Acta Neuropathol (2000) 100:395–402

REGULAR PAPER

Eszter Farkas · Gineke I. De Jong · Rob A. I. de Vos
Ernst N. H. Jansen Steur · Paul G. M. Luiten

Pathological features of cerebral cortical capillaries are doubled in Alzheimer's disease and Parkinson's disease

Received: 21 July 1999 / Revised, accepted: 21 December 1999

Abstract Cerebral capillaries represent a major interface between the general circulation and the central nervous system and are responsible for sufficient and selective nutrient transport to the brain. Structural damage or dysfunctioning carrier systems of such an active barrier leads to compromised nutrient trafficking. Subsequently, a decreased nutrient availability in the neural tissue may contribute to hampered neuronal metabolism, hence to behavioral and cognitive functional deficiencies. Here we focus on the ultrastrucutral abnormalities of cerebral microvessels in Alzheimer's disease (AD; $n = 5$) and Parkinson's diseasse (PD; $n = 10$). The capillary microanatomy in samples from the cingulate cortex was investigated by electron microscopy and severe damage to the vessel walls was observed. Characteristic pathological changes including capillary basement membrane thickening and collagen accumulation in the basement membrane were enhanced in both AD and PD. The incidence of capillaries with basement membrane deposits was two times higher in AD and PD than in age-matched controls. Degenerative pericytes in all groups appeared at a similar frequency. The data indicate that basement membrane deposists, as opposed to pericytic degeneration, represent an important pathological feature of AD and PD and suggest that capillary dysfunction may play a causal role in the development of these two major neurodegenerative diseases.

E. Farkas (✉) · G. I. De Jong · P. G. M. Luiten
Department of Animal Physiology,
Graduate School of Behavioral and Cognitive Neurosciences,
University of Groningen, P. O. B. 14,
9750 Haren, The Netherlands
e-mail: E.FARKAS@biol.rug.nl,
Tel.: +31-50-3632363, Fax: +31-50-3632331

R. A. I. de Vos
Department of Pathology,
Regional Laboratory of Pathology and Microbiology,
Enschede, The Netherlands

E. N. H. Jansen Steur
Department of Neurology, Medisch Spectrum Twente,
Enschede, The Netherlands

Key words Alzheimer's disease · Capillary ultrastructure · Cerebral hypoperfusion · Parkinson's disease

Introduction

Morphological abnormalities of cerebral capillaries and related deficient cerebral circulation observed in dementia, and in Alzheimer's disease (AD) in particular, have gained increasing attention in recent years. Investigation of the influence of altered cerebral circulation and abnormal cerebromicrovascular microanatomy on learning and memory includes both clinical scanning and postmortem examinations, as well as experimental animal studies.

Clinical research can highlight important physiological parameters of the cerebral circulation of patients by the use of non-invasive scanning. Single photon emission computed tomography (SPECT) studies demonstrated that the regional cerebral blood flow of demented subjects was considerably decreased compared to controls. The reduction in flow rate was found to be most pronounced in the hippocampus and temporal cortex, regions which are known to be first and most severely affected in AD [3, 10, 15, 32]. In addition, the degree of hypoperfusion in the hippocampus correlated well with the stage of dementia [32]. The remarkable finding that insufficient cerebral circulation is associated with memory deficits and cognitive impairment stimulated further research in laboratory animals. By occluding the carotid arteries, the negative effect of decreased cerebral blood flow on cognitive processes was reproduced in rats [9, 13, 34]. The created chronic experimental cerebral hypoperfusion resulted in impaired spatial memory of the animals in a water maze paradigm and the increase of errors in the later phase of learning in the radial maze spatial memory test, both of which are indicative of hippocampal dysfunction [9, 34].

These data show that a sufficient cerebral perfusion appears to be essential for proper memory processing. With a lower perfusion rate, the nutrient transport to the brain may not be adequate, which may cause hampered neuronal metabolism and consequent cognitive disturbances.

Indeed, the rate of cerebral metabolisms of oxygen and glucose and the density of glucose transporter sites in the cerebral capillary walls were found to be distinctly reduced in AD [18, 21–23, 31]. Such deprivation of the neuronal tissue can derive from either the lower flow rate itself (implying a reduced volume of blood reaching the brain capillaries) or the compromised permeability of the capillary walls due to abnormal structural features [12]. Most probably, the two factors are dynamically and progressively connected and equally jeopardize nutrient trafficking in the brain.

Cerebral hypoperfusion has been implicated in the development of cerebral capillary damage [8, 9] and the morphological characterization of capillaries in dementia has also revealed distinctive pathology. Structural damage to brain microvessels in AD and Pick's disease was described at the light microscopic level as twisting, tortuous structure, fragmentation and atrophy of capillaries, wherease in amyotrophic lateral sclerosis/parkinsonism-dementia complex, mainly severe fragmentation of the vessels was encountered [5]. The data suggest that, although capillary damage obviously accompanies cognitive deficiencies, it is not specific to a particular type of dementia. Capillary damage would rather appear as a general, dementia-associated pathological property.

The irregular appearance of brain capillaries seen under the light microscope relates to alterations in the microvessel walls observed by electron microscopy (EM). EM examination of cerebral microvessels in humans was mainly restricted to AD where the observed microanatomical irregularities of endothelial cells, capillary basement membrane (BM) and pericytes were extensively described [6, 8, 36]. BM pathology can occur in the form of thickening on the abluminal surface of capillaries and is thought to be the result of either increased secretion or decreased turnover of BM components. The abnormal folding and layering of the BM leads to BM duplication, while BM splitting creates vacuoles within the BM, often filled with collagen fibers [24, 36]. Pericytic degeneration can usually be identified at its earlier stages by inclusion bodies accumulating in the cytoplasm and a totally disintegrated intracellular structure with the progress of damage [7].

