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Review

Giant cell arteritis: A review of classification, pathophysiology, geoepidemiology and treatment

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ABSTRACT

Giant cell arteritis is a chronic vasculitis affecting large and medium-sized arteries, most commonly the temporal and other cranial arteries. Temporal artery biopsy has long been the gold standard for establishing the diagnosis of giant cell arteritis. There is growing evidence that simultaneous color Doppler and duplex ultrasonography of temporal arteries of GCA patients represents a valid alternative for this somewhat invasive procedure. Ultrasonography and other imaging modalities such as magnetic resonance imaging and positron emission tomography have also provided evidence that involvement of the aorta and its proximal branches is much more common in giant cell arteritis than previously appreciated; it will be important to clarify whether these patients need to be treated more aggressively. It has long been known that patients with giant cell arteritis face a markedly increased risk of developing aortic aneurysms and of dying from aortic dissection. This raises important questions as to whether patients should be screened regularly for extra-cranial large-vessel involvement and whether and how treatment of patients with positive screening results should be adjusted. In this review we discuss the pathophysiology of this disease and also the issues of epidemiology and sex differences.

Contents

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1. Introduction

Giant cell arteritis (GCA) is a chronic systemic vasculitis affecting large and medium-sized arteries containing an elastic lamina. It is also called Horton's disease after the physician who gave the first detailed description of pathologically confirmed GCA in 1932. Another name is temporal arteritis because GCA commonly affects the superficial temporal arteries along with the ophthalmic, posterior ciliary and vertebral arteries, while the intracranial arteries are usually spared. In these vessels, arteritis causes intimal hyperplasia, leading to stenosis or occlusion and resulting in a variety of cranial ischemic manifestations. It has long been recognized, however, that GCA is a truly systemic disease and can affect large vessels outside the cranium, particularly the aorta and its proximal branches. Involvement of extra-aortic large vessels most often affects the upper extremities, in particular the subclavian, axillary, and proximal brachial arteries. Lower extremity vasculitis is somewhat less frequent and most often involves the internal iliac artery; common, superficial and deep femoral arteries; and the popliteal and anterior tibial arteries [1,2]. As in cranial arteries, arteritis in these vessels can lead to stenosis and occlusion, resulting in ischemic manifestations. In contrast, when GCA affects the aorta, it does not cause obstruction, but instead can result in aortic dilatation and aneurysm formation, which may ultimately lead to aortic dissection or rupture.

There is considerable overlap between GCA and polymyalgia rheumatica (PMR), with co-occurrence being 38 times more frequent than would be expected if they were truly independent syndromes [3]. In Scandinavian countries, the term GCA encompasses the syndromes of temporal arteritis and PMR occurring either alone or together. Approximately 30–50% patients with GCA have symptoms of PMR before, concomitant with, or after the diagnosis of GCA [3–10]. PMR is characterized by aching and morning stiffness in the neck, shoulder and pelvic girdle, accompanied by a systemic inflammatory response, manifested as elevated acute phase reactants. Rapid response to corticosteroids is one of its diagnostic criteria, but generally lower doses (initially 10–20 mg/d) than are used for the treatment of GCA are sufficient. Like GCA, PMR affects almost exclusively people over the age of 50 years, and women more frequently than men, but it is at least 2–4 times more frequent than GCA [3,11,12]. The immunogenetics of the two disorders show some overlap, but also some clear differences [13]. Therefore, the precise nature of the relationship between the two syndromes remains to be elucidated.

2. Epidemiology

GCA is the most common type of vasculitis affecting people aged ≥50 years. It very rarely affects people younger than 50 years of age, and the incidence rises markedly with increasing age, peaking in the eighth decade of life. Incidence rates of TA/GCA vary between 1 and $30/10^5$ aged ≥50 years (see also Table 1). The highest frequencies have been reported from Scandinavian countries and populations of predominantly Scandinavian descent, such as Minnesota, U.S.A. [6,14], but also the UK [3]. Incidence rates in southern Europe and Israel are intermediate. GCA seems to be infrequent in people of African, Asian, Hispanic and Arab descent, but data are sparse and somewhat conflicting [14–18]. Prevalence of GCA is difficult to define and the few available studies have yielded >100-fold differences in prevalence estimates, the highest reported frequency being $278/10^5$ population >50 years in Olmsted County [14]. Of note, large autopsy studies strongly suggest that even this may constitute a considerable underestimate and that the true prevalence of GCA may be ~1% [19]. In most populations of northern European descent, the female:male ratio is 2.5 or higher, but the female predominance is less pronounced in Israel and other Mediterranean countries [20,21], and an essentially even sex distribution has been reported from northern Spain, India, and Turkey [5,22,23].

