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Cerebrovascular involvement in systemic AA and AL amyloidosis: a clear haematogenic pattern

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Abstract Amyloid deposits in cerebral vessels are common in β-amyloid diseases (Alzheimer's disease, congophilic amyloid angiopathy, Down's syndrome and hereditary cerebral amyloidosis with haemorrhage of the Dutch type). We report of 20 autopsies on patients who had died with systemic amyloidosis of the AA, Aλ and Aκ types: the brains were examined for the occurrence of amyloid. Vascular amyloid was detected in choroid plexus (in 17 of 20 cases), infundibulum (5 of 8), area postrema (6 of 11), pineal body (3 of 7) and subfornical organ (2 of 3), but not in cortical and leptomeningeal vessels. Immunohistochemical classification of the cerebral amyloid and the systemic amyloid syndrome showed identity proving the same origin of both. The distribution is indicative of a haematogenic pattern of amyloid deposition in systemic amyloidosis and is different from that in Alzheimer's, prion, ATTR and cystatin C diseases. It corresponds to areas of the brain with a "leaky" blood–brain barrier. Additionally, all the cases with AA amyloidosis exhibited an Aβ coreactivity in choroid plexus vessels. In one exceptional case, Aβ reactivity of AA amyloid also occurred outside of the brain.

Key words Systemic amyloidosis · Brain · Circumventricular organs · Choroid plexus · Immunohistochemistry · Aβ colocalization.

Introduction

Virchow [57] and later Lubarsch [38] never reported amyloid deposition within the brain in systemic amyloidosis, and more recent authors have also reported negative findings in larger series [47]. However, reports of the absence or rare occurrence [28] of cerebral amyloid in such cases relate to leptomeningeal, cortical and basal ganglia vessels, which are routinely examined. However, in 1914 Askanazy [1] had called attention to a regular and selective involvement of choroid plexus vessels. Later, vascular depositions in systemic amyloidosis were described in the infundibulum [2, 7, 25, 28] and the area postrema [28]. Such depositions thus seem to occur only in special regions of the brain that lack a tight blood–brain barrier (circumventricular organs) or in structures located outside the barrier, in the choroid plexus. However, information on the frequency of this manifestation of the disease is lacking.

Amyloidosis is a chemically heterogeneous group of disorders (for review see [4]). The majority of systemic cases involve deposition of amyloid A protein (AA), mostly following chronic inflammatory disease and of immunoglobulin light chain (AL) amyloidosis in cases of multiple myeloma or benign monoclonal B-cell proliferation or without any other apparent disease. In some extraordinary cases with peripheral neuropathy there is extensive involvement of the brain, with deposition on the outer and inner surface of brain and spinal cord, in meningeal and choroidal vessels with some formation of plaques [6, 7, 24]. Some of these cases are familial amyloid polyneuropathies with (ATTR) amyloid deposits of variant transthyretin (prealbumin) origin [21, 52, 53, 56]. Still other cases of systemic amyloidosis with cerebral deposition are at present unclassified [16, 39, 45]. Finally, more than one kind of amyloid may be found in the same patient, both in peripheral organs [19, 35, 46] and in brain, as shown in 4 cases by Ishihara et al. [21]. These authors demonstrate by immunohistochemistry the β-protein (Aβ) type of meningeal and cortical vascular amyloid and AA or AL amyloid deposits in the choroid plexus identical with the peripheral amyloid type found. Thus, in such cases the meningocortical vessels follow the pattern of the age-dependent Aβ amyloidosis that develops independently of the systemic amyloid disease.

We report the frequency of cerebrovascular amyloid depositions with particular reference to the regions with

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Table 1 Clinicopathological data of the examined cases and the results of the immunohistochemical classification (*n.a.* not available for immunohistochemistry, *0* no deposits of amyloid detected

Case	Autopsy	Age	Sex	Underlying disease	Amyloid type	
					Peripheral	Cerebral
1	219/70	66	f	Chronic glomerulonephritis[a]	n.a.	AA
2	466/71	30	m	Chronic pyelonephritis, haemophilia	n.a.	AA
3	19/76	56	m	Crohn's disease	n.a.	AA
4	27/76	50	f	Chronic polyarthritis	AA	AA
5	391/77	61	m	Chronic pyelonephritis	n.a.	AA
6	349/80	47	m	Crohn's disease	AA	AA
7	177/83	69	f	Chronic polyarthritis	AA	AA
8	213/86	61	m	Chronic pulmonary tuberculosis	AA	AA
9	87/93	59	m	Psoriasis, colitis	AA	AA
10	278/72	60	m	Chronic pyelonephritis	n.a.	Aλ
11	482/74	67	m	No underlying disease	n.a.	Aλ
12	185/83	43	f	Crohn's disease	Aλ	Aλ
13	392/83	59	f	Monoclonal gammopathy, IgA, λ	Aλ	Aλ
14	198/84	59	f	No underlying disease	Aλ	0
15	327/85	51	m	No underlying disease	Aλ	Aλ
16	199/88	68	m	No underlying disease	Aλ	Aλ
17	134/91	69	m	Multiple myeloma, λ light chains	Aλ	0
18	223/78	62	m	No underlying disease	n.a.	Aκ
19	256/82	65	m	Multiple myeloma, κ light chains	Aκ	0
20	36/83	72	m	No underlying disease	Aκ	Aκ

[a] No other disease is known from clinical or autopsy data

higher permeability in 20 cases of systemic AA and AL amyloidosis. We show that cerebral involvement is common. The immunohistochemical identity of the cerebral and the visceral amyloid type was established in every case tested.

Materials and methods

Systemic amyloidosis was examined in 20 consecutive autopsy cases (14 men, 6 women) from 1970 to 1994 (Table 1), in all of which amyloid was present in peripheral organs (kidneys, liver, spleen, adrenals, heart and others). Underlying diseases identified at autopsy were: 11 chronic inflammatory diseases, 3 B-cell neoplasia and 6 amyloidoses of undisclosed cause. The ages at death ranged from 30 to 72 years. For immunohistochemical classification selected paraffin blocks of formalin-fixed kidney, spleen or liver were used. Formalin-fixed paraffin-embedded brain specimens of the frontoparietal cortex and choroid plexus were screened with Congo red in all cases (which had had no clinical signs of cerebral disease), of the infundibulum in 8 cases, of the area postrema of the IV ventricle in 11 cases, and of the pineal body in 7 cases. In addition, the subfornical organ and subcommissural organ were investigated in 3 cases, each by serial sections. The anatomical sites from which the examined specimen were taken are depicted in Fig. 1.