Although the listed abnormalities at the EM level were reported mainly in AD, the question is raised whether such microvascular disintegration is a specific feature of AD or more common to other neurodegenerative diseases, with particular attention to several types of dementia. Preliminary studies from our lab have already indicated that cerebrocortical microvessels show BM thickening, vacuolization and precytic degradation in clinical Parkinson's disease with cortical Lewy bodies (PD) and cerebrovascular disease (CVD), in addition to AD [8, 17]. Here we provide an extended overview of the aberrations of cerebral capillary walls in AD and PD with or without AD-like neuropathology.

Table 1 Neuropathological characterization of the patients included in the study (*AA* amyloid angiopathy, *Amyl* cerebral amyloid deposits, *B* brain stem predominant Lewy bodies, *BP* blood pressure, *HT* hypertenison, *ecAS* extracerebral atherosclerosis, *icAS* intracerebral atherosclerosis, *L* limbic Lewy bodies, *LB* Lewy Body, *N* neocortical Lewy bodies, *NFT* neurofibrillary tangles, *SN pathol* substantia nigra pathology)

Case no.	Age (years)	Gender	Clinical diagnosis	BP	LB score	NFT	Amyl.	CERAD	Braak stage	AA	Vascular factors	SN Pathol
1	67	M	Septichaemia	100/60								
2	66	M	Myocardiac infarct	HT								
3	64	M	Myocardiac infarct	HT								
4	63	M	Myocardiac infarct	160/75								
5	78	F	Lung cancer	130/75								
6	77	M	Alzheimer's	170/80	–	+++	+++	Definite	V	+	–	–
7	78	F	Alzheimer's	160/90	–	+++	+++	Definite	V	±	ecAS++	–
8	87	F	Alzheimer's	180/85	–	++	+++	Probable	IV	–	–	–
9	83	M	Alzheimer's	170/90	–	++	+++	Probable	IV	+	–	–
10	85	M	Alzheimer's	150/75	–	+++	+++	Definite	V	+	ecAS++	–
11	68	F	Parkinson's	140/70	N	–	+	–	III	–	icAS+	+++
12	76	F	Parkinson's	170/75	L	–	–	–	II	–	–	+++
13	77	M	Parkinson's	–	N	–	+++	–	III	–	icAS+	+++
14	68	M	Parkinson's	125/85	L	+	+++	Possible	II	–	–	+++
15	85	F	Parkinson's	150/90	B	–	+	–	I–II	+	–	+++
16	64	M	Parkinson's	160/60	L	–	–	–	0	–	icAS+, micro-infarct BG	+++
17	66	M	Parkinson's	130/70	N	+	+++	Probable	III	+	–	+++
18	70	F	Parkinson's	150/80	N	++	+++	Definite	IV	+	–	+++
19	80	F	Parkinson's	175/80	N	++	+++	Probable	III	+	ecAS++, icAS+	+++
20	86	F	Parkinson's	190/95	L	+	++	Probable	III–IV	+	–	+++

Materials and methods

EM investigation was performed on human post-mortem tissue samples obtained from the cingulate cortex of AD patients ($n = 5$), PD patients ($n = 6$), PD with cerebral pathology of AD (PDd, $n = 4$), and non-demented age-matched controls (C, $n = 5$). The composition of the four groups is shown in Table 1. The groups randomly consisted of both male and female patients ranging from 63 to 87 years old. The clinical diagnosis of the patients was confirmed by routine post-mortem analysis of the brains. The neuropathological examination determined the presence and distribution of Lewy bodies in the brain stem, limbic regions and the neocortex according to previously defined guidelines [14, 29]. Furthermore, the allocortical spread of neurofibrillary tangles (NFT), indicating Braak stages, and the distribution of neocortical plaques in view of the age and clinical history of the patients (CERAD scale) were carefully evaluated [3, 30]. The experimental groups were formed based on the assessed neuropathological data.

Samples were collected at autopsy in Karnovsky fixative (2% glutaraldehyde and 1% paraformaldehyde in 0.1 M phosphate buffer, pH 7.4) and transferred to fresh solution prior to EM. Tissue blocks were cut into 50-µm sections with a vibratome and routinely embedded in glycine ethylether. Samples covering the entire cortical depth were embedded and were cut to semithin thickness followed by azur and methylene blue staining for layer orientation. Non-serial, ultrathin sections were collected on 200-mesh copper grids and were contrasted with 5% aqueous uranyl acetate and Reynold's lead solution. Cortical capillaries were examined with a Philips 201 electron microscope.

