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Basement membrane proteins, apolipoprotein E and glycosaminoglycans in pituitary adenomas and their correlation to amyloid

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Abstract The aim of the study was to confirm earlier reports of the association of amyloid deposits in growth hormone (GH)-producing adenomas of the pituitary and the presence of glycosaminoglycans, basement membrane proteins and apolipoprotein E (apo E). Serial sections from 17 amyloidotic and 11 nonamyloidotic, sparsely granulated, GH-producing adenomas obtained from patients presenting with acromegaly were stained with Congo red and Alcian blue, and also with antisera directed against fibronectin, collagen IV, laminin and apo E. Glycosaminoglycans were found in capillaries of every adenoma and were also related spatially to amyloid deposits. Immunostaining of both nonamyloidotic and amyloidotic adenomas demonstrated the presence of fibronectin, collagen IV and laminin in the basement membranes of surrounding nonadenomatous tissue and tumour vessels. In approximately half the amyloidotic adenomas, each basement membrane protein presented with a distinct spatial relationship to amyloid deposits. Apo E was found in 88% of the amyloidotic adenomas within the amyloid deposits, and in six cases intracellular immunostaining was also evident in folliculo-stellate cells. The results are consistent with the presence of glycosaminoglycans, basement membrane proteins and apo E in the amyloid deposits of pituitary adenomas.

Key words Amyloid · Basement membrane proteins · Apolipoprotein E · Glycosaminoglycans · Pituitary adenoma

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Introduction

About 41% of all pituitary adenomas reveal deposits of amyloid [26]. Amyloid deposits have been described as perivascular and interstitial, and their morphology as filamentous, stellate or spheroid [13, 35]. Amyloid is present in 48% of prolactinomas and 67% of GH-producing adenomas [26].

In nonadenomatous pituitaries of patients aged 85 years and older, amyloid is found with a prevalence of 80% [21]. Previous studies have shown that this local or organ-limited senile interstitial amyloid of the pituitary may be of the same origin as amyloid affecting GH-cell and PRL-cell adenomas [23]. A similar observation has been recorded with regard to deposits of islet amyloid polypeptide (IAPP), which may affect both nonadenomatous islets in non-insulin-dependent diabetes mellitus and insulinomas [37]. Pituitary amyloid has been shown to have a different origin than the amyloid affecting Langerhans' islets and insulinomas [22].

A variety of constituents other than the fibril protein have been identified in amyloid deposits, such as amyloid P component [18, 32], glycosaminoglycans [1, 14, 30], apolipoprotein E [7, 17, 39] and apolipoprotein J [6] and basement membrane proteins [16, 19, 36]. Amyloid P component has been found in the senile amyloid of the anterior pituitary [23] and in the deposits of pituitary adenomas [13]. In recent studies [24], the amyloid of nonadenomatous pituitaries has been found to contain apolipoprotein E, glycosaminoglycans and basement membrane proteins, raising the question of whether these constituents may also be identified in amyloid deposits of pituitary adenomas.

Materials and methods

Twenty-eight GH-producing sparsely granulated adenomas were selected from a collective of 1518 pituitary adenomas surgically removed at the University Hospital of Hamburg (Germany) between 1977 and 1989. The patients had been suffering from acromegaly. All selected adenomas were proven immunohistochemi-

cally to be essentially monohormonal. In 4 adenomas 1% of the tumour cells were immunoreactive for prolactin, in 2 adenomas, 2% and in a single adenoma, 5% of tumour cells.

Twenty adenomas (between 1977 and 1985) had been fixed in Bouin's fixative, dehydrated in graded alcohol and embedded in paraffin, and 8 (1985–1989) had been fixed in 3% buffered glutaraldehyde for 2–6 h, depending on the size of the specimen, then dehydrated and routinely embedded in paraffin. We used 2- to 3-µm-thick serial sections throughout the study.

Amyloid was identified by alkaline Congo Red staining [20]. Glycosaminoglycans were identified using the sodium sulphate alcian blue (SAB) method. The sections were deparaffinized, rehydrated, dipped into acetic alcohol for 90 s and subsequently incubated in SAB stain for 3 h. Afterwards they were rinsed in acetic alcohol, tap water and deionized water and alkalized with saturated sodium tetraborate for 30 min. The washing steps were repeated, and the sections were dipped into saturated picric acid and counterstained with van Gieson's picrofuchsin.