Amyloid was identified as congophilic and green birefringent material according to Puchtler et al. [44]. Immunohistochemical classification [33] was performed on paraffin sections with amyloid deposits using the PAP or ABC method with amino-ethylcarbazole as chromogen, and evaluated blindly. The following seven primary antibodies were applied, which have been shown to be suitable for specific identification of the respective amyloid deposits [50]: monoclonal anti-human AA (mc1) ([31]; available from Dakopatts, Glostrup/Denmark; dilution 1:10), polyclonal anti-human Aλ (HAR) ([33], dilution 1:8000), polyclonal anti-human Aκ(SIN) ([30]; dilution 1:4000), polyclonal anti-human ATTR(TIE) (amyloid of transthyretin origin; [30]; dilution 1:1000), polyclonal anti-human Aβ2M(WOE) (amyloid of β_2-microglobulin origin; [34]; dilution 1:800) and polyclonal anti-human Aβ(RAP) (β-amyloid from Alzheimer's disease; [36]; dilution 1:1000). For the latter and the following antigens a guanidine HCl (6 M) pretreatment was applied to increase the sensitivity.

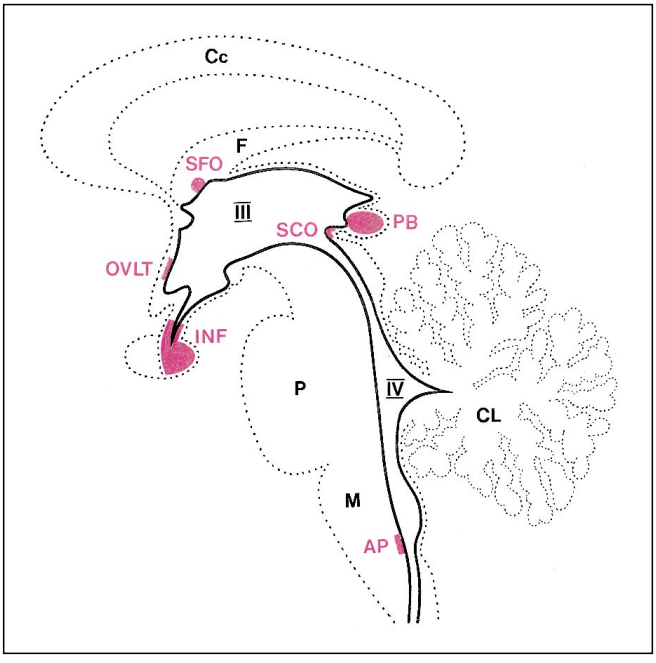

Fig. 1 Location of the circumventricular organs in a sagittal schematic plain of the third (*III*) and fourth (*IV*) ventricle (*AP* area postrema, *Cc* corpus callosum, *CL* cerebellum, *F* fornix, *INF* infundibulum and neurohypophysis, *OVLT* organum vasculosum laminae terminalis, *PB* pineal body, *SFO* subfornical organ, *SCO* subcommissural organ)

In addition, an antiserum against the scrapie-associated prion protein amyloid (AScr) in man was applied. This antiserum against AScr stained specifically the cerebral amyloid plaques of all 7 patients with Creutzfeldt-Jakob and Gerstmann-Sträussler-Scheinker diseases tested immunohistochemically (for method see [31]) on formalin-fixed and paraffin-embedded tissue sections. This antiserum directed against AScr was induced in an outbred rabbit with subcutaneous injections of an emulsion in complete Freund's adjuvant containing 250 µg in 250 µl phosphate-buffered

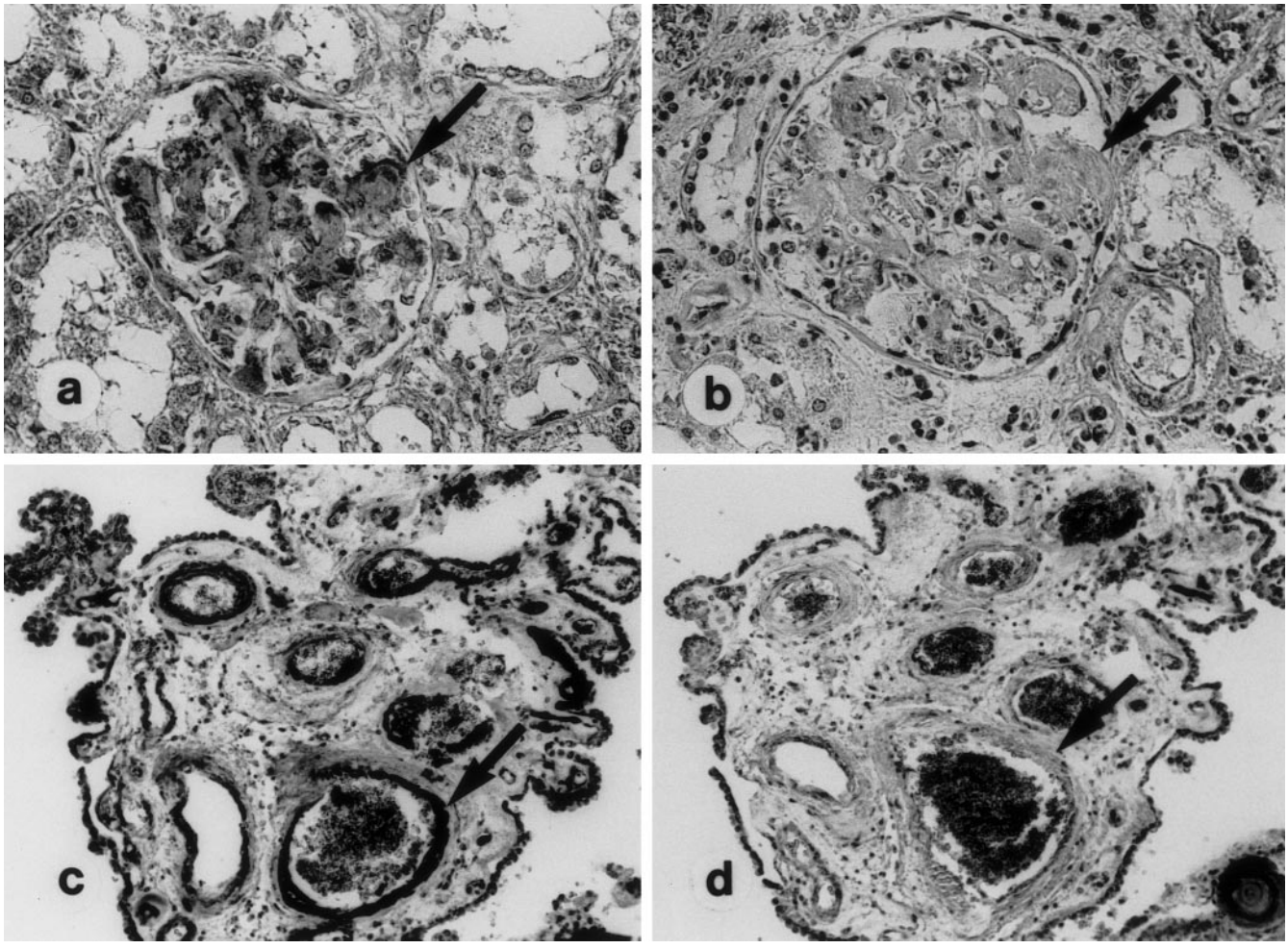

Fig. 2a–d Case 16, Aλ amyloidosis. Identity of the amyloid class in peripheral and cerebral deposits. **a** Kidney, anti-Aλ, positive reaction of glomerular amyloid deposits (*arrow*). **b** kidney, anti-AA, no immunohistochemical staining of the glomerular amyloid (*arrow*). **c** choroid plexus, anti-Aλ, positive reaction of vascular amyloid deposits (*arrow*). **d** choroid plexus, anti-AA, no staining of the deposits in a parallel section (arrow). **a**, **b** ×160, **c**, **d** ×75

