

CASE REPORT

F. Gray · F. Chrétien · P. Cesaro · J. Chatelain
 P. Beaudry · J.L. Laplanche · J. Mikol · J. Bell
 P. Gambetti · J.D. Degos

Creutzfeldt-Jakob disease and cerebral amyloid angiopathy

Received: 23 December 1993 / Revised, accepted: 11 February 1994

Abstract An 83-year-old female with no personal or familial neurological history developed progressive gait and speech disturbance and left motor deficit. She suffered intractable seizures and died 3 months after the onset of neurological signs. Neuropathology showed severe spongiosis and gliosis in the cortex and basal ganglia, and diffuse cerebral amyloid angiopathy. Immunostaining for prion protein (PrP) showed intense PrP positivity in areas of confluent spongiosis and some granular staining in astrocytes. The cortical vessel walls stained positively for β /A4 amyloid but not for PrP amyloid. Both types of amyloid were only observed in pericapillary parenchyma, in areas with severe spongio-

sis. There were only a few tangles and neuritic plaques in the temporal cortex; amyloid plaques were not present either by silver stains or immunostains. There was neither arteriopathic leukoencephalopathy nor cerebral hemorrhage. Immunoblot analysis of brain extracts revealed an abnormal proteinase K-resistant isoform of PrP. Association of Creutzfeldt-Jakob disease and Cerebral amyloid angiopathy in the absence of Alzheimer changes is unusual. The association of PrP and β /A4 amyloid deposits could have been fortuitous in an 83-year-old patient. An etiopathogenic relationship between β /A4 amyloid deposition and PrP accumulation may also be considered.

Supported by a Concerted Action of the European community
 This case was the subject of a preliminary presentation at the eighty-seventh meeting of the British Neuropathological Society [17]

Key words Creutzfeldt-Jakob disease
 Cerebral amyloid angiopathy · Prion protein
 β /A4 amyloid

F. Gray (✉)
 Département de Pathologie (Neuropathologie),
 Hôpital Henri Mondor, F-94010 Créteil cedex, France

F. Gray · F. Chrétien
 Laboratoire d'Anatomie Pathologique (Neuropathologie),
 Hôpital Raymond Poincaré, Garches,
 Faculté de Médecine Paris-Ouest, France

F. Gray · P. Cesaro · J.D. Degos
 Département de Neurosciences Médicales,
 Faculté de Médecine de Créteil, Université Paris-Val de Marne,
 France

J. Chatelain · P. Beaudry · J.L. Laplanche
 Service de Biochimie et de Neurobiologie, Hôpital Saint Louis,
 Paris, France

J. Mikol
 Service Central d'Anatomie et de Cytologie Pathologiques,
 Hôpital Lariboisière, Faculté de Médecine Paris VII, France

J. Bell
 Neuropathology Laboratory, Western General Hospital,
 The University of Edinburgh, UK

P. Gambetti
 Division of Neuropathology, Institute of Pathology,
 Case Western Reserve University, Cleveland, Ohio, USA

Introduction

Prion diseases are characterized by the accumulation of an abnormal protease-resistant isoform of a cell protein, the prion protein (PrP). Human prion diseases include three familial conditions: Gerstmann-Sträussler-Scheinker disease (GSS), familial Creutzfeldt-Jakob disease (CJD) and fatal familial insomnia (FFI) [31]; a sporadic form: sporadic CJD, and two transmitted forms: Kuru [37] and iatrogenic conditions. PrP accumulation is usually demonstrated by immunoblotting [31, 37]. At neuropathological examination, PrP accumulation may be obvious, forming extracellular amyloid deposits such as "Kuru plaques" or "multicentric plaques" in GSS [43]. This particular type of amyloid may be specifically recognized by immunocytochemistry which may also demonstrate small deposits not evident with classical amyloid staining [19, 26].

Cerebral amyloid angiopathy (CAA) is characterized by the deposition of amyloid within the walls of small to medium-sized arteries, in the cerebral cortex and leptomeninges [41]. In most cases, CAA is due to a

deposition of the Alzheimer β /A4 amyloid [41]; it is frequently associated with cortical changes characteristic of Alzheimer-type dementia (AD), i. e. senile plaques and neurofibrillary tangles (NFT), but is not necessarily related to these lesions [15, 43]. Severe CAA may also be responsible for spontaneous non-traumatic petechial and/or larger lobar cortical and subcortical hemorrhages [23], or be associated with leukoencephalopathy [15] or cerebral granulomatous angiitis [16].

