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Amyloid angiopathy of the human brain: immunohistochemical studies using markers for components of extracellular matrix, smooth muscle actin and endothelial cells

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Abstract Cerebral amyloid angiopathies comprise a heterogeneous group of conditions characterised by amyloid deposition in leptomeningeal and cortical vessels. We have studied the deposition of extracellular matrix components in such vessels from controls and ten cases with marked amyloid angiopathy. Arterial vessels which were heavily loaded with amyloid often showed lack of immunostaining to collagen type I, III, V and VI in the amyloid-containing parts of the vessel wall but some immunoreactivity remained in the adventitia. The subintimal region of some arterioles presented a faint staining with collagen V and collagen VI antisera. Immunostaining to collagen IV and laminin revealed normal reactivity in the vascular basal lamina and frequently remaining activity in the media. Immunostaining for actin showed a complete or partial loss of reactivity in the amyloid-containing parts of the media but often there was a thin line of staining at the position of pericytes. The endothelial markers did not reveal any changes compared with controls. In other cerebral microangiopathies, for instance Binswanger's leukoencephalopathy, CADASIL and cases presenting hyalinosis there is a deposition of fibrillary collagens in the wall of afflicted microvessels. Degeneration of smooth muscle cells and absence of marked fibrosis in some of the arterial vessels in cases of amyloid angiopathy may explain why such vessels are susceptible to ruptures and haemorrhages.

Key words Amyloid angiopathy · Alzheimer's disease · Extracellular matrix · Immunohistochemistry · Microangiopathy

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Introduction

Cerebral amyloid angiopathy is an abnormality characterised by deposition of amyloid in the media and adventitia of small vessels in the cerebral cortex and leptomeninges [3, 30, 31]. This angiopathy may occur in cases with the Alzheimer type of dementia [5, 6, 30, 31], non-hypertension intracerebral haemorrhage in the elderly [9], radiation necrosis [27], Down's syndrome and various other brain diseases [30].

Most cases of cerebral amyloid angiopathy are biochemically very closely related to senile plaque amyloid; both lesions contain the β-peptide or A4 protein (β/A4) [3, 5]. Furthermore, immunohistochemical studies have indicated the presence of β-amyloid precursor protein in smooth muscle cells of leptomeningeal vessels in cases with amyloid angiopathy [7, 25, 28]. Two special forms of cerebral amyloid angiopathy are the Icelandic [19] and the Dutch types [17]. The latter type is a hereditary amyloid angiopathy with β/A4 deposition [1]. The Icelandic type of hereditary amyloid angiopathy appears to be caused by an unrelated peptide (gamma-trace or cystatin C) [19].

Degeneration of the media is a major abnormality of cerebral amyloid angiopathy [15, 29, 32]. Ultrastructural studies of the leptomeningeal arteries and arterioles of patients with Alzheimer's disease strongly indicate that β-amyloid deposits originate from smooth muscle cells of the media [34] and indicate that polymerisation into amyloid fibrils takes place in the basal lamina. Myocytes trapped in amyloid deposits degenerate and die.

Amyloid deposits, cell debris and in some cases fibrosis are present in afflicted microvessels of cases with cerebral amyloid angiopathy [32]. However, there has been only one major investigation on the composition of the fibrosis, i.e. the extracellular matrix in cases with cerebral amyloid angiopathy [4]. We have, therefore, characterised the changes which occur in the intracerebral blood vessels of such cases using immunohistochemical markers for various extracellular matrix components. In addition we

have investigated other components of the vessels using markers for endothelial and smooth muscle cells.

Our study is not concerned with the many different architectonic alterations of the terminal cerebral vasculature in Alzheimer patients [2, 14], but with the heavily amyloid-loaded superficial vessels and the arterial vessels which penetrate into the cerebral cortex of cases with severe amyloid angiopathy. These, probably represent the endstage of the angiopathy.

Subjects, materials and methods

Autopsy material was obtained from ten cases (five females, five males, 59–83 years of age) with morphological signs of amyloid angiopathy identified with alkaline Congo stain and β-amyloid immunohistochemistry (Table 1). Five cases had the clinical diagnosis of dementia and met the conventional pathological criteria for Alzheimer's disease [16], one case had Down's syndrome and four cases had amyloid angiopathy of unknown origin. Eight control cases (five males, three females, 28–80 years of age) without signs of brain pathology were used as controls. Four of them had died from heart diseases and four from malignant tumours. The controls have been used in a previous study on the angiopathy seen in cases with Binswanger's encephalopathy [36].