saline of a peptid conjugate to bovine thyroglobulin (Sigma, Deisenhofen, Germany) with carbodiimid (Sigma) as detailed elsewhere [14]and 250 µl of complete Freund's adjuvant (Behring, Marburg, Germany). The synthetic peptid represented position 138–152 (IIHFGSDYEDRYYRE) of the human prion protein [22, 23]. Booster injections were given monthly. Specific antibodies directed against amyloid plaques of patients with spongiform encephalopathies appeared after the second booster injection.

Specificity of all immunohistochemical reactions was ensured by corresponding negative and positive controls. As controls and for comparison we examined 10 biopsies of visceral organs from other patients with AA amyloidosis with the same panel of antibodies and the same technique.

Results

In 13 cases of systemic amyloid the visceral amyloid was classified immunohistochemically as AA in 5, Aλ in 6 and Aκ in 2 cases (Table 1). Because of lack of paraf-

Table 2 Immunohistochemical results of cerebral amyloid in special regions in relation to the peripheral amyloid type (*P* peripheral organs, *CP* choroid plexus vessels, *INF* infundibulum, *AP* area postrema, *PB* pineal body, *SFO* subfornical organ. + Congo red-positive vascular deposits, but not available for immunohistochemistry, *0* no Congo red-stainable material, *n.a.* not available)

Case	P	CP	INF	AP	PB	SFO
1	n.a.	AA	n.a.	0	n.a.	n.a.
2	n.a.	AA	AA	n.a.	+	n.a.
3	n.a.	AA	n.a.	n.a.	n.a.	n.a.
4	AA	AA	n.a.	AA	+	n.a.
5	n.a.	AA	n.a.	n.a.	n.a.	n.a.
6	AA	AA	0	0	n.a.	n.a.
7	AA	AA	n.a.	n.a.	n.a.	n.a.
8	AA	AA	n.a.	AA	n.a.	n.a.
9	AA	AA	AA	+	n.a.	+
10	n.a.	Aλ	+	n.a.	n.a.	n.a.
11	n.a.	Aλ	n.a.	n.a	0	n.a
12	Aλ	Aλ	n.a.	n.a.	n.a.	n.a.
13	Aλ	Aλ	n.a.	n.a.	n.a.	n.a.
14	Aλ	0	0	0	0	n.a.
15	Aλ	Aλ	+	+	n.a.	0
16	Aλ	Aλ	Aλ	Aλ	0	+
17	Aλ	0	n.a.	0	n.a.	n.a.
18	n.a.	Aκ	0	0	+	n.a.
19	Aκ	0	n.a.	n.a.	n.a.	n.a.
20	Aκ	Aκ	n.a.	Aκ	0	n.a.