Association of PrP amyloid and β /A4 amyloid deposition in the same brain has occasionally been described in elderly patients with GSS [6, 21, 32] or CJD [38]. We report a new case with the association of PrP amyloid and β /A4 amyloid in an 83-year-old patient with CJD and CAA in the absence of neuropathological evidence of Alzheimer's disease, cerebral hemorrhages or leukoencephalopathy, raising the possibility of a relationship between the mechanisms of deposition of these two types of amyloid.

Case report

An 83-year-old female with no family history of neurological disorder or relevant past medical history, was admitted to Henri Mondor hospital with a 3-week history of progressive weakness of her left arm, gait ataxia with frequent falls, slurred speech, sleep and memory disturbance. On admission, she was alert and conscious with moderate intellectual slowing, mild disorientation in time and place and intermittent dysarthria. Neurological examination showed a left motor deficit predominantly involving the upper limb; deep tendon reflexes were brisk but symmetrical; plantar responses were equivocal. A grasp reflex was present in the left hand and intermittent myoclonus in the proximal muscles of the left arm. There was no obvious sensory deficit, no signs of cerebellar involvement; cranial nerves were normal. CSF was unremarkable. CT scan, with and without contrast infusion, was normal. EEG revealed a slow wave epileptic focus in the right frontal lobe but no pseudo-periodic activity.

During hospitalization, her condition worsened rapidly, she became confused and drowsy, unable to walk, with severe dysarthria. Myoclonic jerks became permanent bilaterally, she developed generalized intractable epileptic seizures and died from aspiration bronchopneumonia, sepsis, and acute renal failure, 3 months after the onset of neurological signs.

Methods

Postmortem was performed 18 h after death and was restricted to the brain. Samples from the left frontal lobe 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 brain stem and cerebellum perpendicular to their axes.

Blocks from many regions of the cerebral hemispheres, brain stem and cerebellum were embedded in paraffin and in celloidin. Sections were stained with hematoxylin and eosin, Loye stain for myelin, Bodian silver impregnation combined with Luxol fast blue, periodic acid-Schiff, Congo red, and Masson Trichrome.

Immunocytochemistry was performed on selected paraffin sections by an avidin biotin peroxidase technique, utilizing formic acid pretreatment of tissue to enhance amyloid immunoreactivity, using polyclonal antibodies raised against β /A4 amyloid protein (Dako) and Tau protein (courtesy of André Delacourte). PrP was looked for using a polyclonal antibody (1A8, Dr. Hope, Edinburgh Neuropathogenesis Unit) after pretreatment by formic acid and guanidine thiocyanate as previously described [19]. All sections were counterstained with hematoxylin.

Double immunostaining was carried out after pretreatment with formic acid and microwave oven exposure [18] using the monoclonal antibody to PrP 3F4 [23] and a polyclonal anti- β /A4 amyloid (Dako). The monoclonal antibody was shown as a brown color by a peroxidase-antiperoxidase method with 3,3'-diaminobenzidine (DAB) as chromogen. For the polyclonal antibody the product was colored blue using an avidin-biotin system, and naphthol-AS-MX-phosphate/Fast blue BB as chromogen.

Immunoblot analysis was performed on frozen cortical brain tissue homogenized in a 0.32 M sucrose buffer. After incubation with proteinase K at a concentration of 85 μ g/ml, at 37°C for 3 h and precipitation by methanol, the pellet was exposed to 1% sarcosyl, then in a second step to guanidine thiocyanate 3 M. The final pellet was dissolved in 10 μ l of Laemmli sample buffer before electrophoresis in 12% SDS-polyacrylamide gel according to Laemmli [28] and a 2-h protein transfer to immobilon membrane (Millipore). The membrane was then incubated overnight at 4°C with a rabbit polyclonal antibody raised against the hamster PrP 27-30 (RO73, kindly provided by D. Serban and S.B. Prusiner [39]). Immunostaining was obtained using an alkaline phosphatase-conjugated donkey anti-rabbit IgG (Immunoresearch laboratories) shown by nitroblue tetrazolium and 5-bromo-4-chloro-3-indolylphosphate (Amresco). A known neuropathologically verified and PrP-positive CJD brain sample was prepared in the same manner and analyzed on the same gel.

