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Abstract: Giant cell arteritis (GCA) is increasingly being recognized as a systemic vascular disease, not confined to the cranial arteries. Epidemiological studies have shown that almost one-third of the patients with GCA develop serious peripheral vascular complications during long-term follow up, and there is growing evidence that unrecognized extracranial involvement may be even more common. GCA of large- and medium-sized peripheral arteries typically leads to long tapering and occlusion of the arterial lumen due to concentric intimal thickening, sometimes accompanied by spontaneous dissection. Depending on the extent of the arterial obliteration and on the anatomy of the involved arterial segment, this may result in severe ischemia of the limbs during the acute phase of the disease. GCA of the aorta usually remains asymptomatic for many years, and leads to a markedly increased risk of aneurysms and dissections, particularly of the thoracic aorta. Evolving vascular imaging techniques such as duplex ultrasound, computer tomography (CT), magnetic resonance imaging (MRI), and fluorine-18-desoxyglucose positron emission tomography (18F-FDG-PET) have greatly improved our ability to detect and study arterial changes in large-artery vasculitis. Boosted by these advances in vascular imaging, vascular specialists are increasingly involved in the early diagnosis, follow-up and treatment of patients with large-vessel vasculitis.

Key words: duplex sonography; extracranial involvement; fluorine-18-desoxyglucose positron emission tomography; giant cell arteritis; large-vessel vasculitis; magnetic resonance imaging

Introduction

Giant cell arteritis (GCA) is the most common vasculitis of large and medium-sized arteries, affecting almost exclusively individuals over 50 years of age.1,2 In this age-group the prevalence of GCA has been estimated at 200 per 100,000 persons in the United States,3 and an even higher frequency has been reported in northern Europe.4,5 As a result of the aging population in industrialized countries, increasing numbers of patients with GCA can be expected in the near future.

From the initial description by Hutchinson in 1890 and Horton in 19326 until recently, GCA was believed to be predominantly a localized disease, affecting primarily the cranial arteries, particularly the temporal artery (temporal arteritis) and the arteries of the retina and the optic nerve. This pattern of distribution explains many of the classical symptoms of GCA such as tender and swollen temporal arteries, temporal headache, jaw claudication and visual loss. Another characteristic feature of GCA is the frequent occurrence of systemic and musculoskeletal symptoms. Fatigue, weight loss, low-grade fever, polymyalgia rheumatica, arthralgia and tenosynovitis are observed alone or in combination in more than half of the patients with GCA. Laboratory signs of systemic inflammation are characteristic of the disease. An elevated erythrocyte sedimentation rate (ESR) and plasma C-reactive protein (CRP) is almost always present. In addition, many patients have chronic anemia and reactive thrombocytosis.1,2

As a consequence of these typical symptoms, most patients with GCA are initially seen by rheumatologists and ophthalmologists. Traditionally, vascular specialists have been involved in the management of patients with GCA only in exceptional cases with severe extracranial involvement leading to symptomatic peripheral or visceral ischemia. However, this pattern is gradually changing. GCA is increasingly been recognized as a generalized vascular disease potentially leading to serious
Epidemiology of extracranial GCA

Involvement of the aorta and its major branches was recognized early in a subset of patients with GCA.\textsuperscript{7–9} The frequency of clinically manifest, extracranial large-artery involvement is usually quoted to be approximately 10–15%.\textsuperscript{1,2} The true frequency of generalized vascular involvement is, however, controversial. In a population-based cohort followed for a period of 50 years, large-artery complications have been reported in 27% of the patients diagnosed with GCA,\textsuperscript{10} indicating that in the long run almost one-third of GCA patients may develop symptomatic extracranial involvement. Only very few studies have specifically looked for peripheral arterial involvement with a detailed vascular examination and imaging techniques. Large-vessel vasculitis may lead to thickening of the arterial wall without stenosis or to dilatation of the artery and to the formation of aneurysms.\textsuperscript{11} Absent pulses, arterial bruits or symptoms of ischemia may therefore be missing in many cases. Even if arterial obstructions occur, these may remain asymptomatic if they develop slowly. In our clinic we regularly see patients with high-grade stenosis or even occlusion of the subclavian or axillary artery who do not have upper limb claudication. This is particularly the case in elderly patients with reduced physical activity. Moreover, many patients with extracranial large-artery GCA do not have classical symptoms such as headache or jaw claudication, and almost half of these patients were found to have negative temporal artery biopsies.\textsuperscript{12} It is therefore likely that extracranial involvement is underdiagnosed in patients with classical GCA or mistaken for an arteriosclerotic vascular disease in patients without temporal arteritis or typical symptoms of GCA.

