

Cerebral amyloid angiopathy with co-localization of prion protein and beta-amyloid in an 85-year-old patient with sporadic Creutzfeldt–Jakob disease

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Abstract We report on an 85-year-old woman with hypertensive cerebral arteriolosclerosis who presented with rapidly progressive encephalopathy leading to death within 4 months. Magnetic resonance imaging showed mild cortical atrophy consistent with her age and diffuse leukoariosis. Her CSF 14–3–3 protein was positive. Neuropathology showed severe spongiform change and gliosis in the grey matter and immunohistochemistry revealed diffuse prion protein deposition in a predominant synaptic pattern. She had no family history of neurological disorder and genotyping did not show any prion protein gene mutation, in keeping with a diagnosis of sporadic Creutzfeldt–Jakob disease. There was also diffuse amyloid angiopathy involving the cortical and leptomeningeal arterioles of the cerebral hemispheres and cerebellum and the capillaries of the grey matter. The amyloid angiopathy expressed beta-amyloid but

also prion protein and double immunostaining confirmed co-localization of both proteins in many vessel walls. Alzheimer's type pathology was restricted to a few diffuse beta-amyloid plaques in the entorhinal cortex and rare tangles in the hippocampus. Deposition of prion protein in cerebral vessels has been reported in a single case of stop codon 145 mutation of the *PRNP* gene. Co-localization of beta-amyloid and prion protein in the same amyloid plaque has been described in elderly patients with Creutzfeldt–Jakob or Gerstmann–Sträussler–Scheinker diseases but only exceptionally in cerebral amyloid angiopathy. In this patient, hypertensive cerebrovascular disease may have contributed to the failure to eliminate both proteins from the brain.

Keywords Cerebral amyloid angiopathy (CAA) · Beta-amyloid · Prion protein · Creutzfeldt–Jakob disease · Senile dementia Alzheimer's type (SDAT) · Perivascular spaces

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Introduction

Creutzfeldt–Jakob disease (CJD) and Alzheimer's disease (AD) are both characterized by the accumulation of an abnormally folded protein in the central nervous system (CNS). The accumulated protein is composed of PrP^{sc}, a pathologic isoform of the normal cellular prion protein (PrP^c) in CJD and of beta-amyloid (A β) in AD. Cerebral amyloid angiopathy with vascular deposits of A β is a frequent feature of AD [32, 34]. In contrast, deposition of PrP^{sc} in cerebral vessels is an exceedingly rare occurrence reported in a single case of stop codon 145 mutation of the *PRNP* gene in conjunction with abundant tau-positive neurofibrillary tangles [11, 12].

The coexistence of Alzheimer-type pathology in prion diseases has been reported in elderly patients with sporadic CJD [2, 3, 9, 14, 15, 19, 22, 23, 25, 28, 37], in Gerstmann–Sträussler–Scheinker (GSS) disease [1, 6, 13, 17] and more recently in a young patient with iatrogenic CJD [30]. Co-localization of A β and PrP in the same amyloid plaque has been described in elderly patients with GSS [4, 18, 24], in a series CJD patients with concomitant Alzheimer-type pathology [15] and, occasionally, in patients with Alzheimer-type pathology in the absence of spongiform encephalopathy [8, 20, 31]. CAA has been documented in a few case reports of elderly CJD [14, 19, 33] or GSS [18]. When available, immunohistochemistry showed that CAA always expressed A β and not PrP [14, 18]. Co-localization of A β and PrP in vessel walls has only been illustrated in a leptomeningeal arteriole of a CJD patient with severe leptomeningeal CAA [36].

We report a case of sporadic CJD in an 85-year-old patient with hypertensive arteriolosclerosis in whom co-localization of beta-amyloid and prion protein in the vessel walls raises the possibility of a common underlying mechanism of both types of CAA.