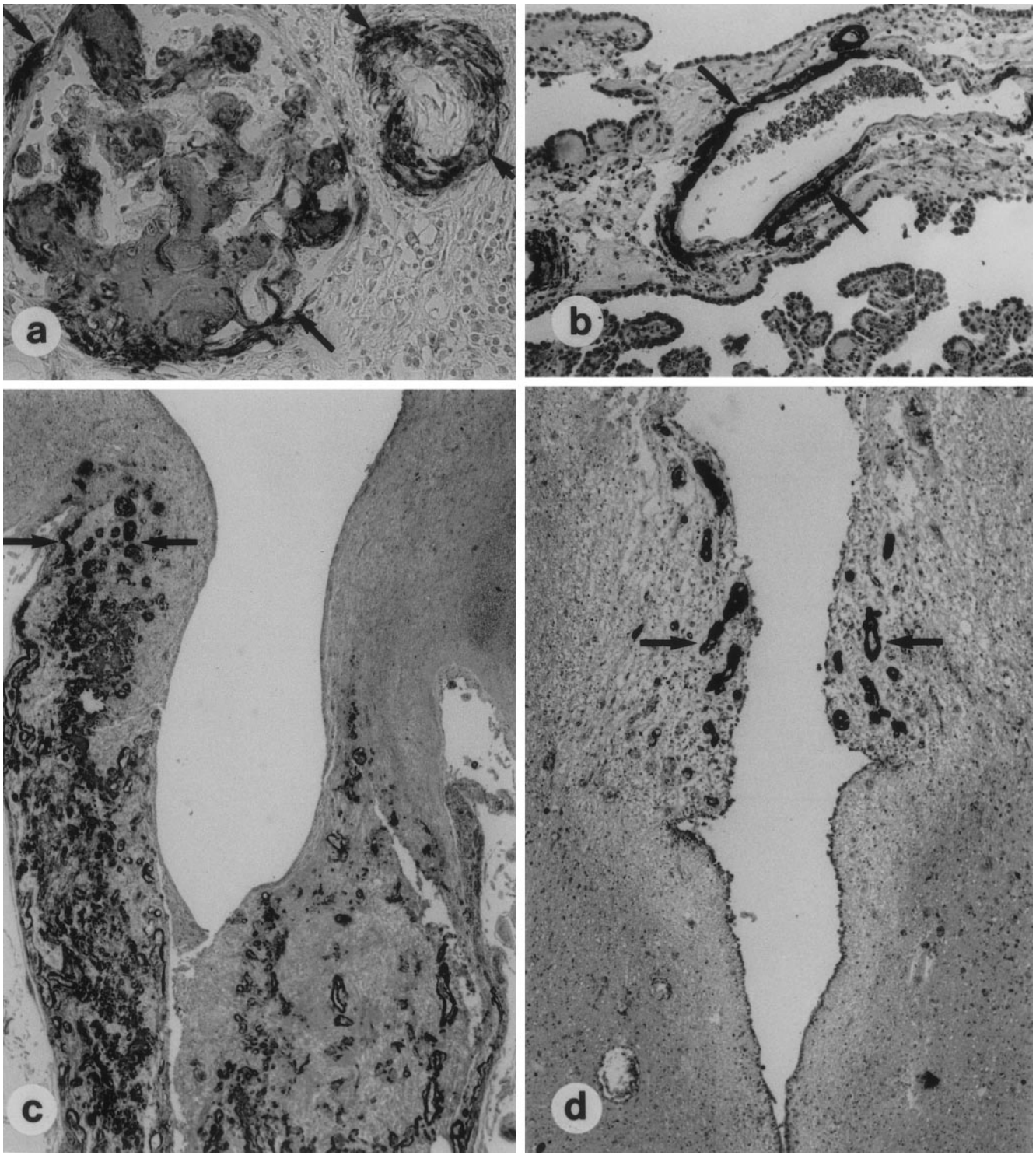

Fig. 3a–d AA amyloidosis. Amyloid in peripheral organs and in various peculiar cerebral locations showing the same intense anti-AA reaction. **a** Case 4, kidney with amyloid in glomerulum (*between arrows*) and artery (*small arrow*). **b** Case 4, choroid plexus containing vessels with AA-reactive deposits (*between arrows*). **c** Case 2, infundibulum surrounding a recessus of the III ventricle with numerous small vessels showing AA-reactive deposits (examples *between arrows*). **d** Case 8, area postrema in the upper part of the figure lining the IV ventricle with AA-reactive deposits in small vessels as indicated by *arrows*. **a–d** Anti-AA, **a** ×160, **b** ×75, **c** ×18, **d** ×45

fin material in 7 cases only Congo red-stained slides were available for diagnosing systemic amyloid deposits.

In all 20 cases of systemic amyloidosis the brain was examined, and in 17 cases (85%) cerebrovascular amyloid was detected. However, the frequency must be specified according to the location. In vessels of the choroid plexus, mostly arteries, amyloid was detected in 17 of 20 cases investigated (85%), in small vessels of the infundibulum in 5 of 8 cases (63%), of the area postrema

Table 3 Colocalizaion of AA and Aβ immunoreactivity according to immunohistochemical results with a panel of antibodies against some of different amyloid types in peripheral organs and in choroid plexus vessels (*n.a.* not available, 0 to ++++ staining intensity with the respective antibody, where 0/++ means the range of the reaction intensity within the same section)

Case	Peripheral organs		Choroid plexus			
	Amyloid class	Anti-Aß	Anti-AA	Anti-Aλ	Anti-Aκ	Anti-Aß
1	n.a.		++++	0/++	0	0/+++
2	n.a.		++++	0	0	++
3	n.a.		+++	0/+	0	++/+++
4	AA	0	+++	0/+	0/+	+++
5	n.a.		+++	0	0	+/++
6	AA	0	+++	0/+	0	++
7	AA	0	++/+++	+	+	++
8	AA	0	++/+++	0	0	++/+++
9	AA	++/+++	++/+++	0/++	0	+/+++
10	n.a.		0	+++	0/++	0
11	n.a.		0	+++	0	0
12	Aλ	0	0	+++	0/+	0
13	Aλ	0	0	+++	0	0
14	Aλ	0	No amyloid			
15	Aλ	0	0	++/+++	0/+	0
16	Aλ	0	0/+	+/+++	0	0
17	Aλ	0	No amyloid			
18	n.a.		0	+	++/+++	0
19	Aκ	0	No amyloid			
20	Aκ	0	0	0	++	0

in 6 of 11 cases (55%), in a few capillaries of the pineal body in 3 of 7 cases (43%) and in vessels of the subfornical organ in 2 of 3 cases (67%). The results are listed in Table 2. Altogether, excluding the choroid plexus, the circumventricular organs were involved in 9 of 14 cases (64%). In the region of the subcommissural organ with intact blood–brain barrier [29] no amyloid could be observed in 3 cases. No amyloid was detectable in leptomeningeal, cortical or white matter vessels in any of the 20 cases. Thus, the relatively frequent cerebrovascular pattern of Aβ amyloid was not present in the cases examined.

Immunohistochemically both systemic visceral and cerebral deposits could be examined in 10 cases. The results showed an identical amyloid class in all cases. Five cases were of AA, 4 of Aλ and 1 of Aκ type (Table 1). As shown in Table 2, the corresponding amyloid protein appeared both in the vessels of the choroid plexus and in those of the special regions of the brain mentioned above (Figs. 2, 3). Other amyloid classes, such as ATTR, Aβ, Aβ2M or AScr, were not present and could not be identified with the respective antibodies. The generalized amyloid in cases 1–3, 5, 10, 11 and 18, which could not be analysed directly, was probably identical to the cerebral vascular amyloid, since deposits of these kinds of amyloid in these peculiar locations have not been reported as independent asymptomatic diseases. Summarizing all cases, therefore, cerebrovascular deposits were detected more frequently in AA (5/5) than in AL amyloidosis (5/8).

Since amyloid in tissue sections is not a pure substance but displays many other proteins adsorbed to the amyloid fibril, including light chains (preferentially λ-light chains), every light chain reaction has to be questioned and checked by means of antibodies against other amyloid proteins. When no other antibody suitable for amyloid classification is reactive, an AL amyloid is the most likely. When, however, an AA reaction is found besides the Aλ reaction, an AA amyloidosis is considered. This rule was formulated after biochemical analyses of cases with double reactions of the same amyloid deposits [32].

In all cases of AA amyloidosis the deposits in choroid plexus vessels exhibited an Aβ reactivity in addition to the AA immunoreactivity (Table 3). The Aβ immunoreactivity was mostly of lower intensity (Fig. 4b), but in case 9 partly of high intensity (Fig. 5c). In contrast to AA amyloid, Aβ colocalization was *not* noted in the choroid plexus amyloid in cases of Aλ or Aκ amyloidosis. The finding of colocalization of AA amyloid and Aß-immunoreactivity was limited to the choroid plexus and was not observed in other cerebral structures examined in cases of AA amyloidosis, such as infundibulum (case 2) and area postrema (cases 4 and 8), with the exception of case 9 only (see below).

The examination of the viscera (Table 3) also revealed no such colocalization, again with the exception of case 9. To answer the question as to whether peripheral amyloid deposits regularly also showed Aβ immunoreactivity, peripheral organ biopsies of additional 10 patients with AA amyloidosis were examined. No Aβ reactivity of AA amyloid deposits was noted.

