Ultrastructural study of florid plaques in variant Creutzfeldt-Jakob disease: a comparison with amyloid plaques in kuru, sporadic Creutzfeldt-Jakob disease and Gerstmann-Straussler-Scheinker disease

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Background: Although the histological features of the amyloid plaques in variant Creutzfeldt–Jakob disease (vCJD) are distinct from those in other forms of prion disease [kuru, sporadic Creutzfeldt–Jakob disease (sCJD) and Gerstmann–Sträussler–Scheinker disease (GSS)], their ultrastructural features have only been described in a single case report. Aims: To study vCJD plaques systematically and compare them with plaques in kuru, sCJD, GSS and Alzheimer disease (AD). Methods: Amyloid plaques were studied by transmission electron microscopy and image analysis in five cases of vCJD, three cases of GSS, two cases of sCJD, one case of kuru and five cases of AD. Immunohistochemistry was performed on paraffin sections from one case of vCJD, two cases of GSS, one case of kuru and two cases of sCJD. Results: The florid plaques in vCJD were either compact or more diffuse; in both forms, the radiating fibrils were organized into thick ‘tongues’, in contrast to kuru plaques. Dystrophic neurites (DNs) containing lysosomal electron-dense bodies or vesicles surrounded florid plaques. Microglial cells were found within florid plaques; occasional amyloid fibrils were identified in membrane-bound pockets of microglial cells. In vCJD, there was significant tau immunoreactivity in DNs around florid plaques while, in sCJD, GSS and kuru, minimal tau immunoreactivity was observed around plaques. Conclusions: The ultrastructure of the florid plaques and DNs in vCJD is more reminiscent of neuritic plaques in AD than kuru or multicentric plaques. These findings may reflect differences both in the strains of the transmissible agents responsible for these disorders and in host factors.

Keywords: amyloid, Gerstmann–Sträussler–Scheinker disease, kuru, plaque, prion protein, sporadic Creutzfeldt–Jakob disease, variant Creutzfeldt–Jakob disease, ultrastructure

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Introduction

Amyloid plaques are a hallmark of transmissible and non-transmissible brain amyloidoses. The former comprise transmissible spongiform encephalopathies (TSEs) or prion diseases, which include kuru [1], Creutzfeldt–Jakob...
disease (CJD) [2], Gerstmann–Sträussler–Scheinker disease (GSS) [3,4] and fatal familial insomnia (FFI) [5]. There are also animal diseases – scrapie in sheep and goats [6], transmissible mink encephalopathy [7], chronic wasting disease (CWD) in deer and elk [8–10], and bovine spongiform encephalopathy (BSE) [11]. Of the non-transmissible amyloidoses, Alzheimer’s disease (AD) [12] and familial British dementia [13] are best recognized.

Human TSEs occur as sporadic, hereditary and infectious (iatrogenic) disorders [14,15]. CJD is a sporadic disorder (sCJD) in around 85% of cases; some 10–15% of CJD cases are hereditary, linked to over 20 mutations in the prion protein gene (PRNP); and the remaining cases are iatrogenic following neurosurgical procedures, administration of human growth hormone and gonadotrophins, and corneal or dura mater transplants [16]. Other familial forms of human TSEs include FFI and GSS. In 1996, a new variant form of CJD (now known as ‘variant’ CJD, or vCJD) was discovered, which results from exposure to BSE, probably by the oral route [17].

Amyloid plaques are restricted to certain subsets of human prion diseases: in sCJD, amyloid plaques occur in approximately 10–15% of cases that have been characterized as the MV2 subtype, according to the codon 129 polymorphism in the PRNP gene and the isoform of the disease-associated prion protein found on Western blot analysis of the brain [18]. These plaques closely resemble those seen in all cases of kuru (hence, kuru plaques) [19,20], but are structurally distinct at the light microscopic level from the florid plaques in vCJD [21] and the multicentric plaques in GSS [3,4,22]. There are no plaques in FFI; indeed, there are only relatively mild pathological changes in FFI anyway. In prion diseases in animals, amyloid plaques are common in different strains of rodent scrapie [23] and occur in all cases of CWD in mule deer [10]. In scrapie in sheep, they are only rarely present, and are absent in BSE in cattle; however, one recent novel form of cattle TSE reported in Italy (bovine amyloidotic spongiform encephalopathy or BASE) is characterized by amyloid plaques in the brain [24]. Most cases of ruminant TSE infections do not give rise to amyloid plaques.

