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Senile amyloidoses of the pituitary and adrenal glands

Morphological and statistical investigations

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Abstract The pituitary and adrenal glands are a functional endocrine unit affected by local or organ-limited senile amyloid syndromes. These occur as interstitial (pituitary only) or intracellular (pituitary and adrenal) varieties. The pituitary and right adrenal glands of each of 108 consecutive autopsy cases of individuals aged 85 years and over were investigated for the prevalence, distribution and immunostaining characteristics of local amyloid. Intracellular amyloid was detected in 77 (71%) pituitaries and 73 (68%) adrenals. Interstitial amyloid was found in 86 pituitaries (80%). Immunohistochemical studies, investigating different amyloid fibril proteins, amyloid P component, ubiquitin, intermediate filaments and pituitary hormones, failed to demonstrate any similarities, and a common origin is unlikely. Statistical analyses demonstrated significant correlations between the occurrences of all three local amyloids. The clinical and histopathological significance of local pituitary and adrenal amyloid remains obscure. The results suggested that the pathogenesis of the local senile amyloidoses of the pituitary and adrenals may be influenced by a common, still uncharacterized variable. It is not clear whether this variable also contributes to the pathogenesis of other senile amyloid syndromes, such as those associated with Alzheimers' disease.

Key words Intracellular amyloid · Pituitary · Adrenal gland · Immunohistochemistry

Introduction

The pituitary and adrenal glands may be affected by local or organ-limited amyloid syndromes occuring as interstitial (pituitary only) or intracellular (pituitary and adrenal) varieties [2, 6, 28, 33]. The incidence of these local or organ-limited disorders increases with age and they are regarded as senile amyloid syndromes [4, 15]. Possible correlations have not been explored and their fibril proteins are not defined [28, 34].

It has been reported that local interstitial pituitary amyloid immunostains with a particular antibody directed against amyloid of λ-light chain origin [26, 27]. This was interpreted as cross-reaction, since an 80% incidence of AL amyloidosis (= immunoglobulin light chain-derived amyloidosis) seemed unlikely in a consecutive autopsy series and local synthesis of immunoglobulins was excluded by in situ hybridizations [26, 27] (A.M. McNicol, unpublished observation). Subsequently, correlations were found between the occurrence of interstitial pituitary amyloid and the prevalence of chronic obstructive pulmonary disease (COPD) and of non-insulin dependent diabetes mellitus (NIDDM) [28]. These observations suggest that the pathogenesis of *local* interstitial pituitary amyloid is influenced by variables that may also relate to COPD and NIDDM.

The pituitary and adrenal glands exemplify a functional endocrine unit in which both components are affected by local amyloid. Immunoreactive antibodies offer the opportunity to specify whether the separately located endocrine amyloid syndromes share a common origin. In addition, a variable linking local interstitial pituitary amyloid with COPD and NIDDM may also affect the hypophysial-adrenal axis and the pathogenesis of their intracellular amyloids.

To answer these questions we investigated local pituitary and adrenal amyloid in a well-defined collection of consecutive autopsy cases, none of which had suffered from generalized AL amyloidosis [26]. In each individual case the pituitary and an adrenal gland were examined for the presence and distribution pattern of local amyloid. The origin of the fibril proteins was classified by immunohistochemistry, and the correlations were investigated between the different local amyloid syndromes as well as between the occurrence of intracellular amyloid and other diseases registered in autopsy reports and clini-

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cal notes. Since local pituitary and adrenal amyloid are senile amyloid syndromes [2, 6, 28, 33], the present study focused on individuals aged 85 years and over.

Materials and methods

The pituitary and right adrenal glands of 108 consecutive autopsy cases of individuals aged 85 years and above were selected irrespective of diseases and cause of death.

The glands were fixed overnight in formalin. Pituitary glands were dissected in standardized planes, producing five pieces with three sectional planes (sagittal, frontal, and transverse) per specimen, as described in detail elsewhere [18, 28]. Specimens from the right adrenal gland were obtained by a representative section through the central portion of the cortex and medulla. The specimens were subsequently embedded in paraffin and 2- to 3-μm-thick sections were used throughout the study.