For molecular genetic study, genomic DNA was purified from frozen cortical brain. The prion protein gene (*PrNP*)-coding region was screened for sequence variations using polymerase chain reaction (PCR) and denaturing gradient gel electrophoresis (DGGE). Oligonucleotide primers and conditions were as previously described in detail [36].

Results

Neuropathological study

Gross examination

Gross examination of the brain did not reveal any macroscopic abnormality. In particular, the brain was not atrophic (1280 g) and did not show any vascular changes. Large intracranial and cervical arteries were unremarkable.

Microscopic examination

Microscopy showed changes characteristic of CJD including severe spongiosis and hypertrophic astrocytic gliosis of the gray matter (Fig.1a). These changes involved the cerebral cortex predominantly, most marked in the occipital, frontal and parietal areas bilaterally.

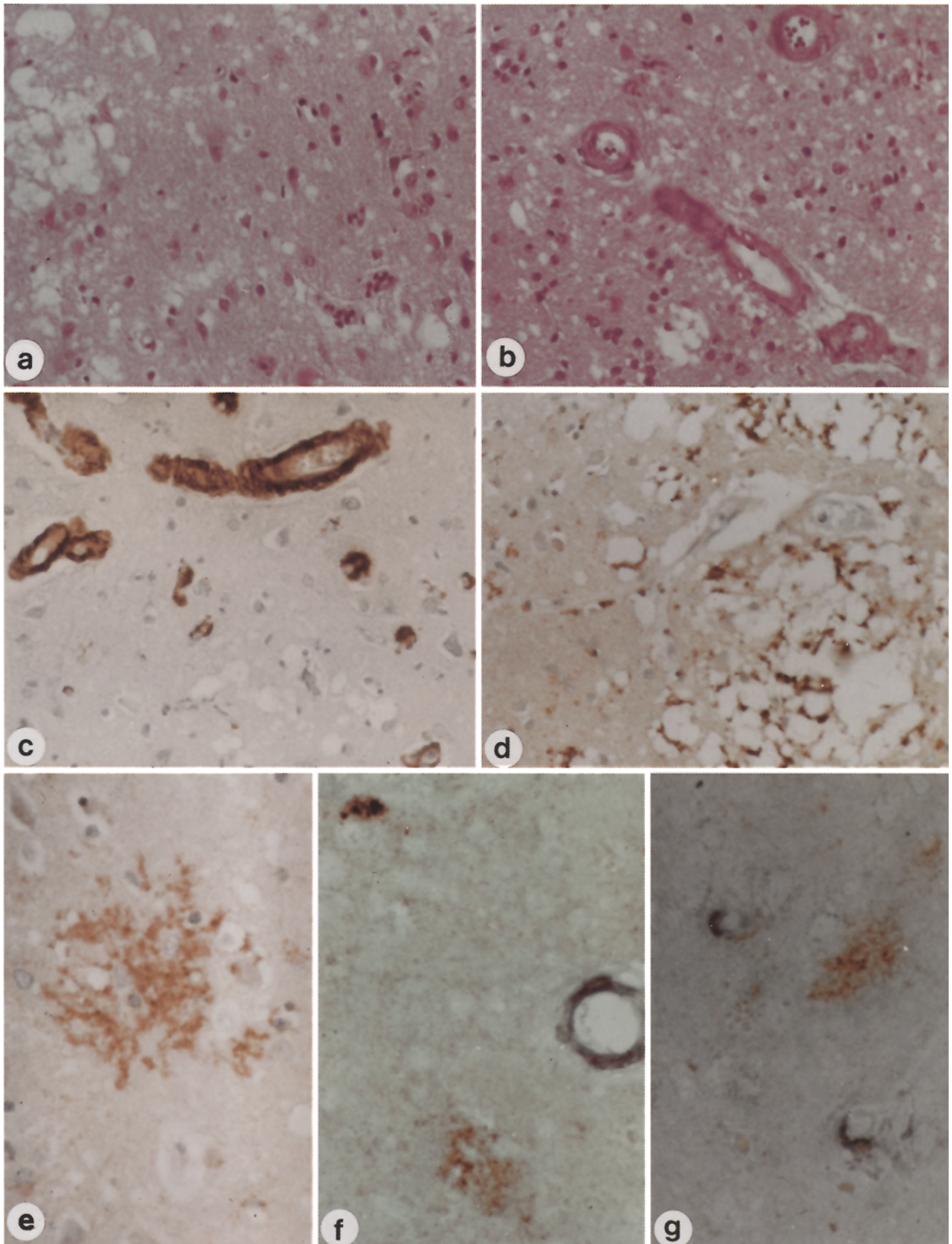


Fig. 1a–g Microscopical changes in the cerebral neocortex. **a** Spongiosis and gliosis characteristic of CJD, there is also neuronal loss. H&E. **b** Cerebral amyloid angiopathy associated with gliosis and spongiosis in the neocortex H&E. **c** Immunocytochemistry for β /A4 amyloid strongly stains the arterioles and capillaries in the neocortex. **d, e** Immunostaining of the PrP is strongly positive in areas of confluent spongiosis (**d**) and reveals parenchymal

deposits forming “plaques” which were not demonstrated by routine techniques (**e**). **f, g** Double immunostaining for β /A4 amyloid (*blue*) and PrP (*brown*). Arterioles (**f**) and capillaries (**g**) only express β /A4 amyloid while PrP is only present in the parenchyma, mostly in areas with spongiosis. **a–g** $\times 100$ (CJD Creutzfeldt-Jakob disease, PrP prion protein)

ally. Ammon's horn was spared and the remaining temporal cortex only mildly affected. Spongiosis and gliosis involved all the cortical layers except the molecular layer and were associated with significant neuronal loss. Similar, although milder changes were also found in the striatum, thalamus and substantia nigra. The cerebellum was less affected; there was mild spongiosis of the molecular layer and occasional loss of Purkinje cells with proliferation of Bergmann glia and axonal "torpedoes".

