Localization, structure and atomar composition of calcifications in temporal arteries

Sirs,

We read with interest the article on calcification of the elastic membrane in temporal arteries (1). Since we recently performed similar investigations, we want to communicate briefly some of our findings that support and expand these observations. Moreover, we want to restrict the interpretation of Nordborg *et al*. (1).

We investigated 92 biopsies of non-arteritic temporal arteries from 61 females and 31 males. In alizarin red-S stained paraffin sections the localization and amount of calcifications were estimated and the mineral component was characterized by ultrastructural investigations and X-ray microanalysis.

Table I exhibits that calcifications were absent in 26% females and 19% males. Predominantly focal or diffuse granular mediacalcinosis, not mentioned by Nordborg *et al.* (1), was observed. In its diffuse form this calcification is characterized by tiny alizarin red granules distributed throughout the muscular wall (Fig. 1 a,b), as formerly described by Fritsch (2). Transmission electron microscopically they represent calcospherites,often composed of irregular small crystals arranged in concentric laminae comparable to Liesegang rings (Fig. 1c); roundish calcospherites of different size are seen with the scanning electron microscope (Fig. 1d). By X-ray microanalysis the granules consist preferentially of calcium and phosphorus with a Ca-P-ratio of 1.6. Furthermore, they are characterized by an unusual high content of magnesium (5.6 atom%) indicating a composition of Whitlockite (3). With increasing age these granules are more often associated with the internal elastic membrane (Table I): aggregates of alizarin red granules conceal this membrane (Fig. 1a). In older individuals lumps of calcifications are present in this region (Fig. 1b). By scanning electron microscopy we found that these sheets are composed of aggregated calcospherites, as they appear isolated in the media (Fig. 1e). These solid calcifications exhibit a calcium and phosphorus content similar to the medial granules; however, they contain lower magnesium values of about 1.5 atom% which nearly corresponds to the composition of bone minerals (4). Mediacalcification imitating Mönckeberg's disease was encountered in 2 biopsies, thus supporting its rarity as described by Castillo *et al.* (5). From Table I no obvious differences between calcifications in females and males can be deduced; nevertheless it should be mentioned that Fritsch (2) described mineralization in the eighth and ninth decade more often in females than in males; however, in the seventh males predominated.

We conclude that granular mediacalcinosis of the temporal arteries corresponds to mediacalcification as it occurs in aortas (6) and femoral arteries (7). It is supposed that the development of calcospherites in these mineralizations is due to calcification of remnants of necrotic or apoptotic cells (6, 8) as recently discussed for the calcification of arteriosclerotic plaques (9). In the temporal arteries there is a tendency of granular accumulations near the elastic membrane - if "dying" cells are more often present in this region than in other zones remains unknown. As in arteriosclerotic plaques (8)