3. Pathogenesis

Geographical variation, seasonal fluctuations and cyclic patterns have been observed in the incidence of GCA, suggesting an environmental, possibly infectious, etiology of the disease [3,6,7,12,14,20]. Indeed, in Denmark, some of the incidence peaks co-occurred with

Table 1
Incidence of temporal arteritis per 100,000.

Country	Years	Biopsy-proven (%)	Incidence overall	Incidence in the population ≥50 years	Incidence in females	Incidence in males	Female:male	Mean age	Age of peak incidence	Reference
US, Olmsted	1950–1999	87.3	n.a.	18.8	24.4	10.3		74.8	≥80	[6]
	1980–84			28.5	38.0	10.1				
	1985–89			20.7	28.6	7.2				
	1990–94			21.4	25.8	16.6				
	1995–2000			18.5	23.6	12.5				
U.S. Shelby	1971–1980	80.8	0.35	1.58	2.43	0.43		72	70–79	[148]
Sweden	1976–1995	100	7.7	22.2	29.8	12.5		n.a.	n.a.	[149]
	1976			9.6	11.6	7.1				
	1986			22.9	29.9	13.9				
	1995			30.1	40.5	17.0				
UK	1990–2001	n.a.	22	n.a.	n.a.	n.a.	2.6	72.8	≥ 80	[3]
Israel	1980–2004	82	n.a.	11.3	13.1	9.1	1.4		≥75	[20]
Spain	1981–2005	100	n.a.	10.13	10.23	9.92		75.0	70–79	[5]
	1981–85			3.18	2.94	3.46				
	1986–90			8.15	6.25	10.37				
	1991–95			10.53	9.57	11.66				
	1996–2000			15.90	17.66	13.82				
	2001–05			12.92	14.72	10.80				
Italy	1980–1988	46.5	2.8	6.9	7.8	5.8		67.6	70–79	[21]
New Zealand	1996–2005	100	n.a.	12.73	21.30	8.80	2.9:1	72.8	≥75	[7]
Iceland	1984–1990	94	n.a.	27.00	36.00	18.00	2.40	71.9	70–79	[91]
Turkey	2002–2008	68.4	n.a.	1.13	1.14	1.1		70	n.a.	[23]

epidemics of *Mycoplasma pneumoniae*, others were partly related to *Chlamydia pneumoniae* and parvovirus 19 epidemics [12]. However, no clear association of GCA with any particular infectious organism has been identified to date. Cases of familial aggregation of GCA, at times with complete sharing of the HLA genotype, suggest that there also is a genetic component [24]. In most populations studied to date, GCA is associated with carriage of HLA-DRB1*04 alleles, most frequently DRB1*0401, but also *0404 [13,25]. An association of PMR with the same alleles has been reported in some populations, but is lacking in others [13]. Rheumatoid arthritis is also associated with the HLA-DRB1*04 haplotype, particularly with alleles that carry the "shared epitope", and homozygosity for this sequence motif strongly increases susceptibility to this autoimmune disease. There are conflicting data on the association of GCA with the shared epitope, but homozygosity is rare in GCA and does not increase disease susceptibility. Other polymorphisms that have been reported to contribute to genetic susceptibility to GCA include genes encoding a variety of cytokines and growth factors, in particular interleukin (IL)-6, interferon (IFN)γ, tumor necrosis factor (TNF)α, IL-10, and vascular endothelial growth factor (VEGF), the enzymes metalloproteinase-9 (MMP-9), endothelial nitric oxide synthase, and myeloperoxidase, and the pathogen-associated molecular pattern recognition receptor toll-like receptor 4 (TLR4), although the results are not always consistent across populations [25].

