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Chemical heterogeneity of amyloid in the carpal tunnel syndrome

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Summary. 140 biopsies from 108 patients afflicted with the carpal tunnel syndrome were studied, 27 of whom showed deposition of amyloid, in 6 of them to such an extent that the amyloid was considered significant in the pathogenesis of the carpal tunnel syndrome. Morphologically, vessels and ligaments were affected and especially the peritendinous structures. As it was always part of generalized amyloidosis, the amyloid in the carpal tunnel consisted immunohistologically of amyloid A in three cases (including one case with simultaneous amyloid deposition of the AA- and the AB-type), of amyloid A$\varkappa$ in one case, of amyloid of prealbumin origin in seventeen cases and of AB-amyloid in eight cases. We also described for the first time the manifestation of generalized senile amyloidosis (ASs) in the carpal tunnel. Deposition of amyloid of β-2-microglobulin type (AB) in the carpal tunnel was particularly frequent and massive.

Key words: Amyloidosis – Carpal tunnel syndrome – Potassium permanganate – Immunohistochemistry – Immunoperoxidase

Introduction

The carpal tunnel syndrome represents a multifaceted condition of varied aetiology and with a pathogenesis which is far from being resolved. The role of amyloid in the carpal tunnel syndrome has been particularly recorded by Bastian (1974); Mohr (1976); and Bjerrum et al. (1984). Various structures in the carpal tunnel are affected in generalized amyloidosis, for instance in plasmocytoma (Glenner 1980a, b; Husby 1983; Pras et al. 1985). A systematic examination of the amyloid in the carpal tunnel structures based on the current biochemically oriented classification of amyloid (Glenner 1980a, b; Cohen and Connors 1987) (see Table 1) has not been previously presented and histochemical and immunohistochemical techniques may aid in further clarifying the chemical nature, the aetiology and the underlying disease in the individual case with amyloidosis. It is the purpose of this paper to report a systematic morphological study on 108 patients afflicted with the carpal tunnel syndrome.

Material and methods

We studied 140 consecutive biopsies of the carpal tunnel retrospectively (unilateral in 76 cases, bilateral in 32 cases) which were obtained between 1975 and 1986 at the Department of Neurosurgery, University of Mainz, FRG. They were scrutinized histologically at the Division of Neuropathology, University of Mainz. Tissue blocks were routinely fixed in 10% neutral formalin and embedded in paraffin. These provided 5 µm thick sections were stained with haematoxylin-eosin, elastica van Gieson, and Congo red according to Puchtler et al. (1962). Yellow-greenish birefringence in polarized light gave evidence of the amyloid.

The degree of amyloidosis was divided into three categories and semiquantitatively evaluated, in that grade I presented scanty speckled amyloid, grade II increased amyloid, and grade III massive occasionally confluent coarsely speckled amyloid.

Histochemically, amyloid containing tissues were treated with $KMnO_4$ according to Wright et al. (1977) which enables the differentiation between $KMnO_4$-sensitive amyloid, i.e., mostly but not exclusively amyloid A, and $KMnO_4$-resistant types of amyloid, i.e. predominantly non amyloid A, as for instance amyloid AL.

Immunhistologically, paraffin sections were digested with pronase followed by application of the avidin biotin method (Polak and van Noorden 1983) and final peroxidase reaction (Taylor 1978; Fujihara et al. 1980; Linke and Nathrath 1980; Levo et al. 1982; Linke 1985; van de Kaa et al. 1986). Our primary antibodies consisted of a mouse monoclonal antibody (mc 1) against amyloid A (Linke 1984, culture supernatant, dilution 1:10), rabbit polyclonal antibodies against light chain

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Table 1. Classification of major amyloid diseases

Type of amyloid	Amyloidogenous protein	Associated clinicopathologic process	Amyloid distribution
AA	Protein AA	Recurrent inflammation malignancies, familial Mediterrarean fever, idiopathic amyloidosis	Generalized
AL	Ig light chain	Immunocyte dyscrasias, idiopathic amyloidosis, extramedullary solitary plasmocytoma	Generalized, localized
AF_p	Prealbumin	Familial systemic amyloidosis, Portuguese type	Generalized
AS_s	Prealbumin	Senile systemic amyloidosis	Generalized
AB	β_2-micro-globulin	Chronic haemodialysis	Generalized
AS_b	β-protein, A_4	Degenerative brain diseases (SDAT etc.)	Organ-limited
AE	Hormone	APUD-endocrine tissue related amyloid	Organ-limited
ASc_2	(atrial natriuretic factor?)	Senile isolated atrial amyloidosis	Organ-limited