Amyloid was identified by the presence of a typical apple-green birefringence in polarized light after alkaline Congo red staining [24], which did not dissappear on rotation of the specimen.

Haematoxylin and eosin (H&E) as well as periodic acid–Schiff stain (PAS) were administered to identify histopathological alterations of the pituitary which differed from amyloid. The histopathological alterations were further classified as described in detail previously [26].

For immunostaining, the peroxidase-anti-peroxidase (PAP) and the avidin-biotin complex (ABC) methods were applied. The sections were deparaffinized in toluene and rehydrated in a graded alcohol series. Endogeneous peroxidase was blocked using 100% methanol supplemented with 1% (v/v) H_2O_2. The specimens were washed in phosphate-buffered saline supplemented with 1% (w/v) bovine serum albumin (Sigma Chemicals, St. Louis, Mo.). Incubation with primary and secondary antibodies was performed in a moist chamber at room temperature, each for 30 min.

The amyloid fibril proteins and amyloid associated proteins were characterized using antibodies directed against amyloid A (AA {mc_1}, dilution 1:30; Dakopatts, Hamburg, Germany), λ light chain (Aλ {HAR}[1], 1:1200, [14, 17]; Aλ {DAKO}, 1:3000, Dakopatts, Hamburg, Germany), κ light chain (Aκ, 1:1000, [14, 17]; Aκ {DAKO}, 1:3000, Dakopatts, Hamburg, Germany), transthyretin (ATTR [TIE][1], 1:600, [13, 14]), β-amyloid (Aβ, 1:25), β2-microglobulin (Aβ2 M, 1:200), ubiquitin (1:25; all three Dakopatts, Hamburg, Germany), and amyloid P component (AP, 1:600, [16]).

Intermediate filaments were characterized with antibodies directed against keratin Kl_1 (dilution 1:100, Immunotech S.A., Marseille, France), desmin (1:50), vimentin (1:5), and neurofilament (1:50, all Dakopatts, Hamburg, Germany).

Pituitary hormones were identified with polyclonal antibodies directed against growth hormone (GH, dilution 1: 300), adrenocorticotropic hormone (ACTH, 1:300), thyroid-stimulating hormone (TSH, 1:800), follicle stimulating hormone (FSH, 1:200), luteinizing hormone (LH, 1:700), prolactin (PRL, 1:300, all Dakopatts, Hamburg, Germany), and α-subunit (1:600, Grässlin and Saeger, Hamburg, Germany).

An antibody directed against S-100 (1:200) was purchased from Dakopatts, Hamburg, Germany.

Specimens provided for immunostaining with anti-Aβ were pretreated with 80% methanoic acid solution for 10 min at room temperature and those provided for anti-ACTH using 1% pronase solution for 10 min at 40°C. Both pretreatments were performed after the blockade of the endogenous peroxidase. The immunoreactions were visualized with 3,3-diaminobenzidine-tetrahydrochloride and the specimens were then counterstained with haematoxylin.

Double staining was performed with immuno- and Congo red staining. Following immunostaining, as described above, the specimens were thoroughly washed and subsequently stained with Congo red according to the procedure of Puchtler et al. [24].

Positive controls included immunostaining of specimens with chemically identified amyloid deposits (AA, Aλ, Aκ, ATTR, Aβ2M) or senile plaques of the brain (Aβ). The consistency between Congo red and immunostained amyloid deposits as examined in serial sections was an additional criterion for specificity. Appropriate immunostaining of intermediate filaments, pituitary hormones and miscellaneous proteins was tested according to the manufacturers' instructions, using well-preserved autopsy and biopsy specimens from the brain, oesophagus, liver (affected by hyalin bodies), mammary gland, myometrium, pancreas, pituitary, prostate, and skin.

Negative controls included omission of the primary antibody and replacement of the primary antibody by normal rabbit or normal mouse serum.

No patient in this group had suffered from generalized AL amyloidosis [26].

The Chi-square test was applied for statistical analyses. The incidences of intracellular pituitary and adrenal amyloids were correlated with the occurrence of interstitial pituitary amyloid, other histopathological alterations affecting the pituitary and the frequency of all recognized diseases documented in hospital notes and postmortem reports [26, 28].