The autopsies were conducted 1–5 days after death. The brain was fixed in 10% formalin for 3–5 weeks. After naked eye inspection of the brain, numerous parts of the cerebral cortex, white matter, basal ganglia, cerebellum and brain stem were taken for microscopical diagnosis.

All the samples were infiltrated with soft paraffin at 54° C overnight, and then embedded in paraplast. Sections of 5 μm were cut and stained with haematoxylin and eosin, Luxol fast blue and by Masson's trichrome method. Other sections were stained with alkaline congo red and examined by polarised light to detect the presence of amyloid by its green birefringence. Still other sections were immunostained with a mouse monoclonal antibody to human β-amyloid (Table 2).

Immunochemistry was performed on samples obtained from the cerebral cortex and leptomeninges in which screening had demonstrated regions with marked amyloid angiopathy. We used a number of primary monoclonal and polyclonal antisera to visualise different components of endothelial cells, smooth muscle actin and components of extracellular matrix, i.e. various components of the blood vessel walls (Table 2).

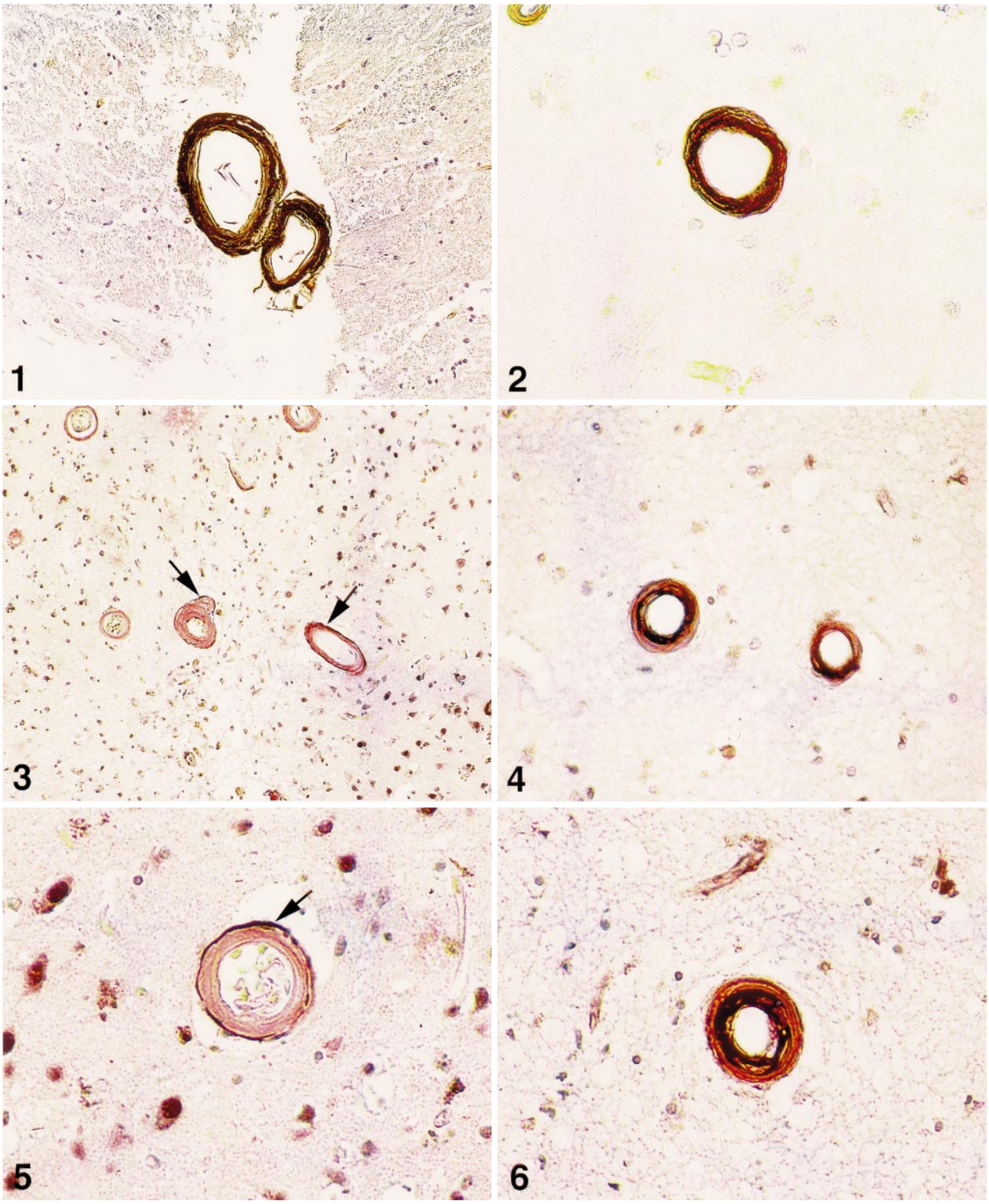
The paraffin sections were exposed to xylol, a series of alcohol concentrations and washed in phosphate-buffered saline (PBS). Endogenous peroxidase activity was blocked with methanol and hydrogen peroxide and the sections were then rinsed in PBS. Un-