In addition, there was diffuse amyloid angiopathy involving the cortical and leptomeningeal arterioles the walls of which were thickened with an acellular, hyaline, eosinophilic material (Fig.1b). This material was positively stained with Congo red and showed characteristic birefringence in polarized light. No inflammatory reaction was observed in and around leptomeningeal and cortical vessels. Amyloid infiltration also involved intracortical capillaries, leaking into the adjacent parenchyma "dyschoric angiopathy". The vessels of the hemispheric white matter, brain stem and cerebellum were unremarkable. Only a few NFT and exceptional neuritic plaques were found in the temporal cortex. There were no amyloid plaques. There were neither senile plaques nor NFT in the neocortex. There was no cerebral hemorrhage either small petechial bleeding or large lobar hematoma. The white matter was unremarkable; in particular there was no obvious myelin pallor.

Immunocytochemistry

Immunocytochemistry showed that the amyloid deposits in arterioles and capillaries were strongly stained with the $\beta/A4$ antibody. The latter did not reveal any amyloid senile plaques (Fig.1c). Immunostaining for Tau protein showed neither senile plaques nor NFT in

the neocortex and only exceptional changes in Ammon's horns.

PrP immunostaining showed intense PrP positivity in areas of confluent spongiosis (Fig.1d) and some granular staining in astrocytes. It revealed a few parenchymal deposits forming "plaques" which were not demonstrated by routine techniques (Fig.1e). The blood vessels were not stained.

Double immunostaining confirmed that the blood vessels only expressed $\beta/A4$ amyloid, while parenchymal areas with severe spongiosis only showed PrP immunoreactivity (Fig. 1f, g). Both proteins were expressed in pericapillary parenchyma, in areas with severe spongiosis; however, even in these places it was obvious that one was vascular while the other was parenchymal.

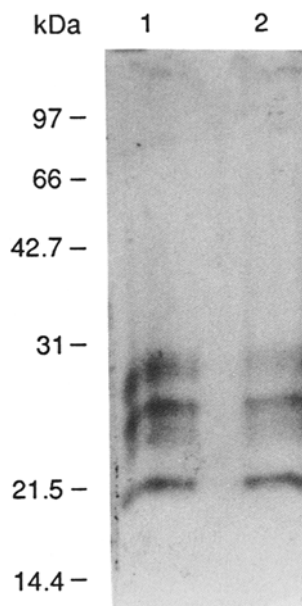
Immunoblot analysis

Immunoblot analysis revealed the presence of the abnormal proteinase K-resistant isoform of PrP, the biochemical hallmark of the spongiform encephalopathies. The pattern of bands (from 27 to 30 kDa) was identical to that obtained from a PrP-positive sporadic CJD brain (Fig. 2).