Results

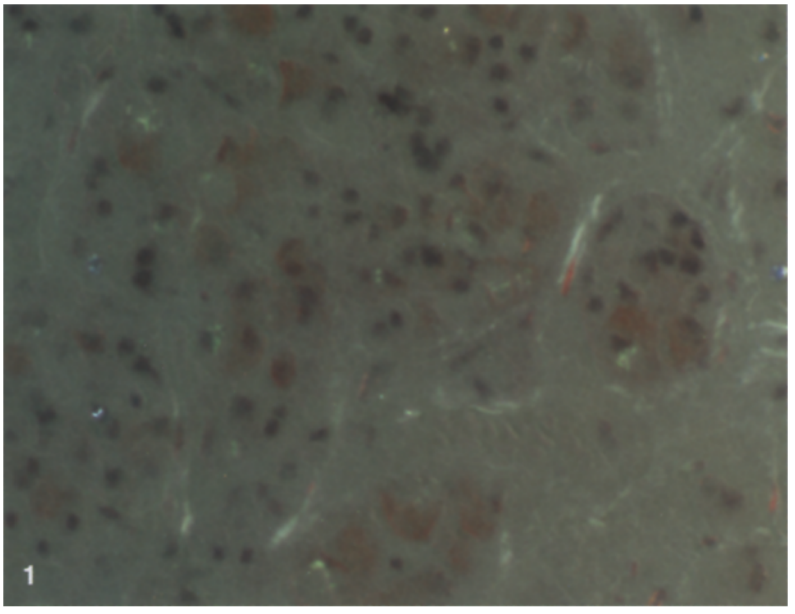
Intracellular amyloid was detected in 77 (71%) pituitaries (Fig. 1). The male-to-female ratio was 1: 2.9, not significantly different from that in the series as a whole (1: 2.5). This amyloid was characterized by the presence of one or two green birefringent needles affecting single cells with no particular recognizable distribution pattern in the anterior lobe.

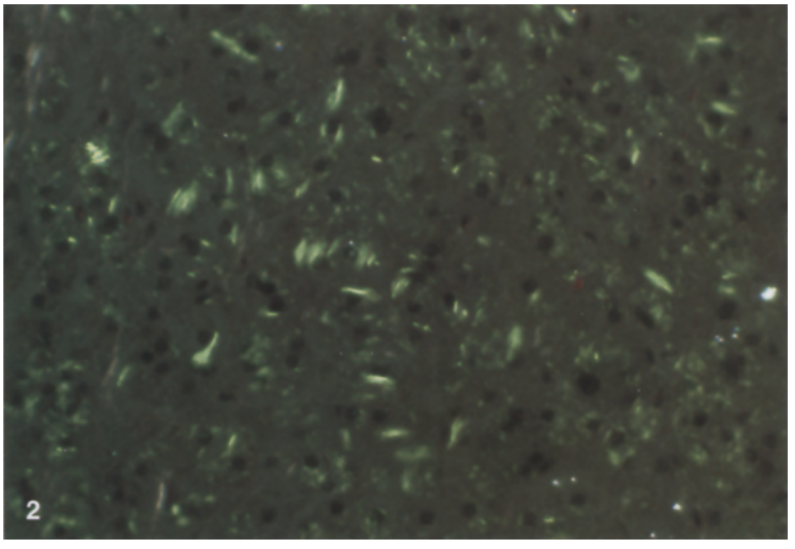
Interstitial pituitary amyloid was detected in 86 (80%) cases and was localized between endocrine cells and capillaries as described previously [26]. Simultaneous occurrence of intracellular and interstitial amyloid was evident in 76 cases. Pituitary cells with intracellular amyloid did not show any significant spatial relationship to interstitial deposits.

