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New Aspects of Thromboangiitis obliterans (von Winiwarter-Buerger's Disease)

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Key Words. Immunovasculitis · Immunohistochemical findings · Anti-elastin antibodies · IgE · Azathioprine

Abstract. The existence of thromboangiitis obliterans as a clinical entity has been a matter of debate for many years. In contrast to other immunovasculitides there is no organ involvement while peripheral vessels are affected. Heavy smokers under 40 years of age have a high predisposition for the disease. The cerebral form shows relapsing brain infarctions which can be visualized in CCT while panarteriography remains negative. Apart from unspecific inflammatory signs in blood and CSF there are distinctive laboratory findings proving the autoimmunological character of von Winiwarter-Buerger's disease. In the serum anti-elastin antibodies, IgE and anticollagen antibody activity are detectable. In 3 patients the authors detected specific immunohistochemical findings in a biopsy specimen of the temporal artery. In addition to platelet-inhibiting substances corticoids in acute and azathioprine in chronic treatment becomes necessary.

In 1879, *von Winiwarter* in Vienna described the segmental inflammatory changings in medium-sized arteries and veins in the amputated leg of a 57-year-old man, a disease he called endarteriitis obliterans. He underlined the possible role of coldness in the development of the gangrene in his case. *Buerger* [1908] changed the term endarteriitis into thromboangiitis obliterans and showed that the stenoses and occlusions in this disease are caused by repeated thromboses. In 19 amputated legs he demonstrated as characteristic findings the alternation of inflammatory thromboses in different states of development and relatively normal segments in the single affected vessel. In these cases he

detected an increased prevalence in Jews of Russian or Polish origin.

During the following years different authors named characteristic features of the disease: (1) A high predisposition for young men under 40 years of age. (2) The vessels of the wrist and hand are often included in the inflammatory process [*Allen*, 1929]. (3) There is a close association between cigarette smoking and the activity of the disease [*Meyer*, 1918; *Silbert*, 1945]. (4) There is often a migratory superficial thrombophlebitis accompanying the vasculitis.

But in spite of all these typical features the existence of thromboangiitis obliterans as a clinical entity has been questioned repeatedly. Especially the differentiation from inflammatory forms of arteriosclerosis gave cause for controversial opinions. One of the reasons for this history of the disease may be the lack of organ involvement in von Winiwarter-Buerger's disease, which is in contrast to almost all other immunovasculitides. In view of this fact it is not surprising that the cerebral form of thromboangiitis obliterans has been put in question even more than the peripheral disease. *Jäger* [1932] was the first to mention the existence of a cerebral involvement in his cases, a few years later *Spatz* [1935] and *Lindenberg and Spatz* [1939] demonstrated two forms of cerebral thromboangiitis obliterans (CTAO): (1) multiple unsystematic cerebral infarctions in involvement of medium-sized vessel, and (2) the symmetrical granular atrophy caused by involvement of small leptomeningeal arteries.

The significance of the second finding had been challenged early when *Fisher* [1957] and later *Zollinger* [1967] demonstrated that different forms of occlusive disease in the small endarteries of the brain result in the same picture. For neuropathologists the differentiation between CTAO and arteriosclerosis was the cardinal problem. The differential diagnosis to other forms of cerebral vasculitis was not as big a problem because pathological studies showed no involvement of the media or the elastica in the inflammatory process in CTAO.

Which are the diagnostic criteria that could help us today in detecting CTAO? In the Neurologic Clinic in Heidelberg we saw, during a period of 12 years, 7 patients suffering from this disease (i.e. 0.05% of all patients and 0.3% of all brain infarctions between 1970 and 1982). All patients were young men and heavy smokers – the onset of neurological symptoms was usually before the thirtieth year. In 3 cases the neuropathological examination confirmed the diagnosis, posthumous. In 3 other patients whom we saw during the last 2 years extensive rheumatological and immunological examinations could be carried out.