Extracranial GCA may have a distribution and clinical presentation similar to Takayasu arteritis.\textsuperscript{13,14} Although histologically similar, GCA and Takayasu arteritis are considered distinct disease entities based on age of onset, distribution of vascular involvement, and clinical presentation.\textsuperscript{15} Takayasu arteritis affects almost exclusively patients younger than 40 years, involves primarily the aorta and its major branches, and generally spares the cranial arteries. These criteria usually allow a clinical differentiation of these two vasculitides. More frequent recognition of aortic and large-artery involvement in GCA is, however, creating an increasing overlap between these disease entities.

Distribution and manifestations of extracranial involvement

Extracranial GCA has most frequently been reported in the aortic arch and in the subclavian and axillary arteries.\textsuperscript{1,2,8,9} Published data on the distribution of extracranial involvement vary, depending on the methodology of the studies. In the retrospective cohort analyzed by Nuenningshoff et al.,\textsuperscript{10} 18% of the GCA patients experienced a large-artery complication due to aortic aneurysm and/or dissection. In the same study, symptomatic stenosis of the subclavian, axillary and/or brachial arteries occurred in 4%, and of the iliac and/or femoral arteries in 0.6%. This low rate of symptomatic peripheral artery stenoses may not reflect the true frequency of peripheral artery involvement. In 72 cases with histologically documented extracranial GCA, Lie found an involvement of the ascending aorta and the aortic arch in 39%, of the subclavian and axillary arteries in 26%, and of the femoropopliteal arteries in 18%.\textsuperscript{16} This study suggests that extracranial GCA involvement of the arteries of the arms and legs may in fact be as common as involvement of the aorta.

GCA of the aorta typically remains asymptomatic during the early phase of the disease and causes serious late complications due to aneurysms and dissections. In a retrospective cohort from Minnesota, patients with GCA were 17.3 times more likely to develop thoracic aortic aneurysms and 2.4 times more likely to develop abdominal aortic aneurysms than individuals of the same age without GCA.\textsuperscript{17} Thoracic aneurysms appear to be particularly dangerous in GCA. Of 41 patients with GCA and thoracic aneurysm, 16 developed an acute aortic dissection and eight died.\textsuperscript{18} In this study the median time between diagnosis of GCA and occurrence of thoracic aneurysm was 7 years. Yearly transthoracic echocardiography and two-view chest radiograph (Figure 1A–C) have therefore been suggested as a screening approach in all patients with GCA.\textsuperscript{19} Unlike aortic involvement, GCA of the peripheral arteries causes luminal narrowing and may cause symptoms of peripheral ischemia during the acute phase of the disease. The most typical extracranial manifestation of GCA is long tapering or occlusion of the axillary artery leading to missing...
arm pulses, decreased blood pressure measurements, axillary bruits, and arm claudication (Figure 2). Symptomatic stenoses of the subclavian and axillary arteries have been reported in 3–15% of patients with GCA. The true frequency of involvement of these arterial segments is, however, unknown since asymptomatic lesions may be rather common. Fortunately, obstruction of the proximal arteries to the arm rarely causes limb-threatening ischemia. Even total occlusions of the subclavian and/or axillary artery may be well tolerated due to sufficient collateralization, and frequently do not require surgical or percutaneous vascular interventions. We have observed severe upper limb ischemia only in rare cases with extensive involvement of the brachial arteries. Inflammatory stenoses of the subclavian artery are almost always distal to the origin of the vertebral artery. Therefore, patients with GCA only rarely develop a subclavian steal phenomenon.