DNA analysis

DNA analysis using PCR and DGGE revealed a methionine-methionine homozygotism at codon 129 of the *PrNP* gene.

Fig. 2 Western immunoblot of proteinase K-treated brain extracts from a neuropathologically confirmed CJD case (lane 1) and our patient (lane 2) revealed with a rabbit polyclonal antibody against scrapie-infected hamster PrP 27-30 (RO 73)



Discussion

In an 83-year-old woman with progressive ataxia, dementia and myoclonic jerks, leading to death within 3 months, immunoblotting and neuropathology confirmed the diagnosis of CJD. Homozigotism at codon 129 of the *PrNP* gene is also often associated with sporadic CJD [34]. Immunostaining for PrP was positive in areas with marked spongiform changes. In addition there was marked CAA, diffuse to the entire hemispheric cortex, expressing $\beta/A4$ amyloid and not PrP, without significant changes of AD.

Association of changes characteristic of spongiform encephalopathies, either CJD or GSS, and senile degenerative cortical lesions including senile plaques, NFT and/or CAA, has been reported in various instances.

The possibility of senile and neuritic plaques in addition to Kuru plaques and multicentric plaques in GSS was mentioned in the initial descriptions of the disease, but NFT were classically absent [4, 42]. However, NFT were found in young patients with a family history and neuropathological changes characteristic of GSS [27, 33] and particularly in the "Indiana kindred" [2, 13, 40].

Immunostaining of the amyloid was performed in the Indiana kindred [12] and in the family of Nochlin [33]; it was strongly immunoreactive with the PrP antibody and negative for the β /A4 amyloid antibody, suggesting that these cases represented just a neuropathological variant of GSS. On the other hand the presence of PrP and β /A4 amyloid was recently demonstrated in elderly patients with GSS [7, 10, 21, 32]. CAA was described in two cases with clinical and neuropathological features consistent with GSS [1, 7]. Both patients were 62 years old and presented with NFT. Immunostaining of the amyloid was performed later in one case [1]; it showed that the vessel wall expressed β /A4 amyloid only, while cortical plaques expressed either PrP or β /A4 amyloid. It is not known whether these were different plaques or whether some could be stained by both antibodies [43]. Two other possible cases were also described by Worster Drought et al. [44] in siblings.

The coexistence of clinical and neuropathological features characteristic of sporadic CJD and Alzheimer's disease has been reported in a few cases [5, 11, 29, 35]. In two cases, amyloid plaques in the cerebral cortex expressed β /A4 amyloid and not PrP; however, abundant PrP was identified by Western blot analysis of brain extracts [5, 35] and one case was transmitted to primates [5]. It is possible that the lack of PrP reaction in those cases only reflected the weaker sensitivity of the method compared to our more recent technique which is able to stain parenchymal PrP in the absence of obvious amyloid deposit [19].

Association of CAA and CJD has been reported in a few cases ([11] case 1; [20, 25, 30]; and [43] cases 18, 20, 21) of which only two [11, 25] are well documented; the others are just mentioned in tables within wider studies. All these cases were over 63 years old. Most of them had cortical changes of AD. In only one case ([43] case 18), as with our case, was CAA not associated with changes of AD. Immunostaining was performed in four cases only [25, 43]. CAA always expressed β /A4 amyloid and not PrP. The latter was expressed in cerebellar Kurur-type plaques in three cases ([43] cases 14, 20 and 21).

Association of PrP accumulation and β /A4 amyloid deposition in the same brain has raised several hypotheses. The possibility that β /A4 amyloid accumulation may be secondary to production of the precursor of β /A4 (β PP) in degenerative neurites [22], around PrP deposits, has been proposed by Bugiani et al. [6] in aged cases of the Indiana kindred with GSS in whom colocalization of both amyloids was observed at the periphery of the amyloid plaques. Such a colocalization was not found in our case making such a mechanism unlikely.