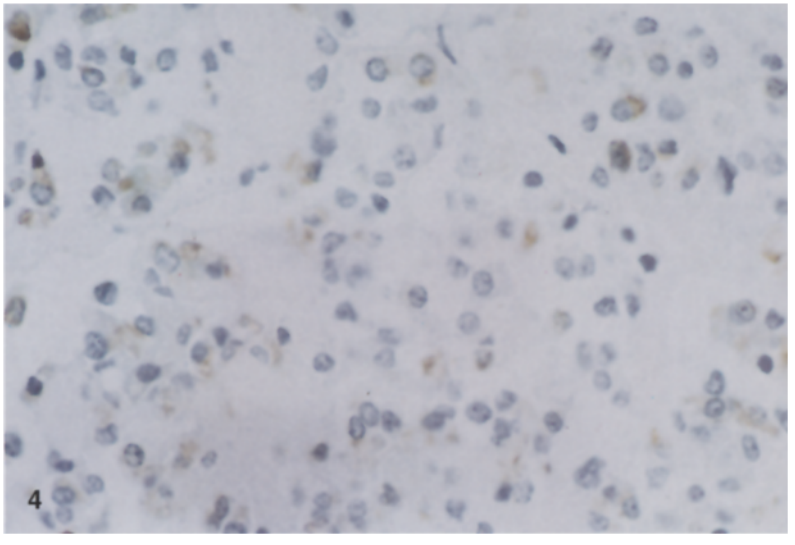
Seventy-three (68%) adrenal glands exhibited intracellular amyloid (Fig. 2) with a male-to-female ratio of 1: 2.8. Bundles of green birefringent needles were deposited in individual cells which were arranged in groups; single amyloid-affected cells were rare. Amyloid was found only in clear cells of the adrenal cortex, most frequently in the zona fasciculata, less commonly in the zona glomerulosa and rarely in the zona reticularis. Interstitial amyloid deposits were not observed in any adrenal gland.

Immunohistochemical studies were performed to elucidate the origin and fibril protein(s) of intracellular amyloid. All positive immunostaining reactions are recorded in Fig. 5. Every amyloid-affected pituitary and 23 consecutive amyloid-affected adrenals were investigated for the presence of any of the five most common fibril proteins, which may present with systemic or generalized deposition (AA, ATTR, Aλ, Aκ and Aβ2M [7, 8]). In addition, 15 pituitaries and 13 adrenals with abundant intracellular amyloid were tested for Aβ, amyloid P component (AP) and ubiquitin.

[1] From a patient's name, from whom the fibril proteins were purified for the production of antibodies







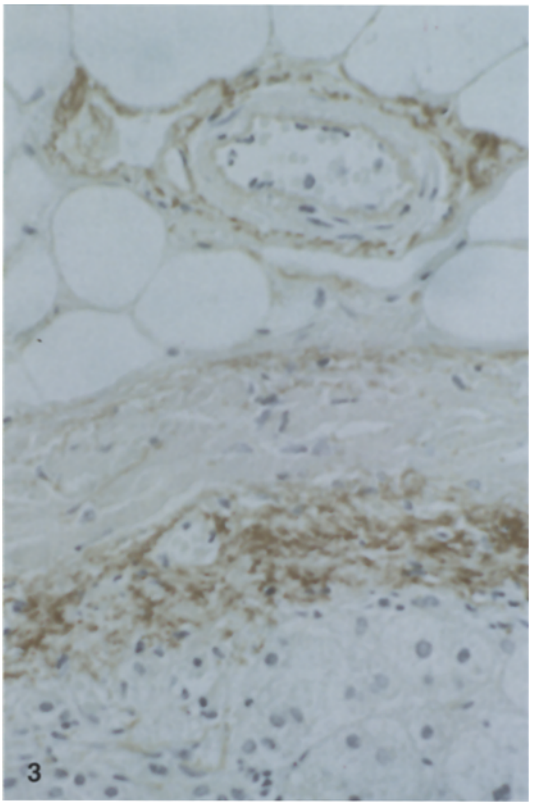


Fig. 1 Intracellular amyloid in endocrine cells of the pituitary. Congo red staining in polarized light, ×350

Fig. 2 Intracellular amyloid deposits in the zona fasciculata of the adrenal cortex. Congo red staining in polarized light, ×350

Fig. 3 Interstitial amyloid deposits in the pituitary immunostained with an antibody directed against amyloid of λ-light chain origin; anti-Aλ {HAR}. Haematoxylin counterstain, ×350

Fig. 4 Intracellular immunostaining of endocrine cells of the pituitary with an antibody directed against cytokeratin. Anti-KL_1, haematoxylin, ×350

