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Age-related accumulation of congophilic fibrillar inclusions in endocrine cells

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Summary. Intracellular fibrillar congophilic inclusions are well known as neurofibrillary tangles in neurons and as Biondi bodies in choroid plexus epithelial cells. Recently similar amyloid-like inclusions in adrenal cortical cells were described (Eriksson and Westermark 1990). This study on 150 adrenal glands confirms these observations. In our material the age-related accumulation of congophilic inclusions starts earlier (in the sixth decade) and reaches a higher incidence (42.7%). We found similar intracellular inclusions in other endocrine organs, for example in the anterior lobe of the pituitary, in the cells of parathyroid glands and in Sertoli cells. The age-related incidence of these fibrillar inclusions in the pituitary was 68%; the co-incidence with interstitial amyloid deposits was 49.5%. Thus the intracellular accumulation of congophilic fibrils in old age is a widespread phenomenon and occurs not only in neurons but also in endocrine cells (adrenal, pituitary and parathyroid glands) and in active secretory cells (choroid plexus and Sertoli cells).

Key words: Congophilic inclusions – Neurofibrillary tangles – Biondi bodies – Pituitary gland – Adrenal gland

Introduction

In old age congophilic fibrillar inclusions are very common in the cytoplasm of different cell types; as neurofibrillary tangles (NFT) in neurons (Bohl et al. 1988), Biondi bodies in epithelial cells of the choroid plexus (Oksche 1974; Eriksson and Westermark 1986) and in ependymal cells and fibrillar inclusions in adrenal cortical cells, recently described by Eriksson and Westermark (1990). In the central nervous system the accumulation of NFT in the cytoplasm of neurons is very often combined with the deposition of amyloid fibrils in the extracellular space of the neuropil and of intracortical and leptomeningeal blood vessels (Bohl et al. 1987). In choroid plexus and in adrenal glands extracellular amyloid deposits only occur in patients with generalized amyloidosis (Bohl et al. 1989; Lack 1990). In the islets of Langerhans the incidence of amyloid deposits is very high in old age (Störkel et al. 1983), but intracellular fibrillar inclusions have not been detected. In order to determine the distribution of cytoplasmic congophilic fibrils and of extracellular amyloid in human tissues, we examined post-mortem specimens of brain, adrenal glands, pituitary glands, parathyroids, pancreas and testes. Histochemical and ultrastructural features of these cytoplasmic inclusions are described and compared to those of the extracellular amyloid. The pathogenesis of similar alterations and their relationship to normal aging are discussed.

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Materials and methods

Autopsy material of the Institute of Pathology, Mainz was used for randomly sampling 150 adrenal bodies, 103 pituitary glands, 200 brains, and from 14 cases parathyroid glands, pancreas and testes. The age distribution is listed in Table 1.

The tissue specimens were fixed in 4% formaldehyde solution, embedded in paraffin, sectioned and stained. The following methods were used: haematoxylin and eosin (H&E), elastic van-Gieson (EvG for connective tissue and elastic membranes), staining method for fibrin according to Pearse (1968), Congo red according to Puchtler (1962), periodic acid-Schiff (PAS), silver impregnation methods according to Campbell et al. (1987) and Gallyas (1971), and the methenamine silver method of Jones (1968). Congo red preparations were investigated in polarized light; photographs were taken with a Nikon photomicroscope (Microphot-FXA).

Selected formalin-fixed samples of adrenal and pituitary glands and of choroid plexus were post-fixed with 1% osmium tetroxide in cacodylate buffer. Then the tissue samples were treated with 1% uranyl acetate and embedded in epoxy resin. Semi-thin sections were stained with paraphenylene diamine and according to Richardson (1960). Ultra-thin sections were contrasted with lead citrate and studied in a Philips electron microscope at 60 kV.