Iliac and femoropopliteal involvement causing ischemic symptoms of the legs has been described in several case reports, but the true frequency of this manifestation is unknown. GCA may cause extensive obstructions of the femoropopliteal and crural arteries, resulting in claudication and even critical limb ischemia. In our experience, severe ischemia requiring vascular surgery or catheter intervention is more frequent in GCA of the lower limbs than of the upper limbs. It is very likely that femoropopliteal GCA is underdiagnosed owing to the similarity and overlap of the arterial occlusions with arteriosclerotic peripheral arterial disease in these elderly patients.

Pathogenesis

GCA is a panarteritis characterized by infiltration of all layers of the arterial wall by T-lymphocytes and macrophages. Multinuclear giant cells are typically found in the proximity of the fragmented internal elastic membrane. Activated CD4+ T cells are the central inflammatory cell in large-vessel vasculitis. Recent studies suggest that the inflammatory process starts in the adventitia, where resident dendritic cells become activated and trigger T-cell response by antigen presentation. The antigens responsible for these events are still unknown. Auto-antigens as well as infectious agents and toxins have been suggested.
Activated CD4+ T cells induce inflammatory infiltrates and activate macrophages mainly through secretion of interferon-γ. Macrophages play a key role in the secretion of cytokines causing systemic inflammation (e.g. interleukin-1 and interleukin-6) and in the local proliferation and damage within the arterial wall. Macrophages in the media cause damage to the arterial wall through secretion of metalloproteinases and reactive oxygen intermediates. These processes lead to fragmentation of the internal elastic lamina, to weakening of the arterial wall, and are probably the basis for development of aneurysms and dissections. When GCA causes arterial stenosis and ischemia, this is due to marked, concentric thickening of the intima. Intimal thickening results from the proliferation of myofibroblasts and secretion of extracellular matrix. Platelet-derived growth factor, vascular endothelial growth factor (VEGF), and metalloproteinases produced by activated macrophages and giant cells play a crucial role in the induction of intimal thickening.

Many questions about the pathogenesis of GCA are still unanswered. Particularly, the initial trigger of the disease remains elusive. Advances in the understanding of the cellular mechanisms of large-vessel vasculitis have, however, provided increasingly detailed explanations for the concentric arterial wall thickening and the tendency to dissection and aneurysm formation typically observed in extracranial GCA. These insights will hopefully generate new therapeutic strategies in the near future.

Physical examination and basic vascular tests in patients with GCA

The classical physical sign of GCA is the swollen, tender temporal artery with decreased or absent pulsation. The specificity of this physical finding for a positive biopsy may be as high as 99%, but the sensitivity is far lower, and an apparently normal temporal artery on physical examination does not rule out a positive biopsy result. Rare, but characteristic complications of extensive involvement of the branches of the external carotid arteries are necrosis of the tongue or of the scalp (Figure 3).

Palpation of pulses, auscultation of peripheral arteries, and bilateral measurements of systolic brachial and ankle artery pressures are simple clinical tests capable of identifying many patients with suspected extracranial involvement. Absent pulses, a difference in systolic blood pressure between arms of more than 10–15 mmHg, or an abnormal ankle/brachial index (< 0.9) indicate hemodynamically significant arterial obstructions. Arterial bruits are the earliest abnormal physical finding due to arterial stenosis, and may be present before the onset of any other symptom. Only 4–5% of GCA patients have been reported to have a diminished radial pulse or a systolic blood pressure difference of more than 10 mmHg between both arms, but 14% had bruits of the subclavian or brachial artery. Typical localizations of arterial bruits in GCA are the carotid arteries, the supra- and infraclavicular region, over the axillary and brachial arteries, and over the orbits. Auscultation of the axillary fossa is particularly useful, since arterial bruits in this region are highly suggestive of large-vessel vasculitis, and almost never due to arteriosclerosis. An abnormal vascular examination of the lower extremities is far less specific for extracranial GCA due to the high frequency of arteriosclerotic peripheral arterial disease in the lower limbs of this elderly population. Differentiation between arteriosclerosis and vasculitis always requires further imaging studies in this arterial region. Physical examination is not highly sensitive for aortic aneurysms, although more than 75% of abdominal aortic aneurysms with a diameter above 5 cm can be palpatated. A diastolic murmur of aortic regurgitation may be the only clinical sign of a thoracic aortic aneurysm and should prompt further evaluation.