In all patients there was an astonishing similarity of the clinical history. They all suffered from repeated brain infarctions of different localization over months or even years. While in cranial computed tomography (CCT) hypodensive areas according to the clinical neurological findings could be demonstrated, there were no pathological changes in the panarteriography of the brain-supporting vessels. Extensive cardiological examinations including echocardiography and in 1 patient even a cardiac-catheter revealed no possible source for repeating brain embolism from the heart. The areas of the medial and the posterior cerebral artery were the regions most often affected. The neurological signs as well as the CCT-findings improved partially within few weeks leaving minor residual symptoms, especially visual

field reductions. Additional findings in 1 patient were major epileptic seizures and an ischemic optic neuritis [*Kessler* et al., 1984]. Another patient – a farmer – twice developed the brain infarctions during work outdoors [*Kessler* et al., 1983].

In all cases unspecific inflammatory changes in blood and/or cerebrospinal fluid (CSF) lead towards a vasculitic process. In CSF an increase of cells up to 100 cells/mm^3 as well as an increased protein concentration about 120 mg/100 ml could be demonstrated in several patients; in some patients at different times of examination the findings were normal as well as pathological. Specific laboratory findings were an increased titre of anti-elastin antibodies of up to 1:1,400 (normal 1:8) and an increased serum IgE of up to 300 U/ml (normal range up to 100 U/ml).

In 3 cases a biopsy of the temporal artery was performed. In all 3 patients there were distinct immunohistochemical findings while the pathohistological examination revealed a morphologically normal vessel wall. The results of the immunohistochemical examination with a direct immunofluorescent technique are shown in table I. An important result is the deposit of immunoglobulins and complement components especially in the vasa vasorum. Early investigators already suggested that the inflammation of the vasa vasorum might be the primary process in von Winiwarter-Buerger's disease [*Buerger*, 1908; *Jäger*, 1932]. The immunohistochemical findings as well as the increase of anti-elastin antibodies and IgE in the serum are signs of an autoimmunological process which one does not find in arteriosclerotic disease. In 20 patients suffering from thrombotic brain infarctions anti-elastin antibody titres and serum IgE were within the normal range. While the presence of anti-elastin antibodies in CTAO seems to be a common and typical finding [*Bollinger* et al., 1979; *Horsch* et al., 1978] the meaning of the increased IgE remains unclear. This immunoglobulin is a sign of an allergic inflammatory process and often found in systemic vasculitis with respiratory tract involvement [*Berlit* et al., 1982].

Table I. Immunohistochemical findings in a biopsy specimen of the temporal artery in 3 patients with CTAO

	IgG	IgA	IgM	C1q	C3b	C3d	C9
Pat. 1							
Intima	–	–	–	+	+	+	–
Elastica interna	–	–	–	–	–	–	–
Media	–	–	–	–	–	–	–
Vas vasorum	–	++	++	–	–	–	–
Pat. 2							
Intima	+	+	+	+	+	+	–
Elastica interna	+	+	–	+	–	–	–
Media	–	–	–	–	–	–	–
Vas vasorum	++	++	++	–	+	+	–
Pat. 3							
Intima	+	+	+	+	+	+	–
Elastica interna	+	+	–	–	–	–	+
Media	–	–	–	–	–	–	–
Vas vasorum	++	++	++	–	+	+	–

Further studies are necessary to clarify the meaning of the immunohistochemical findings in the vessel wall. But in young stroke patients the examination of a biopsy of the temporal artery could be a very helpful diagnostic procedure [*Berlit and Kessler*, 1983] in detecting CTAO. Two preconditions for this procedure are the panarteriography of the brain-supporting vessels performed in advance and a surgical technique for taking the biopsy specimen from a branch of the temporal artery. Taking the possible necessity of a later externa-interna bypass into consider-

Table II. Clinical and laboratory findings in different vasculitides [modified after *Berlit* et al. 1983]

