Cerebral amyloid angiopathy is a pathogenic lesion in Alzheimer’s disease due to a novel presenilin 1 mutation

B. Dermaut,1 S. Kumar-Singh,1 C. De Jonghe,1 M. Cruts,1 A. Löfgren,1 U. Lübke,2 P. Cras,2 R. Dom,5 P. P. De Deyn,4 J. J. Martin3 and C. Van Broeckhoven1

Department of Molecular Genetics, Flanders Interuniversity Institute for Biotechnology, 2Laboratory of Neurobiology and 3Neuropathology, Department of Medicine, 4Department of Neurology, General Hospital Middelheim, Born-Bunge Foundation, University of Antwerp, Antwerpen and 5Laboratory of Neuropathology, University of Leuven, Faculty of Medicine, Leuven, Belgium

Correspondence address: Professor Dr Christine Van Broeckhoven, Department of Molecular Genetics, University of Antwerp (UIA), Department of Biochemistry, Universiteitsplein 1, B-2610 Antwerpen, Belgium
E-mail: cvbroeck@uia.ua.ac.be

Summary
The dense-cored plaques are considered the pathogenic type of amyloid deposition in Alzheimer’s disease brains because of their predominant association with dystrophic neurites. Nevertheless, in >90% of cases of Alzheimer’s disease amyloid is also deposited in cerebral blood vessel walls (congophilic amyloid angiopathy; CAA) but its role in Alzheimer’s disease pathogenesis remains enigmatic. Here, we report a family (family GB) in which early-onset Alzheimer’s disease was caused by a novel presenilin 1 mutation (L282V). This was unusually severe CAA reminiscent of the Flemish amyloid precursor protein (A692G) mutation we reported previously, which causes Alzheimer’s disease and/or cerebral haemorrhages. In family GB, however, the disease presented as typical progressive Alzheimer’s disease in the absence of strokes or stroke-like episodes. Similarly, neuroimaging studies and neuropathological examination favoured a degenerative over a vascular dementia. Interestingly, an immunohistochemical study revealed that, similar to causing dense-cored amyloid plaques, CAA also appeared capable of instigating a strong local dystrophic and inflammatory reaction. This was suggested by the observed neuronal loss, the presence of tau- and ubiquitin-positive neurites, micro- and astrogliosis, and complement activation. Together, these data suggest that, like the dense-cored neuritic plaques, CAA might represent a pathogenic lesion that contributes significantly to the progressive neurodegeneration that occurs in Alzheimer’s disease.

Keywords: familial Alzheimer’s disease; clinicopathological study; presenilin; amyloid angiopathy

Abbreviations: Ab = antibody; Aβ = amyloid β; APP = amyloid precursor protein; CAA = congophilic amyloid angiopathy; MMSE = Mini-Mental State Examination; PSEN = presenilin; SPECT = single-photon emission computed tomography

Introduction
A proteolytic fragment of the amyloid precursor protein (APP), called amyloid β (Aβ), is deposited as extracellular amyloid plaques in the brain of Alzheimer’s disease patients. Amyloid plaques range from non-congophilic diffuse plaques to congophilic compact and often core-containing plaques. The strong association of amyloid cored plaques and only exceptionally diffuse plaques with dystrophic neurites has suggested that the dense-cored plaque is the pathogenic lesion in Alzheimer’s disease (Wisniewski and Terry, 1973; Wisniewski et al., 1989). Besides its deposition in diffuse and cored plaques, Aβ is also present in the walls of cerebral capillaries, arterioles and arteries, and is called congophilic amyloid angiopathy (CAA). Although CAA is found in >90% of autopsied Alzheimer’s disease brains (Glenner et al., 1981), it is highly variable in severity and quantity.