Case report

An 85-year-old female with a long lasting history of hypertension, hypercholesterolemia and supraventricular arrhythmia was referred to hospital because of recent cognitive impairment. She had no family history of dementia or any neurological disorder. She was a former maths teacher, was alert and independent and managed her life and budget adequately. Three months before admission, she made mistakes in her medications and presented with increasing speech and gait disturbances, drowsiness and urinary incontinence. On admission she was confused, somnolent with reduced language. Neurological examination confirmed marked intellectual slowing and revealed akinesia with cog wheel rigidity but no focal neurological signs. EEG showed diffuse slow wave activity and periodic sharp waves. Magnetic resonance imaging (MRI) showed mild cortical atrophy consistent with her age and diffuse leukoaraiosis. Routine blood and serum electrolytes were unremarkable. Cerebrospinal fluid (CSF) contained normal protein and 1 WBC/mm³, and was positive for 14–3–3 protein.

Her status worsened rapidly and she became bedridden, mute and unresponsive. She died 4 months after onset of the neurological signs.

Method

Postmortem was performed 6 h after death and was restricted to the brain. Samples from left frontal lobe and

left cerebellar hemisphere were immediately frozen for molecular biology. Gross examination of the brain was performed after 1 month fixation in 10% buffered formalin on coronal sections of the cerebral hemispheres and sections of the brainstem and cerebellum perpendicular to their axes.

Blocks from many regions of the cerebral hemispheres, brain stem and cerebellum were embedded in paraffin. Sections were stained with haematoxylin and eosin, Bodian silver impregnation combined with Luxol fast blue, periodic acid–Schiff, Congo red and Masson's trichrome.

Immunocytochemistry was performed on selected paraffin sections by an avidin biotin peroxidase technique, after formic acid pretreatment, using monoclonal antibodies raised against A β (beta/A4 amyloid protein, Dako Cytomation, Glostrup, Denmark 1/100), CD68 (Dako Cytomation, Glostrup, Denmark 1/100) and polyclonal antibodies raised against Tau protein (Dako Cytomation, Glostrup, Denmark 1/100) and GFAP (Dako Cytomation, Glostrup, Denmark 1/1,000). Prion protein immunohistochemistry was performed after 25 min hydrated autoclaving in distilled water and 5 min 99% formic acid at 241°C, using a panel of monoclonal antibodies (3F4, Signet, Dedham, MA, USA, 1/500; 12F10, Spibio, Montigny le Bretonneux, France 1/200; 4F2, CEA, Saclay, France, 1/500; SAF32, CEA, Saclay, France, 1/200; BAR233, CEA, Saclay, France, 1/200). Five samples of frontal cortex, occipital cortex, hippocampus, striatum and cerebellum from three non-CJD controls with CAA and one previously reported patient with CJD and CAA [14] were examined according to the same techniques.

For double immunostaining, a monoclonal antibody raised against the prion protein (12F10, Spibio, Montigny le Bretonneux, France 1/200) and a polyclonal antibody raised against A β protein (E50 kindly provided by Dr. T. Ushihara, Tokyo, Japan) were demonstrated using a 488 Goat anti mouse serum (Molecular Probes Interchim, Montluçon, France 1/250) and a CY3 anti-rabbit serum (Jackson ImmunoResearch, West Grove, PA USA 1/500).

The coding sequence of the prion protein gene was sequenced on both strands as previously described [27].