In order to determine the degree of sulphation of the glycosaminoglycans in situ the alcian blue method with varying concentrations of $MgCl_2$ was used [28]. Specimens were deparaffinized, rehydrated and suspended in alcian blue staining solutions for 36 h. The solutions used were 0.03 M, 0.1 M, 0.3 M, 0.7 M, 1.0 M $MgCl_2$.

Autopsy specimens from a patient who had suffered from generalized senile cardiovascular amyloidosis of transthyretin origin (ATTR) served as a control, because ATTR deposits have been shown to contain glycosaminoglycans [30].

The following antisera were used for immunohistochemistry: monoclonal antibodies directed against all alleles of apolipoprotein E (Natutec, Frankfurt, Germany; dilution 1:40), collagen IV (Biogenex, DCS Innovative Diagnostik Systeme, Hamburg, Germany; dilution 1:10), and polyclonal antibodies directed against laminin (Heyl, Berlin, Germany; dilution 1:100) and fibronectin (DAKO, Hamburg, Germany; dilution 1:200). The polyclonal antisera directed against fibronectin and laminin revealed no or negligible (<5%) cross-reactivity with other basement membrane proteins, as stated on data sheets supplied by the manufacturers.

Immunohistochemistry was performed using the peroxidase–anti-peroxidase (PAP) and the avidin–biotin complex (ABC) methods. The sections were deparaffinized in toluene and rehydrated in graded alcohol; 1% buffered H_2O_2 was used to block endogenous peroxidase. Except for anti-apo E, the specimens were treated with 0.1% pronase for 10 min. The sections were washed in phosphate-buffered saline (PBS) supplemented with 1% (w/v) bovine serum albumin (Sigma Chemicals, Deisenhofen, Germany). Incubation with primary and secondary antibodies was performed in a moist chamber at room temperature, for 120 and 30 min, respectively.

The immunoreactions were visualized with 3,3-diaminobenzidine-tetrahydrochloride (Sigma, Deisenhofen, Germany). The sections were counterstained with haematoxylin. Appropriate immunostaining was tested on routinely fixed autopsy and biopsy specimens of kidney, haemangioma and large intestine. Negative controls included omission of the primary antibodies.

Congo Red staining was evaluated using a special polarization microscope with tension-free optics. Amyloid was identified by its typical green birefringence, which did not disappear on rotation of the specimen. An attempt was made to quantify the amyloid. Five fields were randomly selected at the same magnification (×250), and the number of amyloid deposits was counted. It was not possible to count more fields because the smallest specimen did not exceed the size of six high-power fields. The adenomas were classified as containing large (more than 20 amyloid deposits per field; group 1), moderate (10–19 per field; group 2) or small amounts of amyloid (fewer than 10 deposits; group 3).

Results

Seventeen adenomas had amyloid deposits. Eight cases (group 1) yielded large amounts of amyloid (Fig. 1), 5 exhibited moderate amounts (group 2) and 4 specimens contained small amounts (group 3). Eleven adenomas without amyloid served as controls. The pattern of amyloid deposition was not uniform. In 9 cases the amyloid was arranged in stellate masses, whereas in 6 specimens it presented in a filamentous pattern. Two cases demonstrated string-like deposits. Amyloid was deposited both in the vicinity of capillaries and in between adenoma cells.

Glycosaminoglycans were visualized in capillary walls and in amyloid deposits. In order to determine the degree of sulphation, the concentration of $MgCl_2$ was varied. At a concentration of 0.3 M $MgCl_2$, glycosaminoglycans were spatially related to amyloid deposits in 16 cases (94%) (Fig. 2). At a concentration of 0.7 M $MgCl_2$ this correlation was evident in 11 specimens (65%) and in 6 adenomas (35%) staining of GAGs persisted even at 1.0 M $MgCl_2$.

In both nonamyloidotic and amyloidotic adenomas, GAGs were related to basement membranes. At a solution of 0.3 M $MgCl_2$ they were distinct in all cases, while at 0.7 M they were poorly visible in 6 cases. However, in amyloidotic adenomas GAGs occasionally remained detectable in basement membranes in those specimens in which the amyloid deposits were stained, even at concentrations of 0.7 M and 1.0 M $MgCl_2$.

In contrast to the normal anterior pituitary consisting of cell cords surrounded by a network of parenchymatous basement membrane, the adenomatous cells were not organized into cell cords and there was no regular parenchymatous basement membrane (as in previous observations [2]).