The quantitative method used here was previously established in rat and human brain material, and has proved to be an effective approach for evaluating capillary wall alterations as a result of aging and cerebral hypoperfusion [7–9]. The advantage of the method is that it screens systematically the entire depth of the cortex covering all the cortical layers and counting every capillary encountered. Moreover, a high number of microvessels can be investigated to present a general overview of capillary ultrastructure. Approximately 100 capillaries per case were screened throughout the cortical layers focusing on the BM and pericyte pathology as defined below. The analysis was performed blind by two independent investigators. The number of vessels with aberrations was counted directly on the screen of the electron microscope. Only transversely cut microvessels were analyzed and capillaries partially covered by the mesh of the carrying grid were disregarded. The following categories of capillary abnormalities were distinguished based on previously accepted and detailed conditions [7–9]:

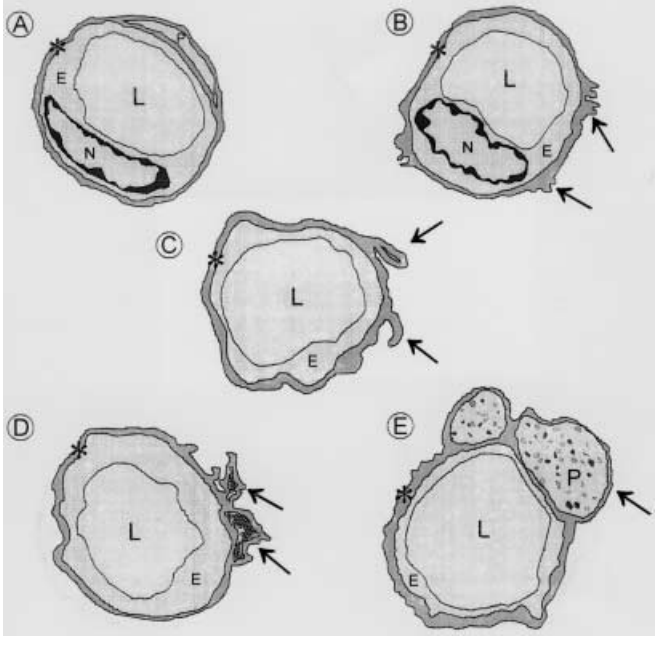

Fig. 1 A–E Schematic drawings representing categories of capillary wall pathology. **A** A healthy capillary. **B** Basement membrane thickening pointed at by *arrows*. **C** Abnormal duplication and branching of the basement membrane. **D** Fibrosis. **E** Pericytic degeneration (*L* capillary lumen, *E* endothelial cell, *N* endothelial nucleus, *P* pericyte, * basement membrane)

1. Local BM thickening (BMT, Fig. 1 B). This was defined as the BM showing local thickening if the luminal and abluminal outline of the BM were not running parallel, as shown in Fig. 1 B. Regions of the BM where the BM splits to embrace pericytes were not considered because the BM appears usually thicker at such segments. In case of the presence of an embedded pericyte, only the outer BM was investigated, the layer separating the endothelial cell and the pericyte was not. Random, irregular branching and folding of the BM (Fig. 1 C) were also considered as BMT. BMT was also determined according to the following measurements: EM photographs of deformed microvessels were randomly taken and the width of the BM was measured at a segment with regular thickness and at a visibly enlarged part of the same vessel. The assessed values for a healthy segment ranged between 126–323 nm, while thickening was indicated between 253–843 nm. The BM was considered to feature BMT when the measured thickness at the enlarged part was at least two times wider than that assessed at the unaffected segment of the same capillary. The method was routinely applied on the EM screen.

2. Fibrosis (Fig. 1 D). The term refers to excessive collagen type IV accumulation between two layers of the BM, identified by its typical periodicity, or collagen invasion to the vascular cells from a split BM (see Fig. 3 C, D). When a capillary demonstrated both BMT and fibrosis, fibrosis overruled BMT and the capillary was counted only as one with fibrosis.

3. Degenerative pericytes (Fig. 1 E). These showed abnormal, fractional inclusion bodies or swelling. Lipofuscin granules in the pericytic cytoplasm were not regarded as aberrant features. The term "deposits" was applied to the merged group of BMT and fibrosis, and "capillary aberrations" for the combination of deposits and degenerative pericytes.

After counting the absolute number of vessels per category, the amount of damaged microvessels was expressed as percentages of the total number of capillaries encountered for each class of vascular pathology. The data was statistically analyzed with the non-parametric Mann-Whitney-U test to define significance values (significance was taken as $P \leq 0.05$).

Results

The ultrastructural abnormalities of cerebral capillaries were examined in post-mortem cingulate cortex samples of three groups of neurological patients. BM deposits (BMT and fibrosis) and pericytic degeneration of AD, PD and PDd cases were compared to those of age-matched controls. Linear correlation between age and the ratio of abnormal capillaries could not be observed. The data of individual cases are summarized in Tables 2 and 3.

Figure 3 B demonstrates typical BMT of an AD patient compared to a normal, control BM (Fig. 3 A). The ratio of microvessels with BMT was doubled in the three pathological groups compared to controls, reaching significant values (Fig. 2 A). A representative example of extensive

Table 2 Summary of the individual data of control cases and AD patients. (*AD* Alzheimer's disease, *deg* degeneration, *BMT* basement membrane thickening)

Case no.	Group	Gender	Age	BMT (%)	Fibrosis (%)	Deposits (%)	Pericytic deg.(%)
1	Control	M	67	3.00	1.00	4.00	41.00
2	Control	M	66	13.25	0.00	13.25	32.53
3	Control	M	64	7.29	5.21	11.46	26.04
4	Control	M	63	8.13	17.89	26.02	26.02
5	Control	F	78	12.00	5.00	17.00	60.00
Mean			67	8.73	5.82	14.35	37.12
SEM				1.82	3.19	3.60	6.35
6	AD	M	77	15.96	4.26	20.21	12.77
7	AD	F	78	36.36	10.23	46.59	11.36
8	AD	F	87	10.64	5.32	15.96	68.09
9	AD	M	83	14.95	16.82	31.77	7.48
10	AD	M	85	14.29	30.25	44.54	33.61
Mean			82	18.44	13.38	31.81	26.66
SEM				4.57	4.77	6.19	11.31
P				**0.028***	0.175	**0.047***	0.347