Table 1 Survey of the material used for immunohistochemical observations on blood-vessel changes in cases showing marked cerebral amyloid angiopathy

Case no.	Diagnosis	Sex	Age at onset of symptoms	Age at death	Cause of death	Other pathological findings
1	Alzheimer's disease	F	59	66	Pulmonary edema	A few lacunes
2	Alzheimer's disease	F	60	83	Pneumonia?	Marked extracerebral arteriosclerosis
3	Alzheimer's disease	F	60	70	Pulmonary emboli	Fracture of the tibia
4	Alzheimer's disease	M	64	67	Respiratory failure	Cerebellar hemorrhage
5	Alzheimer's disease	F	57	66	Pneumonia	
6	Senile dementia	M	70?	75	Pneumonia	Marked extracerebral arteriosclerosis
7	Alcohol abuse, dementia	M	68	70	Respiratory failure	Pulmonary tuberculosis
8	Hypertension	M	?	83	Cardiac failure	Pulmonary tuberculosis
9	Alzheimer's disease	M	73	76	Circulatory failure	
10	Down's syndrome	F	0	59	Respiratory failure	

Table 2 Survey of the antisera used and the product sources. Mouse antisera were monoclonal and the others polyclonal

Protein	Antiserum	Dilutions	Source
Collagen I	Mouse-anti human collagen I	1:500	Paesel & Lorei, Frankfurt, Germany
Collagen I	Goat-anti human collagen I	1:200, 1:300	Southern Biotechnology, Birmingham, Ala.
Collagen III	Goat-anti human collagen type III	1:100	Southern Biotechnology, Birmingham, Ala.
Collagen III	Mouse-anti human collagen type III	1:100	Chemicon International, Temecula, Calif.
Collagen IV	Mouse-anti human collagen IV	1:200, 1:300	Chemicon International, Temecula, Calif.
Collagen V	Goat-anti human collagen V	1:200, 1:300, 1:800	Southern Biotechnology, Birmingham Ala.
Collagen VI	Mouse-anti human collagen type VI	1:100, 1:200	Chemicon International, Temecula, Calif.
Laminin	Mouse-anti human laminin	1:400, 1:600	Chemicon International, Temecula, Calif.
Laminin	Rabbit-anti human laminin	1:1000, 1:1600	Chemicon International, Temecula, Calif.
Actin	Mouse anti-human a-smooth muscle actin	1:100	Dakopatts AB, Glostrup, Denmark
Ulex	Ulex europaeus agglutinin I	1:200	Vector, Burlingame, Calif.
Factor VIII	Chicken anti-human factor VIII	1:1000	Immunsystem AB, Uppsala, Sweden
CD-34	Mouse anti-human endothelial cells	1:25	QBEND 10, Unipath Ltd, Hants, UK
GLUT 1	Rabbit-anti human glucose transporter	1:1000, 1:2000	Chemicon International, Temecula, Calif.
β-Amyloid	Mouse anti-human beta-amyloid	1:50, 1:100	Dakopatts AB, Glostrup, Denmark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◀ **Fig. 1** Intracerebral arterial vessels from one control case. Immunoreactivity to collagen III is present in the adventitia and to a lesser degree in the media

Fig. 2 Intracerebral arterial vessels from a control case. Immunoreactivity to collagen IV is present in the media almost all the way to the lumen of the vessel

Figs. 3, 5 Intracerebral arterial vessels from a case with amyloid angiopathy. Sections are double-stained with alkaline Congo red and immunohistochemistry to collagen III. These vessels containing abundant amyloid show only a small narrow zone of immunoreactivity to collagen III in the outer part of the adventitia *(arrows)*. Compare with Fig. 1