The ultrastructure of kuru and multicentric plaques has been studied for decades, but the florid plaques that are characteristic of vCJD have been described at the ultrastructural level in only one case report [25]. To rectify this situation, we studied vCJD plaques systematically by light and electron microscopy and compared them with plaques in sCJD, GSS, kuru and AD. The hypothesis for this study is that vCJD amyloid plaques possess ultrastructural features different from amyloid plaques occurring in other human prion diseases; these ultrastructural differences are reflected in their unique light microscopic appearances.

Material and methods

Five cases of vCJD, three cases of GSS (one autopsy and two biopsy specimens), two cases of sCJD with plaques and one case of kuru [20] were used in this study. The clinical data of the vCJD cases are summarized in Table 1. One GSS case belonged to the original Austrian ‘H’ family [4,22]; the remaining two cases belonged to the German ‘Sch’ family, which has been previously described [26,27]. Both Austrian and German GSS families were carriers of 102Leu mutation in the PRNP gene; the codon 129 was homozygous for methionine in both the Austrian case and German cases [4,16,28]. All GSS cases fulfilled the neuropathological diagnostic criteria of Budka et al. [29]. Both of the sCJD cases were heterozygous at codon 129 in the PRNP gene. We also used archival brain specimens of a 16-year-old man who died from kuru in 1968 [20]. Furthermore, we studied five well-preserved biopsy and autopsy specimens of Alzheimer disease (AD) from the files of Department of Molecular Pathology and Neuropathology, Medical University, Lodz, Poland.

For electron microscopy, approximately 2-mm³ samples of grey matter from different brain regions were prepared.

Table 1. Basic clinical data on variant Creutzfeldt–Jakob disease (vCJD) cases

<table>
<thead>
<tr>
<th>vCJD cases</th>
<th>96/02</th>
<th>96/03</th>
<th>96/07</th>
<th>96/45</th>
<th>96/110</th>
</tr>
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<tr>
<td>Age (years)</td>
<td>41</td>
<td>29</td>
<td>30</td>
<td>31</td>
<td>35</td>
</tr>
<tr>
<td>Duration (months)</td>
<td>18</td>
<td>23</td>
<td>18</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>Sex</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>PRNP codon 129 genotype</td>
<td>MM</td>
<td>MM</td>
<td>MM</td>
<td>MM</td>
<td>MM</td>
</tr>
</tbody>
</table>

From vCJD, and the GSS case from the H family, we always studied at least four regions – frontal, temporal, occipital cortices and the cerebellum. Wherever possible, four blocks were studied from every region and at least two grids were prepared from every block. From the vCJD cases, we studied collectively 50 blocks. From the brain biopsy of the GSS case from the Sch family, only the frontal cortex was available. From the kuru case, one block from the frontal cortex and one block from cerebellum were studied. From the remaining cases, only single blocks were available. The tissue blocks were immersion-fixed in 2.5% glutaraldehyde for less than 24 h, embedded in Epon and routinely processed for electron microscopy; from a kuru case and one of the sCJD cases, material was reprocessed for electron microscopy from formalin-fixed paraffin-embedded blocks as described previously [30]. Grids were examined and photographed in JEOL JEM 100 CX and JEOL JEM 1011 transmission electron microscopes at 80 kV. Analysis of fibril diameter was performed using iTEM Soft Imaging System for transmission electron microscopy, Olympus, Japan and the diameters of 100 fibrils were measured in each case. For statistical analysis, only cases fixed in glutaraldehyde were included. A non-parametric Mann–Whitney U-test was used to compare group mean values for fibril diameters.

Additionally, we performed immunohistochemistry on paraffin sections of the frontal cortex and cerebellum from one vCJD case, two sCJD cases, two GSS cases and one kuru case. All the paraffin blocks used for immunohistochemistry were obtained from autopsy brain tissue, routinely fixed in 4% formaldehyde and embedded in paraffin. Antibodies used in the study are described in Table 2. For visualization of all immunolabelling, the LSAB+ Kit with horseradish peroxidase (DAKO, Ely, Cambridgeshire, UK) was used.