Results

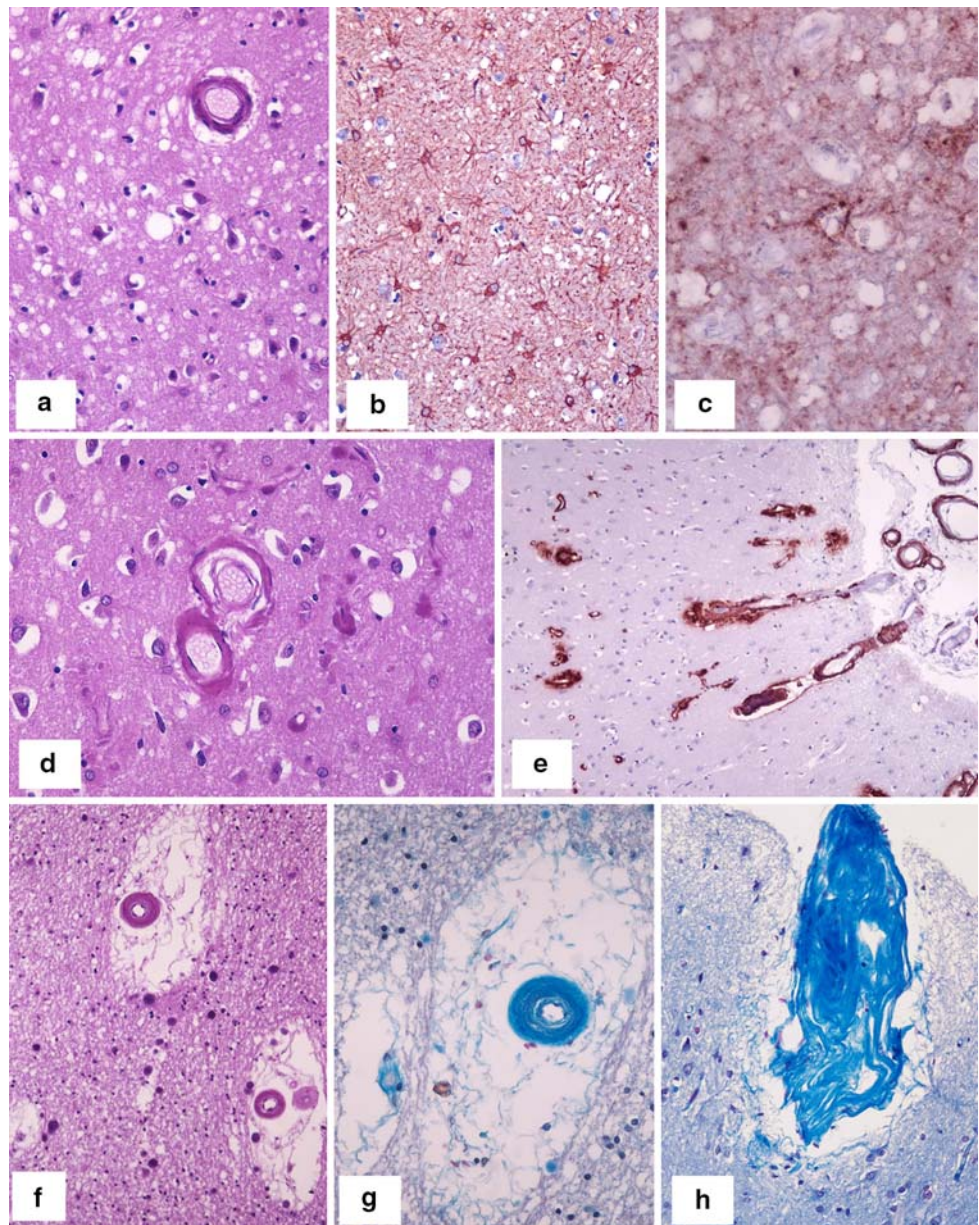
Gross examination of the brain (1,210 g) did not show significant cerebral atrophy or ventricular dilatation. There was slight greyish diffuse discoloration of the cerebral white matter associated with status cribrosus of the white matter of the gyri and of the basal ganglia. There was no significant thinning of the cerebral cortical ribbon which showed occasional microhaemorrhages. The caudate nuclei, substantia nigra and cerebellum were unremarkable. Intracranial vessels showed moderate non-stenosing atherosclerosis.

Microscopy showed changes characteristic of CJD including severe spongiform change (Fig. 1a), reactive astrocytosis (Fig. 1b) and microglial activation in the grey matter. These changes were diffuse in the cerebral cortex including the temporal cortex. Only the hippocampus was partially spared. They were maximal in the deeper layers of the cerebral cortex and were associated with significant neuronal loss. The striatum, thalamus and substantia nigra were also severely affected. In the cerebellum, there was spongiform change and gliosis of the molecular layer and severe loss of granule cells but Purkinje cells were mostly spared. Immunocytochemistry showed a diffuse synaptic [31] expression of PrP in the grey matter; it was mostly perineuronal and also perivacuolar (Fig. 1c). Occasional

plaque-like deposits of PrP were found in the granule cell layer of the cerebellum.