The extent to which CAA plays a role in the progression of typical Alzheimer’s disease is not known, but severe CAA is classically considered an important cause of intracerebral haemorrhage, a prevailing feature in carriers of the Flemish and Dutch variants of APP. In the brains of patients with
hereditary cerebral haemorrhage with amyloidosis of the Dutch type, caused by Dutch APP (E693Q) (Van Broeckhoven et al., 1990), severe CAA is present abundantly and causes recurrent cerebral haemorrhages. In addition to CAA and cerebral haemorrhage, Flemish APP (A692G) patients (Hendriks et al., 1992) also present with Alzheimer’s disease with large cored plaques (Cras et al., 1998). However, cerebral haemorrhage is not limited to Dutch and Flemish APP. Some presenilin (PSEN) mutations also appear to be capable of causing haemorrhagic strokes occasionally. In the Volga-German Alzheimer’s disease family (PSEN2 N1411) (Levy et al., 1995), severe CAA is a consistent feature and cerebral haemorrhage has been reported in one mutation carrier (Nochlin et al., 1998).

However, most cases of hereditary and sporadic Alzheimer’s disease present with progressive dementia and CAA in the absence of its drastic consequences, such as large cerebral haemorrhages and infarcts. Nevertheless, it is difficult to assess how and to what extent CAA per se may contribute to the gradual progressive neurodegeneration seen in Alzheimer’s disease. Detailed clinical and neuropathological descriptions of typical cases of Alzheimer’s disease with unusually severe CAA are therefore likely to contribute to our understanding of the role of CAA in Alzheimer’s disease patients. Here we describe family GB, in which clinically typical early-onset Alzheimer’s disease with unusually severe CAA is associated with a novel PSEN1 mutation (L282V). This paper reports its clinical, molecular genetic, biochemical, neuropathological and immunohistochemical characteristics.

Subjects and methods

Subjects and family ascertainment

Family GB is a three-generation family with two probands (Fig. 1). Blood for DNA extraction and detailed clinical information was available for both probands (III-1 and III-4), who were diagnosed independently in two university hospitals in Belgium. Molecular genetic screening was performed without knowledge of a familial relationship between the two individuals. Brain biopsy and limited clinical information was available for individual II-5. Autopsy and neuropathological examinations were performed in III-4. For individuals I-1, II-1 and II-2, information on the diagnosis of dementia and age at death were provided by the spouse of proband III-1.

Genetic analysis

PCR (polymerase chain reaction)-based screening of the coding exons of PSEN1 was performed on genomic DNA by SSCP (single-strand conformation polymorphism) analysis and direct sequencing as described previously (Cruts et al., 1998). To confirm the presence of PSEN1 L282V in patients and to screen 80 Belgian healthy control individuals, a PCR-based mismatch RFLP (restriction fragment length polymorphism) analysis method was developed (forward mismatch primer 5’-CTCAGGAGACAATGCAACCG-3’; reverse primer 5’-AGCAATTTATCGGGCAACTT-3’), allowing the detection of PSEN1 L282V by MspI digestion. Allele sharing analysis was performed by genotyping the PSEN1 flanking microsatellite markers D14S1028, D14S77, D14S1004, D14S1025 and D14S999 using published primers, one of which was labelled fluorescently. The alleles were separated on 6% polyacrylamide gel containing 8 M urea using an ABI373A automated DNA sequencer (Applied Biosystems, Foster City, Calif., USA). Apolipoprotein E (APOE) genotyping was performed as described (Wenham et al., 1991).