A random association of AD with CJD or GSS cannot be ruled out in elderly cases with clinical and neuropathological features characteristic of both diseases [21], as AD affects 5–7% of individuals over 65 years of age [8] and this prevalence is probably much higher over 80 years of age. However, other authors consider

that one single disease may produce variable neuropathological changes [9]. It is noteworthy that cerebrovascular amyloidosis was observed in 11 of 20 sheep with scrapie [14] and evidence for the experimental transmission of cerebral β -amyloidosis to primates has been recently reported [3].

Deposition of β /A4 amyloid may only represent an age-related phenomenon superimposed on PrP accumulation. This is particularly likely for patients with CAA who all were over 63 years of age and in whom the two types of amyloid deposits involved different structures and never really colocalized. However, the two conditions may interact in some way. A disturbance in the metabolism of β PP or β /A4 due to the accumulation of PrP might have increased the age-related deposition of β /A4 in the blood vessel walls in the 83-year-old woman. It is noteworthy that CAA was only found in areas with changes of CJD and that the severity of both types of change more or less paralleled in the different neocortical areas. On the other hand, CAA may have accelerated the course of CJD. The duration of the neurological disease was indeed very short (less than 6 months) in eight of nine cases with CAA and CJD (L.W. Duchon, personal communication). The short duration of the disease may also account for the absence of any complication of CAA such as hemorrhages, leukoencephalopathy, infarcts or angiitis.

Acknowledgments We are very grateful to Dr. J. Hope for the 1A8 antibody, Dr. R.J. Kascsak for providing the 3F4 antibody, to D. Serban and S.B. Prusiner for their generous gift of the RO73 antibody and also to D. Borchelt and D. Westaway for their advice about the immunodetection of PrP. We wish to thank Prof. Jean Marie Brücher and Dr. Henry Baron for their useful comments on this case, Dr. Catherine Keohane for kindly reviewing the English, Ms. Diane Kofskey for her technical expertise in carrying out double immunostaining, Ms. Linda McArdle for PrP immunostaining, Line Bazeille, Gisèle Corcket, Martine Francesco, Annick Halloche, Véronique Levy and Geneviève Mesnil for histological preparations, Marie Claude Lescs and Lucile Mernier for photography and Leila Breton for secretarial help.

References

1. Adam J, Crow TJ, Duchon LW, Scaravilli F, Spokes E (1982) Familial cerebral amyloidosis and spongiform encephalopathy. *J Neurol Neurosurg Psychiatry* 45: 37–45
2. Azzarelli B, Muller J, Ghetti B, Dyken M, Conneally PM (1985) Cerebellar plaques in familial Alzheimer's disease (Gerstmann-Sträussler-Scheinker variant?). *Acta Neuropathol (Berl)* 65: 235–246
3. Baker HF, Ridley RM, Duchon LW, Crow TJ, Bruton CJ (1993) Evidence for the experimental transmission of cerebral β -amyloidosis to primates. *Int J Exp Pathol* 74: 441–454
4. Boellaard JW, Schlote W (1980) Subakute spongiforme Encephalopathie mit multiformer Plaquebildung. *Acta Neuropathol (Berl)* 49: 205–212
5. Brown P, Jannotta F, Gibbs CJ, Baron H, Guiryo DC, Gajdusek DC (1990) Coexistence of Creutzfeldt-Jakob disease and Alzheimer's disease in the same patient. *Neurology* 40: 226–228
6. Bugiani O, Giaccone G, Verga L, Pollo B, Frangione B, Farlow MR, Tagliavini F, Ghetti B (1993) β PP participates in PrP-amyloid plaques of Gerstmann-Sträussler-Scheinker disease, Indiana kindred. *J Neuropathol Exp Neurol* 52: 64–70