	Poly-arteritis nodosa	Lupus erythematosus	Arteritis temporalis	Allergic granulo-matosis	Wegener's granulo-matosis	Thromboangiitis obliterans
Clinical findings						
CNS	++	++	+	++	+	+
PNS	+++	+	+	++	+	∅
Muscle	+++	++	+++	∅	+	∅
Kidney	++	++	∅	+	+++	∅
Liver	+	+	+	+	+	∅
Heart	++	++	+	+++	+	∅
Lung	+	+	∅	+++	+++	∅
Intestinal tract	++	++	+	+	++	∅
Skin	++	+++	+	++	++	∅
Ankles	++	+++	++	+	+	∅
Peripheral vessels	∅	+	+++	+	+	+++
Age	50–60	30–40	> 50	40–50	40–50	25–35
♂:♀	2:1	1:3	1:2	2,5:1	3:2	6:1
Laboratory findings						
Erythrocyte sedimentation rate	∧∧	∧∧	∧∧∧	∧∧	∧∧∧	∧
Eosinophilia	+	∅	∅	+++	+	∅
C-reactive protein	++	+	+	+	+	++
Rheumatoid factor	++	++	∅	+	+	∅
Anti-elastin antibodies	∅–++	∅–++	∅	∅	∅	+++
Immunoglobulin A	∧∧∧	normal	normal	normal	∧∧	normal
G	normal	∧∧∧	∧	normal	∧	normal
M	normal	normal	∧	normal	∨	normal
E	normal	normal	normal	∧∧	∧∧	∧∧
Complement C3	∨∨	∨∨	∧	normal	normal	normal
C4	∨	∨∨	∧∧	normal	normal	∧∧
HB_sAg/anti-HB_s	++	∅	+	∅	∅	∅
CSF changings	++	++	+	+	∅–+	+
Tissue antigens	?	HLA-B8, A15	HLA-B8, A10	?	HLA-B8	HLA-A9, HLA-B5
Immunohistochemical findings in biopsy specimen from	++ muscle kidney	++ skin	+++ temporal artery	+ skin	++ kidney lung	++ temporal artery

+++ = Usually found; ++ = often found; + = seldom found; ∅ = not found; ∧∧∧ = usually increased; ∧∧ or ∨∨ = often increased or lowered; ∧ or ∨ = seldom increased or lowered.

ation, the main stem of the vessel should be spared.

In addition to these signs of humoral immune mechanisms in thromboangiitis obliterans *Adar* et al. [1983] described an increased stimulation index of cellular sensitivity to human collagen. All these findings are strong arguments for the distinctive character of CTAO as an autoimmunological vasculitis.

Another finding of interest is the greater prevalence of HLA-A9 and HLA-B5 antigens in patients with von Winiwarter-Buerger's disease [*McLoughlin* et al., 1976]. In consis-

tence with the findings of *Buerger* [1908], the disease shows an increased occurrence in Israel and the Orient.

In the differential diagnosis of CTAO one has to think of focal encephalitis in septic brain embolism; a possible cardiac source of emboli to the brain should be excluded by echocardiography and long-term electrocardiography [*Berlit,* 1983]. The typical features of CTAO in comparison to some other vasculitides of the brain are summarized in table II. There are some very distinctive diagnostic criteria that help to make a reasonably certain diagnosis of CTAO: (1) male patients, about 30 years old; (2) strong smokers; (3) relapsing brain infarctions in changing localizations, which can be visualized in CCT; (4) negative results in angiography and cardiologic examinations; (5) unspecific inflammatory signs in blood (blood sedimentation rate, C-reactive protein) and CSF (cells and/or protein elevated); (6) anti-elastin antibodies, IgE and anticollagen antibody activity detectable; (7) distinctive immunohistochemical findings in biopsy of the temporal artery, and (8) signs or history of peripheral vessel involvement.

In therapy the autoimmunological character of CTAO should be taken into account. Apart from the obligatory treatment with platelet-inhibiting substances corticoids in the acute situation of a brain infarction and azathioprine in long-term therapy are necessary. Smoking must be strictly forbidden in patients with CTAO.

Altogether the existence of thromboangiitis obliterans von Winiwarter-Buerger as a clinical entity has been defended by careful studies, and today the question asked by *Zülch* [1969]: 'The cerebral form of von Winiwarter-Buerger's disease – does it exist' should be answered with 'yes'.