Case 9 seems to be unique in that visceral systemic amyloid colocalized with Aβ immunoreactivity. The patient was 59 years of age at his death and had had psoriasis since he was 20. Thirteen years before death he had chronic inflammatory colitis, which was later treated by right-sided hemicolectomy. Progressive renal insufficiency had been manifest for 10 years; dialysis was necessary because of biopsy-proven amyloid nephropathy. Later a renal transplant was performed, with good function of the organ in subsequent 4 years, but for 2 months there had been further renal insufficiency, which was finally life limiting. At autopsy massive amyloid deposits were

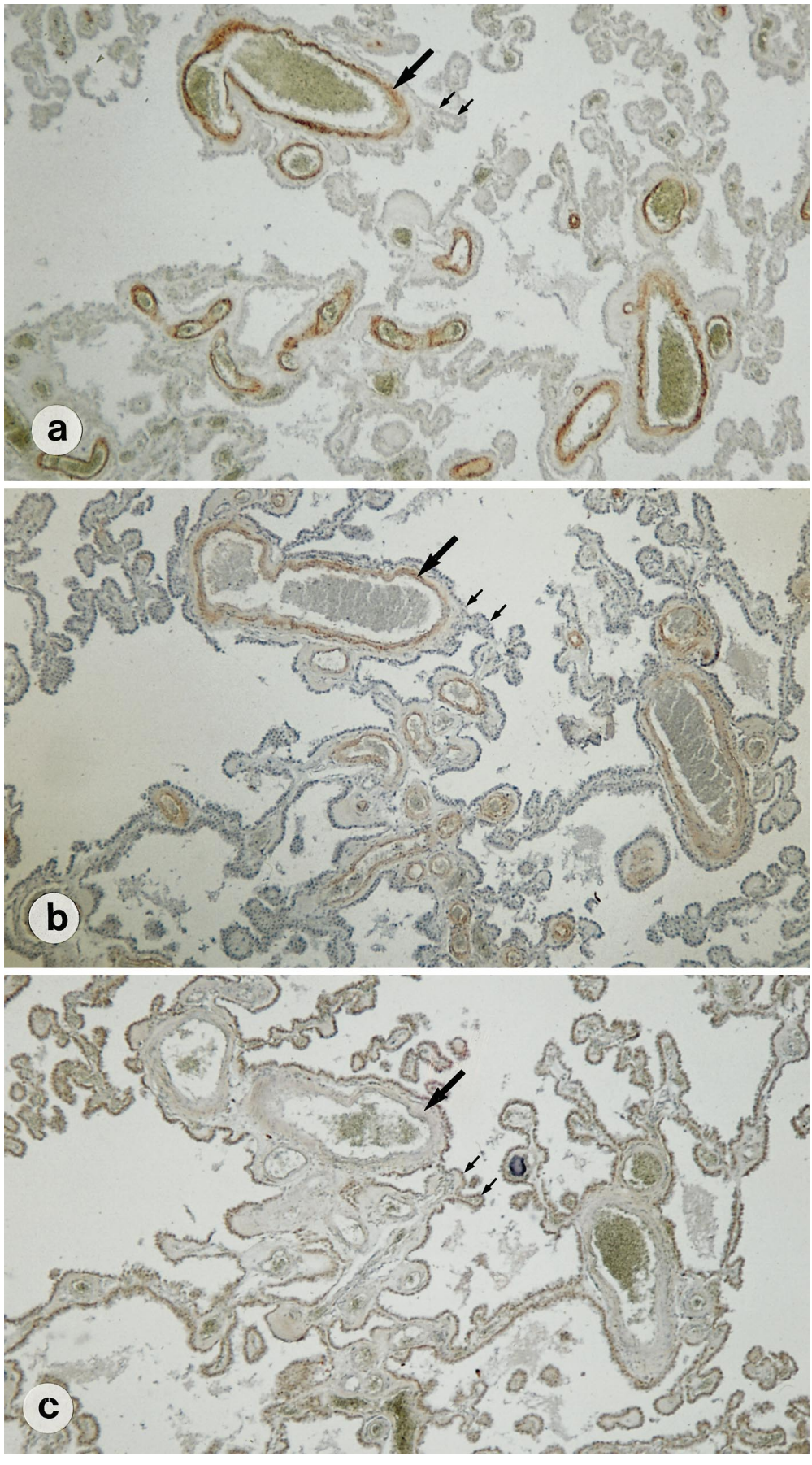

Fig. 4a–c Case 8, AA amyloidosis with colocalized Aβ reactivity in choroid plexus vessels, parallel sections. **a** Anti-AA, intense staining of vascular amyloid deposits (*large arrow*). **b** Anti-Aβ, moderate staining of the vascular deposits in the same area as in **a** (*large arrow*). **c** Anti-ATTR, no reaction of the vascular deposits (see *tip* of *arrow*), but staining of plexus epithelium (*small arrows*; in **a** and **b** *small arrows* indicate unstained plexus epithelium). ×110