Blood inflammatory markers

A marked elevation of the ESR is typical for GCA, and an ESR above 50 mm/h is one of the five American College of Rheumatology 1990 criteria for the
classification of this disease. However, a normal or only slightly elevated ESR does not rule out GCA. In a population-based study, ESR was < 30 mm/h in 3.6%, < 40 mm/h in 5.4%, and < 50 mm/h in 10.8% of patients with untreated GCA. Compared with ESR, CRP levels have the advantage of being unaffected by age and sex and of responding more rapidly to inflammation. There is some evidence that an elevated CRP may be slightly more sensitive than ESR for the diagnosis of active GCA. However, GCA patients with normal CRP but elevated ESR have been reported. In a recent study, only one of 119 patients (0.8%) with biopsy-proven GCA was found to have both normal ESR and CRP. The authors of this study conclude that the use of both tests provides a slightly greater sensitivity for the diagnosis of GCA than the use of either test alone. With this approach, untreated GCA patients without detectable systemic inflammation appear to be very rare.

The use of blood markers of inflammation for the follow-up of disease activity during treatment is more complicated. Studies in Takayasu arteritis have shown that approximately 40% of patients thought to be in remission based on normal ESR and/or CRP have histological signs of active arteritis. These results cast doubt on the validity of currently used blood markers of inflammation for the assessment of disease activity in glucocorticoid-treated large-vessel vasculitis. Interleukin-6 (IL-6) is a promising biologic marker of disease activity, which has been shown to be markedly elevated in GCA before treatment as well as during relapses. In one study, 89% of flares of GCA during treatment were accompanied by increased IL-6, whereas only 58% of these patients had an ESR above 30 mm/h. These findings indicate that IL-6 may be a highly sensitive marker of disease activity in GCA. However, the value of this marker for the practical management of GCA patients has still to be demonstrated in clinical trials.

Vascular imaging

Duplex sonography

Duplex sonography is today the first-line vascular imaging technique for the detection of large-vessel vasculitis. Interest in duplex sonography for the diagnosis of GCA was first triggered by sonographic studies of the temporal artery. Ultrasound transducers with frequencies of at least 10 MHz allow non-invasive imaging of the temporal artery with a degree of spatial resolution unachievable with any other of the currently available imaging techniques. Characteristic signs for temporal arteritis are segmental, concentric, hypoechoic thickening of the arterial wall (‘halo sign’), which may lead to luminal stenosis or total occlusion (Figure 4A and B). Sensitivity and specificity of duplex ultrasound for the diagnosis of GCA is still a matter of debate. Sensitivities above 75% and specificities above 95% have been reported in some studies. Whether duplex ultrasound is indeed more sensitive than the clinical examination of the temporal artery, has however been questioned, and duplex ultrasound has not yet replaced temporal artery biopsy as a diagnostic criterion for GCA in clinical practice. Much of the controversy regarding the reliability of duplex sonography for the detection of temporal arteritis may be due to differences in methodology between published studies. In our experience, duplex sonography of the temporal artery is best performed with a 12–15-MHz ultrasound transducer. Under these conditions, and with sufficient experience of the examiner, we...
regularly detect bioptically confirmed temporal arteritis in clinically unremarkable temporal arteries. As has been suggested in a recent meta-analysis, we consider duplex ultrasound of the temporal arteries a valuable diagnostic test, when used in combination with the clinical probability. Moreover, ultrasound-guided mapping of the temporal arteries has the potential to improve the diagnostic yield of the biopsy.

The contribution of duplex sonography is even more important for diagnosis, assessment of severity and follow-up in extracranial GCA. In the subclavian, axillary, and brachial arteries as well as in the cervical arteries, GCA has a typical sonographic appearance with concentric, hypoechoic wall thickening of long arterial segments eventually leading to tapering of the arterial lumen (Figure 5) or to hypoechoic occlusion. These arteries are easily accessible for duplex sonography with a 5–10-MHz transducer, thus allowing high-resolution imaging of the arterial wall, and exact quantification of the degree of stenosis. In our experience, no additional information is gained by angiography. In extracranial GCA involving the arteries to the arms and/or the cervical arteries, we therefore do not recommend conventional angiography, except in rare cases in which a revascularization procedure is considered. The sonographic appearance of these arteries combined with elevated laboratory markers of systemic inflammation can be considered pathognomonic for large-vessel vasculitis.