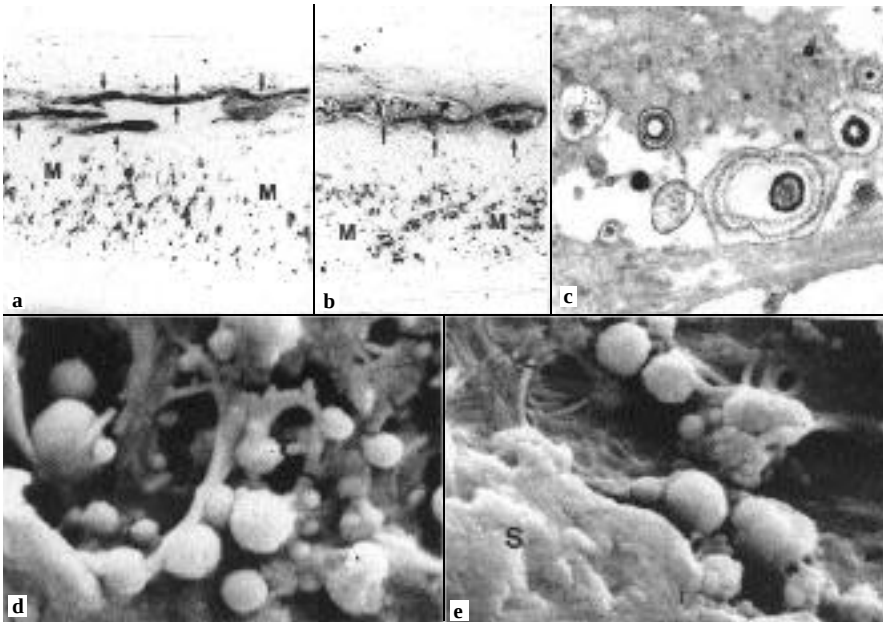

Fig. 1. Calcification of temporal arteries. (**a**) Granular mediacalcinosis (**M**) and accumulation of calcified granules at the elastic membrane (arrows; alizarin red S staining, 160x); (**b**) granular mediacalcinosis (**M**) and granular as well as beginning sheet-like calcification around the elastic membrane (arrows; alizarin red S staining, 160x); (**c**) calcospherites of the media exhibiting Liesegang rings (transmission electron microscopy, 14000x). (**d**) calcospherites of different size in the connective tissue of the media (scanning electron microscopy, 14000x); (**e**) sheet-like calcification (**S**) consisting of calcospherites and calcospherites in the connective tissue of the neighborhood (scanning electron microscopy, 14000x).

Table I. Summary of the results of the morphological investigations on alizarin red S stained sections of 92 temporal arteries (expressed as % unless otherwise indicated).

Number	4	2	11	3	10	4	11	6	8	7	13	8	4	1	61	31
Lumps inside the tunica media ("Mönckeberg-like")									13	14					1.6	3.2
Lumps associated with the internal elastic membrane					10				25	71	38		75		11	5
Granular calcinosis associated with the internal elastic membrane			55	33	70	75	72	33	38	86	77	75	100	100	62	61
Focal or diffuse granular mediacalcinosis	25	100	55	66	80	75	81	50	63	100	92	88	100	100	73	81
No calcification	75		45	33	20	25	18	50	38		8	13			26	19
Gender and age classes (years)	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M
	50-54		55-59		60-64		65-69		70-74		75-79		> 80		Total	

and Mönckeberg's disease (7) calcospherites are precursors of calcified lumps, eventually supported by the secondary appearance of bone-like apatite indicating a biphasic calcification process. Thus, it may be summarized that the calcification in temporal arteries does not differ from the same process occurring in blood vessels not prone to the development of vasculitis. Therefore, we assume that the appearance of two different age-related tissue alterations – calcification on the one hand, arteritis on the other hand – does not necessary implicate a causal relationship.

W. MOHR, *Prof. Dr. med.*

Prof. Dr. med. Winfried Mohr, Department of Pathology, University of Ulm, Albert-Einstein-Allee 11, D-89081 Ulm, Germany.

References

1. NORDBORG C, NORDBORG E, PETURSDOTTIR V, FYHR I-M: Calcification of the internal elastic membrane in temporal arteries:Its relation to age and gender. *Clin Exp Rheumatol* 2001; 19: 565-8.
2. FRITSCH H: Temporalarterienuntersuchungen an 100 unausgewählten Sektionsfällen. Ein Beitrag zur sog. Arteriitis temporalis. *Zbl Allg Pathol* 1964; 106: 147-58.
3. REID JD, ANDERSEN ME: Medial calcification (whitlockite) in the aorta. *Atherosclerosis* 1993; 101: 213-24.
4. MCCANN HG: Determination of microgram quantities of magnesium in mineralized tissues. *Analyt Chem* 1959; 31: 2091-2.
5. CASTILLO BV, TORCZYNSKI E, EDWARD DP: Mönckeberg's sclerosis in temporal artery biopsy specimens. *Br J Ophthalmol* 1999; 83: 1091-2.
6. MOHR W, GÖRZE: Granulare Mediakalzinose der Aorta. Strukturelle Befunde, historischer Rückblick und pathogenetische Bedeutung. *Z Kardiol* 2001; 90: 916-28.
7. MOHR W, GÖRZ E: Morphogenese der Mediakalzinose des Morbus Mönckeberg. Lichtmikroskopische, rasterelektronenmikroskopische und röntgenmikroanalytische Untersuchungsbefunde. *Z Kardiol* 2002 (in press).
8. MOHR W, GÖRZ E: Imitiert die arteriosklerotische Gefässwandverkalkung die Osteogenese? Pathomorphologische Untersuchungen an arteriosklerotischen Beeten. *Z Kardiol* 2002; 91: 212-32.
9. PROUDFOOT D, SHANAHAN CM: Biology of calcification in vascular cells: Intima versus media. *Herz* 2001; 26: 245-51.

Reply

Sirs,

We have read the letter from Professor Winfried Mohr concerning our paper with the title "Calcification of the internal elastic membrane in temporal arteries: its relation to age and gender" which was published in *Clinical and Experimental Rheumatology* 2001; 19: 565-8. We do not agree with Professor Mohr's conclusion that calcification of the internal elastic membrane (IEM) and giant cell arteritis (GCA) are not causally related.