In addition, there was diffuse amyloid angiopathy involving the cortical and leptomeningeal arterioles, both in the cerebral hemispheres (Fig. 1e) and in the cerebellum and capillaries of the grey matter. The arteriolar walls were thickened with an acellular, hyaline and eosinophilic material (Fig. 1a, d) which was congophilic showing characteristic birefringence in polarized light. This infiltration was associated with arteriolar changes with a frequent “double barrel” appearance (Fig. 1d). There were a few microinfarcts and microhaemorrhages in the cerebral cortex. Amyloid infiltration also involved the capillaries and the adjacent parenchyma corresponding to the formerly

Fig. 1 Microscopic changes characteristic of CJD in the frontal cerebral cortex including: **a** spongiform change (H&E, $\times 200$) notice associated amyloid infiltration of an arteriolar wall; **b** hypertrophic astrocytosis (GFAP immunostaining, $\times 200$); **c** diffuse synaptic expression of PrP perivacuolar and perineuronal (3F4 immunostaining, $\times 400$). Cerebral amyloid angiopathy in the hippocampus (**d**) and occipital cerebral cortex (**e**): **d** associated amyloid angiopathy with a double barrel appearance of the lumen of an arteriole and pericapillary deposits (H&E, $\times 200$); **e** immunostaining of beta-amyloid shows involvement of the cortical and leptomeningeal arterioles and peri-capillary deposits in the depth of the cortex ($\times 40$). Microscopic changes characteristic of hypertensive small vessel disease in the white matter of the frontal gyri (**f, g**) and temporal subpial region (**h**): notice concentric fibrous thickening of the vessel walls and luminal stenosis (**f** H&E, $\times 100$; **g** Masson's trichrome, $\times 200$; **h** Masson's trichrome, $\times 200$). There is also dilatation of the perivascular spaces producing *status cribrosus* in the peripheral white matter of the gyri (**f, g**)



so-called “dyschoric angiopathy” (Fig. 1d). The amyloid angiopathy constantly expressed $A\beta$ (Figs. 1e, 2j, l). Expression of PrP in arteriolar walls and pericapillary areas varied according to the region examined. It was more frequent in regions in which PrP deposits were abundant, i.e. in the deeper layers of the frontal (Fig. 2a) and occipital (Fig. 2b, d–f) cortex and in the cerebellum (Fig. 2m). In the hippocampus about half of vessels expressing $A\beta$ also expressed PrP (Fig. 2c, k). PrP expression in arteriolar walls and pericapillary areas was constantly identified using different antibodies but its intensity varied somewhat according to the antibody used. It was stronger using 12F10 (Fig. 2b), SAF32 (Fig. 2e) or 4F2 (Fig. 2f) than with BAR233 (Fig. 2d). Interestingly, in the striatum where only a few pericapillary deposits of $A\beta$ were found (Fig. 2h), occasional arterioles with hypertensive changes (Fig. 2g) within areas of status cribrosus (Fig. 2i), expressed PrP. Fluorescence microscopy of double immunostaining confirmed co-localization of both proteins in the same vessel wall (Fig. 2n–p). In contrast, there was only minimal Alzheimer’s type pathology. A few diffuse amyloid plaques expressing $A\beta$ were found in the entorhinal cortex and tau pathology was limited to rare tangles in the pyramidal layer of the hippocampus. The arterioles showed severe diffuse changes characteristic of hypertensive small vessel disease including arteriolosclerosis (Fig. 1f–h) with concentric fibrous thickening of the vessel walls, luminal stenosis and focal lipohyalinosis. Although widespread, these changes were most marked in the white matter, basal ganglia and leptomeninges (Fig. 1h). They were associated with dilatation of the perivascular spaces producing status cribrosus in the basal ganglia (Fig. 2h, i) and peripheral white matter of the gyri (Fig. 1f, g). There was also diffuse myelin pallor in the deep periventricular white matter.