Table 1. Incidence of age-dependent intracellular congophilic fibrillar inclusions and of extracellular amyloid deposits (percentages in brackets)

Age (years)	Adrenal cortex	Pituitary gland		Choroid plexus Biondi bodies	Alzheimer fibrils	Amyloid plaques
		Amyloid	Fibrils			
41–50	(0) 0/25	(0) 0/5	(0) 0/5	(30) 3/10	(0) 0/9	0[a]
51–60	(7.7) 2/26	(63.6) 7/11	(45.5) 5/11	(69.2) 9/13	(35.7) 5/14	0[a]
61–70	(42.9) 15/35	(63) 17/27	(51.9) 14/27	(95) 19/20	(55.6) 25/45	(30) 23/76
71–80	(54.8) 17/31	(76.5) 26/34	(79.4) 27/34	(100) 21/21	(69.2) 54/78	(56) 46/82
81–90	(90) 27/30	(69.6) 16/23	(91.3) 21/23	(100) 33/33	(88) 22/25	(83) 30/36
91–	(100) 3/3	(100) 3/3	(100) 3/3	(100) 3/3	(100) 4/4	(100) 6/6
n	150	103		111	175	200
Overall incidence:	(42.7) 64/150	(67) 69/103	(68) 70/103	(79.3) 88/111	(62.9) 110/175	(52.5) 105/200

[a] Patients under 61 years of age were not included in this group

Table 2. Ultrastructure of intracellular congophilic fibrillar inclusions and of extracellular amyloid deposits

Type	Diameter width	Structure components	Periodicity	Reference
Neurofibrillary tangles (NFT)	10 nm 16–22 nm 28–36 nm	Two components subunits 6–10 nm two filaments 14–18 nm each	80 nm 70–80 nm 70–90 nm	Ipsen[a] Wisniewski[b] Ohtsubo et al. (1990)
Biondi bodies (choroid plexus)	20 nm 10 nm	Two filaments	Irregular not segmented	Eriksson and Westermark (1986) Oksche 1974
Adrenal cortex	12–15 nm 10 nm	Two filaments of 6 nm each two subunits	Irregular Irregular 65–80 nm	Eriksson and Westermark (1990) Bohl (present study)
Pituitary gland (anterior lobe)	6–9 nm	Two filaments	No periodicity	Bohl (present study)
Amyloid fibrils (extracellular)	7.5–10 nm	Two or more filamentous subunits: 2.5–3.5 nm	Not regularly twisted	Shirahama and Cohen 1986

[a] Signoret JL (1988) Maladie d'Alzheimer, 3rd edn. Ipsen, Paris
[b] Wisniewski HM, Merz PA, Iqbal K (1984) Ultrastructure of paired helical filaments of Alzheimer's neurofibrillary tangles. J Neuropathol Exp Neurol 43:643–656

Immunohistochemical studies were performed on fresh frozen or paraffin-embedded material from one of the severely involved adrenal glands and on one paraffin-embedded pituitary. After incubation with primary antisera the peroxidase-antiperoxidase (PAP) method was used. Congo red staining was performed after the immunohistochemical reactions. The following antisera were used: ubiquitin (dilution: 1:500; Schiffer, Turin, Italy), cytokeratin (dil.: 1:80), vimentin (dil.: 1:10), anti-somatotropic hormone (STH) (dil.: 1:700), anti-adrenocorticotropic hormone (ACTH) (dil.: 1:350; all from Dakopatts, Hamburg, FRG), and anti-prolactin (dil.: 1:800).

Results

One hundred and fifty adrenal glands were investigated histologically. The male to female ratio was 1 to 1.13. Sixty-four (42.7%) contained congophilic fibrillar inclusions in the cytoplasm of their cortical cells. The mean age of the positive cases was 77.7 years (range 55–104), compared with 57.2 years for all patients without inclusions in their adrenal cortical cells (range 15–89 years). The amount of intracellular inclusions obviously increased with age. In some cases all zones of the adrenal cortex were involved; the accumulation seems to occur at first in cells adjacent to the capsule of the gland (zona glomerulosa and exterior zona fasciculata). The congophilic inclusions differ in shape and size; most inclusions are spindle-shaped and as long as the whole cell; some are very thin and short, like needles; others are short but shaped like an eye or like a grain or seed (Braak and Braak 1987) (Fig. 1). The best staining method for these inclusions is Jones' methenamine silver impregnation method (1968), which stains the inclusions black.