Aβ secretion

Site-directed mutagenesis was performed on the full-length PSEN1 cDNA (De Jonghe et al., 1999) cloned in vector pCDNA5/FRT (Invitrogen, Carlsbad, Calif., USA) using the QuickChange site-directed mutagenesis system (Stratagene, La Jolla, Calif., USA) with primers 5’-CTCAGGAGAGAAA-TGAAAACGTTTTTCCAGCTCATTAC-3’ and 5’-GT AAATGAGAGCTGGAAAAACCGTTCAGTGTTC-3’ to introduce the L282V mutation. Human embryonic kidney Flp-In (Flp-In-293; Invitrogen) cells were co-transfected with wild-type or L282V mutant PSEN1 cDNA cloned in pCDNA5/FRT and recombinant Flp recombinate, cloned in pOG44 (Invitrogen) using Lipofectamine (Life Technologies, Gaithersburg, Md., USA) according to the manufacturer’s instructions. Cells were selected for stable integration of the recombinant plasmid in the cell genome by resistance to 400 µg/ml hygromycin. Aβ42 concentrations in eightfold concentrated 24-h conditioned media were measured by sandwich-type ELISA (enzyme-linked immunosorbent assay), using the Innogenest β-amyloid 1–42.
(Innogenetics, Zwijnaarde, Belgium) and Aβ40 concentrations were measured in the same media with the human β-amyloid 1–40 ELISA (Biosource, Camarillo, Calif., USA). A two-tailed unpaired t-test was used to compare the Aβ42/Aβ40 ratio produced by the wild-type and mutant transfectants.

**Histopathology**

A paraffin-embedded biopsy specimen of the frontal cortex was available for case II-5. A post-mortem neuropathological study was performed on case III-4. Macroscopically, frontal cortical atrophy was noted in this case. Tissue was obtained from the superior frontal gyrus, superior temporal gyrus, hippocampus, area striata and cerebellum. After fixation in 4% formaldehyde, tissue was dehydrated and embedded in paraffin. From paraffin-embedded blocks, sections 10 µm thick were sliced and stained with classical histological stains, such as haematoxylin–eosin, cresyl violet, Bodian, Congo red and thioflavin S.

**Immunohistochemistry**

Immunohistochemistry was performed on serial 4 µm sections from the temporal and frontal cortical regions. The following antibodies (Ab) were used: 4G8 (Senetek, Maryland Heights, Md., USA; directed against amino acid residues 18–24 of Aβ); 6E10 (Senetek; raised against Aβ 1–17, recognizes Aβ 5–11), JRF/AβN/11 (specific for N-terminus of Aβ, generated against Aβ residues 1–5), JRF/cAb40/10 (specific for Aβ40), β JRF/cAb42/12 (specific for Aβ42) (Kumar-Singh et al., 2000), 22C11 (against N-terminal APP; Roche), AT8 [Innogenetics; against abnormally phosphorylated PHF (paired helical filament)-tau], ubiquitin (Dako, Glostrup, Denmark), anti-glial fibrillary acidic protein (GFAP; Dako), CD68 (Dako, for microglia). For Aβ immunohistochemistry, sections were preincubated with 98% formic acid for 5 min. APP (22C11) and GFAP immunohistochemistry was performed on sections retrieved in citrate buffer (pH 6) and, before CD68 staining, sections were preincubated with 0.1% pepsin for 20 min at 37°C. Blocking sera (rabbit and goat sera), link antibodies (biotinylated rabbit anti-mouse and goat anti-rabbit) and horseradish peroxidase–avidin–biotin complex were used at recommended dilutions (Dako). Sections were immersed in 0.03% hydrogen peroxide in methanol and incubated for 0.5 h to block endogenous peroxidase, and were then preincubated with normal sera diluted 1 : 5. Sections were incubated overnight (16 h) at 4°C with the primary Ab, followed by 0.5 h incubations with first biotinylated secondary Ab and then by horseradish peroxidase-conjugated avidin–biotin diluted 1 : 1 : 100. Sections were finally treated with peroxidase substrate solution containing 0.01% hydrogen peroxide and 0.05% DAB (diaminobenzidine tetrahydrochloride), counterstained with Harris haematoxylin and coverslipped in DPX. All dilutions were made in 0.1 M PBS (phosphate-buffered saline) containing 0.1% bovine serum albumin. Immunohistochemistry, involving the detection of more than one antigen, was done using species-specific or IgG subtype-specific secondary Ab conjugated directly with biotin, horseradish peroxidase, alkaline phosphatase or galactosidase (Southern Biotechnology, Birmingham, Ala., USA). This was followed by colour development using one of the following chromogens (Roche): DAB, AEC (3-amino-9-ethylcarbazole), fast red, BCIP/NBT (5-bromo-4-chloro-3-indolyl phosphate/nitroblue tetrazolium solution) and X-gal (5-bromo-4-chloro-3-indolyl-β-d-galactopyranoside), as described elsewhere (Kumar-Singh et al., 2000).