Genetic molecular study of frozen material did not show any mutation on the prion protein gene. The patient was homozygous for valine at the polymorphic codon 129 of *PRNP*. Immunoblotting of PrP performed on frozen cerebellum tissue identified PrP type 2A as classified by Parchi et al. [26].

Discussion

In this 85-year-old patient with a long history of hypertension who presented with a rapidly progressive encephalopathy leading to death in 4 months, neuropathology showed a combination of three different types of changes.

1. Diffuse arteriolar changes characteristic of hypertensive small vessel disease [21] associated with status cribrosus of the basal ganglia and peripheral cerebral white matter, and leucoencephalopathy with radiological leukoariosis, consistent with subcortical arteriosclerotic encephalopathy or Binswanger disease [7].
2. The classical triad of CJD in the grey matter including spongiform change, severe astrocytosis and neuronal loss, together with diffuse synaptic deposits of PrP in the absence of any known mutation of the *PRNP* gene and of any recognized exposure to iatrogenic risk factors was diagnostic of sporadic CJD. The clinical profile including ataxia at onset and the neuropathological features including predominant subcortical and cerebellar involvement and prominent perineuronal PrP staining with a few plaque-like focal deposits were consistent with the VV genotype at codon 129 of the *PRNP* and type 2 PrP^{sc}.
3. Diffuse CAA with both arteriolar and pericapillary deposits was associated with some secondary changes including cortical microinfarcts and micro haemorrhages [32], but with minimal Alzheimer’s type pathology.

The short duration of the disease strongly suggests that CJD was the main if not the only cause of dementia. In the absence of neuritic plaques and significant tau pathology, AD may be excluded according to the CERAD criteria [16] and it seems likely that the arteriosclerotic encephalopathy had evolved silently, long before the onset of the neurological signs.

The coexistence of Alzheimer-type pathology in prion diseases has been reported, mainly in elderly patients with sporadic CJD [2, 3, 9, 14, 15, 19, 22, 23, 25, 28, 37] one of whom also had alpha-synuclein inclusions [35], or in Gerstmann–Sträussler–Scheinker (GSS) disease [1, 6, 17] particularly in the Indiana kindred [13] and more recently in a young patient with iatrogenic CJD who underwent dura mater graft after a traumatic open skull fracture and in whom amyloid deposits were likely to be related to the childhood trauma [30]. CAA was mentioned in a few series [23, 37] and documented in rare case reports of elderly CJD [14, 19, 33] or GSS [18]. It was usually associated with abundant amyloid plaques in the cerebral cortex but in one case, as in the present one, amyloid plaques were not detected [14]. Immunohistochemistry, performed in two cases [14, 18] showed that CAA always expressed $A\beta$ and not PrP.

The association of PrP deposits and $A\beta$ deposits in arteriolar walls and around capillaries, with areas of co-localization of both proteins on double immunostaining, is an original finding.

Vascular deposits of PrP in the walls of small and medium-sized parenchymal and leptomeningeal vessels and in the perivascular neuropil associated with abundant neurofibrillary lesions in the cerebral grey matter has been reported in one single Japanese case with an Y145STOP mutation on a Met 129 allele of the *PRNP* gene [11, 12].