**Table 2.** Antibodies used for immunohistochemistry on paraffin sections

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Company</th>
<th>Clone</th>
<th>Host</th>
<th>Dilution</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA DR</td>
<td>DAKO</td>
<td>CR/3/43</td>
<td>Mouse IgG1</td>
<td>1:100</td>
</tr>
<tr>
<td>GFAP</td>
<td>DAKO</td>
<td>Polyclonal</td>
<td>Rabbit</td>
<td>1:3000</td>
</tr>
<tr>
<td>APP</td>
<td>Chemicon</td>
<td>22C11</td>
<td>Mouse IgG1</td>
<td>1:500</td>
</tr>
<tr>
<td>NFP</td>
<td>DAKO</td>
<td>2F11</td>
<td>Mouse IgG1</td>
<td>1:50</td>
</tr>
<tr>
<td>Tau</td>
<td>Pierce endogen</td>
<td>AT8</td>
<td>Mouse IgG1</td>
<td>1:200</td>
</tr>
<tr>
<td>PrP</td>
<td>Cayman</td>
<td>12F10</td>
<td>Mouse IgG2a</td>
<td>1:500</td>
</tr>
<tr>
<td>Ubiquitin</td>
<td>DAKO</td>
<td>Polyclonal</td>
<td>Rabbit</td>
<td>1:200</td>
</tr>
</tbody>
</table>

HLA DR, human leucocyte antigen DR; GFAP, glial fibrillary acidic protein; APP, amyloid precursor protein; NFP, neurofilament protein.

**Results**

Plaques in specimens of GSS and sCJD were of two major types: the first was stellate unicentric kuru plaques composed of a dense centre of interwoven fibrils and radiating fibrils at the periphery, and they were seen in both GSS and sCJD (Figure 1). The second type was found only in GSS specimens – multicentric plaques composed of several merging unicentric plaques (Figure 2). A particular plaque type – unicentric stellate amyloid plaques (florid plaques) – were readily identified in all vCJD specimens (Figure 3): they were most abundant in the occipital cortex and the cerebellum. These were either compact (resembling kuru plaques) or more diffuse; even in the more compact plaques, the radiating fibrils were organized into thick ‘tongues’ in contrast to kuru plaques. Irrespective of the region studied, no obvious differences were seen in the general ultrastructural features of the plaques in vCJD. The radiating tongues of amyloid that give the florid plaque a stellate appearance were also thicker than those in GSS and vCJD. It was noteworthy that, apart from florid plaques, smaller amyloid (fibrillar) structures – which have been called cluster plaques – were also seen in vCJD; however, it is impossible to be sure that those are not the poles of larger plaques cut tangentially. Numerous empty vacuoles were seen within and around florid plaques, which appeared as rather dilated ‘empty’ processes (as judged by remnant of subcellular organelles like mitochondria within them) and not typical ‘spongiform’ vacuoles. The latter term is used to describe ‘empty’ spaces containing curled membrane fragments and ‘fluffy’ material [31]. Thus, the nature of vacuoles surrounding florid plaques remains uncertain.

To demonstrate differences in amyloid fibril thickness, we performed analysis of fibril diameter using a morpho-
Figure 1. Gerstmann–Sträussler–Scheinker disease. (a, b, c) Different views of amyloid plaques. Note that some plaques are surrounded by a pale 'halo' composed of astrocytic processes (c, arrowheads). (c) Dystrophic neurites around a plaque (arrows).
metric system for transmission electron microscopy by measuring the diameters of 100 fibrils in every case. The mean diameter of a single fibril in GSS was 17.64 nm (range 12–22.99 nm) while, in vCJD, it was 21.37 nm (range 17.23–24.37 nm) and in AD – 14.24 nm (range 11.41–17.35 nm). As normality assumption for data distribution was not met for the AD and vCJD groups (Shapiro–Wilk W test significant) and variances could not be assumed as equal (Levene’s test for equality of variances significant for all three between groups comparisons), a non-parametric Mann-Whitney U-test was used to compare groups’ means as a post hoc procedure after a Kruskal–Wallis one-way analysis of variance ($\chi^2 = 215.2$; df = 2, $P < 0.001$).