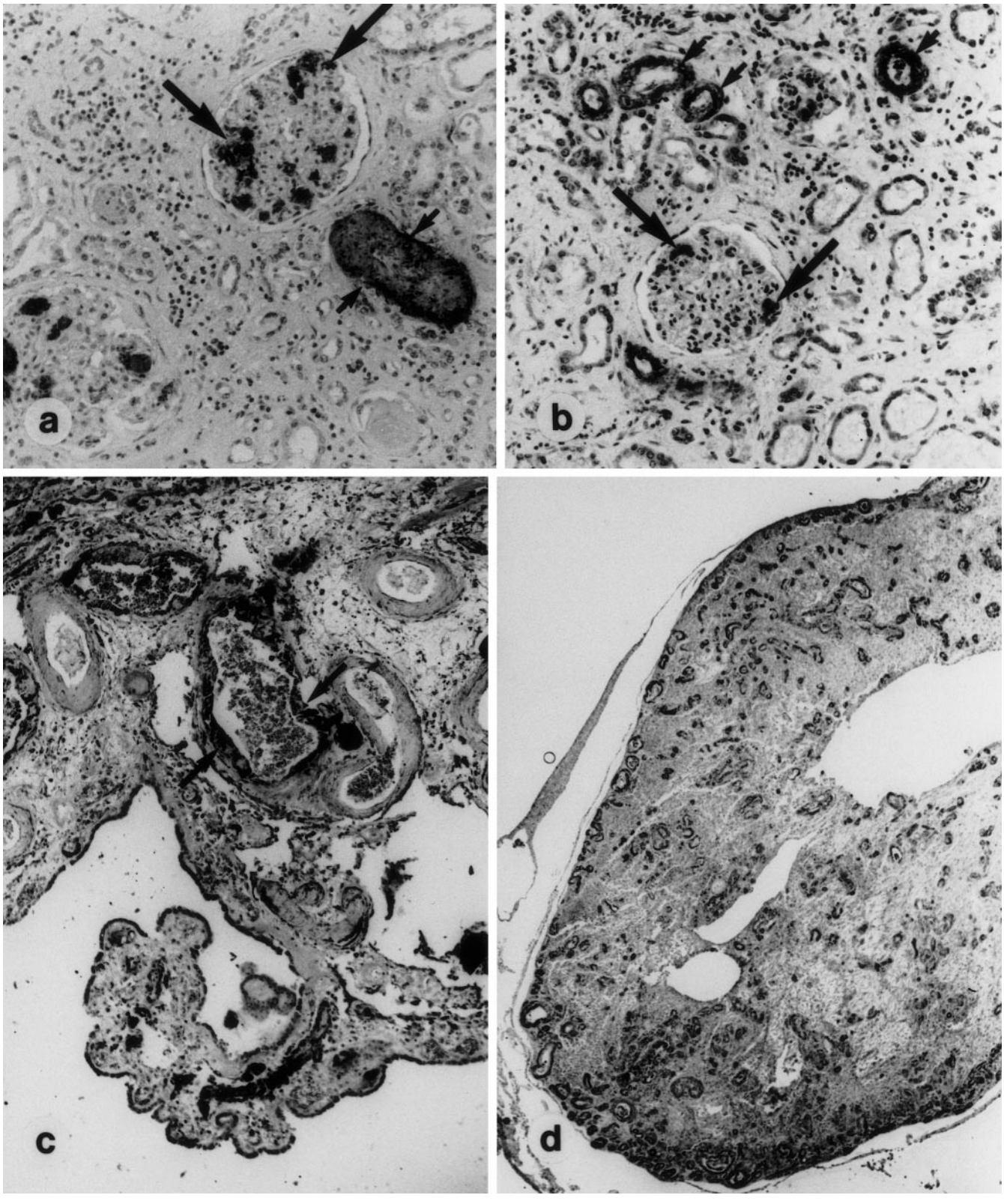

Fig. 5a–d Case 9, AA amyloidosis with strong Aβ reactivity in all locations. **a** Transplanted kidney, anti-AA, intense staining of glomerular (*large arrows*)and arterial (*small arrows*) amyloid deposits. **b** Transplanted kidney, anti-Aβ, intense staining of glomerular (*large arrows*) and arterial (*small arrows*) AA amyloid deposits. **c** Choroid plexus, anti-Aβ, intense staining of vascular AA amyloid deposits (example *between arrows*). **d** Infundibulum, anti-Aβ, intense staining of numerous vascular AA amyloid deposits throughout the section. **a–c** ×120, **d** ×20

found in the autochthonous kidneys, lesser amounts in the transplanted kidney and in the submandibular gland, thyroid gland, spleen, liver, adrenals, bile ducts, colon, pancreas, peripheral nerves, prostate, and testes, and trace-like amounts in the myocardium. The immunohistochemical findings, including those recorded in the brain, are shown in Tables 2 and 3. The results revealed strong labelling with the anti-AA antibody and a strong Aβ reactivity in both the original and the transplanted kidney as well as in the choroid plexus and infundibulum (Fig. 5).

In all cases examined plexus epithelium showed a consistent immunohistochemical reaction independent of the type of systemic amyloid. Since these cells are the site of intense transthyretin synthesis [17] they stained diffusely with the anti-ATTR antibody (Fig. 4c), as shown by other authors [20, 26, 49]. The reaction was not congruent with the intracellular age-related Congo red-staining protein fibrils and Biondi rings, which seem to consist of a special type of intracellular amyloid [8, 9] with Aβ features [42, 58]. Corresponding to this a weak cytoplasmic anti-Aβ reactivity was seen in 6 of our cases (5/9 being of the AA and 1/8 of the AL class).

Discussion

The data presented demonstrate that cerebral amyloid deposits in special regions are very common in systemic AA and AL amyloidoses, as we found in 17 of our 20 cases (85%). The amyloid deposits described are of the same chemical amyloid class as the visceral amyloid in all 10 cases comparatively examined by immunohistochemistry. AA amyloid deposits in vessels of the choroid plexus show immunohistochemical coreactivity with antigenic determinants of Aβ amyloid in all 9 cases examined in the absence of Alzheimer's disease (evaluated by clinical data and neuropathological findings), whereas visceral and the other cerebral AA amyloid deposits revealed this colocalization in only 1 of 5 cases, or 1 of 15 cases if the 10 visceral biopsies are included.

These findings suggest that cerebral and visceral amyloid deposits in systemic amyloidoses have the same origin and arise by the same pathogenesis. The AA amyloid deposits originate from the acute phase serum protein (aSAA) and the AL amyloid derives from monoclonal immunoglobulin light chains [13, 27]. These circulating precursors, infiltrating some cerebral vessels, may either represent intact amyloidogenic proteins, which may be cleaved locally within the tissue [13], or represent precleaved preamyloid fragments, as demonstrated by light chain intermediates [11].

In contrast to the systemic nature of the amyloid described here, with a characteristic haematogenic distribution pattern of the cerebral deposits, local tumour-like amyloid deposits or amyloidomas of the Aλ type, causing severe clinical symptoms, are reported as likely to have originated from a plasma cell clone restricted to the brain [10, 37, 48, 55].

Other cerebrovascular amyloid diseases, such as the frequent Aβ amyloidoses, the ATTR amyloidoses of different hereditary, mostly polyneuropathic syndromes (the non-relevant hereditary cystatin C-type Icelandic cerebral amyloidosis was not examined) and prion protein diseases were excluded in our series by investigation with specific antibodies.

Since amyloid is only detected at sites where the blood–brain barrier is not tight, such as in the small areas of the circumventricular organs [29] around the III and IV ventricles (Fig. 1), the circulating precursor molecules may pass through the fenestrated endothelium of these vessels, being processed and deposited as amyloid between the endothelial and glial basement membranes.

There are no data on the frequency of amyloid deposition in systemic amyloidoses within the special vessels of infundibulum or area postrema. We found an involvement in 9 of 14 cases (64%), with identity to the visceral amyloid class in all 6 cases comparatively tested. In the epiphysis cerebri and in the subfornical organ we further observed amyloid; this has not been reported previously.

The frequent involvement of vessels of the choroid plexus in systemic amyloidoses [1] is presumably due to the fact that these vessels are outside the barrier to the cerebrospinal fluid built up by the plexus epithelium. They follow visceral amyloid expansion. The immunohistochemical identity of these deposits with visceral amyloid has been demonstrated in 9 cases of systemic AA and AL amyloidosis by Ishihara et al. [21]. We can confirm this in 10 further cases.

Our results together with those of Ishihara et al. [21] show that the choroid plexus vessels were involved in all 7 AA cases examined (100%) and in 12 of 19 AL cases (63%). This quantitative difference, which needs to be verified by observations in a larger number, may be related to the different organ distribution pattern known to occur in the two amyloid syndromes, AL being discontinuous [5].

In other systemic (hereditary) amyloidoses, including variant ATTR and apolipoprotein A I (AApoAI), choroid plexus vessels are also affected [15, 21, 53, 54].

In contrast, the involvement of meningocortical vessels has rarely been described in systemic amyloidoses. Rukavina [47] found no case in a collection of 56 cases, Mathews [40] 2 cases in 50 and Lampert [28] 1 case among 36. The meningocortical vessels in cases of this kind may be found on immunohistochemical or chemical investigation to be affected by another amyloid protein, the Aβ type [21, 49]. In a few cases the protein belongs to other types, including transthyretin in senile systemic amyloidosis [21], type I familial amyloidotic polyneuropathy [21, 53], a familial ATTR syndrome with central neurological deficits [18, 56] and familial oculoleptomeningeal amyloidosis [43, 51]. They are of the gelsolin type in type IV familial amyloidotic polyneuropathy [41]. Grey matter and white matter vessels may also be affected in prion diseases [12]. In systemic AA and AL amyloidosis no case has yet been reported with immunohistochemically verified depositions of the visceral amyloid type in meningocortical vessels. Similarly, in our cases there

was no involvement of this vascular domain, where apparently the intact blood–brain barrier prevents the permeation of the circulating precursor proteins through the vessel wall.