The thickening of the arterial wall may decrease during treatment and become more echogenic. However, some degree of thickening and stenosis usually persists even in patients in complete remission, and recanalization of occluded arterial segments does not occur. The sonographic appearance of the arterial wall is therefore an unreliable parameter for the assessment of disease activity. Sequential sonographic follow-up of patients with extracranial GCA is nonetheless essential to rule out a progression of stenoses or involvement of previously normal arterial segments during treatment.

Less is known about the sonographic appearance of GCA of the femoropopliteal and crural arteries. Only very few studies report the sonographic appearance of lower limb GCA. Moreover, interpretation of vascular imaging is hampered by the high rate of concomitant arteriosclerosis in this vascular region. Undoubtedly, femoropopliteal GCA may have the same sonographic appearance as in the arteries of the upper limbs and the cervical arteries. Figure 6 shows the typical hypoechoic, concentric wall thickening in the superficial femoral artery of a 67-year-old patient with GCA. Figure 7 shows an example of a spontaneous dissection of the superficial femoral artery in a 65-year-old woman with

Figure 5 Color-coded duplex sonography in a 68-year-old woman with extracranial GCA. Longitudinal view of the left axillary artery showing tapering of the lumen due to concentric, hypoechoic thickening of the arterial wall.

Figure 6 Color-coded duplex sonography in a 67-year-old man with extracranial GCA of the lower extremities. Longitudinal view of the left superficial femoral artery showing a high-grade stenosis due to hypoechoic thickening of the arterial wall.
critical ischemia of her left foot due to histologically confirmed extracranial GCA. The proneness of extracranial GCA to dissections is known from aortic aneurysms. However, spontaneous femoropopliteal dissection has not previously been reported as a manifestation of GCA.

A major advantage of duplex ultrasound over angiographic techniques is its ability to visualize the pathological thickening of the arterial wall, even if it does not cause arterial narrowing. By systematically performing a complete vascular ultrasound in all our patients with GCA, we are just starting to appreciate the variety of vascular morphology in large-vessel vasculitis. A frequent finding we have observed in these patients is a non-occlusive, concentric thickening of the arterial wall of medium echogenicity, accompanied by beaded, highly echogenic inclusions lining the innermost arterial layer (Figure 8A and B). Interestingly, we find this characteristic appearance almost

Figure 7 Color-coded duplex sonography in a 65-year-old woman with extracranial GCA of the upper and lower extremities. Longitudinal view of the left superficial femoral artery showing a spontaneous dissection of the arterial wall with two perfused lumens.

Figure 8 Duplex sonography of the superficial femoral artery of a 56-year-old woman presenting with a 3-month history of fever of unknown origin. The longitudinal view (A) and cross-section (B) show marked thickening of the arterial wall of medium echogenicity and beaded, highly echogenic inclusions lining the innermost arterial layer. The arterial wall thickening did not lead to stenosis of the lumen, and the patient had normal pulses and systolic ankle pressures. 18F-FDG-PET confirms marked tracer-uptake in the femoropopliteal arteries consistent with large-vessel vasculitis (C).

exclusively in the femoropopliteal arteries of patients with a non-occlusive course of the disease. The histological correlate to these sonographic changes is still unknown.

**Computer tomography and magnetic resonance imaging**

Computer tomography (CT)\(^45\)--\(^47\) and magnetic resonance imaging (MRI)\(^48\)--\(^53\) have been shown to detect the inflammation in the arterial wall as well as luminal narrowing and aneurysms in patients with large-vessel vasculitis. In addition, CT- and MR-angiography (MRA) can provide detailed non-invasive information on the luminal anatomy, and the distribution of arterial stenoses and occlusions. Particularly, MRA is steadily replacing conventional angiography for obtaining a comprehensive overview of the involved vascular regions in large-vessel vasculitis.