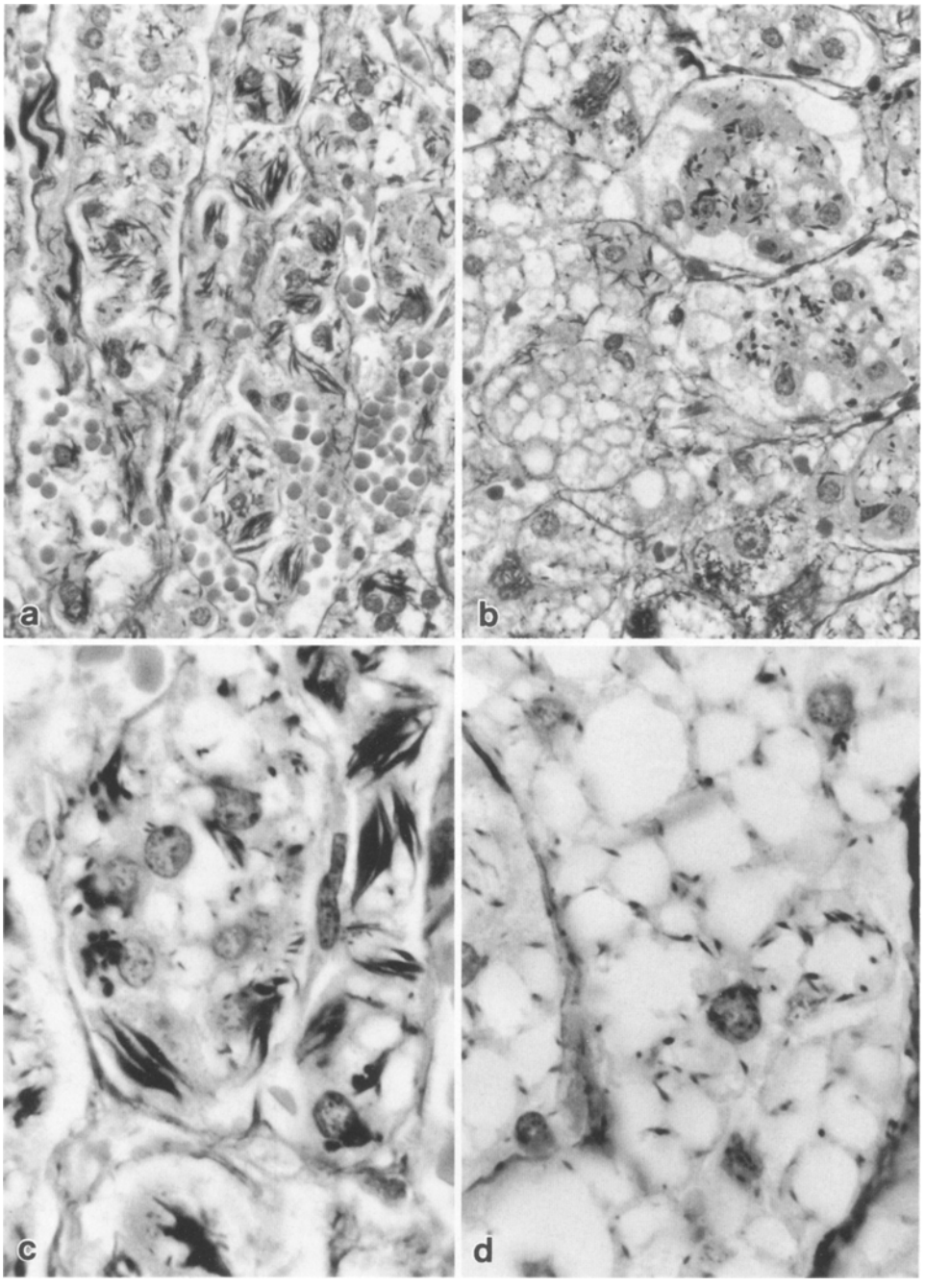

Fig. 1a–d. Adrenal cortical cells with intracellular congophilic and argyrophilic fibrillar inclusions. **a** Many cortical cells contain small fusiform bundles of argyrophilic fibrils (zona fasciculata). Jones' methenamine silver, ×625. **b** Another type of inclusion is short and small like grains or seeds, resembling argyrophilic grains in cerebral cortex, ×625. **c, d** Higher magnifications of other regions, similar to **a** and **b**. ×1560

They are slightly positive after the PAS reaction and can also be stained with the silver impregnation method of Campbell et al. (1987). In Gallyas (1971) and Gomori preparations the inclusions were unstained, as well as in H&E, EvG and Pearce preparations. However they are easily stained with Congo red and give a distinct green birefringence in polarized light.

The analysis of the underlying diseases showed no correlation between the incidence and amount of these intracellular congophilic inclusions and special well-defined diseases. The portion of positive cases – corresponding to age – was nearly the same in all groups of main diseases. Many drugs had been given in the course of the fatal illness; however, pharmacotherapy did not appear to be related to the development of these fibrillar inclusions. The only positive correlation that could be detected was that with age. There were 4 adrenal glands from patients with generalized amyloidosis. Extracellular amyloid deposits were found in the adrenal cortex or in the capsule. The incidence and amount of intracellular congophilic fibrils was not higher than expected according to age. Immunohistochemical preparations showed negative results for ubiquitin, cytokeratin and vimentin. The case histories of severely affected patients did not contain any hints of a functional disturbance of the adrenal cortex.