Firstly, we have presented ample light- and electron microscopical evidence that, in the course of the inflammatory process in GCA, foreign-body giant cells do attack, engulf and degrade IEM calcifications in temporal arteries. These giant cells express HLA-DR, and IL-2R-expressing lymphocytes gather around them and may be found in pockets on the giant cell surface (1-5). Furthermore, morphological evidence indicates that this occurs in the initial phase of the inflammatory process (1). We are well aware of the fact that,using special staining methods, finely dispersed calcification may be found also in the media of temporal arteries. However, the assessment of such media calcification was beyond the scope of the present investigation, since the foreign-body giant cell reaction was constantly, and without exception, directed at IEM calcifications.

Secondly, although more common in cranial arteries, GCA is a generalized inflammatory disorder which may affect any medium-size or large artery in the body. As vascular pathologist and rheumatologist, repectively, we do see GCA not only in temporal arteries but also in the aorta and other arteries. Thus, we recently examined a case in which the femoral arteries were affected, causing vascular stenosis and threatening bilateral gangrene of the lower extremities. IEM calcification and foreign-body giant cell reaction was noticed at the border between media and intima. In the aorta, the inflammatory reaction in GCA is directed at calcified, atrophic lesions within the media. We did not have the opportunity to do electron microscopy on aortic tissue, but light-microscopically the granulomatous and foreign-body giant-cell reaction is found at the margins of such atrophic lesions, in which there is loss of smooth-muscle cells, loss of undulation of the elastic lamellae and heavy calcification (6). Thus, also the morphology of giant cell aortitis, indicates the pathogenetic relationship between calcification and GCA.

The similarities in terms of age and sex distribution between the temporal IEM calcifications and GCA do support our previous morphological observation that calcification of elastic membranes, be it in temporal arteries, the aorta or elsewhere, is involved in the pathogenesis of GCA.

C. NORDBORG, *MD*

E. NORDBORG, *MD*

Address correspondence to: Claes Nordborg, Head of Vascular Pathology and Neuropathology, Sahlgrenska University Hospital, S-413 45, Göteborg, Sweden.

References

1. NORDBORG E, BENGTSSON B-Å,NORDBORG C: Temporal artery morphology and morphometry in giant cell arteritis. *APMIS* 1991; 99: 1013-23.
2. NORDBORG E, BENGTSSON B-Å, PETURSDOTTIR V, NORDBORG C: Morphological aspects on giant cells in giant cell arteritis. An electron microscopic and immunocytochemical study. *Clin Exp Rheumatol* 1997; 15: 129-34.
3. NORDBORG E, NORDBORG C: The inflammatory reaction in giant cell arteritis. An immunohistochemical study. *Clin Exp Rheumatol* 1998; 16: 165-8.
4. NORDBORG C, NORDBORG E, PETURSDOTTIR V: The pathogenesis of giant cell arteritis; Morphological aspects. *Clin Exp Rheumatol* 2000; 18 (Suppl. 20): S18-S21.
5. NORDBORG C, NORDBORG E, PETURSDOTTIR V: Giant cell arteritis. Epidemiology, etiology and pathogenesis. *APMIS* 2000; 108:713-24.
6. PETURSDOTTIR V, NORDBORG E, NORDBORGC: Atrophy of the aortic media in giant cell arteritis. *APMIS* 1996; 104: 191-8.

The central role of actinically degenerate elastic tissue

Sirs,

We thoroughly enjoyed the article "Calcification of the internal elastic membrane in temporal artieries: Its relation to age and gender" by C. Nordborg, E. Nordborg, V. Petursdottir and I.M. Fyhr. Their emphasis on the internal elastic membrane or lamina (IEM) in temporal artieries as being a target for the inflammatory process in giant cell arteritis (GCA) is a proposition with which we would agree. We are not so convinced that calcification is necessary and would regard it as coincidental to the cause.

In several articles (1-4) John O'Brien and I have drawn attention to the central position of the IEM in the pathology of GCA,postulating that degenerate elastic tissue due to elastosis/elastolysis is the prime antigen with flow-on consequences to the elastic laminae of arteries elsewhere. We further postulated that actinic radiation over a lifetime acting upon the elastic laminae of superficial vessels such as the temporal arteries is a significant, if not the prime cause of this elastic tissue damage leading to GCA in those predisposed. Like the authors we do not dispute age, sex, racial or hereditary factors, but we wholeheartedly agree that the IEM is the prime target.

Elastic tissue can be difficult to investigate. The interest of cosmetic firms is engaged in relation to wrinkling and respiratory physicians also have an interest, but we are not aware of many basic studies on elastic tissue and its autoimmune potential with flow-