* $P \leq 0.05$

Table 3 Summary of the individual data of PD cases with or without dementia (*PD* Parkinson's disease, *dem* dementia)

Case no	Group	Gender	Age	BMT (%)	Fibrosis (%)	Deposits (%)	Pericytic deg. (%)
11	PD	F	68	16.13	8.60	24.73	54.84
12	PD	F	76	16.09	2.30	18.39	4.60
13	PD	M	77	29.41	2.94	32.35	26.47
14	PD	M	68	3.64	34.55	38.18	28.18
15	PD	F	85	24.66	8.90	33.56	42.47
16	PD	M	64	20.41	11.22	31.63	22.45
Mean			73	18.39	11.42	29.76	29.84
SEM				3.62	4.85	2.88	7.05
P				**0.045***	0.273	**0.018***	0.584
17	PD + dem.	M	66	13.83	6.83	20.21	63.83
18	PD + dem.	F	70	30.77	19.23	50.00	5.77
19	PD + dem.	F	80	24.49	0.00	24.49	38.78
20	PD + dem.	F	86	16.19	25.71	41.90	24.76
Mean			75.5	21.32	12.83	34.15	33.29
SEM				3.89	5.87	7.06	12.22
P				**0.014***	0.268	**0.050***	0.624

* $P \leq 0.05$

fibrosis is shown in Fig. 3C and D. The ratio of vessels with such collagen accumulation remarkably increased in AD, PD and PDd but showed considerable variance among individual cases (Fig. 2B). The combination of BMT and fibrosis, defined as deposits in the capillary walls may provide a more objective approach to describe BM pathology, as the two features are considered to be progressively related. Deposits in the BM exhibited a remarkable and significant increase in AD, PD and PDd, as shown in Fig. 2C. The number of capillaries with deposits in these three groups was more than two times higher than that of controls. On the other hand, degenerative pericytes were encountered to a similar proportion in all groups including the controls, suggesting no specific involvement of pericytic degradation in any of the studied neurological conditions (Fig. 2D). An example of a degenerative pericyte is shown in Fig. 3E.

In general, the cerebral capillaries of AD, PD and PDd patients were affected, and demonstrated specific BM pathology. Disease-related vascular damage was restricted to the BM and did not involve the pericytes. Deposits in the capillary walls, as well as BMT were highest in the PDd group, although this group did not differ significantly from either the AD or the PD patients.

The control group that we assembled was not strictly age-matched due to limitations at performing autopsy. However, all cases exceeded the age of 60 years and were considered aged. A correlation analysis was performed to rule out that the vascular aberrations observed here present an age-related phenomenon: no significant correlation could be seen between the age of the patients and any of the defined categories of cerebral capillary damage. Fig. 4 shows a representative correlation graph concerning the percentage of intact capillaries.

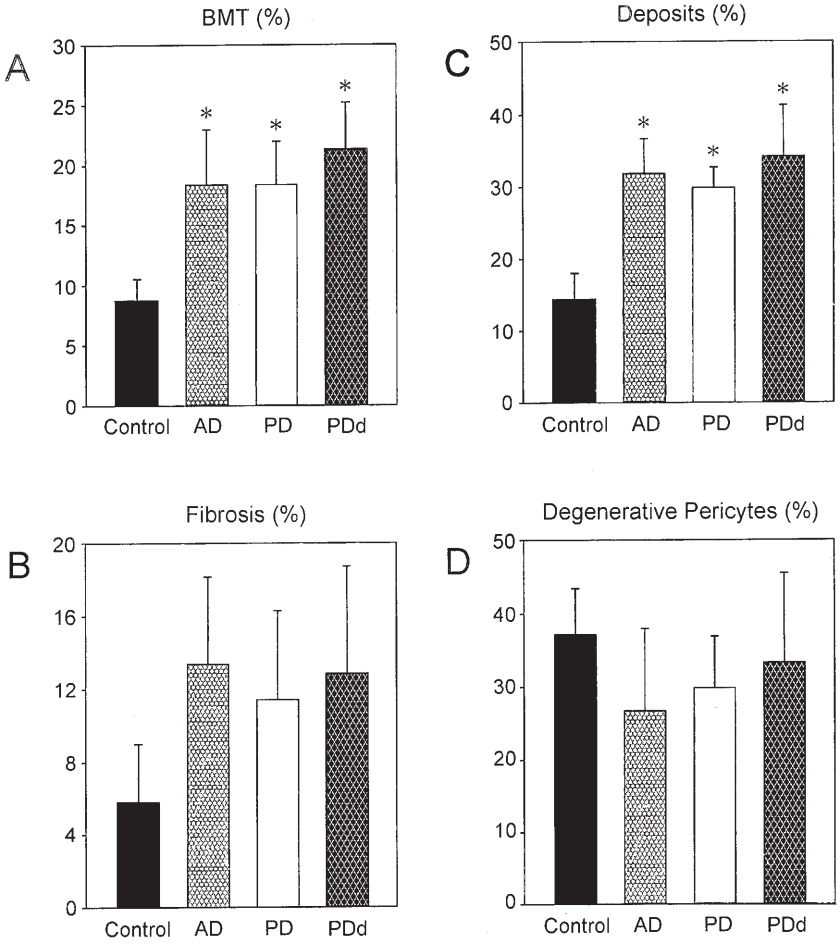

Fig. 2 Ultrastructural BM abnormalities in neurological disorders compared to controls. * ≤ 0.05 (*AD* Alzheimer's disease, *PD* clinical Parkinson's disease with cortical Lewy bodies, *PDd* PD with typical AD neuropathology, *BMT* basement membrane thickening)