In the pituitary glands (Figs. 2, 4) the incidence of congophilic fibrils in epithelial cells is still higher than

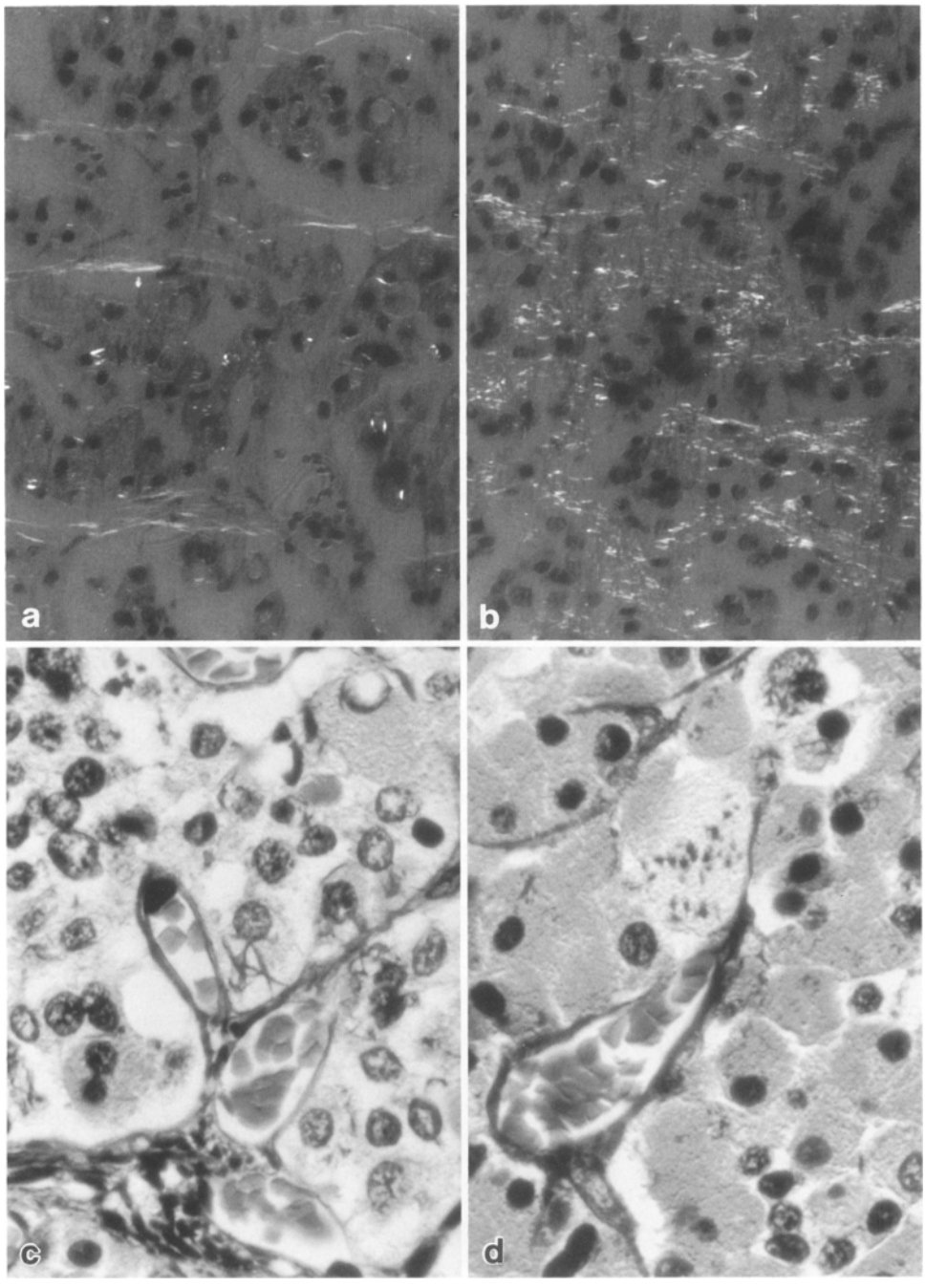

Fig. 2a–d. Anterior lobe of the pituitary gland (adenohypophysis).
a Typical green birefringence of small congophilic intracellular fibrillar inclusions. Congo red, ×500.
b Amyloid deposits in extracellular space. Congo red, ×500.
c, d In some pituitary cells there are small bundles of black fibrils, resembling Biondi fibrils and congophilic inclusions in adrenal cortical cells. In others only grain-like inclusions lie in the cytoplasm, similar to Braak's argyrophilic grains in human cerebral cortex. Jones' methenamine silver, ×1000