Although CT is excellent for the detection of arterial wall inflammation in the aorta and its proximal branches\(^45\)--\(^47\) (Figure 9), it has the disadvantage of exposing the patient to iodinated contrast medium and radiation. This is particularly relevant in young patients with Takayasu arteritis. For these reasons, and due to the fast advances in MR-technology, MRI is becoming the preferred method for obtaining a comprehensive overview of the involved vascular regions in large-vessel vasculitis.

In addition to increased arterial wall thickness, MRI detects edema\(^49\) and enhanced uptake of ferromagnetic contrast medium in the inflamed arterial wall.\(^51\) Edema appears hyperintense in T2-weighted and STIR images, and marked enhancement of the arterial wall becomes evident in gadolinium-assisted MRI (Figure 10). The degree of arterial wall edema and contrast enhancement has been shown to correlate with systemic inflammation\(^48\),\(^51\) and to regress during treatment.\(^49\),\(^52\),\(^54\),\(^55\) These studies suggest that MRI is superior to duplex ultrasound for the assessment and follow-up of disease activity.

CT and MRI have become indispensable for the evaluation of aortitis and aortic aneurysms in GCA and other inflammatory large-artery disorders such as Takayasu arteritis, periaortitis, and inflammatory aortic aneurysm. MRA is already being widely used for the evaluation of peripheral arterial disease. Today’s high-end MR-scanners produce good quality angiographies that can clearly depict the typical tapered stenoses of large-vessel vasculitis (Figure 2). Morphological analysis of the arterial wall of medium-sized and small arteries is feasible with modern MR-technology, but these applications must still be considered experimental. Presently, duplex sonography is more widely available and offers superior resolution of the arterial wall and better quantification of the degree of stenosis in these peripheral arterial segments.

**Digital subtraction angiography**

Digital subtraction angiography (DSA) is still considered the gold standard for the diagnosis of obliterating arterial disease. A long, smooth or beaded
appearance of arterial stenoses is suggestive of vasculitis on angiography. However, these findings are not specific. Beaded stenoses are also typical of fibromuscular dysplasia medial type, and long, smooth arterial narrowing may be seen in other non-inflammatory conditions such as post-interventional myointimal hyperplasia, ergotism or after dissection. Angiographic diagnosis of femoropopliteal GCA is particularly difficult due to the similarity and overlap with arteriosclerotic peripheral arterial disease. Characteristic tapering of the artery or beaded configuration of the stenosis are missing in many patients. Extensive involvement of the deep femoral artery (Figure 11A) and spontaneous dissection (Figure 11B) may indicate GCA in this vascular region. The angiographic appearance of GCA may, however, be almost indistinguishable from arteriosclerotic vascular disease. This is particularly the case in patients with extensive obliteration of the femoropopliteal and crural arteries.

At our institution we perform DSA only in patients with severe ischemia, in whom we consider revascularization. With increasing use of duplex sonography, MRI and CT, DSA has become dispensable for the majority of patients with suspected extracranial GCA, and would therefore represent an unnecessary exposure of the patients to the risks of arterial puncture, iodinated contrast medium and radiation.

Fluorine-18-desoxyglucose positron emission tomography
Fluorine-18-desoxyglucose positron emission tomography (18F-FDG-PET) has recently shown promising results for the detection of arterial wall inflammation in large-vessel vasculitis. 18F-FDG-PET can be used as a whole-body...
screening tool, and this method has the potential of detecting arteritis in very early stages, before the occurrence of manifest arterial stenosis. Accordingly, several studies have demonstrated the usefulness of 18F-FDG-PET for the detection of large-vessel vasculitis in patients with fever of unknown origin or unexplained systemic inflammation but without clinically manifest vascular symptoms.68,69