Anti-collagen IV stained vascular basement membranes and any remaining parenchymatous basement membranes in the pituitary adenomas. Capillary basement membranes were particularly well visualized, and the walls of larger blood vessels were also reactive. In 9 adenomas (53%) collagen IV immunostained amyloid deposits; in cases with a stellate amyloid pattern it was interesting to note that staining was less intense in the centre of the deposit than in peripheral areas (Fig. 3). Some deposits in some adenomas were not immunostained.

Like anti-collagen IV, anti-laminin stained vascular basement membranes as well as parenchymatous basement membranes in all adenomas. Immunostaining was more intense in basement membranes than in amyloid deposits, which were immunoreactive in 10 cases (59%) (Fig. 4).

Anti-fibronectin stained serum and vascular basement membranes and also nuclei in several cases. In 9 adenomas (53%) amyloid deposits were reactive but the staining was less intense than in serum and basement membranes (Fig. 5).

Anti-apo E immunoreactivity was more intense in serum than in vessel walls. Deposits in 15 (88%) amyloidotic cases were immunoreactive for apo E (Fig. 6); in several specimens the centre of the deposits showed less reaction than the periphery, but other deposits in the same adenomas revealed homogenous staining patterns. Intracellular immunostaining was found in six amyloidotic adenomas, the cytoplasm of folliculo-stellate cells being reactive.

Fig. 1 GH-cell adenoma: multiple deposits of amyloid. Congo red staining, polarization, ×330

Fig. 2 GH-cell adenoma: three medium-sized deposits of amyloid (*arrows*). Alcian blue staining, 0.3 M $MgCl_2$, ×535

Fig. 3 GH-cell adenoma: collagen IV in deposits of amyloid (*long arrow*) and vessel walls (*short arrow*). Anti-collagen IV, counterstain haematoxylin, ×535

Fig. 4 GH-cell adenoma: laminin in amyloid plaques (*long arrow*) and vessel walls (*short arrows*). Anti-laminin, counterstain haematoxylin, ×535

Fig. 5 GH-cell adenoma: fibronectin in amyloid deposits (*long arrow*) and vessel walls (*short arrow*). Anti-fibronectin, counterstain haematoxylin, ×535

Fig. 6 GH-cell adenoma: apolipoprotein E in amyloid plaques. Anti-apo E, counterstain haematoxylin, ×535