in the adrenals (see Table 1). All different types of cells are involved, acidophilic, basophilic and chromophobe cells as demonstrated in Jones' preparations, but acidophilic cells are less affected. These findings were verified by means of an immunohistochemical demonstration of hormone production, combined with a later Congo red staining. In many cases, age-dependent interstitial amyloid deposition in the pituitary was detected. The coincidence of extracellular amyloid and intracellular congophilic fibrils was calculated at 49.5%. As shown in Table 1, the incidence of both increases with age. Immunohistochemical reactions for ubiquitin, vimentin and cytokeratin were also negative.

At least 7 different regions from 200 brains were stained with Congo red to look for extracellular amyloid deposits (plaques); in 175 cases silver impregnation methods were used to detect intracellular NFT; and in 111 cases Campbell and Congo red preparations of the choroid plexus were used to demonstrate Biondi bodies in choroid plexus epithelial cells and ependymal cells. The incidence of amyloid deposits, NFT and Biondi bodies gradually increases with age (Table 1).

Similar congophilic intracellular fibrillar inclusions were found in epithelial cells of parathyroid glands in 5 of 14 cases and in Sertoli cells of atrophic testes in 1 case. In parathyroid glands we found additional extracellular amyloid deposits in 6 cases (out of 14). The pancreatic islets of Langerhans contained only interstitial