In GSS, the mean value for fibril diameter ($17.6 \pm 2.5$ nm) was significantly larger than in AD ($14.2 \pm 1.4$ nm). Mann–Whitney U-test, $P < 0.001$. In vCJD, the group mean value ($21.4 \pm 1.8$ nm) was significantly bigger than in both GSS ($P < 0.01$) and AD ($P < 0.001$). Thus, the statistical analysis showed significant differences between these groups. The mean values for fibril diameters in kuru plaques in cases of kuru and sCJD were 23.40 and 27.06 nm, respectively, although these values were not statistically analysed due to the changes evoked by different fixation conditions from vCJD, GSS and AD cases. Fibrils from amyloid material retrieved from paraffin blocks are usually much thicker than in corresponding material directly fixed in glutaraldehyde; e.g. in GSS plaques, the fibril diameter from paraffin-embedded tissues is approximately 50 nm, approximately three times more than from the non-paraffin-embedded material. From these observations, we may therefore speculate that the real diameter of amyloid fibrils in kuru plaques from a case of kuru may be around 7–8 nm, consistent with data already published from material directly fixed in glutaraldehyde, which give a fibril diameter of 7 nm [32].

Interestingly, florid plaques were neuritic – i.e. they contained dystrophic neurites; the latter contained lysosomal electron-dense bodies or vesicles (Figure 3). Dystrophic neurites (DNs) were found either at the margin of plaques or immersed within the centre of the plaque.

Figure 2. Amyloid plaques in (a) variant Creutzfeldt-Jakob disease (vCJD) in comparison to (b) Gerstmann–Sträussler–Scheinker disease. Note the vacuoles (arrowheads) around the vCJD plaque (a).
florid plaques of vCJD, DNs were also observed, mainly at the plaque margins. Microglial cells (Figure 4), not unlike those in GSS [33], were found within vCJD plaques and, in certain specimens, amyloid fibrils were clearly present in membrane-bound pockets of microglial cells. In two specimens from the temporal cortex in vCJD, Hirano bodies were found in cell processes in the neuropil close to florid plaques (Figure 5). In kuru, astrocytic processes were frequently seen at the margin of plaques. The ultrastructural differences between the various types of plaques are illustrated in Figure 6 and summarized in Table 3.

Recently, we realized that autophagy is an important contributor to the pathology of TSEs [34,35]. To this end, we observed many multivesicular bodies, which are involved in the process of microautophagy, in the vCJD cases [36]. Those subcellular organelles were often found within electron-lucent vacuoles of different sizes located at the margin of florid plaques (Figure 7). In AD, the ultrastructure of amyloid plaques was similar to that in earlier descriptions [37], with dense amyloid cores surrounded by corona of DNs; in contrast to the DNs of TSEs, those in AD contained paired helical filaments (PHFs).
Table 3. Comparison of ultrastructural features in various types of amyloid plaques in human TSEs

<table>
<thead>
<tr>
<th></th>
<th>Florid plaques (vCJD)</th>
<th>Kuru plaques (sCJD)</th>
<th>Multicentric plaque cores (GSS)</th>
<th>Kuru plaques (kuru)</th>
<th>Aβ plaques (AD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plaque size</td>
<td>Large</td>
<td>Medium*</td>
<td>Small, forming larger clusters</td>
<td>Small*</td>
<td>Various sizes</td>
</tr>
<tr>
<td>Average fibril diameter (range)</td>
<td>21.37 nm(17.23–24.37)</td>
<td>9–10 nm†</td>
<td>17.64 nm(12.6–22.99)</td>
<td>7–8 nm†</td>
<td>14.24 nm(11.41–17.35)</td>
</tr>
<tr>
<td>Dystrophic neurites</td>
<td>+++</td>
<td>Single</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Vacuoles</td>
<td>+++</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Microglia</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Astrocytic processes</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+</td>
</tr>
</tbody>
</table>

*In specimens retrieved from paraffin blocks.
†Estimated.