No Aβ immunoreactivity has been reported in choroid plexus vessels, as we have found in cases of AA amyloidosis. Since this reactivity pattern was not demonstrated in circumventricular or in visceral amyloid of AA type (in a total of 14 cases, with the only exception of case 9) and in non-AA type amyloid (8 cases), this codeposition of AA and Aβ reactivity needs further attention.

Finally, the frequent involvement of special regions of the brain lacking a tight blood–brain barrier in systemic AA and AL amyloidosis is comparable to the situation in some other systemic diseases, including haemochromatosis [3] and primary oxalosis (personal observation, unpublished), with a similar exclusive distribution of depositions. This haematogenic pattern in both types of systemic amyloidoses can be distinguished from that in brain-specific Aβ amyloidosis. The situation is different again in cases with systemic ATTR amyloidosis, in which the involvement of both choroidal and meningocortical vessels and of the outer and inner surface of the brain [21, 52, 53] results from the synthesis of the regular or mutant transthyretin by both liver and choroid plexus epithelium. There is circulation of the protein in plasma as well as in cerebrospinal fluid.

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References

1. Askanazy M (1914) Zur Physiologie und Pathologie der Plexus chorioidei. Verh Dtsch Pathol Ges 17:85–103
2. Bekker GM (1983) Changes of the nervous system in amyloidosis (in Russian). Zh Nevropatol Psikhiatr 83:1181–1184
3. Cammermeyer J (1947) Deposition of iron in paraventricular areas of the brain in hemochromatosis. J Neuropathol Exp Neurol 6:111–127
4. Castaño EM, Frangione B (1988) Biology of disease. Human amyloidosis, Alzheimer disease and related disorders. Lab Invest 58:122–132
5. Cohen AS (1967) Amyloidosis. N Engl J Med 227:522–530, 574–583, 628–638
6. Da Silva Horta J, Dias Coelho MR (1960) Localisations de substance paramyloide dans le système nerveux central. Arch Vecchi Anat Patol 31:163–178
7. Diezel PB (1962) Amyloide Strukturen im Nervensystem. Proc IVth Int Congr Neuropathol, vol 1, Thieme, Stuttgart, pp 136–141
8. Eriksson L, Westermark P (1990) Characterization of intracellular amyloid fibrils in the human choroid plexus epithelial cells. Acta Neuropathol 80:597–603
9. Eriksson L, Westermark P (1991) Choroid plexus amyloid. In: Natvig JB, Førre Ø, Husby G, Husebekk A, Skogen B, Sletten U, Westermark P (eds) Amyloid and amyloidosis. (VIth Int Symposium on Amyloidosis) Kluwer Academic, Dordrecht Boston London, pp 761–764
10. Eriksson L, Sletten K, Benson L, Westermark P (1993) Tumor-like localized amyloid of the brain is derived from immunoglobulin light chain. Scand J Immunol 37:623–626
11. Eulitz M, Linke RP (1993) The precursor molecule of a Vλ II-immunoglobulin light chain-derived amyloid fibril protein circulates precleaved. Biochem Biophys Res Commun 194: 1427–1434
12. Ghetti B, Piccardo P, Spillantini MG, Ichimiya Y, Porro M, et al (1996) Vascular variant of prion protein cerebral amyloidosis with τ-positive neurofibrillary tangles: the phenotype of the stop codon 145 mutation in PRNP. Proc Natl Acad Sci USA 93:744–748
13. Glenner GG (1980) Amyloid deposits and amyloidosis – the β-fibrilloses. N Engl J Med 302:1283–1292
14. Goodfriend TL, Levine L, Fasman GD (1964) Antibody to bradykinin and angiotensin: a use of carbodiimid in immunology. Science 144:1344–1346
15. Guimaraes A, Monteiro L, Coutinho P (1980) Pathology of the autonomic nervous system in Andrade type of familial amyloidotic polyneuropathy. In: Glenner GG, Pinho e Costa P, Falcão de Freitas A (eds) Amyloid and amyloidosis. (3rd Int Symposium on Amyloidosis) Excerpta Medica, Amsterdam Oxford Princeton, pp 139–146
16. Haberland C (1964) Primary systemic amyloidosis. Cerebral involvement and senile plaque formation. J Neuropathol Exp Neurol 13:135–150
17. Herbert J, Wilcox JN, Pham KC, et al (1986) Transthyretin: a choroid plexus-specific transport protein in human brain. Neurology 36:900–911
18. Herrick MK, De Bruyne K, Horoupian DS, Skare J, Vanefsky MA, Ong T (1996) Massive leptomeningeal amyloidosis associated with a Val30Met transthyretin gene. Neurology 47:988–992
19. Hoshii Y, Takahashi M, Ishihara T, Uchino F (1994) Immunohistochemical classification of 140 autopsy cases with systemic amyloidosis. Pathol Int 44:352–358
20. Inoue T, Matsushima T, Fukui M et al (1988) Immunohistochemical study of intracranial cysts. Neurosurgery 23:576–581
21. Ishihara T, Nagasawa T, Yokota T et al (1989) Amyloid protein of vessels in leptomeninges, cortices, choroid plexuses, and pituitary glands from patients with systemic amyloidosis. Hum Pathol 20:891–895
22. Kitamoto T, Tateishi J (1988) Immunohistochemical confirmation of Creutzfeldt-Jakob disease with a long clinical course with amyloid plaque core antibodies. Am J Pathol 131:435–443
23. Kretschmar HA, Stowring LE, Wetswang D, Stubblebine WD, Prusiner SB, DeArmond SJ (1986) Molecular cloning of human prion protein cDNA. DNA 5:315–324
24. Krücke W (1950) Das Zentralnervensystem bei generalisierter Paramyloidose. Arch Psychiatr Nervenkr 185:165–192
25. Krücke W (1959) Die Paramyloidose. Erg Inn Med 11:299–378
26. Kuchelmeister K, Bergmann M (1992) Colloid cyst of the third ventricle. An immunohistochemical study. Histopathology 21:35–42
27. Kyle RA, Gertz MA (1995) Primary systemic amyloidosis: clinical and laboratory features in 474 cases. Semin Hematol 32:45–59
28. Lampert PW (1968) Amyloid and amyloid-like deposits. In: Minckler J (ed) Pathology of the nervous system, vol 1. McGraw-Hill, New York, pp 1113–1121
29. Leonhardt H (1980) Circumventriculäre Organe. In: Oksche A (ed) Handbuch der mikroskopischen Anatomie des Menschen, vol IV/10: Neuroglia I. Springer, Berlin Heidelberg New York
30. Linke RP (1982) Immunohistochemical identification and cross reactions of amyloid fibril proteins in senile heart and amyloid in familial polyneuropathy. Clin Neuropathol 1:172–182
31. Linke RP (1984) Monoclonal antibodies against amyloid fibril protein AA. Production, specificity, and use for immunohistochemical localization and classification of AA-type amyloidosis. J Histochem Cytochem 32:322–328
32. Linke RP (1985) Immunochemical typing of amyloid deposits after microextraction from biopsies. Appl Pathol 3:18–28