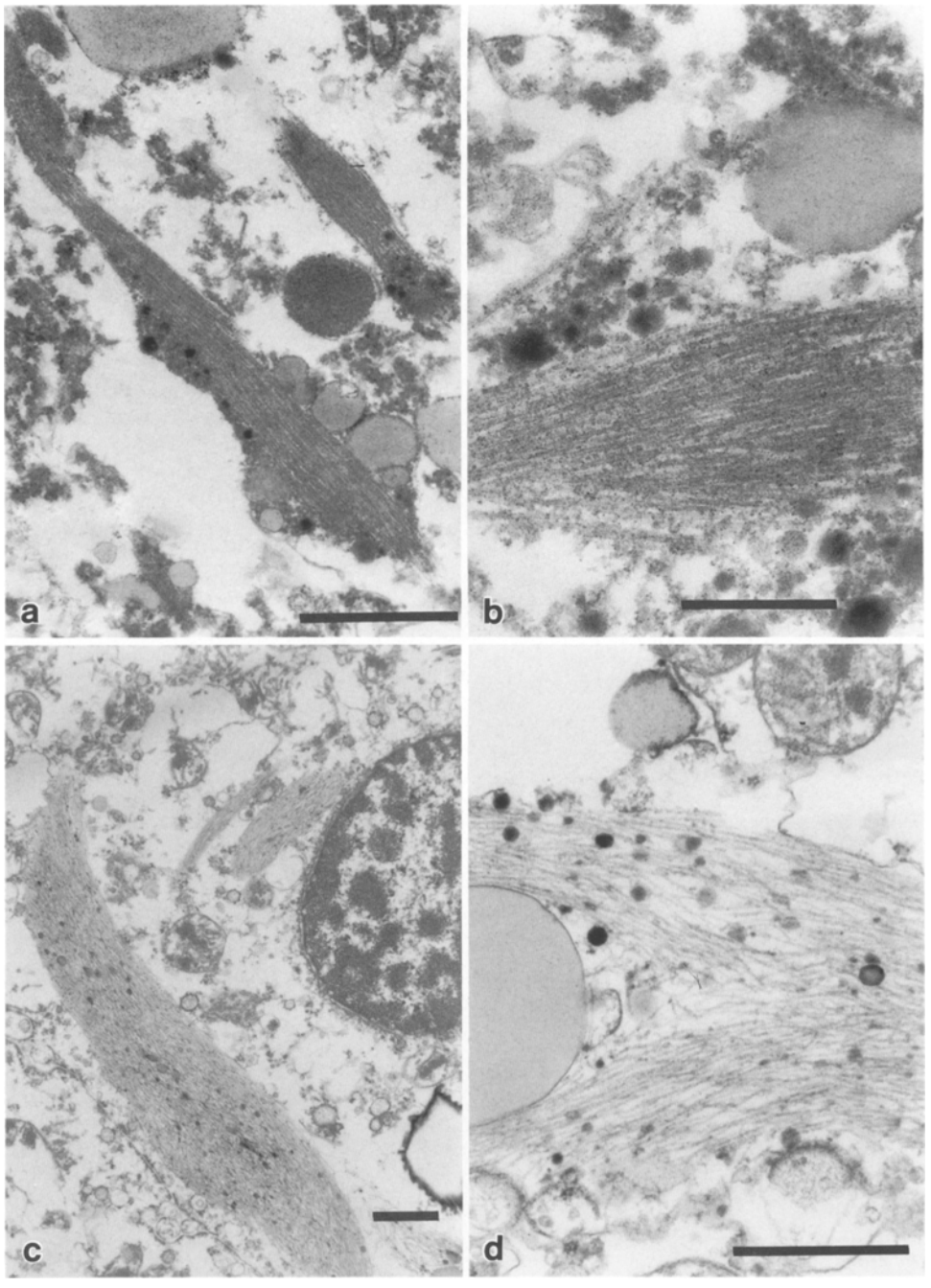

Fig. 3a–d. Ultrastructure of intracellular fibrillar inclusions in adrenal cortical cells (**a, b**) and of Biondi bodies in choroid plexus epithelia (**c, d**). The scale bar in **a, c** and **d** represents 1 μm, in **b** 0.5 μm.
a Densely packed fibrils are forming long bundles in the cytoplasm and are often related to lipid droplets and pigment granules. ×27500.
b The fibrils are composed of two straight subunits; there is no membrane around the fibrillar aggregations. ×54400
c The typical Biondi bodies resemble closely to the adrenal gland inclusions. ×11360.
d The fibrillar bundle contains a lipid droplet and many small electron dense pigment granules. ×30400

amyloid deposits; intracellular congophilic inclusions were not found with certainty. The evaluation proved difficult as a consequence of advanced autolytic changes in most cases.

Electron microscopical studies (Fig. 3) of 2 severely affected adrenal glands revealed that the congophilic inclusions contained long parallel fibrils with a mean diameter of about 10 nm. These fibrils were composed of two filamentous subunits with a diameter of 4–5 nm, which were not regularly twisted. Sometimes there was an irregular periodicity of about 65–80 nm. These filamentous inclusions lay within the cytoplasm and had no membranous capsules. Very often they showed a relationship to lipopigment droplets. Fibrillar intracellular inclusions in the anterior lobe of the pituitary gland proved to be of similar ultrastructural appearance with a diameter of 6–9 nm (Table 2, Fig. 4).

Discussion

Our results indicate that the intracellular accumulation of congophilic fibrils in cells of the nervous system (neurons, choroid plexus cells, ependymal cells) and in cells of the endocrine system (anterior pituitary gland, adrenal cortex, and parathyroid gland) is a phenomenon of aging. With increasing age the incidence and the amount of these congophilic fibrils are gradually rising. The process in the different cells begins at various ages but final-