Discussion

We have shown in the present study that the capillary ultrastructure in the limbic cingulate cortex of AD, PD and PDd patients is severely compromised. In addition to dementia-related disorders, PD is also shown here to be subject to cerebrovascular microanatomical alterations, particularly BM depositions. The cingulate cortex proves to be a proper area for investigation because neuropathological alterations characteristic of AD or PD, namely neuritic plaques, NFT or Lewy bodies, can be all observed in the region. The spread of NFT, an accepted marker for the pathological staging of AD, covers the complete limbic cortex with the progression of the disease and affects the entire isocortex at the later stages [3]. The appearance of Lewy bodies, the cortical lesion that can accompany PD, concerns the cingulate gyrus, as well [4].

Research on capillary anatomy and cortical regional cerebral perfusion rate has chiefly focused on their relationship with dementia; therefore, information about the phenomenon in other human neurological disorders is relatively scarce. However, PET studies showed decreased regional cerebral blood flow (rCBF) and oxygen utilization in PD [28]. Moreover, Kawabata et al. [27] conducted SPECT examinations and found that the rCBF of PD subjects with or without dementia was significantly reduced in the temporal and parietal cortices or the frontal and temporal cortices, respectively. Varma et al. [42] also showed cortical blood flow alterations in PD with dementia. The described observations appear to be rather similar to AD in that the temporal, parietal and frontal cortical lobes are primarily affected [10, 15, 32].

To place our pathological results into a physiological context and to be able to hypothesize cause-effect relationships, experimental animal studies are needed. Bilateral, chronic carotid artery occlusion in rats (2VO) has proved to be a cerebral hypoperfusion model that creates dementia-like symptoms such as learning impairment and memory deficits. Besides the typical spatial memory deficits demonstrated by water maze and radial maze tasks in 2VO rats [9, 34], sypmtoms of progressive neurodegeneration similar to that seen in human dementia have also been observed, such as characteristic apoptotic pyramidal cell damage in the hippocampus CA1, the primary site of neuropathological changes in AD [1, 3, 13]. Furthermore, additional features of AD, such as increased immunoreaction to glial fibrillary acidic protein and amyloid precursor protein accumulation, were reported after 2VO [13, 25]. The described hypoperfusion-related cog-