7. Courten-Myers de G, Mandybur TI (1987) Atypical Gerstmann-Sträussler syndrome or familial spinocerebellar ataxia and Alzheimer's disease? *Neurology* 37: 269–275
8. Cross PS, Gurland BJ (1986) The epidemiology of dementing disorders. Contract report prepared for the Office of Technology Assessment. US Congress
9. Duchen LW (1992) Current status review: cerebral amyloid. *Int J Exp Pathol* 73: 535–550
10. Farlow MR, Yee RD, Dlouhy SR, Conneally PM, Azzarelli B, Ghetti B (1989) Gerstmann-Sträussler-Scheinker disease. I. Extending the clinical spectrum. *Neurology* 39: 1446–1452
11. Gaches J, Supino-Viterbo V, Foncin JF (1977) Association de maladies d'Alzheimer et de Creutzfeldt-Jakob. *Acta Neurol Belg* 77: 202–212
12. Ghetti B, Tagliavini F, Masters CL, Beyreuther K, Giaccone G, Verga L, Farlow MR, Conneally PM, Dlouhy SR, Azzarelli B, Bugiani O (1989) Gerstmann-Sträussler-Scheinker disease. II. Neurofibrillary tangles and plaques with PrP-amyloid coexist in an affected family. *Neurology* 39: 1453–1461
13. Giaccone G, Tagliavini F, Verga L, Frangione B, Farlow MR, Bugiani O, Ghetti B (1990) Neurofibrillary tangles of the Indiana kindred of Gerstmann-Sträussler-Scheinker disease share antigenic determinants with those of Alzheimer disease. *Brain Res* 530: 325–329
14. Gilmour JS, Bruce ME, Mackellar A (1986) Cerebrovascular amyloidosis in scrapie-affected sheep. *Neuropathol Appl Neurobiol* 12: 173–183
15. Gray F, Dubas F, Rouillet E, Escourolle R (1985) Leukoencephalopathy in diffuse hemorrhagic cerebral amyloid angiopathy. *Ann Neurol* 18: 54–59
16. Gray F, Vinters HV, Le Noan H, Salama J, Delaporte P, Poirier J (1990) Cerebral amyloid angiopathy and granulomatous angitis: immunohistochemical study using antibodies to the Alzheimer A4 peptide. *Hum Pathol* 21: 1290–1293
17. Gray F, Chrétien F, Mikol J, Bell J (1994) Creutzfeldt-Jakob disease (CJD) and cerebral amyloid angiopathy (CAA) (abstract). *Neuropathol Appl Neurobiol* (in press)
18. Hashimoto K, Mannen T, Nukina N (1992) Immunohistochemical study of kuru plaques using antibodies against synthetic prion protein peptides. *Acta Neuropathol* 83: 613–617
19. Hayward PJ, Bell JE, Ironside JW (1994) Prion protein immunocytochemistry: the development of reliable protocols for the investigation of Creutzfeldt-Jakob disease. *Neuropathol Appl Neurobiol* (in press)
20. Hogenhuis LAH, Joosten EMG, Jaspar HHJ, Kemp B (1977) Myoclonus in encephalopathy associated with cerebrovascular congophilic angiopathy. *Excerpta Med Int Congr Ser* 427: 181
21. Ikeda S, Yanagisawa N, Allsop D, Glenner GG (1991) A variant of Gerstmann-Sträussler-Scheinker disease with β -protein epitopes and dystrophic neurites in the peripheral regions of PrP immunoreactive amyloid plaques. In: Natvig JB, Forre O, Husby G, et al (eds) *Amyloid and amyloidosis 1990*. Kluwer Academic, Dordrecht, pp 737–740
22. Iverfeldt K, Walaas SI, Greegard P (1993) Altered processing of Alzheimer amyloid precursor protein in response to neuronal degeneration. *Proc Natl Acad Sci USA* 90: 4146–4150
23. Jellinger K (1977) Cerebrovascular amyloidosis with cerebral hemorrhage. *J Neurol* 214: 195–206
24. Kascsak RJ, Rubenstein R, Merz PA, Tonna-DeMasi M, Fersko R, Carp RJ, Wizniewski HM, Diring H (1987) Mouse polyclonal and monoclonal antibody to scrapie-associated fibril proteins. *J Virol* 61: 3688–3693
25. Keohane C, Peatfield R, Duchen LW (1985) Subacute spongiform encephalopathy (Creutzfeldt-Jakob disease) with amyloid angiopathy. *J Neurol Neurosurg Psychiatry* 48: 1175–1178