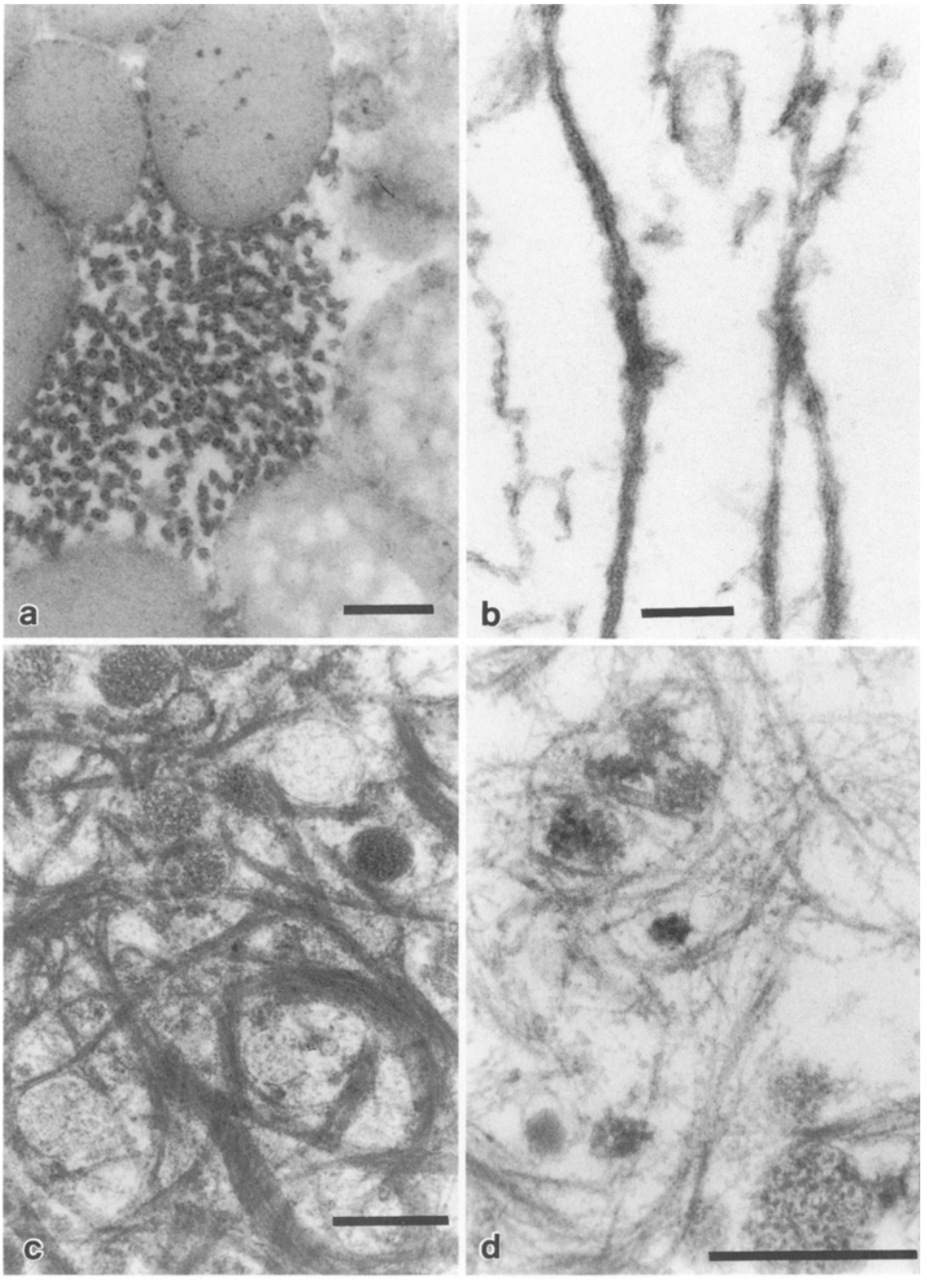

Fig. 4a–d. Ultrastructure of intracellular congophilic fibrillar inclusions in adrenal cortical cells (**a, b**) and in anterior lobe epithelial cells of the pituitary gland (**c, d**). The scale bar represents in **a** and **b** 0.1 μm, in **c** and **d** 0.5 μm.
a Cross-section of a bundle of fibrillar inclusions in the cytoplasm at a higher mangification. ×154700.
b Longitudinal section of a small group of fibrillar inclusions. Sometimes two or more fibrils are irregularly twisted one around the other. There is no regular periodicity. ×159600.
c In epithelial cells of the pituitary gland small bundles of densely packed fibrils form an irregular network in the cytoplasm, surrounding the secretory granules. ×40000.
d Sometimes single fibrils or only small groups of fibrils are loosely arranged. There is no membrane around them. ×72000

ly the incidence reaches 100%. In adrenal cortical cells, congophilic inclusions appeared for the first time in our material at the age of 55 years. In this decade, 7.7% of all cases already showed these intracellular birefringent filaments in the cortex of their adrenal glands. Beyond the age of 90 years all patients were involved. Eriksson and Westermark (1990) had found an overall incidence of 36% (compared with 42.7% of our material) starting in the 8th decade (from 70 to 79: 31%).

The accumulation of Biondi bodies begins earlier: the youngest patient was 41 years old. Above the age of 65 years all brains in our autopsy material contained Biondi bodies in their choroid plexus.