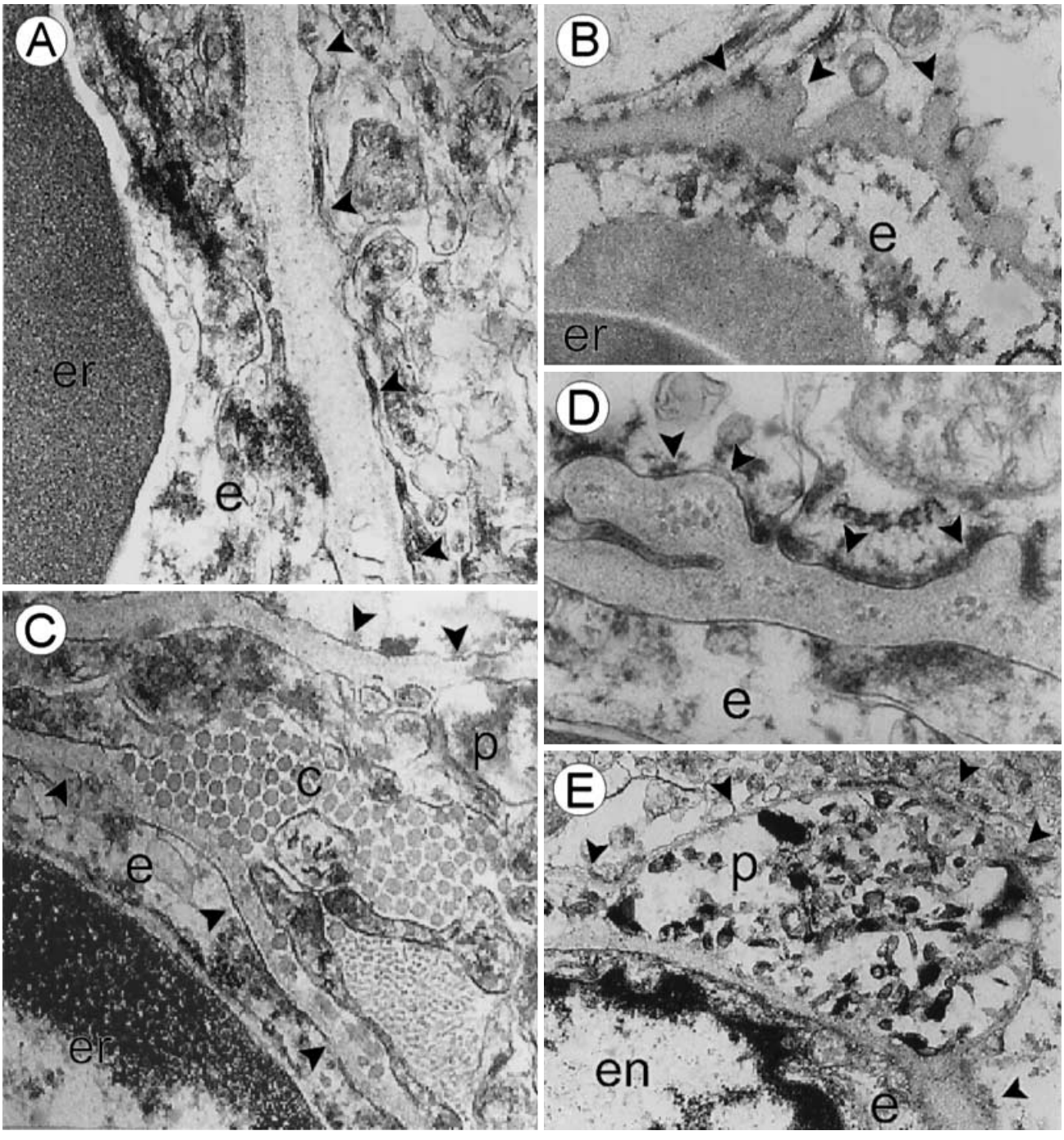

Fig. 3 A–E Photomicrographs demonstrating illustrative pathological ultrastructural alterations of human cerebral capillary walls. The BM in each photograph is indicated by *arrowheads*. **A** A healthy capillary of a control sample. **B** BM thickening of an AD patient. **C** Transversely cut collagen bundles invading the pericytic cytoplasm. **D** BM duplication with transversely cut collagen fibers. **E** A swollen, degenerating pericyte with inclusion bodies in the cytoplasm (*er* erythrocyte in the capillary lumen, *e* endothelial cytoplasm, *en* endothelial nucleus, *p* pericyte). **A** × 36,000; **B** × 26,5000: **C** × 54,5000; **D** × 48,000; **E** × 12,500

nitive malfunction was also accompanied by cerebral capillary damage as demonstrated by De Jong et al. [8, 9]. Considering all these the experimental data, a group of properties reminiscent of particular aspects of AD is assembled [11]. Therefore, it is tempting to speculate that the ultrastructural capillary abnormalities in human samples presented here and previously by others [6, 8, 36] are most likely associated with chronic cerebral hypoperfusion. Since cerebral hypoperfusion in animals causes massive capillary damage in the brain [8, 9], the alterations in rCBF possibly act as a causal factor inducing microvessel malformations not only in AD but also in PD and PD with dementia.

Morphological capillary abnormalities can not only be linked to cerebral hypoperfusion but may also account for compromised metabolic rates in the neural tissue. Re-

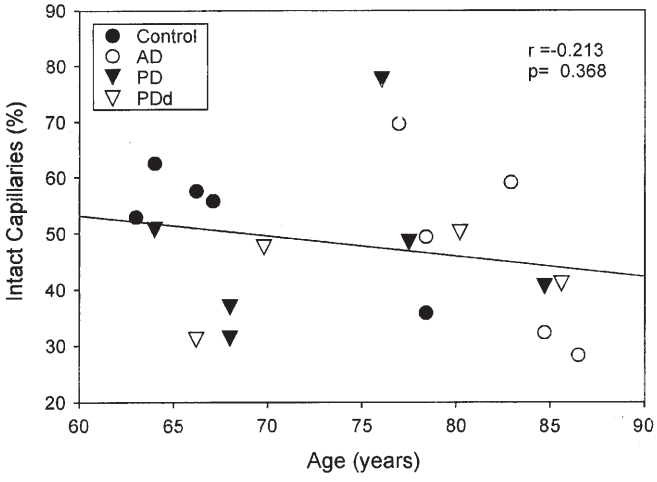

Fig. 4 Correlation between the age of the individual patients and the percentage of intact capillaries in the examined samples from the cingulate cortex

duced glucose metabolism in AD brains is a well-established phenomenon [2, 37]. Although the existence of reduced glucose metabolism in PD is a topic of debate, and contradicting PET results are available [16, 35, 38], PD with dementia has consistently been shown to be accompanied by reduced cerebral glucose metabolism [35, 38, 41]. A lower metabolic rate for glucose may be caused by hypoglycemia (resulting from the above-described hypoperfusion) or defective transport through distorted capillary walls. Both the physical features of capillaries, such as BMT shown here, and the functional damage to endothelial transport molecules can explain the latter possibility. Glucose transporters of the endothelial cells (GLUT-1) suffer dramatic changes in AD, as indicated by the lower level of GLUT-1 in the cerebral cortex [21, 22, 31], but GLUT-1 density measurements in PD have, to our best knowledge, not yet been reported.

Microvascular atrophy can be evoked not only by cerebral hypoperfusion but also by compromised metabolic routes of microvascular cells. The components of the capillary BM (collagen type IV, laminin and heparan sulfate proteoglycan) are secreted by the three cell types of the microvessels: the endothelial cells, the pericytes and the astrocytes [44]. Perlmutter and Chui [36] suggested that the production of these molecules may be under the influence of toxic external stimuli. Prominent examples are β-amyloid action on endothelial cells leading to endothelial dysfunction [39, 40] or the effect of oxygen free radicals on endothelial cells causing chromosomal aberrations and the induction of micronuclei [26]. Thus, the effect of β-amyloid or oxidative stress can alter the internal metabolism of the endothelial cells, which may imply, among others, a corrupt production of BM constituents. Oxidative stress is considered to be a contributing factor in the development of both AD and PD [19, 20, 33]. In addition to inducing neuronal damage, accumulating oxygen radicals may interfere with capillary ultrastructure by expressing a toxic influence on endothelial metabolism in AD and PD.