26. Kitamoto T, Tateishi J, Tashima T, Takeshita I, Barry RA, DeArmond SJ, Prusiner SB (1986) Amyloid plaques in Creutzfeldt-Jakob disease stain with Prion protein antibodies. *Ann Neurol* 20: 204–208
27. Kornfeld M (1984) Gerstmann-Sträussler syndrome with features of Alzheimer's disease: two entities or one? (abstract). *J Neuropathol Exp Neurol* 43: 321
28. Laemmli UK (1970) Cleavage of structural proteins during the assembly of the head of bacteriophage T4. *Nature* 227: 680–685
29. Liberski PP, Papierz W, Alwasiak J (1987) Creutzfeldt-Jakob disease with plaques and paired helical filaments. *Acta Neurol Scand* 76: 428–432
30. Masters CL, Gajdusek DC, Gibbs CJ (1981) Creutzfeldt-Jakob disease virus isolations from the Gerstmann-Sträussler-Scheinker syndrome, with an analysis of the various forms of amyloid plaque deposition in the virus-induced spongiform encephalopathies. *Brain* 104: 559–588
31. Medori R, Tritschler HJ, LeBlanc A, Villare F, Manetto V, Chen HY, Xue R, Leal S, Montagna P, Cortelli P, Tinuper P, Avoni P, Mochi M, Baruzzi A, Hauw JJ, Ott J, Lugaresi E, Autilio-Gambetti L, Gambetti P (1992) Fatal familial insomnia, a prion disease with a mutation at codon 178 of the prion protein gene. *N Engl J Med* 326: 444–449
32. Miyazono M, Kitamoto T, Iwaki T, Tateishi J (1992) Colocalization of prion protein and „ protein in the same amyloid plaques in patients with Gerstmann-Sträussler syndrome. *Acta Neuropathol* 83: 333–339
33. Nochlin D, Sumi SM, Bird TD, Snow AD, Leventhal CM, Beyreuther K, Masters CL (1989) Familial dementia with PrP-positive amyloid plaques: a variant of Gerstmann-Sträussler syndrome. *Neurology* 39: 910–918
34. Palmer MS, Dryden AJ, Hughes J, Collinge J (1991) Homozygous prion protein genotype predisposes to sporadic Creutzfeldt-Jakob disease. *Nature* 352: 340–341
35. Powers JM, Liu Y, Hair LS, Kascsak RJ, Lewis LD, Levy LA (1991) Concomitant Creutzfeldt-Jakob and Alzheimer diseases. *Acta Neuropathol* 83: 95–98
36. Ripoll L, Laplanche JL, Salzmann M, Jouvét A, Planques B, Dussaucy M, Chatelain J, Beaudry P, Launay JM (1993) A new point mutation in the prion protein gene at codon 210 in Creutzfeldt-Jakob disease. *Neurology* 43: 1934–1938
37. Roberts GW, Clinton J (1992) Prion disease: the spectrum of pathology and diagnostic considerations. In: Prusiner SB, Collinge J, Powell J, Anderton B (eds) *Prion diseases of humans and animals*. Ellis Horwood, Chichester, pp 215–240
38. Roberts GW, Lofthouse R, Allsop D, Landon M, Kidd M, Prusiner SB, Crow TJ (1988) CNS amyloid proteins in neurodegenerative diseases. *Neurology* 38: 1534–1540
39. Serban D, Taraboulos A, DeArmond SJ, Prusiner SB (1990) Rapid detection of Creutzfeldt-Jakob disease and scrapie prion proteins. *Neurology* 40: 110–117
40. Tagliavini F, Prelli F, Ghiso J, Bugiani O, Serban D, Prusiner SB, Farlow MR, Ghetti B, Frangione B (1991) Amyloid protein of Gerstmann-Sträussler-Scheinker disease (Indiana kindred) is an 11 kDa fragment of prion protein with an N-terminal glycine at codon 58. *EMBO J* 10: 513–519
41. Vinters HV (1987) Cerebral amyloid angiopathy. A critical review. *Stroke* 18: 311–324
42. von Seitelberger F (1981) Sträussler's disease. *Acta Neuropathol (Berl)* [Suppl] 7: 341–343
43. Watanabe R, Duchen LW (1993) Cerebral amyloid in human prion disease *Neuropathol Appl Neurobiol* 19: 253–260
44. Worster-Drought C, Hill TR, McMenemey WH (1933) Familial presenile dementia with spastic paralysis. *J Neurol Neurosurg Psychiatry* 14: 27–34