TSEs, transmissible spongiform encephalopathy; vCJD, variant Creutzfeldt–Jakob disease; sCJD, sporadic Creutzfeldt–Jakob disease; GSS, Gerstmann–Sträussler–Scheinker disease; AD, Alzheimer disease.
Figure 6. Comparison of plaque ultrastructure in (a) variant Creutzfeldt–Jakob disease (vCJD), (b) Gerstmann–Sträussler–Scheinker disease and (c) Alzheimer’s disease. Amyloid is labelled by arrows in (c) and (d), the latter also showing a dystrophic neurite (DN) in vCJD.
While the search for tubulovesicular structures (TVSs), the only disease-specific particles found in all TSEs at the level of electron microscopy [38], was not the aim of this study, we readily found them in all GSS specimens [39], but not in autopsy vCJD specimens. In contrast, TVSs were previously readily found in a brain biopsy vCJD specimen [40].

Immunohistochemistry for glial fibrillary acidic protein (GFAP) showed astrocytosis in all cases in both cerebral and cerebellar cortex. In the cerebellum, astrogliosis was most pronounced in the kuru case. The GFAP-positive cell processes were observed around the plaques and in the peripheral part of the plaques in kuru and, to a lesser degree, in sCJD. In vCJD and GSS, the astrocytic processes surrounded the plaques, but did not penetrate into the plaques. Immunohistochemistry for human leucocyte antigen DR (HLA-DR) revealed the presence of HLA-DR-positive microglial cells around the plaques in all cases. In GSS and vCJD, there was also significant HLA-DR immunoreactivity in the central parts of the plaques. Immunohistochemistry for amyloid precursor protein (APP) showed high numbers of APP-positive structures corresponding to DNs around the plaques in vCJD and GSS. In kuru and sCJD, we also observed some APP-positive distended processes, but they were dispersed throughout cortex and not gathered around the plaques. Immunohistochemistry for ubiquitin also revealed DNs at the plaque margin as well as some dispersed abnormal neurites in vCJD and in GSS. In kuru and sCJD, the number of ubiquitin-positive DNs was much lower and the intensity of staining for ubiquitin around the plaques was less intense (Figure 8). Similar results were obtained following immunohistochemistry for phosphorylated neurofilament proteins (NFP), which also demonstrated some axonal swellings in the cerebellar cortex in both vCJD and GSS. These structures were distributed randomly, not around the plaques. An interesting observation was made on immunohistochemistry for hyperphosphorylated tau with the AT8 anti-tau antibody. In vCJD, there was significant immunoreactivity in DNs around the plaques and some AT8-positive structures were also dispersed in the cerebral and, to a lesser degree, the cerebellar cortex (Figure 9a). In sCJD, GSS and kuru, immunoreactivity for tau was much less intense and was restricted to the periphery of the plaques, but not in the neuropil (Figure 9b–d).

Discussion

We describe herein the spectrum of amyloid plaques in vCJD. The most characteristic plaques of vCJD are florid plaques – stellate structures surrounded by vacuoles, visible in haematoxylin and eosin sections in light microscopy. Those plaques differ from unicentric kuru plaques of sCJD and multicentric plaques of GSS. Florid plaques are also unicentric, but they were of a less compact structure than kuru plaques, with constituent amyloid fibrils being thicker than those of sCJD/GSS. The diameter of the single fibril of a florid plaque measured in situ is much higher than in the amyloid plaques of GSS or AD. Merz et al. [41] showed that fibrils isolated from AD brain were 4–8 nm in diameter and fibrils from GSS brain were 7–9 nm. Those results also showed that AD fibrils are thinner in comparison with GSS. The differences between our numbers and those showed in Merz et al.’s [41] paper are most probably evoked by the different methodology of experiments (isolation and negative staining vs. fixed tissues and positive staining).

As in the plaques of GSS, but unlike most plaques of sCJD, florid plaques are neuritic – they contain DNs accumulating electron-dense lysosomal bodies and vesicles.
but many of these abnormal structures are mixed with amyloid fibrils. Thus, a subpopulation of DNs are situated not at the periphery of the plaque, but more often within the centre. The latter situation is not unusual in AD, where in a reconstruction of plaques using confocal laser microscopy, Masliah et al. [42] elegantly demonstrated that DNs are located at the plaque centre and their spurious location at the periphery reflects the plane of the section, not the real plaque structure. The plaque pathology in vCJD may, however, reflect the latter situation, as there are many more plaques in vCJD than in sCJD or even GSS, and thus there are more planes at which these plaques are sectioned for electron microscopy. In any case, the problem of whether small DNs within the plaque centre is an intrinsic characteristic of the florid plaque of vCJD, as already suggested in a case report from France [25], or an artefact of sectioning, requires computer-based image analysis for final elucidation. The ultrastructure of florid plaques of vCJD is reminiscent of neuritic plaques in AD, in spite of the obvious difference that a proportion of DNs in AD contain PHFs. It must be stressed, however, that a high proportion of DNs in AD do not contain PHFs [43].