AA: Amyloid, type A; AL: Amyloid, immunoglobulin light chain derived, A$\varkappa$- and Aλ-isotypes; AF_p: Amyloid, familial Portuguese type; $AS_{s,\ b,\ c}$: Amyloid, senile type, systemic, brain, cardiac; AB: Amyloid, β_2-microglobulin derived; AE: Amyloid, endocrine type

amyloid of the $\varkappa$ and λ types (dilutions 1:1200 and 1:3000) and against prealbumin (Linke 1982; Linke 1985), the amyloidogenic protein of the systemic senile amyloidosis and the familial amyloidoses (dilution 1:2000).

Rabbit polyclonal antibody against human beta-2 microglobulin (Dakopatts Co., D-2000 Hamburg, dilution 1:250) was used to identify the amyloid of the AB-type which most often is associated with chronic haemodialysis. Antibodies were diluted so that amyloid appeared to be distinct against minimal background staining. Conventional positive and negative controls were prepared. Each specimen that was Congo red positive was tested with each of the above mentioned antibodies.

The individual underlying disease and clinical data associated with amyloid formation were recorded from each patient who had amyloid in his or her carpal tunnel.

Results

The specimens contained parts of the retinaculum flexorum, perineurial fat and connective tissue, peritendinous and synovial structures in varying frequency and composition. Among 140 tissue specimens we found amyloid to a varying degree in 27 cases (19%). Semiquantitatively, amyloid of grade I was present in 8 cases, of grade II in 13 cases, and of grade III in 6 cases.

The amyloid, being Congo red-positive and with yellow-greenish birefringence, had formed small specks or bands within the vessel walls of capillaries, small arteries and veins (Fig. 1c). Large plaques of amyloid marked sections of the media and adventitia of thick veins (Fig. 1d). Small circumscribed specks of amyloid were also found around capillaries in fat (Fig. 1e) and partially embedded in the loose vascularized connective tissue along the internal surface of tendinous sheaths and synovia (Fig. 1a, b).

Disseminated amyloid was also encountered in the connective tissue amongst tightly packed collagen, for instance in the retinaculum flexorum, where the external surface of collagen bundles was particularly affected. Occasionally, however, a massive diffuse deposition of amyloid was also seen (Fig. 1f).

Ten specimens were sensitive to $KMnO_4$, 17 were resistant (Table 2). Two of the 10 sensitive specimens were completely decolored of Congo red indicating amyloid of the AA-type. This result correlated with the information that one patient had systemic amyloidosis associated with rheumatoid arthritis whilst in the other patient no amyloid A inducing disease was found (idiopathic AA-amyloidosis). The remaining 8 Congored-positive specimens were reduced in Congo red binding to a degree that they had to be classified als $KMnO_4$-sensitive. They were all from patients who had undergone chronic haemodialysis. In one of these cases two different types of amyloid (AA-amyloid and AB-amyloid) were later detected immunohistochemically. The $KMnO_4$-method failed in distinguishing both types because they both were found to be sensitive towards $KMnO_4$. Of the 17 $KMnO_4$-resistant only one belonged to a patient affected by a plasmocytoma of the light chain kappa type while in the remaining 16 patients no association between the amyloid and the underlying disease was apparent.