Figs. 4, 6 Intracerebral arterial vessels from a case with amyloid angiopathy. Sections are double-stained with alkaline Congo red and immunohistochemistry to collagen IV. These vessels which are heavily stained for amyloid show immunoreactivity to collagen IV in the media and almost all the way to the lumen of the vessels. Compare with Fig. 2 (control) and Figs. 3, 5 (collagen III)

specific protein binding was blocked with 1% bovine serum albumin, horse serum or swine serum. For some of the techniques we used treatment with protease (0.05% in PBS, 10 min) to unmask antigenic sites in the tissue (collagen I, III, IV, V, laminin). The primary antiserum was then applied (dilutions 1 : 100–1 : 1600). The appropriate dilutions and exposure time were determined in preliminary experiments to achieve optimal staining quality and these parameters varied for the different antisera used.

The sections were rinsed in PBS, exposed to secondary antibodies and rinsed again in PBS. Antibodies bound to antigens were located in the sections by the avidin-biotin-peroxidase complex method (Vectastain ABC Kit, Vector Laboratories, Burlingame, Calif.) using 3-amino-9-ethylcarbazol or 3,3,-diaminobenzidine tetrahydrochloride as the chromogen. To intensify the reaction product we applied in some of the methods (actin, ulex, factor VIII and CD34) the nickel enhancement procedure according to Shu et al. [26]. It is a combination of the nickel ammonium sulphate technique [11] and the glucose-glucose oxidase method to obtain a continuous release of hydrogen peroxide [12]. It results in a very dark and easily visible reaction product. Cell nuclei were stained by haematoxylin or nuclear fast red. Negative control stainings were performed by omitting the primary antibody from the immunohistochemical procedure; otherwise the technique was identical to that described above.

For the entire material we used parallel sections stained for amyloid and various immunohistochemical markers. In addition, double stainings were performed to demonstrate the presence of amyloid and the expression of collagen type III or IV in one and the same vessel (see Figs. 3–6). To that end the sections were first stained with alkaline Congo red and then immunostained with monoclonal antisera to collagen type III or IV (Table 2).

Results and comments

Controls

Collagen I antiserum immunostained the adventitia of arterioles but the media was not or only faintly stained. Occasionally, there was a weak staining of capillaries and venules. Collagen III antiserum showed a similar but somewhat weaker immunostaining (Fig. 1). Collagen type V immunostaining disclosed reaction particularly in the adventitia and media of the arterioles as well as in the walls of many capillaries and venules. Collagen VI immunostaining gave a weak positive signal in the media.

Immunostaining with antisera to the basal lamina components, collagen IV and laminin demonstrated one intensely stained line between the intima and media of arterioles and several fine lines in the media, obviously representing basal lamina (Fig. 2). The staining was present also in the walls of the capillaries.

The staining for smooth muscle actin demonstrated concentric layers of immunoreactive cells in the media corresponding the smooth muscle cells and an inner thin line presumably representing pericytes. This inner layer was also present in veins. Occasional immunoreactive cells were present in capillaries. All the endothelial markers showed distinct immunostaining at the position of the endothelial cells.

Cerebral amyloid angiopathies

The angiopathy involved leptomeningeal and cortical arteries and arterioles. We identified first vessels with a strong congophilic appearance, thickened walls and marked β-amyloid immunostaining. Such vessels, immunostained for smooth muscle actin, showed in all the cases a complete or partial loss of staining in the media but there was often a remaining thin line of immunoreactivity in the intima.

Staining with antisera to collagen type I, III, V and VI of the heavily amyloid-loaded arterial vessels often was negative particularly in the media (Figs. 3, 5). However, immunoreactivity was still present in the adventitia of many of these vessels (Figs. 3, 5), proving that the lack of immunostaining in the media was not a histotechnical failure. It should be pointed out that the media of some amyloid-containing arterial vessels were immunopositive. In addition, in some of the markedly amyloid-containing arterioles a faint immunostaining to collagen V and collagen VI was visible in the inner part of the media.

Immunostaining for collagen IV and laminin revealed moderately intense staining of the vascular basal lamina and frequently of the media (Figs. 4, 6). Such immunoreactivity often surrounded amyloid-containing regions of the media as demonstrated in Figs. 4 and 6.