We found that capillaries with deposits occurred considerably more frequently in AD, PD and PDd than in controls, but the incidence of degenerating pericytes was not disease specific. Our data for pericytes do not agree with those of previous reports describing AD-associated, β-amyloid-induced damage to pericytes in cell culture [43]. The source of this discrepancy may lie in the methodological approach, although our theory that the presence of degenerating pericytes does not relate to dementia is supported by the lack of correlation between existing pericytic degeneration and learning performance in rats [9]. Thus, BM deposits, rather than pericytic irregularities, represent a crucial microvascular pathological property in neurological disorders.

We conclude that in addition to the neural tissue, the cerebral capillary network is also prone to structural degradation under neurological conditions like AD, PD and PDd. The microvascular BM suffers the most pronounced and dramatic damage as opossed to pericytes and emerges as a central target of vascular pathological changes in these disorders. The described structural BM malformations can lead to pathophysiological consequences such as compromised nutrient transport, insufficient neuronal metabolism and subsequent cognitive disturbances. Because of the multiple consequences, cerebral capillary damage must be considered a significant property or contributing factor in the development of AD, and possibly PD.

Acknowledgements The valuable contributions of Annelies Klink and Carolien Rozenmuller are highly appreciated. This work was supported by grants from The Netherlands Science Foundation (NWO) grant no. 970-10-005 and The Netherlands Science Foundation NWO-OTKA grant no. 048-011-006.

References

1. Bennet SA, Tenniswood M, Chen JH, Davidson CM, Keyes MT, Fortin T, Pappas BA (1998) Chronic cerebral hypoperfusion elicits neuronal apoptosis and behavioral impairment. Neuroreport 9:161–166
2. Blesa R, Mohr E, Miletich RS, Hildebrand K, Sampson M, Chase TN (1996) Cerebral metabolic changes in Alzheimer's disease: neurobehavioral patterns. Dementia 7:239–245
3. Braak H, Braak E (1991) Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol 82:239–259
4. Braak H, Braak E, Yilmazer D, Vos RAI de, Jansen ENH, Bohl J (1996) Pattern of brain destruction in Parkinson's and Alzheimer's diseases. J Neural Transm 103:455–490
5. Buée L, Hof PR, Delacourte A (1997) Brain microvascular changes in Alzheimer's disease and other dementias. Ann NY Acad Sci 826:7–24
6. Claudio L (1996) Ultrastructural features of the blood-brain barrier in biopsy tissue from Alzheimer's disease patients. Acta Neuropathol 91:6–14
7. De Jong GI, Weerd H de, Schuurman T, Traber J, Luiten PGM (1990) Microvascular changes in aged rat forebrain. Effects of chronic nimodipine treatment. Neurobiol Aging 11:381–389
8. De Jong GI, De Vos RIA, Jansen Steur ENH, Luiten PGM (1997) Cerebrovascular hypoperfusion: a risk factor for Alzheimer's disease? Animal model and postmortem human studies. Ann NY Acad Sci 826:56–74