Applying the five antibodies directed against amyloid resulted in a positive reaction in each of the histochemically proven amyloid specimens, thus classification of the amyloid was possible in each specimen (Table 2). In two cases and one case

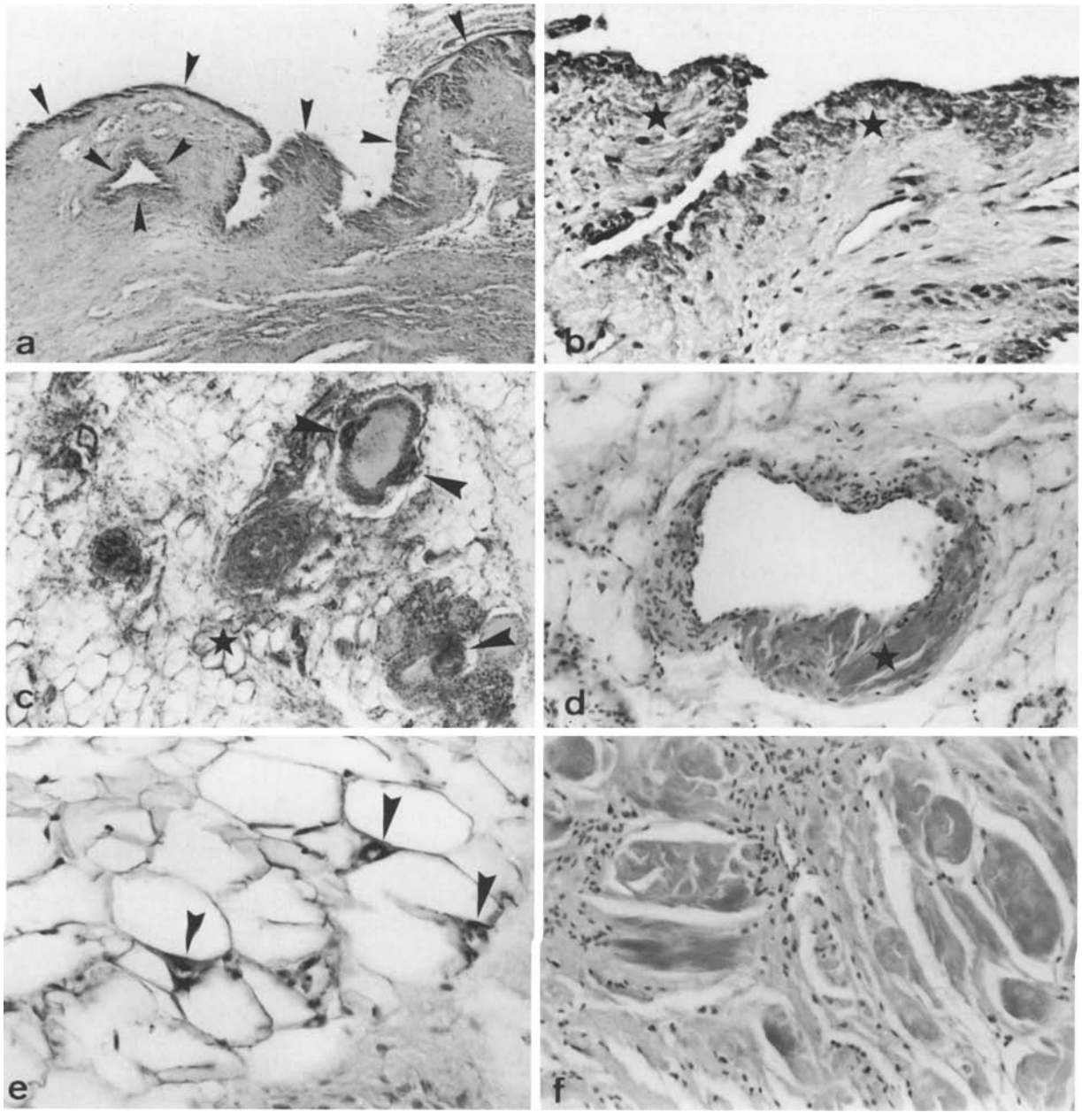

Fig. 1a. Peritendineum of a patient with chronic haemodialysis, superficial band-like amyloid infiltration (▾), grade III, Congo red, ×70; **b** Peritendineum of a patient with chronic haemodialysis, superficial band-like amyloid infiltration (*), grade III, Congo red, ×280; **c** Fatty tissue in senile systemic amyloidosis with spotty amyloid infiltration of veneous vessel walls (▾) and interstitial amyloid infiltration around fat cells (*), grade III, Congo red, ×70; **d** Spotty amyloid infiltration of a veneous vessel wall in senile systemic amyloidosis (*), grade III, Congo red, ×180; **e** Fatty tissue with amyloid deposits around small capillaries (▾) in amyloidosis AA type, grade III, Congo red, ×280; **f** Amyloid accumulation in collagen bundles of the retinaculum flexorum, in amyloidosis of the AL (kappa) type, grade III, Congo red, ×180