**Results**

Clinical, neuropathological and molecular genetic results are summarized in Table 1.

**Case histories**

**Patient III-1 (proband 1)**

The patient had a known history of hypertension. At the age of 45 years the first symptoms of memory impairment were noticed. Five years later the patient was referred to a neurologist because both at home and at the workplace negligent and inaccurate behaviour was observed. At that time, the patient was also noticed to react more slowly and was having difficulty in comprehension. At neurological examination, an insecure, adynamic and apathetic man with cognitive impairment and aphasia was observed. A Mini-Mental State Examination (MMSE) score of 21 out of 30 was calculated. Cognitive deficits were most pronounced in short-term recall, calculation, word finding and comprehension. Further clinical examination revealed a slightly propulsive and insecure shuffling gait, sporadic myoclonus in the hands, mild rigidity in the upper limbs and positive frontal release signs. On MRI and CT scanning, cortical and subcortical atrophy were observed, together with a widened cisterna magna. Single photon emission computed tomography (SPECT) revealed a diffuse pattern of hypoperfusion. EEG was characterized by short paroxysms of generalized slow-wave activity that increased with hyperventilation. Six months later, marked anosognosia was observed. A MMSE of 18 out of 30 was calculated and it was mentioned that the patient had become severely short-tempered. The extrapyramidal syndrome, as reflected in upper limb cogwheel rigidity, bradykinesia and propulsive shuffling gait, had become more marked and was most prominent on the right side. Severe paratonia of the lower limbs was observed. The primitive reflexes were still provokable. There was no evidence of a cerebellar syndrome as tests on coordination remained normal. Nine months after initial examination, the MMSE had dropped to 12 out of 30 despite symptomatic treatment with tacrine. Clinical neurological examination remained largely unaltered: a prominent frontal...
and extrapyramidal syndrome was still observed and the patient had become completely helpless. About 2 years later the patient was admitted to the hospital because of recurrent epileptic seizure-like episodes, for which valproic acid was prescribed. By then the patient had progressed into a nearly vegetative state with generalized rigidity, hyperactive deep tendon reflexes with outspoken diffusion, strongly positive primitive reflexes and generalized myoclonus. At this stage a CT scan showed cerebellar and cerebral atrophy as well as periventricular ischaemic white-matter lesions. SPECT demonstrated diffuse hypoperfusion of the brain with two regions of clearly decreased perfusion, in the right parieto-occipital region and the left hemisphere. Nine months later, 9 years after disease onset, the patient died at the age of 54 years.

There was a family history of dementia as both parents (II-1 and II-2) were reported to have been demented. The father (II-1) died at the age of 83 years and the mother (II-2) at 54 years.

**Patient III-4 (proband 2)**

The first symptoms of cognitive impairment were noticed at the age of 41 years. Four years later symptoms of confused behaviour and disorientation, as a result of already severe memory impairment, were observed. In her job as a mathematics teacher, she started to give all students maximum scores. At home financial problems had arisen and at neurological consultation a depressed, aphasic, apractic and obese woman who was disoriented in time and space was observed. Further examination revealed dysmetria and an MMSE score of 15 out of 30. In the main, difficulty in text comprehension, arithmetic and imprinting was observed. Constructional apraxia was also seen. However, no other neurological symptoms were noted to accompany the dementia syndrome. Pneumoencephalography showed moderate ventricular dilatation and cortical atrophy. EEG showed frontotemporal slow-wave activity. The patient was diagnosed as having Alzheimer’s disease. At this time a brain biopsy was taken; it confirmed the diagnosis of Alzheimer’s disease and the patient died the same year. The family history revealed dementia with early onset in the father (I-1).