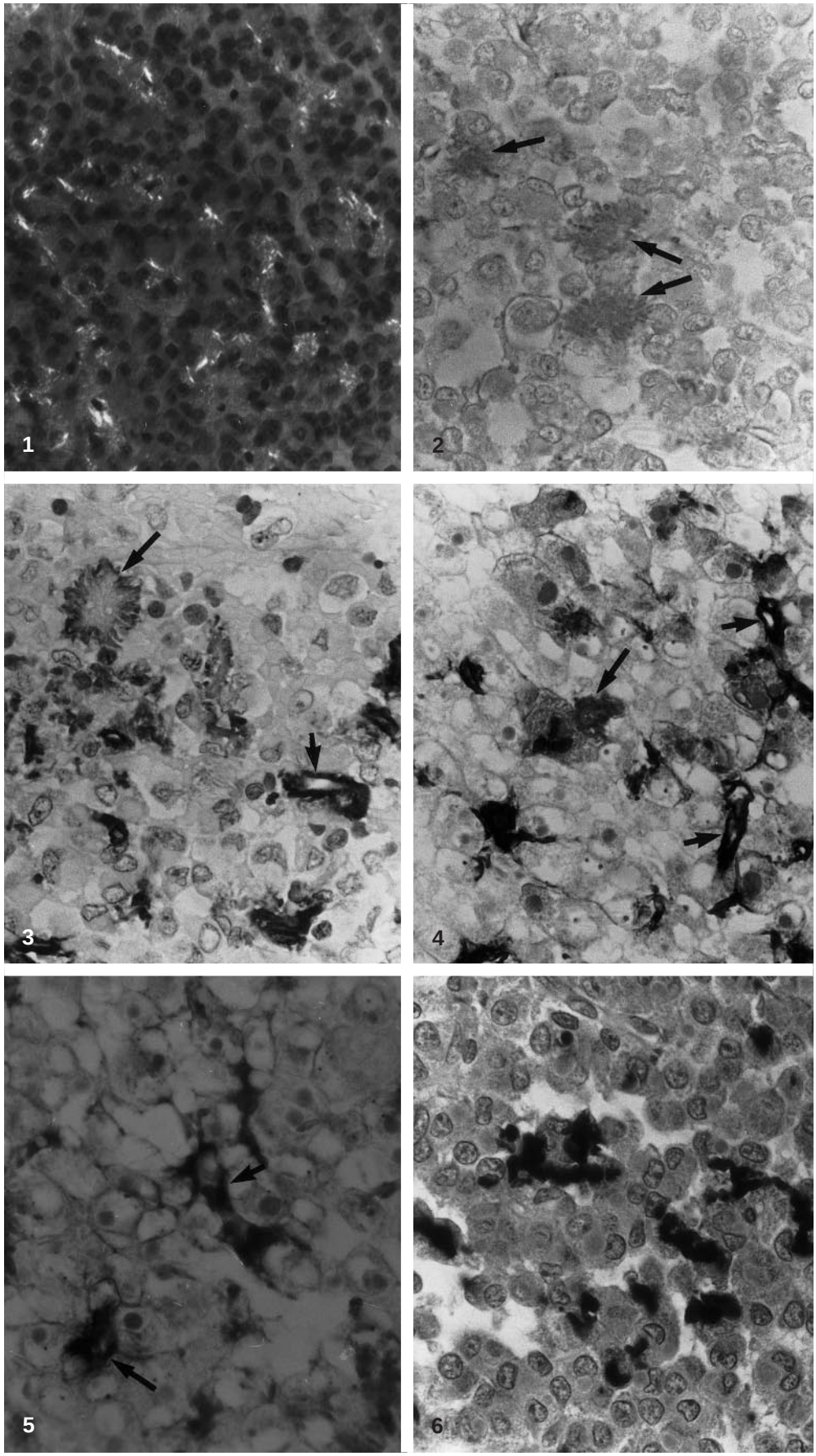

Table 1 Correlation of the degree of amyloid deposition to the presence of basement membrane proteins, apolipoprotein E and glycosaminoglycans (+ positive immuno-/or histochemical staining of amyloid, – no immuno-/or histochemical staining of amyloid, *group 1* more than 20 amyloid deposits per high power field, *group 2* 10–20 deposits per high power field, *group 3* less than 10 deposits per high-power field)

	Collagen IV	Laminin	Fibronectin	Apolipoprotein E	0.3 M $MgCl_2$	0.7 M $MgCl_2$
Group 1						
7/82	+	+	+	+	+	–
3526/79	–	–	–	–	+	+
130/87	–	+	+	+	+	–
79/82	+	–	–	+	+	+
15/84	–	+	+	+	+	+
75/79	+	–	–	+	+	–
84/88	–	+	+	+	+	+
10/80	+	–	+	–	+	+
Group 2						
57/82	+	+	+	+	+	–
42/85	–	+	+	+	–	+
30/82	+	+	–	+	+	+
26/83	–	+	+	+	+	+
114/81	+	–	–	+	+	+
Group 3						
30/79	–	–	–	+	+	+
108/89	–	–	–	+	+	+
53/81	+	–	–	+	+	–
9/81	+	+	+	+	+	–

Table 1 summarizes the correlation of the degree of amyloid deposition to the presence of GAGs, basement membrane proteins and apo E.

In nonamyloidotic adenomas, apo E was found in vessel walls and plasma. Intracellular immunoreactivity was not found. Immunostaining for laminin, collagen IV and fibronectin was related only to basement membranes.

Discussion

The histochemical and immunohistochemical studies presented here give morphological evidence for the presence of glycosaminoglycans, basement membrane proteins and apo E in the amyloid deposits of GH-synthesizing and GH-secreting adenomas. This type of amyloid is thus comparable to other amyloid syndromes, in particular to local interstitial pituitary amyloid, which was previously reported to be of the same origin as the amyloid affecting pituitary adenomas [23, 24]. This was recently shown to derive from prolactin [8, 38]. The presence of probably PRL-derived amyloid in so-called monohormonal GH-secreting adenomas [25] requires further clarification.

The origin of the different amyloid-associated components is not clear. Apo E is a circulating protein synthesized mainly by liver and cells of the reticuloendothelial system and has been identified in many different types of amyloid [17, 39]. A local origin has been proposed because cells of the reticuloendothelial system are found in close proximity to amyloid deposits [29, 34], but our previous attempts have failed to demonstrate apo E-immunostaining in reticuloendothelial cells of the nonadenomatous amyloidotic pituitary (in folliculo-stellate cells [24]). The observation of intracellular apo E-immunostaining of the folliculo-stellate cells in pituitary adenomas is the first evidence that the apo E may be of local origin. These cells have previously been shown to be activated and hypertrophic in pituitary adenomas [27]. Phagocytosis of amyloid may also explain the pattern of immunostaining. Future immunoelectron microscopic investigations may help to differentiate beween these possibilities.