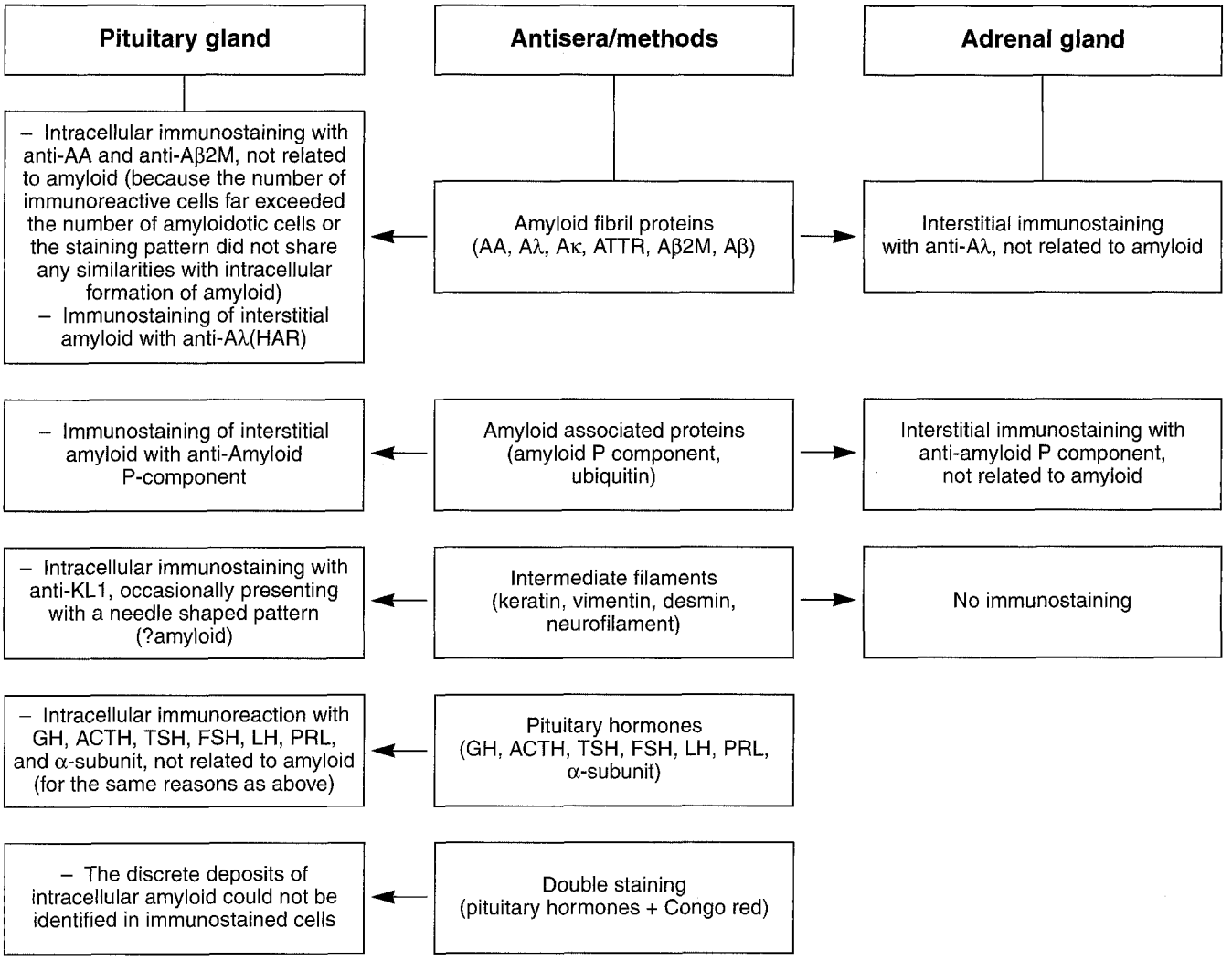


Fig. 5 A summary of the immunohistochemical investigations of interstitial pituitary amyloid, intracellular pituitary amyloid and intracellular adrenal amyloid. For further details see Materials and methods and Results

Immunostaining with anti-AA demonstrated a fine, granular pattern in the endocrine cells of the anterior lobe. Intracellular immunostaining with anti-Aβ2 M was homogeneous. AA- and Aβ2M-immunoreactive cells were evenly distributed upon the anterior lobe. Interstitial pituitary amyloid was immunostained by anti-Aλ {HAR} (Fig. 3) and anti-AP, but not by anti-Aλ {DAKO}, as described in detail elsewhere [26]. In contrast, immunostaining of the adrenal was observed with anti-Aλ {HAR} (2 cases) and anti-AP (13 cases) in the interstitium of the medulla, cortex and capsule, which was *not* related to amyloid deposits.