**Genetics and Aβ secretion**

SSCP analysis of exon 8-containing PCR fragments of *PSEN1* from both probands (III-1 and III-4) showed aberrant patterns.
Presenilin 1 L282V and amyloid angiopathy

Table 2 Genotypes of PSEN1 flanking microsatellite markers in the 2 PSEN1 L282V carriers (III-1 and III-4)

<table>
<thead>
<tr>
<th></th>
<th>D14S1028</th>
<th>D14S77</th>
<th>D14S1004</th>
<th>D14S1025</th>
<th>D14S999</th>
</tr>
</thead>
</table>

Allele sizes are given in base pairs and shared alleles are underlined.

Fig. 2 [99mTc]HMPAO scan image of patient III-4 showing multiple regions of reduced perfusion in the left frontal, parietal, temporal and parieto-occipital regions, with extension of the perfusion defect to the right temporoparietal cortex.

Direct sequencing of the PCR fragments demonstrated a C→G transversion in exon 8 resulting in a Leu (CTT) to Val (GTT) substitution at codon 282 of PSEN1 (L282V). The APOE genotype was ε3ε4 for both patients. Genotype analysis of the polymorphic microsatellite markers D14S1028, D14S77, D14S1004, D14S1025 and D14S999, located near PSEN1 (Cruts et al., 1995), showed that the two probands shared at least one allele for each of these markers (Table 2). The mutation was absent in 160 Belgian control chromosomes. Measurement of Aβ42 and Aβ40 levels in medium of HEK-293 cell lines stably expressing mutant and wild-type PSEN1 cDNA showed a twofold increase in the Aβ42/Aβ40 ratio for L282V compared with wild type (6.6 ± 0.5 versus 3.3 ± 0.7%; P = 0.02).

Histopathology and immunohistochemistry

Marked neuronal loss in all layers accompanied by cortical atrophy was noted in the superior temporal gyrus, superior frontal gyrus and area striata. Similarly, pyramidal cell loss and pycnotic neurones were evident in layer III of the entorhinal cortex. Thioflavin S and Congo red staining of brain sections showed fluorescence and apple-green birefringence under polarized light, respectively, in the dense-cored plaques and blood vessels. Neurofibrillary tangles, recognized by silver stains and Ab for hyperphosphorylated tau, were noted in the entorhinal cortex, fields CA1 and CA2 of the hippocampus and in the neocortex, mostly in association with neuritic amyloid plaques. Neuritopil threads recognized by AT8 were also abundant in all these regions, especially in the entorhinal cortex. Rarely, granulovacuolar degeneration was evident in neocortical regions. In the molecular layer of the dentate gyrus, mild spongiosis was noticed together with amyloid plaques and CAA. The amyloid deposits were abundantly present, both as dense-cored plaques and diffuse plaques, in all regions analysed. Double immunohistochemistry showed that the dense-cored senile plaques were associated with astroglial proliferation and activated microglia. Besides neuritic plaques, diffuse plaques (preamyloid) were also noted in all brain regions analysed, including the subpial region and cerebellum (Fig. 3).

Staining serial neocortical and hippocampal sections for Ab specific for C-termini Aβ40 and Aβ42, Aβ middle portion (4G8; Aβ 17–24) and Ab directed to the N-terminus demonstrated that vascular amyloid and amyloid in the compact cores was full-length Aβ40, whereas those in the diffuse plaques were N-truncated Aβ42 (Fig. 4).