33. Linke RP, Nathrath WBJ (1980) Klassifizierung von Amyloid-Krankheiten an der Biopsie. Anwendung der Immunperoxidase-Technik. Münch Med Wochenschr 122:1772–1776
34. Linke RP, Hample H, Bartel-Schwarze S, Eulitz M (1987) β_2-Microglobulin, different fragments and polymers thereof in synovial amyloid in long-term hemodialysis. Biol Chem Hoppe-Seyler 368:137–144
35. Linke RP, Kunert U, Lobeck H, Hample H, Eulitz M (1988) Chemical analysis of beta$_2$-microglobulin derived amyloid in patients on long-term hemodialysis. In: Isobe T, Araki S, Uchino F, Kito S, Tsubura E (eds) Amyloid and amyloidosis. Plenum Press, New York London, pp 611–616
36. Linke RP, Schifferegger R, Kretschmar H, Gerhard L (1991) Antigenic heterogeneity of cerebral amyloid deposits in Alzheimer's disease. In: Natvig JB, Førre Ø, Husby G, Husebekk A, Skogen B, Sletten U, Westermark P (eds) Amyloid and Amyloidosis. (VIth Int Symposium on Amyloidosis) Kluwer Academic, Dordrecht Boston London, pp 741–744
37. Linke RP, Gerhard L, Lottspeich F (1992) Brain-restricted amyloidoma of immunoglobulin λ-light chain origin clinically resembling multiple sclerosis. Biol Chem Hoppe-Seyler 373: 1201–1209
38. Lubarsch O (1929) Zur Kenntnis ungewöhnlicher Amyloidablagerungen. Virchows Arch Pathol Anat 271:867–889
39. Marinesco G (1931) Sur une affection particulière simulant, au point de vue clinique, la sclérose en plaque et ayant pour substratum des plaques spéciales du type sénile. Arch Roum Pathol Exp Microbiol 4:41–69
40. Mathews WH (1954) Primary systemic amyloidosis. Am J Med Sci 228:317–333
41. Meretoja J, Teppo L (1971) Histopathological findings of familial amyloidosis with cranial neuropathy as principle manifestation. Report of three cases. Acta Pathol Microbiol Scand [A] 79:432–440
42. Miklossy J, Kraftsik R, Pillevuit O, Lepori D, Genton C, Bosman FT (1998) Curly fiber and tangle-like inclusions in the ependyma and choroid plexus – a pathogenetic relationship with the cortical Alzheimer-type changes? J Neuropathol Exp Neurol 57:1202–1212
43. Petersen RB, Tresser NJ, Richardson SL, Gali M, Goren H, Gambetti P (1995) A family with oculoleptomeningeal amyloidosis and dementia has a mutation in the transthyretin (abstract). J Neuropathol Exp Neurol 54:413
44. Puchtler H, Sweat F, Levine M (1962) On the binding of Congo red by amyloid. J Histochem Cytochem 10:355–364
45. Ritama V (1954) Amyloidosis of the cerebellar cortex in a diabetic. Ann Med Intern Fenn 43:51–67
46. Röcken C, Saeger W, Linke RP (1993) Mehrere unterschiedliche Amyloidtypen bei einer 93jährigen Patientin. Kasuistik eines Sektionsfalles. Pathologe 14:42–46
47. Rukavina JG, Block WD, Jackson CE, et al (1956) Primary systemic amyloidosis: a review and an experimental, genetic, and clinical study of 29 cases with particular emphasis on the familiar form. Medicine (Baltimore) 35:239–334
48. Schröder R, Linke RP, Voges J, Heindel W, Sturm V (1995) Intracerebral Aλ amyloidoma diagnosed by stereotactic biopsy. Clin Neuropathol 14:347–350
49. Sillus M, Saeger W, Linke RP, Müller D, Voigt C (1993) Cerebral amyloid angiopathy. Frequency, significance and immunohistochemistry. Zentralbl Pathol 139:2107–2115
50. Strege RJ, Saeger W, Linke RP (1998) Diagnosis and immunohistochemical classification of systemic amyloidoses. Report of 43 cases in an unselected autopsy series. Virchows Arch 433:19–27
51. Uitti RJ, Donat JR, Rozdilsky B, Schneider RJ, Koeppen AH (1988) Familial oculoleptomeningeal amyloidosis. Report of a new family with unusual features. Arch Neurol 45:1118–1122
52. Ushiyama M, Ikeda S, Yanagisawa N (1991) Prealbumin type cerebral amyloid angiopathy in familial amyloid polyneuropathy. In: Natvig JB, Førre Ø, Husby G, Husebekk A, Skogen B, Sletten U, Westermark P (eds) Amyloid and amyloidosis. (VIth Int Symposium on Amyloidosis) Kluwer, Dordrecht Boston London, pp 667–670
53. Ushiyama M, Ikeda S, Yanagisawa N (1991) Transthyretin-type cerebral amyloid angiopathy in type I familial amyloid polyneuropathy. Acta Neuropathol 81:524–528
54. Van Allen MW, Frohlich JA, Davis JR (1969) Inherited predisposition to generalized amyloidosis. Clinical and pathological study of a famliy with neuropathy, nephropathy, and peptic ulcer. Neurology (Minneap) 19:10–25
55. Vidal RG, Ghiso J, Gallo G, Cohen M, Gambetti PL, Frangione B (1992) Amyloidoma of the CNS. II. Immunohistochemical and biochemical study. Neurology (Minneap) 42:2024–2028
56. Vidal R, Garzuly F, Budka H, Lalowski M, Linke RP, Brittig F, Frangione B, Wisniewski T (1996) Meningocerebrovascular amyloidosis with a novel transthyretin mis-sense mutation at codon 18 (TTRD 18 G). Am J Pathol 148:361–366
57. Virchow R (1858) Vorlesungen über Pathologie. Die Cellularpathologie in ihrer Begründung auf physiologische und pathologische Gewebelehre. Hirschwald, Berlin
58. Wen GY, Rudelli RD, Kim KS, Wisniewski HM (1988) Tangles of ependyma–choroid plexus contain β-amyloid protein epitopes and represent a new form of amyloid fiber. Arch Neurol 45:1298–1299