The presence of neuritic dystrophy and occasional Hirano bodies in processes around the florid plaques of vCJD suggests that they might represent a neuronal reaction to the abnormal accumulation of amyloid. However, these changes are not present around other forms of PrP amyloid plaques, suggesting that differences in the conformation and arrangement of the amyloid fibres in different
forms of human prion disease may influence these reactions, or that there are other plaque constituents in vCJD that potentiate the neuronal reaction. Previous studies have suggested that tau accumulates within neuritic processes around plaques in some human prion diseases, including vCJD [44] and GSS [45]; on the other hand, the DNs in sCJD have been previously reported to accumulate NFP rather than tau [46].

Our immunohistochemical studies confirmed the presence of microglial cells, astrocytic processes and dystrophic neurites at the periphery of the plaques. Immunoreactivity with the AT8 antibody revealed hyperphosphorylated tau at periphery of the plaques in vCJD, in a distribution that is consistent with DNs. This finding is also reminiscent of AD plaques but, in contrast to AD, no PHF were observed within DNs in vCJD on electron microscopy. In contrast to a previous report [44], tau immunoreactivity in or around the plaques in kuru, GSS and sCJD was also observed. This difference is probably due to the lack of plaques in sCJD cases studied by Giaccone et al. [44]. To our knowledge, this is the first report on hyperphosphorylated tau immunoreactivity in sCJD and kuru.

All our GSS and vCJD cases were homozygous for methionine at codon 129 of the PRNP gene. Thus, we cannot conclude that the differences in plaque ultrastructure result from differences in PRNP codon 129 polymorphism as suggested by Cervenakova et al. [47]. All described kuru cases with plaques were homozygous for methionine or for valine [47,48]. However, the number of studied kuru cases was small, and the influence of the presence of valine at codon 129 on the clinical course and pathology of prion diseases require further investigation.

**Figure 9.** Differing patterns of ubiquitin immunoreactivity around amyloid plaques in human transmissible spongiform encephalopathies in neurites and in thread-like structures in the surrounding neuropil (anti-ubiquitin antibody with haematoxylin counterstain, × 600). (a) Variant Creutzfeldt–Jakob disease; (b) sporadic Creutzfeldt–Jakob disease; (c) Gerstmann–Sträussler–Scheinker disease; (d) kuru.
In conclusion, we can say that there are three types of amyloid plaques in vCJD observed by light microscopy: florid plaques, small kuru plaques (cluster plaques) and amorphous plaques. Ultrastructurally, all consist of thick amyloid fibrils, different from the amyloid fibrils seen in other human prion diseases. The florid plaques are not only surrounded by vacuoles, but also contain DNs, microglial cells and occasional Hirano bodies at their border; thus, the ultrastructural composition of florid microglial cells and occasional Hirano bodies at their only surrounded by vacuoles, but also contain DNs, other human prion diseases. The florid plaques are not amyloid fibrils, different from the amyloid fibrils seen in amorphous plaques. Ultrastructurally, all consist of thick florid plaques, small kuru plaques (cluster plaques) and amyloid plaques in vCJD observed by light microscopy: PRNP fined to cases that are heterozygous at codon 129 in the ance. In sCJD, kuru plaques are characteristically con- influences quantitative characteristics of amyloid pathology is the same ‘kuru plaque’ irrespective of the experimental model selected [53]. Thus, the strain difference influences quantitative characteristics of amyloid plaques, but not necessarily their ultrastructural appearance. In sCJD, kuru plaques are characteristically confined to cases that are heterozygous at codon 129 in the PRNP gene (as in our cases) [18]. Furthermore, the agent that causes vCJD is also the cause of BSE in cattle, which is characterized by a virtual absence of amyloid plaques in the brain [43], further highlighting the importance of host factors in the pathological phenotype of this group of disorders.

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