of simultaneous amyloid deposition (as described before) the amyloid was labelled with the anti-AA-antibody (Fig. 3e), in principle corresponding to histochemical $KMnO_4$-sensitivity. One specimen labelled with the A$\varkappa$-antibody was also $KMnO_4$-resistant and showed the most intensive deposition (grade III) within vessel walls (Fig. 3a), synovial areas (Fig. 2a, c) and the bundles of collagen fibrils. The anti-Aλ antibody failed to react with any amyloid, apparently because this type of amyloid was not present among our material. In specimens the amyloid reacted with the anti-AF-antibody corresponding to histochemical $KMnO_4$-resistance, both in small mural plaques of vessels

Table 2.

Case	Patient	basic disease	Age	Amyloid grade	$KMNO_4$	Anti AA	Anti Aκ	Anti Aλ	Anti AF/ASs	Anti AB
1	1	diabetes mellitus	56	I	sensitive	+	–	–	–	–
2	2	rheumatoid arthritis	63	II	sensitive	+	–	–	–	–
3	3	plasmocytoma	76	III	resistant	–	+	–	–	–
4	4	unknown	55	II	resistant	–	–	–	+	–
5	4	unknown	55	II	resistant	–	–	–	+	–
6	5	arteriosclerosis	85	III	resistant	–	–	–	+	–
7	6	arteriosclerosis	66	I	resistant	–	–	–	+	–
8	7	arteriosclerosis	78	I	resistant	–	–	–	+	–
9	8	unknown	74	I	resistant	–	–	–	+	–
10	9	coxarthropathy	58	II	resistant	–	–	–	+	–
11	9	coxarthropathy	66	II	resistant	–	–	–	+	–
12	10	degenerative arthritis	73	I	resistant	–	–	–	+	–
13	11	diabetes mellitus	70	I	resistant	–	–	–	+	–
14	12	arteriosclerosis	73	II	resistant	–	–	–	+	–
15	13	carcinoma of the pancreas	68	I	resistant	–	–	–	+	–
16	14	spondylopathy	72	II	resistant	–	–	–	+	–
17	15	arteriosclerosis	83	II	resistant	–	–	–	+	–
18	16	cardiopathy	79	II	resistant	–	–	–	+	–
19	17	carcinoma of the prostate	75	I	resistant	–	–	–	+	–
20	18	haemodialysis	56	II	sensitive	–	–	–	–	+
21	18	haemodialysis	56	II	sensitive	–	–	–	–	+
22	19	haemodialysis	78	III	sensitive	–	–	–	–	+
23	19	haemodialysis	78	III	sensitive	–	–	–	–	+
24	20	haemodialysis	54	III	sensitive	–	–	–	–	+
25	21	haemodialysis, M. Bechterew	43	III	sensitive	+	–	–	–	+
26	22	haemodialysis	48	II	sensitive	–	–	–	–	+
27	23	haemodialysis	69	II	sensitive	–	–	–	–	+

(Fig. 3b–d) and in one instance in an especially pronounced manner within collagenous connective tissue (Fig. 3c). Amyloid in eight specimens showing weak $KMnO_4$-sensitivity and being marked by anti-beta-2- microglobulin antibody in patients who had undergone chronic haemadialysis (see above) had diffusely infiltrated the peritendineum (Fig. 2b) and the retinaculum flexorum (grades II or III, respectively) (Fig. 3f). The antibody also marked subtle deposits along the muscular lamina basalis or the vascular medial layer. In one of these patients chronic haemadialysis had been performed because of renal insufficiency due to histologically confirmed amyloidosis associated with Bechterew's disease (amyloid A). The carpal tunnel tissue of this patient, however, did contain both, small amounts of amyloid of the AA-type in small vessel walls and large amounts of amyloid of the AB-type in the peritendineous tissue.

Discussion

In the past, Bastian (1974); Mohr (1976); and Bjerrum et al. (1984) have reported on amyloid deposits in the carpal tunnel, indicating a frequency of 2% to 8%. By contrast, our unselected material gave an incidence of 19%, possibly because of methodological differences (step-sections, selection of patients). The problem of the quantity of the amyloid seen in the specimens studied is also closely related to section techniques. Based on our semiquantitative results, 8 specimens showed grade I, 13 specimens grade II, and 6 specimens grade III. All were in individual sections infrequently associated with extensive amyloid deposits.

What is the significance of the amyloid deposits as regards the pathogenesis of the carpal tunnel syndrome? When amyloid is massively deposited (grade III) it is conceivable that the effect of a mass with subsequent narrowing of the carpal tunnel may impart direct mechanical damage on the median nerve. Conversely, in grade I with amyloidosis with only single plaques or groups of plaques this mechanism appears unlikely. In these instances, we consider the deposition of amyloid an epiphenomenon that is associated with the idiopathic carpal tunnel syndrome or the coincidence of two independent diseases lasting in carpal tunnel syndrome.

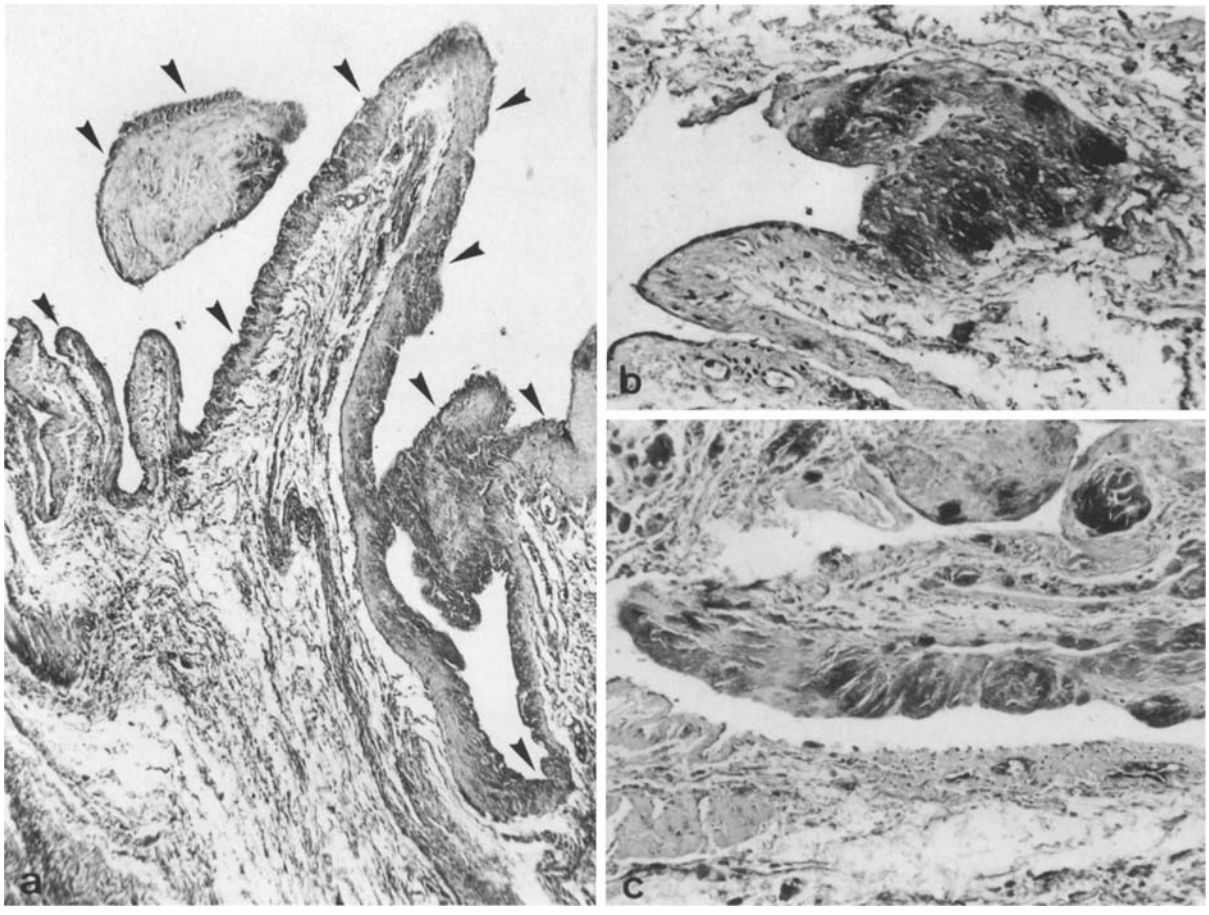

Fig. 2a. Peritendineum with band-like superficial amyloid deposits (▾), grade III, staining with an anti-amyloid light chain kappa antibody, peroxidase reaction, ×55; **b** Peritendineum with spotty superficial amyloid deposits, grade III, staining with an anti-β-2-microglobulin-antibody, peroxidase reaction, ×180; **c** Peritendineum with spotty superficial amyloid deposits, grade III, staining with an anti-amyloid light chain kappa antibody, peroxidase reaction, ×110

How may our findings conform with the currently valid concept of amyloidosis? (Glenner 1980; Schneider and Thoenes 1982; Cohen and Connors 1987). This is based on biochemical differences of the amyloid fibrils and the underlying associated diseases (Table 1). The different amyloidogenic proteins mark a certain type of amyloid like AA, AL, AFp, ASs, and AB, which most often develops as part of a generalized amyloidosis while types ASb, AE, and ASc2 are characterized by organ limited amyloid deposits. The latter types are without significance in amyloid of the carpal tunnel and are only enumerated for the sake of completeness.

The first typing of amyloid in the carpal tunnel was carried out by the histochemical $KMnO_4$-treatment, according to Wright et al. (1977) which differs between sensitive and resistant types of amyloid. We found two $KMnO_4$-sensitive specimens (loss of Congo-red staining), which were, according to the literature (van Rijswik and van Heusden 1979) classified as AA amyloid. Of the remaining specimens, we found 17 to be $KMnO_4$-resistant as occurs in plasma cell dyscrasia associated with amyloidosis of the AL type and in the familial and senile systemic amyloidoses of AFp-ASs-type (Pitkänen et al. 1984; Kitamoto et al. 1985, 1986). In eight cases, classification with the $KMnO_4$ technique was difficult because, in spite of considerable alteration of color intensity ($KMnO_4$-sensitivity), there was still some remaining colorability with Congo red and yellow-greenish birefringence in polarized light, so that this type can be classified as weak $KMnO_4$-sensitive. It is remarkable to note that the patients who contributed these eight specimens all had undergone haemodialysis. Thus, our study confirms those of Gorevic et al. (1985); Morita et al. (1985) and Shirahama et al. (1985). Applying modern immunohistochemical techniques allows us, when using re-

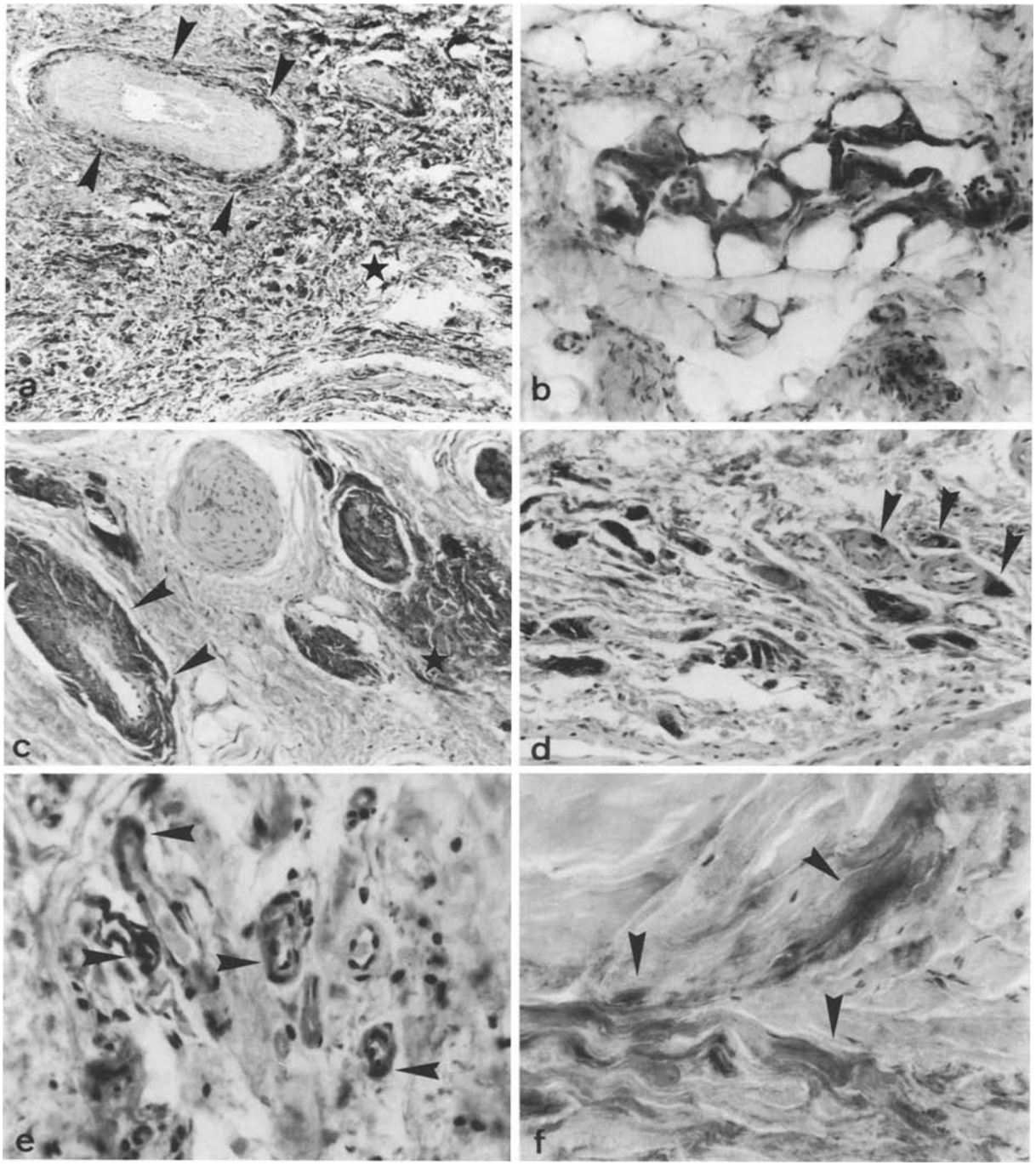

Fig. 3a. Perivascular (adventitial) (▾) and diffuse interstitial (*) amyloid deposition in the peritendineous connective tissue, grade III, staining with an anti-amyloid light chain kappa antibody, peroxidase reaction, × 70; **b** Fatty tissue with interstitial (pericapillary) amyloid infiltration, grade III, staining with an anti-amyloid prealbumin antibody, peroxidase reaction, × 180; **c** Severe and diffuse amyloid infiltration in and around vessel walls (▾) and in the surrounding connective (collageneous) tissue (*), grade III, staining with an anti-amyloid prealbumin antibody, peroxidase reaction, × 110; **d** Spotty amyloid infiltration in the walls of small vessels and capillaries (▾), grade III), staining with an anti-amyloid prealbumin antibody, peroxidase reaction, × 180; **e** Band-like amyloid deposits around small capillaries (▾) in the peritendineum connective tissue, grade II, staining with an anti-amyloid A antibody, peroxidase reaction, × 360; **f** Spotty amyloid deposits in the collagen tissue (▾), grade II, staining with an anti-β-2-microglobulin antibody, peroxidase reaction, × 280

spective antibodies, to type amyloid within the tissue according to the biochemical classification (Fujihara et al. 1980; Linke and Nathrath 1980; Levo et al. 1982; Linke 1985; van de Kaa et al. 1986). So far, single communications have reported on amyloid in the carpal tunnel in plasma cell dyscrasia associated with AL-amyloidosis (Glenner 1980a, b; Husby 1983; Pras et al. 1985) in single forms of hereditary amyloid neuropathy (Lambird and Hartmann 1969) and furthermore more recently in haemodialysis patients (Jain et al. 1979; Assenat et al. 1980; Emery et al. 1983; Schwarz et al. 1984a, b; Walts et al. 1985).

Our systematic studies, however, revealed that in principle amyloid of chemically different types may be found in the carpal tunnel. We thus observed type A amyloid in three patients within capillary walls and at the margin of collagen bundles of the retinaculum flexorum, corresponding to the $KMnO_4$-sensitivity. In two of these cases a typical amyloid inducing basic disease existed (rheumatoid arthritis, Bechterew's disease) whilst one case remained unresolved in this point. In accordance with Husby (1983), 20% of patients with AL amyloidosis are to develop a carpal tunnel syndrome, thus we expected a numerable amount of cases in our biopsies investigated. Surprisingly among our 27 cases with carpal tunnel amyloid we only found one patient with an A$\varkappa$ amyloid immunohistochemically and none with an Aλ amyloid. In this instance, the massive deposition of amyloid (grade III) with diffuse infiltration in all morphological components of the carpal tunnel was particularly remarkable, characteristic of cases with massive amyloid production and tissue concentration (Schneider 1980).

Amyloid of the prealbumin-type represents the largest group of our specimens from the carpal tunnel (16 cases). The anti-AF-antibody we used is directed against the amyloidogenic protein prealbumin, the different fragments of which have been demonstrated in familial amyloid neuropathy (Skinner and Cohen 1981; Dalakas and Engel 1981; Wallace et al. 1986) and in senile (systemic) amyloidosis (Sletten et al. 1980; Linke 1982; Pitkänen et al. 1984; Cornwell et al. 1987). A peak is found in the seventh decade in our patients indicating that these had systemic senile amyloidosis, especially as there was no clinical evidence of a familial amyloid neuropathy. Only in the two younger patients (55 and 58 years old) might an early manifestation of systemic senile amyloidosis be considered. This is mainly marked by perimyo- and pericytic deposition of amyloid in small blood vessels, in heart, and lungs (Störkel et al. 1983). Localisation of amyloid of this type within the carpal tunnel has not yet been reported.

Recently, deposition of amyloid in the carpal tunnel has been reported from patients undergoing chronic haemodialysis (Jain et al. 1979; Assenat et al. 1980; Emery et al. 1983; Schwarz et al. 1984a, b; Walts et al. 1985). The frequency is reported between 50 and 100%. Eight out of 12 of our specimens from patients undergoing haemodialysis contained amyloid. We always found marked deposition of amyloid (grades II and III), which followed the mode of deposition already described as obvious thickening amyloid infiltration especially of the tendinous sheaths. This may be of pathogenetic significance in the development of the carpal tunnel syndrome.

Studies by Gorevic et al. (1985); Morita et al. (1985); Shirahama et al. (1985); Gejyo et al. (1985); Connors et al. (1985) Chanard et al. (1986) and Linke et al. (1986, 1987) demonstrated that the non-dialysable and thus accumulating protein beta-2-microglobulin with a molecular weight of 11.8 kilo-dalton and fragmented β-2-microglobulin represents the amyloidogenic protein in patients undergoing chronic haemodialysis. Moreover it has been found in amyloid kidney stones of uraemic patients prior to chronic haemodialysis (Linke et al. 1986).

Deposits of amyloid have also been described in the synovia of large joints and in bones (Bardin et al. 1985; Huaux et al. 1985; Herve et al. 1985; Munoz-Gomez et al. 1985; Di Raimondo et al. 1986; Casey et al. 1986; Fenves et al. 1986) and one may assume that this represents a new type of generalized amyloidosis. In the context of our study, it is interesting to note that one patient on haemodialysis with renal biopsy-proven generalized amyloidosis of the AA-type had small amounts of amyloid of the AA-type and large plaques of the beta-2-microglobulin type in his carpal tunnel indicating a preferential localisation of the latter type of amyloid within the carpal tunnel.

In summary we may state that 19% of patients afflicted with a carpal tunnel syndrome have amyloid in their carpal tunnel, that marked deposits of amyloid (grade III) were found in 22% of the positive cases. Only these massive deposits are considered significant in the aetiopathogenesis of the carpal tunnel syndrome.

Amyloid within the carpal tunnel only occurs associated with generalized amyloidosis, and the deposits of amyloid are precisely typable immunohistochemically. Involvement of the carpal tunnel in association with generalized senile amyloidosis is described here for the first time. Immunohisto-

chemical typing of the amyloid allows conclusions on hitherto unknown underlying diseases.

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