9. De Jong GI, Farkas E, Plass J, Keyser JN, Torre JC de la, Luiten PGM (1999) Cerebral hypoperfusion yields capillary damage in hippocampus CA1 that correlated to spatial memory impairment. Neuroscience 91 : 203–210
10. DeKosky ST, Shih WJ, Schmitt FA, Coupal J, Kirkpatrick C (1990) Assessing utility of single photon emission computed tomography (SPECT) scan in Alzheimer disease: correlation with cognitive severity. Alzheimer Dis Assoc Disord 4 : 14–23
11. De la Torre JC (1999) Critical treshold cerebral hypoperfusion causes Alzheimer's disease? Acta Neuropathol 98 : 1–8
12. De la Torre JC, Mussivand T (1993) Can disturbed brain microcirulation cause Alzheimer's disease? Neurol Res 15 : 146–153
13. De la Torre JC, Fortin T, Park GAS, Butler KS, Kozlowski P, Pappas BA, Socarraz H de, Saunders JK, Richard MT (1992) Chronic cerebrovascular insufficiency induces dementia-like deficits in aged rats. Brain Res 582 : 186–195
14. De Vos RAI, Jansen ENH, Stam FC, Ravid R, Swaab DF (1995) 'Lewy body disease': clinico-pathological correlations in 18 consecutive cases of Parkinson's disease with and without dementia. Clin Neurol Neurosurg 97 : 13–22
15. Eberling JL, Jagust WJ, Reed BR, Baker MG (1992) Reduced temporal lobe blood flow in Alzheimer's disease. Neurobiol Aging 13 : 483–491
16. Eberling JL, Richardson BC, Reed BR, Wolfe N, Jagust WJ (1994) Cortical glucose metabolism in Parkinson's disease without dementia. Neurobiol Aging 15 : 329–335
17. Farkas E, De Jong GI, De Vos RAI, Jansen Steur ENH, Luiten PGM (1999) Cerebral microvascular breakdown in Alzheimer's disease and experimental hypoperfusion. In: Iqbal K, Swaab DF, Winblad B, Wisniewski HM (eds) Alzheimer's disease and related disorders. Wiley, New York, pp 165–170
18. Fukuyama H, Ogawa M, Yamaguchi H, Yamaguchi S, Kimura J, Yonekura Y, Konishi J (1994) Altered cerebral energy metabolism in Alzheimer's disease: a PET study. J Nucl Med 35 : 1–6
19. Gorman AM, McGowan A, O'Neill C, Cotter T (1996) Oxidative stress and apoptosis in neurodegeneration. J Neurol Sci 139 [Suppl] : 45–52
20. Gsell W, Strein I, Krause U, Riederer P (1997) Neurochemical abnormalities in Alzheimer's disease and Parkinson's disease – a comparative review. J Neural Transm Suppl 51 : 145–159
21. Harik SI (1992) Changes in the glucose transporter of brain capillaries. Can J Physiol Pharmacol 70 [Suppl] S 113–S 117
22. Horwood N, Davies DC (1994) Immunolabelling of hippocampal microvessel glucose transporter protein is reduced in Alzheimer's disease. Virchows Arch 425 : 69–72
23. Kalaria RN (1996) Cerebral vessels in aging and Alzheimer's disease. Pharmacol Ther 72 : 193–214
24. Kalaria RN, Pax AB (1995) Increased collagen content of cerebral microvessels in Alzheimer's disease. Brain Res 349 : 352
25. Kalaria RN, Bhatti SU, Lust WD, Perry G (1993) The amyloid precursor protein in ischemic brain injury and chronic hypoperfusion. Ann NY Acad Sci 695 : 190–193
26. Karlhuber GM, Bauer HC, Eckl PM (1997) Cytotoxic and genotoxic effects of 4-hydroxynonenal in cerebral endothelial cells. Mutat Res 381 : 209–216
27. Kawabata K, Tachibana H, Sugita M (1991) Cerebral blood flow and dementia in Parkinson's disease. J Geriatr Psychiatry Neurol 4 : 194–203
28. Leenders KL, Wolfson L, Gibbs JM, Wise RJS, Causon R, Jones T, Legg NJ (1985) The effects of L-DOPA on regional cerebral blood flow and oxygen metabolism in patients with Parkinson's disease. Brain 108 : 171–191
29. McKeith IG, Galasko D, Kosaka K, Perry EK, Dickson DW, Hansen LA, Salmon DP, Lowe J, Mirra SS, Byrne EJ, Lennox G, Quinn NP, Edwardson JA, Ince PG, Bergeron C, Burns A, Miller BL, Lovestone S, Collerton D, Jansen ENH, Ballard C, de Vos RAI, Wilcock GK, Jellinger KA, Perry RH (1996) Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. Neurology 47 : 1113–1124
30. Mirra SS, Heyman A, McKeel D, Sumi SM, Crain BJ, Brownlee LM, Vogel FS, Hughes JP, Belle G van, Berg L (1991) The consortium to establish a registry for Alzheimer's disease (CERAD). Part II. Standardization of the neuropathologic assessement of Alzheimer's disease. Neurology 41 : 479–486
31. Mooradian AD, Chung HC, Shah GN (1997) GLUT-1 expression in the cerebra of patients with Alzheimer's disease. Neurobiol Aging 18 : 469–474
32. Ohnishi T, Hoshi H, Nagamachi S, Jinnouchi S, Flores II. LG, Futami S, Watanabe K (1995) High-resolution SPECT to assess hippocampal perfusion in neuropsychiatric diseases. J Nucl Med 36 : 1163–1169
33. Owen AD, Schapira AH, Jenner P, Marsden CD (1997) Indices of oxidative stress in Parkinson's disease, Alzheimer's disease and dementia with Lewy bodies. J Neural Transm Suppl 51 : 167–173
34. Pappas BA, Torre JC de la, Davidson CM, Keyes MT, Fortin T (1996) Chronic reduction of cerebral blood flow in the adult rat: late-emerging CA1 cell loss and memory dysfunction. Brain Res 708 : 50–58
35. Peppard RF, Martin WR, Clark CM, Carr GD, McGeer PL, Calne DB (1990) Cortical glucose metabolism in Parkinson's and Alzheimer's disease. J Neurosci Res 27 : 561–568
36. Perlmutter LS, Chui HC (1990) Microangiopathy, the vascular basement membrane and Alzheimer's disease. Brain Res Bull 24 : 677–686
37. Rapoport SI, Horwitz B, Grady CL, Haxby JV, De Carli C, Schapiro MB (1991) Abnormal brain glucose metabolism in Alzheimer's disease, as measured by position emission tomography. Adv Exp Med Biol 291 : 231–248
38. Sasaki M, Ichiya Y, Hosokawa S, Otsuka M, Kuwabara Y, Kato M, Goto I, Masuda K (1992) Regional cerebral glucose metabolism in patients with Parkinson's disease with or without dementia. Ann Nucl Med 6 : 241–246
39. Thomas T, Thomas G, McLendon C, Sutton T, Mullan M (1996) β-Amyloid-mediated vasoactivity and vascular endothelial damage. Nature 380 : 168–171
40. Thomas T, McLendon C, Sutton ET, Thomas G (1997) Cerebrovascular endothelial dysfunction mediated by beta-amyloid. Neuroreport 8 : 1387–1391
41. Vander Borght T, Minoshima S, Giordani B, Foster NL, Frey KA, Berent S, Albin RL, Koeppe RA, Kuhl DE (1997) Cerebral metabolic differences in Parkinson's and Alzheimer's diseases matched for dementia severety. J Nucl Med 38 : 797–802
42. Varma AR, Talbot PR, Snowden JS, Lloyd JJ, Testa HJ, Neary D (1997) A 99mTc-HMPAO single-photon emission computed tomography study of Lewy body disease. J Neurol 244 : 349–359
43. Verbeek MM, Waal RM de, Schipper JJ, Van Nostrand WE (1997) Rapid degeneration of cultured human brain pericytes by amyloid beta protein. J Neurochem 68 : 1135–1141
44. Zarow C, Barron E, Chui HC, Perlmutter LS (1997) Vascular basement membrane pathology and Alzheimer's disease. An NY Acad Sci 826 : 147–160