The 15 amyloid-affected pituitaries and 13 amyloid-affected adrenals were investigated for evidence of intermediate filaments, such as keratin, vimentin, neurofilament (NFT) and desmin. The intracellular immunoreaction observed in the anterior pituitary with anti-keratin Kl_1 was most commonly a homogeneous staining pattern. In addition, a needle-shaped staining pattern was evident, which shared some similarities with the feature of intracellular amyloid (Fig. 4). However, many more pituitary cells stained for keratin Kl_1 than were affected by intracellular amyloid. Vimentin was found in folliculo-stellate cells, with a staining pattern that differed significantly from the appearance of intracellular amyloid deposition.

An attempt was made to determine whether pituitary amyloid was related to a particular pituitary hormone or to a distinct endocrine cell type (Fig. 5). Intracellular immunostaining of pituitary hormones (GH, ACTH, TSH, FSH, LH, and PRL) and α-subunit was achieved in each of the 24 pituitaries investigated. The staining pattern was consistent with the presence of the hormones in situ and did not share any similarities with intracellular formation of amyloid. No differences were observed in the staining patterns of affected or nonaffected pituitaries.

Doublestaining, with Congo red and immunostaining with antibodies directed against pituitary hormones failed; discrete deposits of intracellular amyloid could not be identified in immunostained cells.

The prevalence of interstitial pituitary amyloid correlated significantly with the occurrence of intracellular amyloid in the pituitary ($P<0.0001$) *and* the adrenal

Table 1 Frequency of other diseases documented in hospital notes and postmortem reports and of other histopathological alterations of the pituitaries of the current collection which were correlated with the occurrence of intracellular pituitary *and* adrenal amyloid

Other disease documented in hospital notes and postmortem reports		Histopathological alterations in autopsy pituitaries	
Chronic obstructive pulmonary disease	103	Regressive changes	108
Atherosclerosis	96	Microfollicles	107
Cardiac failure	96	Cysts	60
Arterial hypertension	44	Local fibrosis	50
Diverticulosis	43	Scars	13
Malignant tumour	42	Diffuse fibrosis	14
Tuberculous scars	35	Necrosis	4
Non-insulin dependent diabetes mellitus	22	Erdheim's squamous epithelia	14
Benign prostatic hyperplasia	21	Cysts of the intermediate zone	90
Osteoarthritis	18	Basophil invasion of posterior lobe	76
Other chronic infectious diseases	11	Hyperplasia	11
Endocarditis	10	Adenomas	12
Gastric ulcer	7		
Liver cirrhosis	6		
Cardiac arrhythmia	5		
Aortic sclerosis	4		
Renal insufficiency	4		
Anaemia	3		
Chronic pancreatitis	3		
Chronic pyelonephritis	3		
Duodenal ulcer	3		
Bronchial asthma	1		
Cushing's syndrome	1		
Myelodysplastic syndrome	1		
Psoriasis	1		
Rheumatoid arthritis	1		
Thyroiditis	1		

($P<0.0001$; Table 1). The prevalence of intracellular pituitary amyloid, in turn, correlated significantly with the occurrence of intracellular amyloid in the adrenal ($P<0.0001$).

However, no correlations were found between the occurrence of intracellular amyloid either in the pituitary or the adrenal and any other histopathological alteration affecting the pituitary (Table 1). Furthermore, no correlations were evident between the prevalences of intracellular amyloid either in the pituitary or the adrenal and any other disease documented in this series of cases (Table 1).

The statistical analyses are summarized graphically in Fig. 6.