3.1. Histopathology

The typical histopathology of GCA consists of an inflammatory infiltrate in all three tunics of the arterial wall with giant cells forming granulomas in the media, particularly at the intima–media border [26,27]. The elastic lamina is fragmented or obliterated, and medial vascular smooth muscle cells are destroyed. The arterial lumen can be partially or completely occluded due to intimal hyperplasia, which leads to the ischemic complications commonly observed in GCA. There is considerable variation in the histopathology not only between patients, but also within the same sample. Giant cells may be absent both in the early evolving state and in the late healing phase of the disease, consequently they are detected in ~60–70% of samples. In the late stages, the intima may no longer be infiltrated or the infiltrate may be sparse. In the media, smooth muscle cells are eventually replaced by fibrous tissue.

3.2. Dendritic cells

There are data suggesting that inappropriate activation, maturation and retention of dendritic cells (DCs) in the adventitia constitutes one of the earliest steps in the pathogenesis of GCA and that subsequent events are dependent on DC-induced T cell activation [28,29]. Of note, the toll-like receptor (TLR) profile of DCs in large and medium-sized human arteries is vessel-specific [30], while the type of arteritis resulting from TLR ligation is ligand-specific [31]. This provides further evidence that bacterial agents may be involved in the triggering of GCA and affords some insights into the tissue tropism of the various forms of vasculitides.

3.3. T lymphocytes

Several lines of evidence indicate that GCA is a T cell-mediated disease. 1) The infiltrate in the arterial wall of patients with GCA consists primarily of T cells and macrophages, with few to no B cells [32,33]. Polymorphonuclear cells, in particular neutrophils, are rare and most often completely absent. The T cells are predominantly of the CD4+ phenotype, although CD8+ T cells can constitute up to 46% of the infiltrating T lymphocytes in individual patients [34]. The highest number of both CD4 and CD8 T cells was found in the adventitia, followed by the intima, whereas few lymphocytes were detected in the media. In addition, 2) GCA is associated with specific HLA-DRB1 alleles; 3) the formation of granulomas is known to be dependent on T lymphocytes, particularly the CD4+ subset; 4) T cells infiltrating GCA lesions show signs of activation such as MHC class II and CD25 (IL-2 receptor) expression [32,33]; 5) there is evidence of selective clonal T cell expansions in temporal artery biopsy specimens obtained from GCA patients, which are not detected in peripheral blood from these patients [34–36], and 6) depletion of T cells in an experimental model of temporal arteritis attenuated inflammation [37]. These and other studies provide evidence that the immune response in GCA is driven by one or more antigen(s) that is/are enriched in temporal artery tissue of GCA and PMR, but not in uninflamed temporal arteries [35]. Note, however, that the T cell expansions are oligoclonal or polyclonal and there is limited overlap in the usage of specific Vβ gene segments between patients [34], and no sequence homology was detected in the TCR β chains of different patients [35]. This suggests that there is highly diverse TCR usage in the response to one or a few antigens, or that multiple antigens are involved.

There is some evidence that two types of T cells play an important role in GCA: Th1 and Th17 cells. Temporal artery tissue from patients with GCA expresses significantly higher levels of IFNγ mRNA compared to control specimens without evidence of arteritis [38,39]. There are data suggesting that a chronic course of GCA is attributable to the relative resistance of IFNγ expression to corticosteroid therapy [39]. However, this is not fully supported by other findings [40]. Furthermore, IFNγ mRNA in the arterial lesions of GCA patients has been found to correlate with the presence of giant cells, ischemic complications, and neoangiogenesis [41,42]. Nonetheless, according to data from 8 patients with GCA, IFNγ-producing T cells represent only 2–4% of T lymphocytes infiltrating the temporal arteries, are almost exclusively localized in the adventitia, and show evidence of recent antigen-specific activation [43]. Unfortunately, these data have not been independently confirmed in a larger patient sample, and it is currently unclear how CD4+ T cells localized mainly in the adventitia orchestrate the formation of granuloma and the activation of macrophages predominantly at the media–intima junction.

The IL-17 family of cytokines usually plays a role in host defense against a variety of bacteria and fungi, but has also been implicated in a variety of other inflammatory responses, including autoimmune diseases and vasculopathies. It has been shown that IL-17 is expressed in temporal arteries of untreated GCA patients, but not in uninflamed arteries and that IL-17+ cells are expanded in the peripheral blood of GCA patients [39]. