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Thickness of endoneurial vessel basal lamina area in chronic idiopathic axonal polyneuropathy

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Abstract For chronic idiopathic axonal polyneuropathy (CIAP), even after extensive evaluation, no cause has yet been found. Considering the age and sex distribution of patients with this disease, it is possible that vascular disease plays a role in the development of this polyneuropathy. As endoneurial vessel abnormalities can be related to ischemia, we investigated endoneurial vessels in sural nerve biopsies of 18 patients with CIAP. As controls we used sural nerves of 4 patients with diabetes mellitus, 6 patients with hereditary motor and sensory neuropathy type II (HMSN type II) and 10 autopsy cases. Basal lamina area thickness, endothelial cell area, lumen area, and the number of basal laminae, endothelial cells and periendothelial cell nuclei were investigated. Basal lamina area thickness, endoneurial cell area and number of endothelial cell nuclei in CIAP were increased in comparison with HMSN type II, whereas the basal lamina area thickness of patients with CIAP and diabetes mellitus were in the same range. The structure of the basal lamina area in CIAP differed from diabetes mellitus; in diabetes mellitus there was a larger number of lamellae, whereas in CIAP there was an increase in collagen. There was no correlation between basal lamina area thickness and age. In CIAP patients with peripheral vascular disease of the legs, basal lamina area thickness was increased. The relation between basal lamina area thickening and peripheral vascular disease of the legs in CIAP may indicate a role for ischemia in the development of this polyneuropathy.

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Introduction

In a substantial number of elderly patients with axonal neuropathy, no cause can be found after extensive evaluation [6, 23]. We have denominated this condition chronic idiopathic axonal polyneuropathy (CIAP). In our group of patients with CIAP, the mean age of onset was 56.5 years and there was a male predominance [27]. Given the occurrence of peripheral vascular disease in elderly patients [5, 32], it can be hypothesized that ischemia plays a role in the development of CIAP.

Ischemia is thought to play a role, together with metabolic abnormalities, in the development of diabetic neuropathy. The observed multifocal myelinated fiber loss in diabetic neuropathy is considered as indicative for ischemic neuropathy [8]. Abnormalities of endoneurial vessels such as basal lamina area thickening and endoneurial cell hypertrophy have been documented in diabetes mellitus [4, 8, 10, 13, 14, 17, 21, 22, 24, 36, 37, 38], and a positive correlation between these vessel wall abnormalities and severity of diabetic neuropathy has been found [14]. Basement membrane thickening is also observed in other conditions in which ischemia is thought to be an important pathogenic factor, such as hypoxic neuropathy in chronic obstructive pulmonary disease [2, 28], and peripheral arterial disease of the legs [9, 29].

To find out whether increased thickness of the basal lamina area was present in CIAP, we measured the endoneurial vessels in sural nerve biopsies of 18 patients with CIAP. We searched for endoneurial vessel wall abnormalities and determined the distribution of myelinated fiber loss. Results were compared with sural nerves of 4 patients with diabetes mellitus with a distal symmetric sensory polyneuropathy, 6 patients with hereditary motor and sensory neuropathy type II (HMSN type II), in which a vascular pathogenesis is unlikely, and 10 autopsy con-

trols without a neuromuscular or vascular disease. In addition, we determined the presence of vascular disease in patients with CIAP to investigate a relationship between basal lamina area thickness and clinical symptoms and signs of vascular disease.

Patients and methods

Patients

Sural nerve biopsy specimens from 18 patients with CIAP, 4 patients with diabetes mellitus, and 6 patients with HMSN type II as well as sural nerves from 10 autopsy controls, matched for age, were included in this study (Table 1). In all CIAP patients polyneuropathy was characterized by axonal degeneration and no cause was found after extensive clinical and laboratory evaluation [27]. Diabetes mellitus was chosen as a control group because endoneurial vessel abnormalities have been described in this condition [4, 8, 10, 13, 14, 17, 21, 22, 24, 36, 37, 38]. HMSN type II was chosen because in this hereditary polyneuropathy a vascular pathogenesis is unlikely, and there is axonal degeneration, as in CIAP. The medical records of the autopsy controls were reviewed; patients with either vascular diseases or diseases that may cause polyneuropathy (i.e., diabetes mellitus) were excluded. The cause of death of the autopsy controls examined was carcinoma without signs of polyneuropathy in 5 patients, acute infection in 3 patients and road accidents in 2 patients. The 4 patients with diabetes mellitus all had a symmetrical distal sensory polyneuropathy. HMSN type II was definitely diagnosed according to standard criteria [15, 34]. The study was approved by the ethics committee of our hospital and all patients gave informed consent prior to their inclusion in the study.

Vascular evaluation

In 18 patients with CIAP an extensive vascular history was taken. Manifest vascular disease was defined as the prevalence of ischemic cardiac disease or stroke. The ankle brachial index (ABI) was determined as an indicator for peripheral arterial disease. The ABI is the ratio between the systolic blood pressure in the ankle and in the arm. An ABI of over 1.00 is considered as normal. An ABI below 0.95 at rest or after exercise was considered as an indicator for (asymptomatic) peripheral arterial disease.

Biopsies

Sural nerve biopsy specimens were taken at the level of the ankle and part of the sample was fixed in 2% buffered glutaraldehyde, postfixed in osmium tetroxide and embedded in Epon. In the autopsy controls, the sural nerve was taken at less then 24 h postmortem (mean postmortem time 11.5 h, SD 6.4 h). Transverse 1-μm sections were stained with p-phenylenediamine for light microscopy. Transverse ultrathin sections of a representative area of the 1-μm sections were stained with uranyl acetate and lead citrate and viewed in an electron microscope (Jeol). All endoneurial and subperineurial vessels identified in the EM sections were photographed at a magnification of × 1,500–4,000, adjusted to the size of the vessel. Vessels that were cut obliquely, i.e., if the ratio between the largest and smallest diameter differed more than 1 : 3, were excluded [13].

Table 1 Patient characteristics. Data are expressed as means with SD in parentheses (*CIAP* chronic idiopathic axonal polyneuropathy, *DM* diabetes mellitus, *HMSN II* hereditary motor and sensory neuropathy type II, *mf* myelinated fibers)

Diagnosis	CIAP	DM	HMSN II	Autopsy controls
Age (years)	63.0 (7.1)	64.3 (13.5)	56.8 (11.6)	65.5 (9.6)
Male/female	15/3	3/1	4/2	7/3
Density of mf	4332 (946)	3403 (1930)	3340 (967)	5900 (1498)

Morphometry

Electron micrographs of patients and controls were mixed and blinded for the diagnosis. The circumference of the lumen, endothelial cells and the total vessel were drawn on the photos and measured with a digitizing tablet connected with a personal computer. The area of the measured objects was calculated using Sigma Scan software. Basal lamina area thickness (BLAT) was calculated by subtraction of the radius of a circle equivalent of lumen and endothelial area (EA), from the radius of a circle equivalent of the total vessel area (VA) ($BLAT = \sqrt{VA/\pi} - \sqrt{EA/\pi}$).

The endothelial cell area was calculated by subtraction of the lumen area from the endothelial and lumen area. The numbers of endothelial and periendothelial cell nuclei were counted in every vessel. Basal laminae were counted at four different sites: two at the longest and two at the shortest axis; the mean number of laminae was calculated. Using the light microscope, the endoneurial vessel density was calculated by counting the number of endoneurial vessels and measuring the total intrafascicular area in slides with cross-sections of the whole biopsy. In these sections, the densities of myelinated nerve fibers were calculated and the distribution of different myelinated fibers was studied, as multifocal myelinated fiber loss is considered a hallmark of ischemic neuropathy [7]. To measure the variability of myelinated fiber density, the index of dispersion (ID) and coefficient of variation (CV) were calculated, according to Dyck et al. [7]. Briefly, the nerve was divided in square frames with an area of 2,434 μm^2. In every third square the number of myelinated fibers was counted. One third of the fascicles of every biopsy was measured. The ID was calculated as $ID = A_H s^2/x$, where A_H is the harmonic mean of the frame areas, and x and s the mean and standard deviations of the densities. The CV was calculated as $CV = s/x$.

Data analyses

The number of photographed vessels per patient varied between 4 and 13. To consider an equal number per patient in the analysis, 4 vessels of each patient were chosen with help from a random digit table. A Kruskal-Wallis analysis for non-parametric values was used for analysis of the differences in four groups. Mann-Whitney U test for non-parametric values was used for analysis of subgroups (SPSS, Illinois).

Results

Light microscopy

All patients with CIAP, HMSN type II and diabetes mellitus had a myelinated fiber loss of predominantly large myelinated fibers, indicative of axonal degeneration. The myelinated fiber densities of the autopsy controls were in the same range as densities found by Jacobs and Love [16] in controls of the same age (Table 1). The ID and CV of all patient groups indicated a random distribution of myelinated fiber loss. Capillary density of endoneurial

Table 2 Results from Kruskal-Wallis analysis for non-parametric values. Data are expressed as medians or means and SD (in parentheses) (*BLAT* basal lamina area thickness, *EA* endothelial cell area, *LA* lumen area, *lam* number of lamellae, *EN* endothelial cell nuclei, *PN* periendothelial cell nuclei, *Cap dens* capillary density, *ID* index of dispersion, *CV* coefficient of variation)

	CIAP	DM	HMSN II	Autopsy controls	*P* value
Median BLAT	3.9	3.9	2.7	2.9	0.03
Median EA	36.3	42.8	24.1	53.0	0.009
Median LA	20.1	21.1	10.6	24.6	NS
Median lam	3.8	5.4	3.3	3.4	0.06
Median EN	1	2	1	1	0.03
Median PN	1	0.5	1	0.5	NS
Cap dens	17.1 (3.4)	17.6 (7.5)	17.8 (3.9)	19.7 (4.7)	NS
ID (SD)	0.98 (0.25)	1.36 (0.80)	1.43 (0.46)	1.01 (0.39)	NS
CV(SD)	0.38 (0.06)	0.56 (0.24)	0.40 (0.10)	0.35 (0.11)	NS

vessels in the whole biopsy was similar among all patient groups (Table 2).

Electron microscopy

In the 18 CIAP patients, 146 vessels (mean 8.7, SD 2.4, per patient), in 4 diabetes mellitus patients, 35 vessels (mean 8.8, SD 0.96, per patients), in 6 HMSN patients, 49 vessels (mean 8.2, SD 3.1, per patient) and in 10 autopsy controls, 79 vessels, (mean 7.9, SD 2.2, per patient) could be identified. There was a difference in basal lamina area thickness according to a Kruskal-Wallis analysis (P = 0.03) (Table 2). In a subgroup analysis, there was a statistically significant difference between basal lamina area thickness of CIAP and HMSN type II patients (P = 0.01). The difference between CIAP and controls showed a trend towards a larger basal lamina area thickness in CIAP (P = 0.08). The basal lamina area thickness of CIAP and diabetes mellitus were in the same range, but there was a trend towards a larger number of lamellae present in the basal lamina area in diabetes mellitus (P = 0.07), whereas in CIAP the increase of the basal lamina area thickness consisted more of collagen. The difference in basal lamina area structure between CIAP and diabetes is shown in Fig. 1 a and b. A trend towards a difference in the number of lamellae was also found among all patient groups (P = 0.06) (Table 2). The number of lamellae was larger in CIAP than in HMSN type II (P = 0.04), and similar to that in autopsy controls. There was also a difference between the number of endothelial cell nuclei (P = 0.03) (Table 2). A larger number of endothelial cell nuclei was found in CIAP than in HMSN type II and autopsy controls (P = 0.05) and a similar number in comparison with diabetes mellitus. There was a difference between endoneurial cell area among the four groups (P < 0.01). In the subgroup analysis, there was a trend towards a smaller endothelial cell area in CIAP in comparison with autopsy controls. The enlargement of the endothelial cell area in autopsy controls is probably due to postmortem swelling. Endothelial cell area between CIAP and diabetes mellitus was similar, but larger than that in HMSN type II. There was no difference in lumen area among the four groups. There was no relation between basal lamina area thickness and amount or type of myelinated fiber loss.

No difference was found between basal lamina area thickness of patients younger or older than 60 years.

Vascular disease

Thirteen (72%) of the CIAP patients showed evidence of vascular disease; 10 (56%) had manifest vascular disease [6 (33%) with cardiac disease and 4 (22%) with cerebral ischemia], 3 (17%) had an abnormal ABI, and 4 (22%) had both manifest vascular disease and abnormal ABI. Four (22%) patients had only risk factors for vascular disease and one (6%) had no signs of vascular disease. The basal lamina area thickness of patients with and without abnormal ABI is shown in Fig. 2. The basal lamina area thickness was enlarged in CIAP patients with a lowered ABI (P < 0.01), but was similar in patients with and without manifest vascular disease.

Discussion

In this study, endoneurial vessels of the sural nerves of patients with CIAP were compared with those of patients with diabetes mellitus, HMSN type II and autopsy controls. The basal lamina area of endoneurial vessels was enlarged in CIAP in comparison with HMSN type II and autopsy controls, while basal lamina area thickness in CIAP and diabetes mellitus was in the same range. The endothelial cell area and the number of endothelial cell nuclei were increased in CIAP compared with HMSN type II and similar to those in diabetes.

The structure of the vessel walls seemed to vary between CIAP and diabetes mellitus; there was a larger number of continuous lamellae in diabetes mellitus, while in CIAP, the basal lamina area thickening seemed more homogeneous (Fig. 1 a, b). This difference in structure of the basal lamina area has also been found in a study comparing diabetes mellitus and HMSN type I, where the basal lamina area was enlarged in both conditions, but the laminae were more discontinuous in HMSN type I [3]. Lamina reduplication of the endoneurial vessel wall has often been described in diabetes mellitus [14]. The exact mechanism of this phenomenon is unknown, but resistance to proteolytic degradation has been given as an ex-

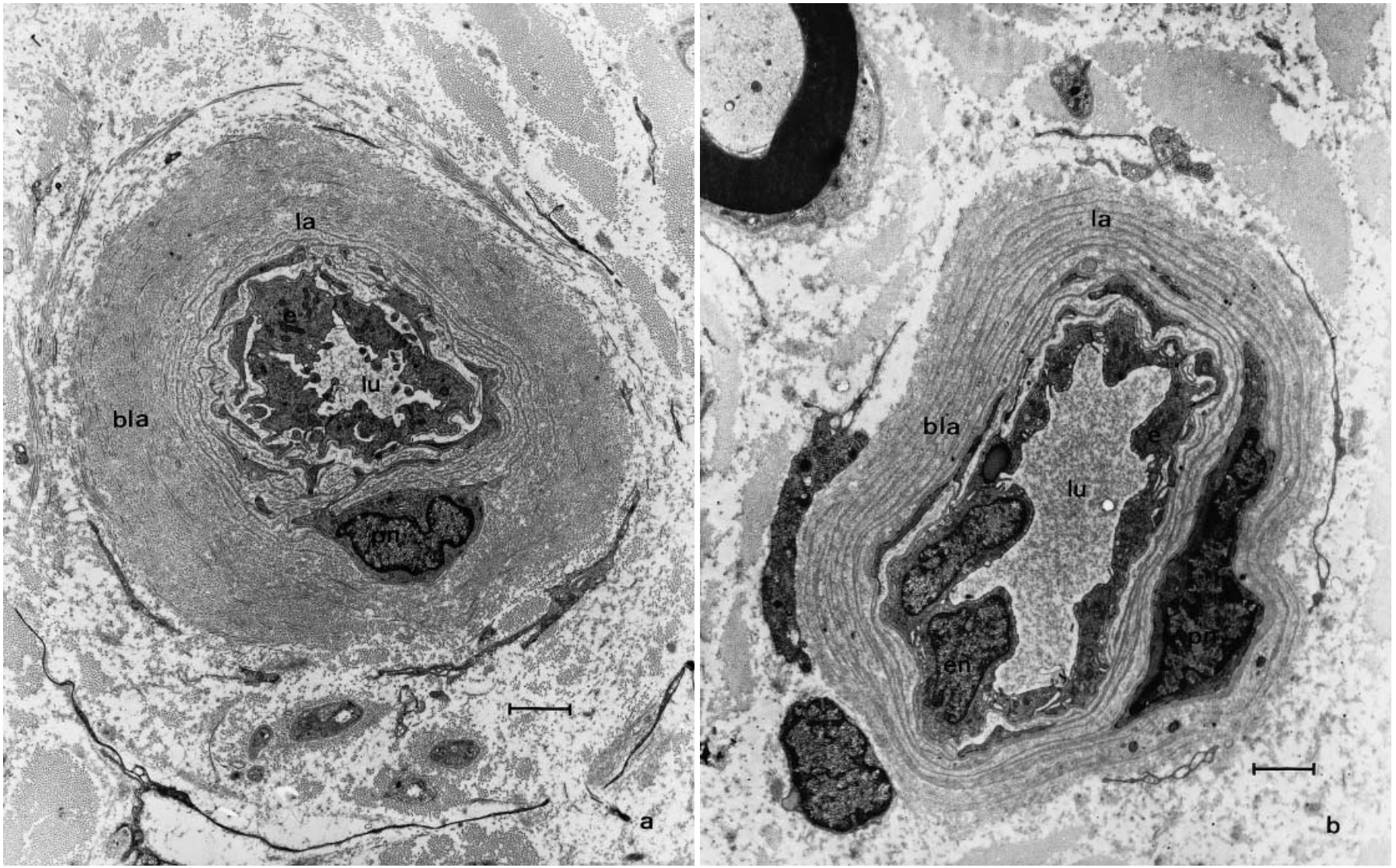

Fig. 1 **a** Endoneurial vessel of patient with CIAP and **b** with diabetes mellitus. Note the difference between number of laminae in the enlarged basal lamina area (*lu* lumen, *e* endothelial cell, *en* endothelial cell nucleus, *pn* periendothelial cell nucleus, *la* lamina, *bla* basal lamina area. *Bars* **a**,**b** 2 μm

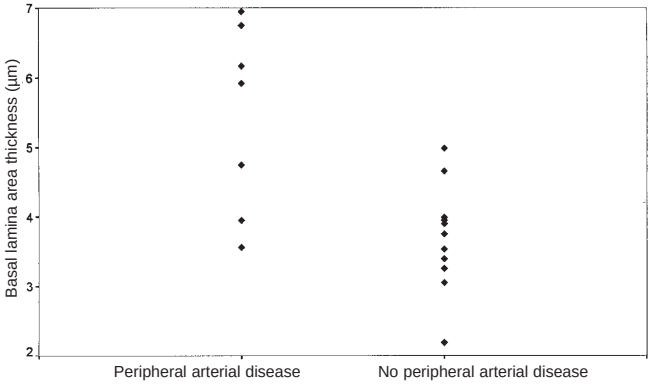

Fig. 2 Basal lamina area thickness in patients with and without peripheral arterial disease

planation for this persistence of laminae in diabetes mellitus [18]. Possibly, the metabolic derangements which are present in diabetes mellitus, but not in CIAP and HMSN type I, form an explanation for these differences in structure.

Endoneurial vessel abnormalities have been observed in a number of conditions, in many of which ischemia and hypoxia play a role, such as hypoxic neuropathy in chronic obstructive pulmonary disease [2, 28], almitrine neuropathy in chronic obstructive pulmonary disease [11] and peripheral arterial disease [9, 29]. However, the same abnormalities of the endoneurial vessel have also been described in conditions in which ischemia is not likely, e.g., polyneuropathy associated with paraproteinemia [25, 31, 33], where an immune reaction in the vessel wall is considered as the pathophysiological mechanism [20, 26] and in HMSN type I [3]. The mechanisms leading to endoneurial vessel wall abnormalities such as basal lamina area thickening and increased endoneurial area are still unknown and are probably heterogeneous, considering the variety of conditions in which they are observed. Endoneurial vessel wall abnormalities may alter the blood nerve barrier causing increased capillary filtration of albumin [35], IgG and IgM [30]. Together with an increased diffusion distance this could then cause damage to the endoneurium. In diabetes mellitus, it has been observed that the development of endoneurial vessel wall abnormalities precedes the development of diabetic neuropathy [14], and that axonal degeneration did not cause basal lamina area thickening [1]. These findings suggest that basal lamina area thickening is not a secondary phenomenon to neuropathic changes in the peripheral nerve.

Basal lamina area thickening does not seem to be related to normal aging. Giannini and Dyck [12] could not find a relation between age and basal lamina area thickness in sural nerves of a control group with a mean age of 35 years, (range 20–66 years). Jacobs and Love [16] described an association between lamina reduplication and age over 60 years, but did not observe obvious basal lamina area thickening. In our study also, no relation between age and basal lamina area thickness was found.

Could hypoxia induce basal lamina area enlargement? The observations in chronic obstructive pulmonary disease [2, 28] and peripheral arterial disease [9, 29] are in agreement with this hypothesis. In our study, there was a large variation among basal lamina area thickness in patients with CIAP. It was remarkable that an increased basal lamina area thickness was more often present in patients with (subclinical) peripheral arterial disease.

Clustering of myelinated fiber loss, as is seen in experimental neuropathies of an ischemic nature [7] and to a lesser extent in diabetes mellitus [8], is considered indicative for ischemic neuropathy. It is, however, uncertain if this finding is a sign for ischemia, since it has also been observed in patients with HMSN type I [19]. In our study, we could not demonstrate a spatial loss of myelinated fibers in any of the groups.

In conclusion, our study shows that the basal lamina area and endothelial cells of endoneurial vessels are enlarged in patients with CIAP compared with controls and that the abnormalities are in the same range as in diabetes mellitus. The significance of these findings is, however, not certain. Endoneurial vessel wall abnormalities are often found in conditions in which ischemia plays a role in the development of the polyneuropathy. In our study the basal lamina area was enlarged in patients with (subclinical) peripheral arterial disease. These results may, therefore, indicate a role for ischemia in the development of CIAP.

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