Most interesting was the extensive CAA in all regions analysed, including the neocortex, hippocampus and cerebellum. 4G8 stained amyloid in thickened arteries and arterioles in a concentric fashion and most of the vessels were associated with strong perivascular amyloid deposition. Staining for smooth-muscle actin demonstrated that smooth muscle cells were lost from arteries. We noted all the associated characteristics of dense-cored plaques with CAA, especially with its perivascular deposits. Such deposits showed dystrophic neurites stained with ubiquitin and AT8 as well as specific markers for astro- and microgliosis and complement activation. Co-staining sections with Congo red and microglial markers showed a strong association of microglia with CAA. Severe to moderate white matter loss was present in the neocortical regions. Pathology in the cerebellum was severe and associated with focal loss of Purkinje cells. A remarkable arrangement of linear streaks of amyloid arranged perpendicularly to the interfolial fissures in the outer molecular layer of the cerebellum was associated with severe CAA that was present parenchymally and in the...
leptomeninges and cerebellar fissures. Occasional compact, burnt-out cored plaques in the Purkinje cell layer and amyloid streaks in the molecular layer were associated with ubiquitin-positive dystrophic neurites and with CAA and its perivascular deposits (Fig. 5).

The biopsy specimen of the affected father also demonstrated severe CAA and cored plaque pathology, the CAA having all the characteristics described for the proband III-4 (Fig. 3).

Discussion

We describe a novel PSEN1 mutation (L282V) resulting in early-onset Alzheimer’s disease that is neuropathologically characterized by unusually severe CAA. The causal nature of PSEN1 L282V is strongly supported by the autosomal dominant transmission pattern of Alzheimer’s disease in this family, the absence of the mutation in 160 Belgian control chromosomes, the sharing of alleles between the two probands at PSEN1 flanking markers (Table 2) and the increased in vitro Aβ42 secretion by cells expressing mutant compared with wild-type PSEN1. Moreover, this mutation is located in the functionally important membrane-associated part of the large sixth hydrophilic loop of the PSEN1 protein, where ~30% of mutations are clustered (http://molgen-www.uia.ac.be/ADMutations/). Although this domain is highly conserved between PSEN1 and its homologues PSEN2 and Caenorhabditis elegans sel-12, L282 is one of the few non-conserved amino acids within this region. Interestingly, another amino acid substitution at the same codon (L282A) has been reported previously, although without clinical or pathological details, as the cause of early-onset Alzheimer’s disease in a Spanish family with a mean onset age of 43 years (Aldudo et al., 1998). The mean ages at onset (44.3 ± 3.1 years, range 41–53 years) and death (53.5 ± 3.3 years, 49–57 years) in family GB, as well as the additional clinical features of myoclonus and frontal, extrapyramidal or cerebellar signs, have been noted previously for early-onset Alzheimer’s disease caused by PSEN1 mutations (Martin et al., 1991; Lippa et al., 2000).

The most remarkable finding in family GB, however, was the presence of a prominent CAA that was as severe as in our Flemish APP A692G family reported previously (Hendriks et al., 1992). We do not yet understand why a
subset of mutations either in APP (Flemish or Dutch) or in PSEN1 or PSEN2, here or described elsewhere (Ikeda et al., 1996; Mann et al., 1996; Yasuda et al., 1997; Nochlin et al., 1998; Singleton et al., 2000), present with abundant amyloid angiopathy. CAA leading to strokes has also been described in cases of Down syndrome (Donahue et al., 1998). Clearly, a specific pathoclisis for vessels to deposit amyloid is more complex than a simple increase in A\textbeta{}40 levels. Indeed, we show here in a heterologous in vitro assay that PSEN1 L282V, like all pathogenic PSEN mutations, increases A\textbeta{}42 specifically. However, we also demonstrate that the precise A\textbeta{} composition of CAA varies between the cortex and cerebellum. In contrast to the neocortex, where CAA is chiefly composed of full-length A\textbeta{}40, in the cerebellum the CAA load consists predominantly of A\textbeta{}42, and it is not always full-length. It is of interest that a recent systematic neuropathological study of early-onset PSEN1 Alzheimer’s disease showed a strong correlation between CAA and the PSEN1 mutation codon position. It was demonstrated that a severe degree of CAA was much more frequent among cases in which the PSEN1 mutation occurred after codon 200 (Mann et al., 2001). Although it is difficult to understand such a molecular clustering of PSEN1 mutations associated with severe CAA, our study seems to confirm this interesting observation.