Discussion

Two pathophysiological mechanisms may explain the occurrence of intracellular amyloid: interstitial amyloid fibrils may be phagocytosed [32] or amyloid fibrils may be assembled within the cell [20, 30, 32]. Amyloid assembled within a cell may remain cell bound, but may also be excreted. Its intracellular assembly may induce cell death with subsequent, "residual", interstitial deposition [20]. Phagocytosis of intracellular amyloid is unlikely in the pituitary and adrenal, since the deposits were found in endocrine cells and, in addition, the adrenal gland lacked interstitial deposits and therefore an extracellular source.

Intracellular assembly may lead to extracellular deposition as described, but no evidence of interstitial deposits was found in the adrenals. However, in the pituitary gland the presence of interstitial deposits made this explanation possible. Intracellular amyloid in conjunction with interstitial deposits have been found in various amyloid syndromes [1, 5, 9, 10, 19, 20, 23, 30, 32]; in each of these the fibrils found inside the cell were interpreted as of the same origin as the interstitial deposits. With the aid of a particular antibody (anti-Aλ {HAR}) that cross-reacts with interstitial pituitary amyloid in a unique fashion [26, 27], we were able to test the similarity of intracellular and interstitial pituitary amyloid and the possibility of a common origin. However, no intracellular immunostaining was observed and a difference in the origin of intracellular and interstitial pituitary amyloid is most probable.

Similar observations were made in pituitary adenomas. Two structurally and immunochemically distinct types of amyloid were found in pituitary adenomas [11, 12]. The less common deposit had a spheroidal shape, immunostained with a panepithelial antibody (mAB 5-lu) and was thought to originate from intermediate filaments [11, 12]. The second and more common type formed stellate or perivascular deposits, did not stain with a panepithelial antibody [11, 12], but was immunoreactive for anti-Aλ {HAR} [27]. Based on these observations, immunostaining with antibodies directed against intermediate filaments was performed to test whether intracellular amyloid in the "normal" pituitary may be the equivalent of spheroid amyloid in adenomas. Of all four antisera applied, only a panepithelial antiserum directed against cytokeratin demonstrated immunostaining of endocrine cells in the pituitary. The pattern of immuno-

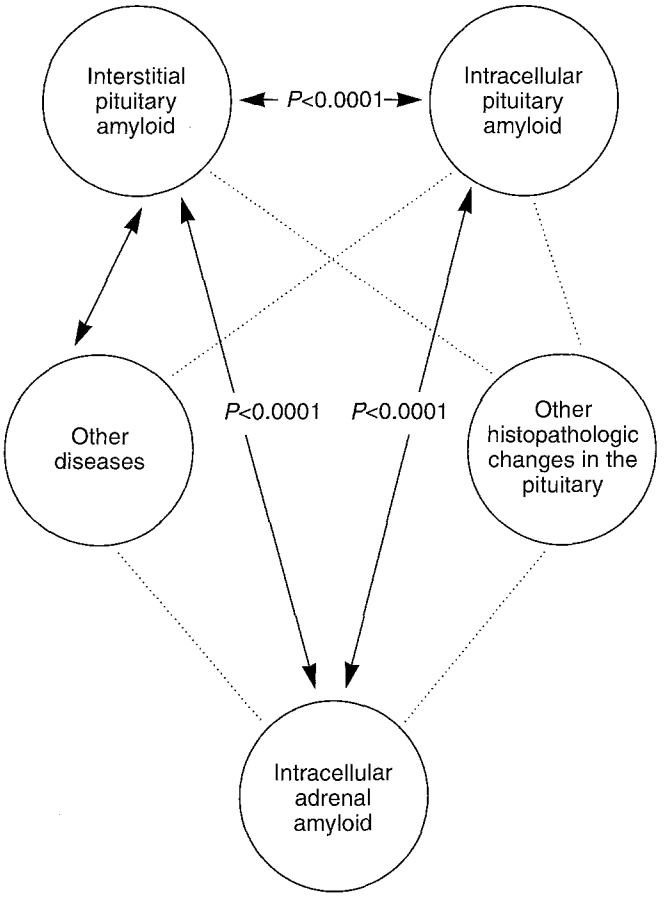


Fig. 6 A summary of the statistical analyses to correlate the occurrences of local pituitary and adrenal amyloid with each other, with the prevalence of other histopathological alterations affecting the pituitary, and with diseases documented in hospital notes and postmortem reports. The correlation studies between interstitial pituitary amyloid and other histopathological alterations ($P<0.02$) and other diseases ($P<0.03$) have been described in detail elsewhere [26, 28]. The *solid line* (——) represents significant correlations; the *dotted line* (·····) marks non-significant correlations

staining occasionally shared similarities with the pattern of intracellular amyloid. An interstitial immunostaining was not achieved with this antiserum. However, we could not disprove the notion that intracellular pituitary amyloid may originate from intermediate filaments and that its origin may differ from interstitial deposits.