References

Adar, R.; Papa, M.Z.; Halpern, Z.; Mozes, M.; Shosan, S.; Sofer, B.; Zinger, H.; Dayan, M.; Mozes, E.: Cellular sensitivity to collagen in thromboangiitis obliterans. New Engl. J. Med. *308:* 1113–1116 (1983).

Allen, E.N.: Thromboangiitis obliterans: methods of diagnosis of chronic occlusive arterial lesions distal to the wrist with illustrative cases. Am. J. med. Sci. *178:* 237–244 (1929).

Berlit, P.; Die kardiale Hirnembolie. Nervenarzt *54:* 389–399 (1983).

Berlit, P.; Kessler, C.: Immunhistologische Diagnostik bei Schlaganfällen. Psycho *9:* 386 (1983).

Berlit, P.; Kessler, C.; Storch, B.; Krause, K.H.: Immunvaskulitis und Nervensystem. Nervenarzt *54:* 497–503 (1983).

Berlit, P.; Möller, P.; Krause, K.H.: Eosinophile Polyneuritis und allergische Angiitis. Nervenarzt *53:* 714–720 (1982).

Bollinger, A.; Hollmann, B.; Schneider, E.; Fontana, A.: Thromboangiitis obliterans: Diagnose und Therapie im Licht neuer immunologischer Befunde. Schweiz. med. Wschr. *109:* 537–543 (1979).

Buerger, L.C.: Thrombo-angiitis obliterans: a study of the vascular lesions leading to presenile spontaneous gangrene. Am. J. med. Sci. *136:* 567–580 (1908).

Fisher, M.C.: Cerebral thromboangiitis obliterans. Medicine, Baltimore *36:* 169–209 (1957).

Horsch, A.K.; Brechmeier, P.; Robert, L.; Horsch, S.: Anti-Elastin-Antikörper bei der Thrombangiitis obliterans (Morbus v. Winiwarter-Buerger). Verh. dt. Ges. inn. Med. *40:* 1758–1761 (1978).

Jäger, E.: Zur pathologischen Anatomie der Thrombangiitis obliterans bei juveniler Extremitätengangrän. Virchows Arch. path. Anat. Physiol. *284:* 526–583 (1932).

Kessler, C.; Berlit, P.; Reuther, R.; Schwechheimer, K.: Zur Differentialdiagnose der Thrombangiitis obliterans v. Winiwarter-Buerger. Nervenarzt *54:* 85–91 (1983).

Kessler, C.; Reuther, R.; Berlit, P.; Carls, C.; Hoffmann, W.: CAT-Scan and immunohistochemical findings in a case of cerebral thromboangiitis obliterans (Buerger's disease). Eur. Neurol. *23:* 7–11 (1984).

Lindenberg, R.; Spatz, H.: Über die Thrombangiitis

obliterans der Hirngefässe. Virchows Arch. path. Anat. Physiol. *305:* 531–557 (1939).

McLoughlin, G.A.; Helsby, C.R.; Evans, C.C.; Chapman, D.M.: Association of HLA-A9 and HLA-B5 with Buerger's disease. Br. med. J. *ii:* 1165–1166 (1976).

Meyer, W.: Etiology of thrombo-angiitis obliterans (Buerger). J. Am. med. Ass. *71:* 1268–1272 (1918).

Silbert, S.: Etiology of thromboangiitis obliterans. J. Am. med. Ass. *129:* 5–17 (1945).

Spatz, H.: Über die Beteiligung des Gehirns bei der v. Winiwarter-Buerger'schen Krankheit. Dt. Z. Nervenheilk. *136:* 86–141 (1935).

Winiwarter, F. von: Über eine eigentümliche Form der Endarteriitis und Endophlebitis mit Gangrän des Fusses. Arch. klin. Chir. *23:* 202–226 (1879).

Zollinger, H.U.: Adaptive Intimafibrose der Arterien. Virchows Arch. path. Anat. Physiol. *342:* 154–167 (1967).

Zülch, K.J.: The cerebral form of von Winiwarter-Buerger's disease: does it exist? Angiology *20:* 61–69 (1969).

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