18F-FDG-PET was shown to have a sensitivity of 92% and a specificity of 100% for the initial diagnosis of Takayasu arteritis, and to correlate with clinical disease activity during follow-up.61 Vascular tracer uptake in the aorta and in peripheral arteries was detected by 18F-FDG-PET and also in patients with GCA.23,59,62,63,65,67 In a recent study, Blokhmans et al.63 found a positive vascular 18F-FDG uptake in 29 of 35 (83%) patients with biopsy proven GCA, who did not have clinical symptoms of peripheral ischemia. Increased 18F-FDG uptake was most frequent in the subclavian artery (74%), followed by the aorta (51%) and the femoral arteries (37%). This study reinforces impressively the assumption that GCA is a generalized vascular disease in the majority of patients (Figure 12). The interpretation of 18F-FDG-PET in GCA is, however, more difficult than in Takayasu arteritis. GCA patients are usually old and frequently have concomitant arteriosclerosis. Arteriosclerotic vascular disease has been shown to cause enhanced vascular 18F-FDG uptake.58,69 Only very few studies of 18F-FDG uptake in vasculitis included an age-matched control group. In one study,67 18F-FDG uptake of the thoracic aorta and subclavian arteries was positive in 54% of GCA patients and in 2% of controls. However, 77% of the patients with GCA and 23% of controls had enhanced vascular 18F-FDG uptake in the femoral arteries. This study indicates that 18F-FDG-PET may have a good specificity for extracranial GCA of the aorta and the proximal arteries to the arms, but that positive results have to be interpreted with caution in the femoropopliteal region. Duplex ultrasound proved very useful for the interpretation of 18F-FDG-PET in our patients with GCA. In our experience, femoropopliteal 18F-FDG uptake can be regarded as an indication of extracranial GCA only in patients without generalized arteriosclerosis and with the typical sonographic signs of vasculitis (Figure 8A–C).

Widespread use of 18F-FDG-PET is restricted by high costs, limited availability and the relatively high radiation burden. Moreover, the specificity of 18F-FDG uptake in peripheral arteries of patients with GCA requires further study. 18F-FDG-PET is nonetheless a very promising technique for the evaluation of large-vessel vasculitis in selected patients. In vasculitis patients presenting with unspecific symptoms such as fever of unknown origin or chronic anemia and thrombocytosis, 18F-FDG-PET is already today an important diagnostic tool. 18F-FDG-PET may also become a very useful method for monitoring disease activity in patients with persistent systemic inflammation or with progression of the disease in spite of immunosuppressive treatment.

**Medical treatment**

When treating patients with GCA, the primary aim is to prevent progression of vascular damage and serious vascular complications by suppression of the inflammatory process. Glucocorticoids remain the mainstay of treatment in GCA. Virtually all patients respond to initial glucocorticoid treatment with quick resolution of systemic symptoms and normalization of the laboratory signs of inflammation. Many years of experience have shown that glucocorticoid treatment is effective in halting the inflammatory process and in preventing the progression of the disease. Prednisone is usually started at doses between 40 mg and 60 mg per day, although occasional patients require higher initial doses to attain remission.1,2 In a recent study, induction treatment with a 3-day course of 15 mg/kg i.v. methylprednisolone was superior to standard treatment with oral prednisone started at 40 mg per day.70 Initial treatment with high-dose i.v. glucocorticoid pulses resulted in a more stable remission, subsequently allowing more rapid tapering of oral glucocorticoids, and a lower cumulative glucocorticoid dose. Parenteral, high-dose glucocorticoids have previously been suggested for the initial treatment of GCA patients presenting with acute visual loss,71 although this treatment regimen is controversial.72 Patients with extracranial GCA, who are at a high risk of severe peripheral arterial complications, might also benefit from a higher initial glucocorticoid dose. However, this hypothesis has not yet been investigated in a clinical study.