Vessels with the characteristics demonstrated in Figs. 3–6 were seen in the leptomeninges and in the cerebral cortex of all the cases. The endothelial cell markers did not reveal any clear-cut pathology of the amyloid-containing vessels, i.e. factor VIII, ulex, CD34 and glucose transporter 1. All these markers showed clear-cut staining of the endothelial cells both in controls and in the heavily amyloid-loaded type of vessels.

Discussion

The present study was carried out to characterise by immunohistochemistry various collagen subtypes and some other components of the extracellular matrix in arterial vessels from cases presenting severe amyloid angiopathy. The most significant findings were: (1) the absence of im-

munostaining to fibrillary collagens in the media of many markedly amyloid-containing arteries and arterioles, and (2) the presence of immunoreactivity to collagen IV and laminin at the vascular basal lamina and frequent staining of the media.

The deposition of amyloid seen in cases with cerebral amyloid angiopathy has previously been investigated by histochemistry, immunohistochemistry and electron microscopy [3, 7, 28, 29, 32–35]. It is known that the amyloid is first found close to basal laminas at the junction of the media and the adventitia. The changes then gradually occupy the entire media sparing the endothelial cells and their basal lamina [3]. The amyloid encircles and separates each individual smooth muscle cell which exhibits signs of cell degeneration [15, 32, 34]. The smooth muscle cells thus appear to produce the compound which finally causes their death, i.e. a cellular suicide mechanism.

The arteries and arterioles we focused on obviously represent the end-stage of the pathological process since immunostaining to smooth muscle cell actin was lost in the media of the amyloid-loaded vessels. Degeneration of smooth muscle cells of the media in other cerebral microangiopathies is usually associated with depositions of various components of the extracellular matrix [37], which probably strengthen and stabilise the diseased vessel wall. In view of the fact that haemorrhages due to vascular rupture occur in cases with cerebral amyloid angiopathy [3, 32], it is of interest to define the changes which may occur in the various components of the vascular extracellular matrix of such cases.

There are only a few previous studies on changes of the extracellular matrix in cases of amyloid angiopathy of the human brain and most of these concern the basal lamina of terminal vessels [21, 22, 34] rather than the arteries and arterioles [4]. Our study shows that immunoreactivity to the basal lamina components, collagen type IV and laminin remains in the media of the vessels heavily loaded with amyloid. In addition, the vascular basal lamina shows normal staining for these markers. The presence of basal lamina components remaining in the media of afflicted vessels is of interest since the idea has previously been proposed that amyloidogenesis in such vessels may be facilitated by extracellular proteins including basal lamina products [7].

There was an absence of immunostaining to collagen type I, III, V and VI in the media of many markedly amyloid-containing arteries and arterioles. In other microangiopathies including Binswanger's leukoencephalopathy, CADASIL and cases presenting hyalinosis, there is often an increase in immunostaining to these collagen types [36, 37]. Amyloid angiopathy is an important cause of brain lesions in afflicted individuals [3, 5, 32]. Cerebral amyloid angiopathy often declares its presence by producing intracerebral haemorrhage [5, 8, 18] and ischaemic injury to the brain [5, 8, 20]; in some cases white matter degeneration may occur [10]. Media degeneration in association with low amounts of extracellular matrix may make these vessels vulnerable and more easily susceptible to rupture than in other microangiopathies in which various collagens are deposited, and thus strengthen the vessel wall [23, 24, 36, 37]. Furthermore, the media degeneration in the arteries and arterioles probably makes these vessels less responsive to humoral and neurogenic influences. Since the amyloid angiopathy preferentially involves larger surface vessels and penetrating arteries and arterioles, brain perfusion may be jeopardised [14].

We would like to point out that in each of the cases presented here many amyloid-containing vessels were also present in which the immunoreactivitiy to fibrillary collagens remained. The cause of this variation is unknown. One explanation may be that the different changes reflect a temporal evolution of the microangiopathy. In a forthcoming investigation based on material with a milder degree of amyloid angiopathy we will address this question in detail.

In the present study we did not find any obvious changes with regard to the expression of the endothelial cell markers in the arterial amyloid-containing vessels. However, many previous investigations have demonstrated structural and functional endothelial cell changes in the capillary bed from cases with Alzheimer's disease [2, 13, 14]. An intact endothelial cell layer of the arteries and arterioles will counteract the formation of thrombosis which is rarely seen in the amyloid-loaded vessels.

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