that of elk and human. Other causes for heterogeneity may be related to the C-terminal glycolipid anchor that may contain various numbers of sialic acids or the presence of additional minor N-terminal cleavage sites, all of which may have contributed to some overlapping two-dimensional spots of human, elk, and deer PrPSc.

In conclusion, the parallel study of CWD that naturally occurs in elk and deer and of prion disease occurring in humans with or without a history of potential exposure to CWD reveals substantial differences in the type and distribution of the histological lesions as well as in the pattern of PrP immunohistochemistry. Similar findings have been reported when natural BSE and vCJD were compared. However, in BSE and vCJD the basic characteristics of PrPSc, such as protein type based on the size of the PK-resistant PrPSc fragment, and the glycoform ratio are similar. This is consistent with the notion that BSE PrPSc serves as template for the human PrPSc associated with vCJD. In contrast, although the size of the PK-resistant PrPSc fragment of CWD matches most closely that of sCJDMM1, the glycoform ratio of CWD PrPSc is different from that of the PrPSc associated with sCJDMM1 as well as all non-familial human prion diseases except for vCJD. Furthermore, CJDMM1 cases potentially exposed to CWD also had the same glycoform ratio as the other sporadic cases. These findings suggest that PrPSc associated with CJDMM1 (as well as sCJDMM1 and sCJDVV1) in several individuals (15) who were potentially exposed to CWD is not derived from the CWD PrPSc and therefore in these individuals CJD was not acquired from CWD. This conclusion is in agreement with the results of a recent experimental study on the transmissibility of elk CWD to various transgenic mice (39). Although CWD could be transmitted to transgenic mice expressing the elk PrP in a PrP knock-out background following an incubation of 118–143 days, none of the transgenic mice expressing the human PrP manifested prion disease during their lifespan following intracranial inoculation of CWD-affected brain homogenate, indicating that there is a substantial species barrier for transmission of elk CWD to humans. A recent report has shown that CWD can be transmitted to squirrel monkeys, a non-human primate (40). However, squirrel monkeys may not be used as a suitable model of human transmission of CWD. Although at present transmission of CWD to humans may be doubtful, should it occur it is likely that the PrPSc associated with this human prion disease may have a glycoform ratio similar to that of CWD. However, the resulting histopathology and PrP immunostaining patterns cannot be predicted. It is therefore important that the study of cases affected by non-familial CJD includes detailed analysis of the PrPSc characteristics.

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