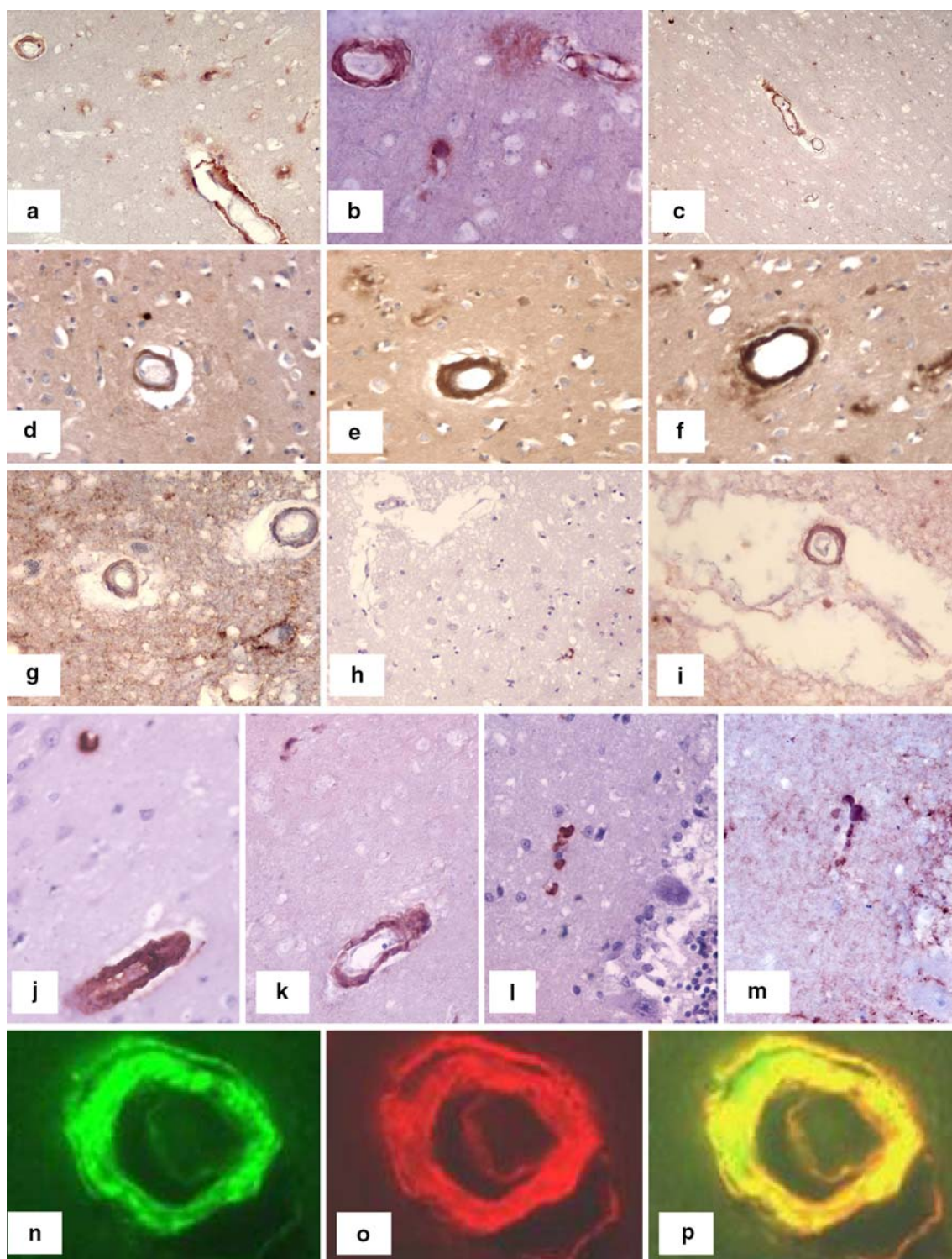


Fig. 2 Beta-amyloid and prion protein deposition in the vessel walls. PrP immunostaining showing positivity of arteriolar walls and capillary deposits in the deep cortical layer of the frontal cortex (**a** 12F10, $\times 200$) occipital cortex (**b** 3F4, $\times 300$) and temporal cortex (**c** 12F10, $\times 100$). PrP immunostaining in the occipital cortex using different antibodies shows variation in the staining intensity according to the antibody used (**d** BAR233, $\times 300$) (**e** SAF32, $\times 300$) (**f** 4F2, $\times 300$). PrP and A β immunostaining in the striatum showing PrP deposition in the walls of arterioles within status cribrus (**g** 3F4, $\times 300$; **i** 12F10, $\times 200$) whereas A β immunohistochemistry only shows rare capillary