Attempts to specify the endocrine cell type affected or a probable hormonal origin of intracellular pituitary amyloid using double staining or immunostaining alone failed. Various different protohormones have been shown to form local amyloid deposits, such as calcitonin in medullary cancer of the thyroid, insulin following subcutaneous injection in individuals who suffer from diabetes mellitus, islet amyloid polypeptide in the islets of Langerhans, and atrial natriuretic peptide in the atria [34]. However, a hormonal origin is still possible in the pituitary, but was not demonstrated immunohistochemically for either intracellular or interstitial amyloid [2, 26, 33, 35].

Intracellular adrenal amyloid did not stain with antibodies (including anti-Aλ {HAR}) directed against known amyloid fibril proteins or against intermediate filaments, and the precursor protein remains obscure.

Further attempts were then made to specify the occurrence of amyloid-associated proteins such as AP or ubiquitin. AP was found in the deposits of all interstitial amyloid syndromes studied, including interstitial pituitary amyloid [21, 22]. However, no intracellular immunostaining was detected in the pituitaries and adrenals affected by intracellular amyloid, which is a further difference between intracellular and interstitial amyloid. Ubiquitin is occasionally present in amyloid deposits [3] but was virtually absent in the local hypophysial and adrenal deposits in our collection.

Our morphological investigations on pituitary and adrenal amyloid have failed to demonstrate any relation between interstitial and intracellular amyloid. Intracellular pituitary amyloid was found in endocrine cells which were not significantly related spatially to interstitial pituitary deposits. Therefore, phagocytosis or excretion of fibrils is probably excluded. Interstitial and intracellular pituitary amyloid showed dissimilar immunohistochemical characteristics and a common origin is even less likely. Further differences were observed regarding intracellular adrenal amyloid.

Subsequent statistical analyses demonstrated significant correlations between all three local endocrine amyloids (interstitial pituitary amyloid, intracellular pituitary amyloid and intracellular adrenal amyloid, as summarized in Fig. 6). However, no correlations were found between the occurrences of intracellular amyloid and other histopathological alterations of the pituitary or other diseases, in particular COPD and NIDDM. In contrast, the appearance and amount of *interstitial* pituitary amyloid correlated with the occurrence of COPD and NIDDM, as reported previously [28]. We cannot explain these correlations.

The statistical analyses imply that the correlations between COPD and interstitial pituitary amyloid and between NIDDM and interstitial pituitary amyloid do not affect the occurrence of intracellular amyloid. Multiple, probably independent, variables may influence the appearance and amount of local pituitary and adrenal amyloid.

Apart from local pituitary and adrenal amyloid [2, 6, 25, 29, 31, 33], many more different senile amyloid syndromes have been described, including senile systemic amyloidosis, senile aortic amyloid, seminal vesical amyloid, amyloid associated with Alzheimer's disease, amyloid of the pancreatic islets, and isolated atrial amyloid [4, 15]. However, little attention has been paid to their inter relationships. Yamada et al. [35] described a correlation between the occurrence of amyloid in the brain (senile plaques) and interstitial amyloid affecting the pituitary and amyloid in the islets of Langerhans. Our own immunohistochemical investigations demonstrated that interstitial pituitary amyloid does not originate from β-amyloid or islet amyloid poylpeptide [28]. Therefore, common, probably systemically acting, variables may indeed exist that influence the pathogenesis of different se-

nile amyloid syndromes, such as those in the case of the pituitary and adrenal gland. It is not clear what kind of pathophysiological mechanism characterizes the correlation between local or organ-limited pituitary and adrenal amyloid or how it may affect the pathogenesis of other senile amyloid syndromes.

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