The initial prednisone dose should be continued until systemic symptoms have disappeared, and blood markers of inflammation have returned to normal. This usually takes 2–4 weeks. There is no consensus on how quick the prednisone dose should be tapered after initial remission is obtained. We usually reduce the dose by 10 mg every 2 weeks until the dosage reaches 20 mg/day, then by 2.5 mg every 2 weeks until a dosage of 10 mg/day. Below 10 mg/day we recommend a slower reduction by approximately 1 mg every 4 weeks. The aim is to achieve a low maintenance dose – possibly below 7 mg/day – without inducing relapses. The total duration of glucocorticoid treatment is usually 2 years. Unfortunately, 30–50% of the patients will experi-
ence relapses during reduction of the glucocorticoid dose. These patients require high doses of glucocorticoids over long periods of time, and are at great risk to suffer serious treatment-related side effects and complications. Adjunctive treatment with cyclophosphamide, dapsone, and azathioprine has been tested in individual patients and small trials, but the glucocorticoid-sparing effect of these drugs is not convincing. Methotrexate was studied in three randomized, double-blind, placebo-controlled trials. Only one of these trials could demonstrate a benefit of methotrexate treatment. Anti-TNF-α agents have recently shown promising results in patients with difficult-to-treat Takayasu arteritis. However, the first randomized, double-blind, placebo-controlled trial of infliximab in GCA was discontinued early due to lack of efficacy. These studies emphasize that long-term medical treatment of patients with GCA remains a clinical challenge. We usually treat the first relapses by increasing the prednisone dose to 20–40 mg/day and attempt slow dose-reduction anew. After several relapses, methotrexate is considered the first-line corticosteroid-sparing agent by most clinicians, in spite of the weak evidence for its efficacy. It is our impression that patients with generalized disease and extensive extracranial involvement require higher glucocorticoid doses and more aggressive immunosuppressive treatment than patients with localized disease. Possibly, these patients may represent a subgroup which would benefit from anti-TNF-α treatment in a similar way as has been shown in Takayasu arteritis. However, prognosis and response to treatment has not yet been studied systematically in extracranial GCA.

Aspirin and anticoagulants have been shown to reduce the risk of ischemic complications in patients with newly diagnosed GCA. In addition to its antithrombotic effects, aspirin may have beneficial anti-inflammatory actions in large-vessel vasculitis. Whether antithrombotic treatment has a clinically relevant effect on top of glucocorticoids in preventing disease progression and new ischemic events during treatment, is however unknown. It is probably prudent to treat patients with extracranial GCA with an anti-platelet agent in addition to glucocorticoids, particularly in cases with symptoms of ischemia. The potential benefit of antithrombotic treatment has, however, to be individually weighted against increased risk of bleeding.

**Vascular interventions**

The decision to perform invasive vascular procedures in patients with large-vessel vasculitis is always difficult. As a general rule, elective vascular reconstruc-

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not at risk. As in Takayasu arteritis, surgical revascularization is probably superior to percutaneous intervention in GCA patients with critical limb ischemia.

Aortic aneurysms of patients with GCA are generally treated according to the same recommendations as for arteriosclerotic aneurysms. Epidemiological data on the natural history of GCA-related aneurysms is insufficient to allow for specific recommendations in these patients. Unlike in arteriosclerosis, aneurysms of GCA patients affect more frequently the thoracic aorta and appear to be more prone to dissection. These factors make screening more difficult, and suggest that follow-up examinations may be warranted at shorter intervals in these patients.

**Future perspectives**

Today, modern vascular diagnostic techniques allow us to perform detailed non-invasive studies of the true degree of extracranial involvement in patients with GCA. Preliminary data suggest that GCA may in fact be a generalized vascular disease in the majority of patients. Systematic studies are now needed to characterize the distribution of symptomatic and asymptomatic peripheral arterial involvement in these patients. These studies will help to clarify the impact of extracranial involvement on the course of the disease, the response to treatment, and the prognosis of these patients.

Increasing insight into the pathophysiology of large-vessel vasculitis will generate new treatment strategies, which will have to prove their ability not only to suppress laboratory signs of inflammation, but also to stop the progression of vascular damage. Subjective symptoms and global markers of inflammation such as ESR or plasma CRP have long been recognized as insufficient surrogate parameters for disease activity. Again, modern vascular diagnostics offers new opportunities to monitor non-invasively disease activity in the arterial wall, thus greatly facilitating the evaluation of the efficacy of new treatments.

It is very likely that peripheral arterial disease of the lower-limb arteries due to large-vessel vasculitis has long been underestimated or misinterpreted as an aggressive form of obliterating arteriosclerosis. Catastrophic outcomes are no rarity in these patients, and are usually the consequence of delayed diagnosis and treatment. Increasing engagement of vascular medicine in the interdisciplinary management of patients with large-vessel vasculitides will hopefully improve the prevention and treatment of serious vascular complications.

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