Regardless of its precise constituents or biomechanism(s) of formation, and in contrast to Flemish Alzheimer’s disease, or as would be expected from its severity, CAA does not lead to strokes or stroke-like episodes in family GB. Other known consequences of CAA, e.g. white matter lesions (Wallin, 1998; Roks et al., 2000), are also not detected, at least early in the disease progression. Instead, we show here that the pathological correlates of CAA, in terms of its association with dystrophic neurites and inflammatory gliosis, are similar to those of cored plaque pathology. In our view, the most straightforward interpretation of this observation is that CAA triggers a perivascular neurodegenerative response and therefore it might, like the neuritic cored plaque, represent a pathogenic lesion in the Alzheimer’s disease brain. A similar explanation was suggested recently in a neuropathological study of two cases with senile dementia presenting with CAA and perivascular tau pathology in the absence of neuritic cored plaque (Vidal et al., 2000). Moreover, the present study is also in line with our recent
Fig. 5 Double immunohistochemistry suggesting a neurodegenerative role of CAA in the cognitive decline in Alzheimer’s disease. Neurites accumulating (A) phosphorylated tau stained by AT8 (brown) and (B) ubiquitin, in association with anti-Aβ antibody (blue) in CAA and perivascular plaques, indicating a ‘neuritic’ role for CAA. Staining (C) microglia and (D) astroglia for specific Ab (brown) shows the same pattern of glial reactivity with CAA (anti-Ab antibody, blue) as for dense-cored plaques (arrow in C). (E) Similarly, complement C1q reactivity was present in both CAA and dense-cored plaques (arrow). In the cerebellum, ubiquitin-positive dystrophic neurites (brown) showed an equal magnitude of association with both dense-cored plaques (F) and CAA (blue) (G), and amyloid streaks in the molecular layer (blue) (H) paralleled and were associated with blood vessels (CD31/34, brown). Scale bars = 20 μm.
demonstration that the unusually large dense cored plaques in Flemish Alzheimer’s disease (Cras et al., 1998), are most probably derived from stenosed vessels (Kumar-Singh et al., submitted for publication). A role of concomitant minor vascular lesions that cumulatively lead to the progressive decline in Alzheimer’s disease might explain, in part, the increasingly recognized close overlap between Alzheimer’s disease and vascular dementia (Kalaria and Ballard, 1999), especially the linear progressive variant of vascular dementia (Pantoni et al., 1996). However, this overlap between Alzheimer’s disease and vascular dementia can also be explained by hypoxic injury due to amyloidogenic stenosing vessels or by direct toxicity incurred by the accumulation of full-length Aβ in CAA, similar to that deposited in dense-cored plaques. Moreover, the close link between CAA and a neurodegenerative-like decline shown in our study and the known effects of cerebrovascular strokes, such as strokes in Alzheimer’s disease (Snowdon et al., 1997), should prompt the reconsideration of the clinical diagnosis of Alzheimer’s disease, as such events are normally considered to be exclusion criteria.

In conclusion, we suggest that, besides the classical pathological Alzheimer’s disease hallmark of dense-cored plaques with neuritic pathology, the presence of CAA, although not necessary, should be considered a contributing factor in the progressive cognitive decline in Alzheimer’s disease.

Acknowledgements
We wish to thank Dr F. Van Genechten and Dr L. Swerts for sharing clinical information. Financial support was received from the Fund for Scientific Research Flanders (FWO-F), DWTC Interuniversity Attraction poles (IUAP) and the International Alzheimer’s Research Foundation (IARF). M.C. and C.De J. are postdoctoral fellows and B.D. is a Ph.D. fellow of the FWO-F.

References


Received April 18, 2001. Revised June 18, 2001. Accepted July 7, 2001