GAGs accumulate in all types of amyloid studied [30], and we can now add the amyloid of pituitary adenomas to this list. In 94% of adenomas GAGs were identified and spatially related to amyloid deposits. The proportions of sulphated GAGs (chondroitin sulphate and dermatan sulphate) and highly sulphated GAGs (heparan sulphate or keratan sulphate) may vary in different organs as well as in different types of amyloid [10, 18, 30]. In this study, the GAGs were differentiated into sulphated GAGs and highly sulphated GAGs by means of the alcian blue method with varying concentrations of $MgCl_2$: sulphated GAGs such as heparan sulphate only stain at concentrations up to 0.6 M $MgCl_2$. Highly sulphated GAGs, such as keratan sulphate, also stain at concentrations of 0.8 M $MgCl_2$ [18, 28]. In 65% of adenomas highly sulphated GAGs were demonstrated in association with amyloid, whereas in nonamyloidotic adenomas highly sulphated GAGs were not found. These results imply an absence of highly sulphated GAGs in pituitary adenomas, correlating with findings in nonadenomatous pituitaries [24]. However, when amyloid is formed, highly sulphated GAGs are deposited in more than half of the cases. The question remains as to whether they are synthesized locally or delivered from organs other than the pituitary.

The significance of the basement membrane in the pathogenesis of amyloidosis is intriguing. Amyloid is often seen closely associated with basement membranes, and alterations of the basement membrane (lamina densa malformation) have been documented in different amyloid syndromes, including localized cutaneous amyloidosis [9], AA glomerular amyloid [16] and Alzheimer's disease [19]. It has been suggested that an interaction beween basement membrane proteins and amyloid precursor proteins or amyloid fibril proteins may influence the onset and progress of fibril formation and deposition [11, 12]. Basement membrane proteins have been demonstrated in depositions of AA-amyloid [16], AL-amyloid [36] and cerebral Aβ-amyloid [19].

In nonadenomatous pituitaries, local interstititial amyloid is commonly spatially related to basement membranes [33]. Previously, we demonstrated the presence of fibronectin, collagen IV and laminin in amyloidotic pituitaries [24], where the basement membrane proteins were also found within amyloid deposits, but we were unable to exclude the possibility that scattered residual basement membrane fragments were stained in the deposits. Pituitary adenomas are different, as they do not show a reticular network or a similar integrity of "normal" nonadenomatous basement membranes [2–4]. In nonamyloidotic adenomas fibronectin, collagen IV and laminin were found only in tumour vessels or the vascular and periacinar basement membranes of the surrounding nonadenomatous endocrine tissue. Thus, the presence of basement membrane proteins in the amyloid deposits of pituitary adenomas is unlikely to be due to residual basement membrane fragments. It is more likely that the spatial relationship is due either to a local overproduction following stimulation by the deposition of amyloid or precedes and precipitates the formation of amyloid. In some cases, especially those of group 3, laminin and fibronectin were not found in the deposits. This observation may be explained in two ways: either the amyloid deposits were too small and present only in some but not all serial sections, or laminin and fibronectin are not deposited in the early stages of amyloid formation. An observation in support of the latter interpretation is the presence of collagen IV at the periphery of the amyloid deposits. Again, synthesis and assembly of basement membrane proteins may follow amyloid deposition, indicating the age of a particular deposit. Accumulating amyloid may stimulate the synthesis of collagen IV, which is then deposited at the periphery. Most of the constituents associated with amyloid (apo E and amyloid P component) are distributed evenly throughout the deposits. However, a peripheral distribution has also been described for dermatan sulphate proteoglycan (decorin), and it has been suggested that decorin may contribute to controlling the size of amyloid deposits in Alzheimer's disease [31]. However, whether the assembly of basement membrane proteins perpetuates the formation of amyloid or limits its size is unknown.

These studies demonstrate the presence of glycosaminoglycans, basement membrane proteins and apo E in amyloid deposits of pituitary adenomas, as found in other amyloid syndromes of different origin. Thus, amyloidotic adenomas become comparable with other amlyoid diseases, particularly those of the nonadenomatous gland. The integrity and composition of basement membranes and connective tissue show great differences between normal and tumour tissue and even with different pituitary adenomas [2, 3, 5]. Pituitary adenomas may serve as an autologous model to investigate the significance of basement membrane proteins in the pathogenesis of amyloid formation and deposition. So far, the interaction of basement membrane proteins and fibril proteins has been investigated in animal models or in vitro assays [15].

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