deposits (**h**, $\times 75$); notice that the arteriole within status cribrus (*top*) is not stained. Serial sections of the hippocampus immunostained for beta-amyloid (**j** $\times 300$) and prion protein (**k** 3F4 $\times 300$) showing deposits of both proteins in the walls of a capillary (*top*) and an arteriole (*bottom*). Serial sections of the cerebellar cortex immunostained for beta-amyloid (**l** $\times 400$) and prion protein (**m** 3F4, $\times 400$) showing deposits of both proteins in the walls of a capillary. Double immunostaining for prion protein (**n** 12F10) and beta-amyloid (**o**) showing co-localization of both types of deposits in an arteriolar wall (**p**, $\times 1,000$)

This mutation was not found in our patient who, although elderly, had only minimal tau pathology.

In a wider study of cerebrovascular P-glycoprotein expression in CJD, the authors mentioned one case with severe leptomenigeal CAA who showed occasional small arteries with a co-localization of A β and PrP within the vessel wall [36].

Co-localization of A β and PrP in the same plaques has already been described in elderly patients with GSS [4, 18, 24] one of whom also had CAA expressing A β [18], and in 11 of 12 CJD patients with concomitant Alzheimer-type pathology [15]. There are several suggestions as to how this develops. The possibility that A β accumulation may be secondary to production of the precursor of A β in degenerative neurites around PrP deposits has been proposed in aged cases with GSS [4, 18] in whom the “hybrid” plaques had a PrP expressing core whereas A β was identified at the periphery. In contrast, in the “compound plaques” of elderly patients with co-existing CJD and AD, PrP accumulated at the periphery of A β plaques [15]. It was proposed that pre-existing A β acts as a microenvironmental factor influencing PrP^{res} genesis in CJD by promoting aggregation of one amyloidogenic protein onto a core composed by the other. A comparable mechanism was proposed to explain co-localization of A β and AL λ amyloid in cerebral blood vessel walls, in five patients suffering from CAA and spontaneous intracranial haemorrhage [10].

PrP immunoreactivity has been identified mainly at the periphery, but also throughout the A β plaques of non-CJD patients with AD, using different antibodies [8, 20, 31]. Disappearance of PrP staining after pre-treatment of the section with proteinase K in some cases [8], or negative Western blot analysis in others [20, 31] supports the view that these deposits represent normal cellular PrP. We believe our case is most unlikely to be due only to normal cellular PrP, since we did not find PrP positivity in the vessel walls of three controls with CAA examined using the same techniques. Furthermore, we did not observe PrP positivity in the vessel walls of a previously published case of CJD and CAA in whom double immunostaining clearly showed the vessel wall deposits only expressed A β whereas PrP expression was found only in the cerebral parenchyma, away from vessels [14]. Our findings were reproducible using different types of PrP antibodies particularly 12F10, the immunoreactivity of which is more disease-specific, restricted to cases of prion diseases [20]. Moreover, co-localization of PrP and A β in the vessel walls was not a constant finding and the proportion of vessels expressing both PrP and A β varied according to the region examined. In the hippocampus in which CJD changes and parenchymal PrP deposits were mild, many vessels only expressed A β . In contrast, PrP deposits were present in the walls of occasional arterioles

of the striatum showing hypertensive angiopathy and no A β deposition.

Another mechanism might explain the accumulation of both proteins in the vessel walls of our case. Capillary and artery basement membranes have recently been shown to act as “lymphatics of the brain” for drainage of fluid and solutes [5], particularly A β [29, 39]. Cerebrovascular disease may be a major factor in the failure of A β elimination from the ageing human brain due to loss of pulsation in arteriosclerotic arteries which abolishes the force necessary for protein drainage [40]. In our case, accumulation of A β was probably an age-dependent phenomenon and elimination of A β and insoluble prion protein resulting from CJD might have been impaired by severe hypertensive arteriosclerosis. This is compatible with the theory that drainage of disease-related prion protein follows the same route as that of A β , as already suggested for the only case with vascular deposits of PrP [38].

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