The ultrastructure of these congophilic fibrils in endocrine cells and in choroid plexus epithelial cells seemed to be similar but probably not identical (Oksche 1974; Eriksson and Westermark 1986; Eriksson and Westermark 1990). The fibrils are composed of two filamentous subunits with a diameter of about 6 nm each (Eriksson and Westermark 1990). The width of the whole fibril is in the mean 10–15 nm. Eriksson and Westermark (1986) reported a diameter of 20 nm for Biondi bodies but Oksche (1974) found a mean width of 10 nm. In most cases there was no regular periodicity. We found an irregular periodic twisting of about 65–80 nm in the adrenal cortical cells. These measurements are similar to the characteristic data from paired helical filaments (PHF) called left handed in NFT, as described by

Crowther and Wischik (1986) and Ohtsubo et al. (1990). Most authors have found a diameter of 15–20 nm and an irregular periodicity of 70–80 nm for PHF. The latest measurement of Ohtsubo et al. (1990) resulted in higher values: fibrils of 28–36 nm in diameter composed of filamentous subunits of 14–18 nm were noted. This is probably a consequence of the special technique they used (quick freeze, deep edge and replica method).

In contrast to these intracellular fibrils the amyloid deposits in all localized or generalized forms of amyloidosis occur in the extracellular space. The ultrastructure of amyloid fibrils is not identical to that of PHF (Shirahama and Cohen 1986). The width of amyloid fibrils amounts to 7.5–10 nm; they are composed of two or more filamentous subunits with a diameter of 2.5–3.5 nm and these components are not regularly twisted. We know of 24 different types of amyloid which are supposed to be different in their biochemical composition (Castano and Frangione 1988). The precursor proteins and even the amino acid sequences of some special types of amyloid are already known, notably the biochemical nature of the A4 or β-amyloid in senile brains or in Alzheimer brains (Glenner and Wong 1986; Dyrks et al. 1988). The biochemical nature and molecular structure of PHF, of Biondi bodies and of congophilic fibrils in endocrine cells are unknown. Many different components of PHF have been detected (Dyrks et al. 1988). There seems to be a greater heterogeneity in the chemical composition of intracellular fibrils; in general they are more complex than extracellular amyloid filaments.

Is it justified to classify the intracellular congophilic fibrillar accumulations as amyloid fibrils? There are contrary opinions in the literature: Eriksson and Westermark (1990) first described the congophilic inclusions in adrenal cortical cells as amyloid. Kirschner et al. (1986) found a cross beta conformation by X-ray diffraction of PHF and extraneuronal amyloid fibres in Alzheimer's disease. We prefer to restrict the term "amyloid" to extracellular deposits of fibrillated proteins, where the exact composition and molecular structure of the cytoplasmic accumulation of congophilic material is not known since there are ultrastructural differences and dissimilarities in their staining properties.

Can the pathogenesis of extracellular amyloid deposits and of intracellular congophilic fibrils be related to one other? In some tissues we find both alterations in normal aging: extracellular amyloid deposits (Saeger et al. 1983; Störkel et al. 1983; Tashima et al. 1988) and intracellular accumulation of congophilic tangles (our study). This occurs in the brain, in the pituitary gland (anterior lobe) and in the parathyroid gland. In our cases intracellular congophilic fibrils without extracellular amyloid deposits occurred in the adrenal cortex, in the choroid plexus and in ependymal cells. In generalized amyloidosis with involvement of the adrenal glands and of choroid plexus tissues, the incidence and amount of intracellular fibrils do not seem to be increased. The distribution patterns of amyloid plaques and NFT are not always identical in the central nervous system. These observations suggest that the pathogenetic mechanisms are not closely related to each other.

The biochemical composition is always quite different, as indicated by the results of the immunohistological methods. These failed to give specific reactions with antibodies to some of the most common types of amyloid (Eriksson and Westermark 1990).

One of the most important questions is: does the intracellular accumulation of congophilic fibrillar material disturb cell function? Is there a disease correlated with the amount of cytoplasmic filamentous deposits? In the central nervous system most authors (Khachaturian 1985) have found a correlation between the location and amount of NFT and the severity of clinical symptoms in cases of Alzheimer's disease and senile dementia of Alzheimer type. But functional impairment of the choroid plexus and of ependymal cells associated with Biondi bodies is not known, and there is no specific disease associated with the augmentation of intracellular congophilic fibrils in adrenal cortical cells (Lack 1990), in the endocrine cells of the pituitary or of the parathyroid glands (Westermark 1986). Thus the accumulation of congophilic fibrils in the cytoplasm of several cell types merely seems to be a phenomenon of individual aging; the cellular age does not seem to be the decisive factor.

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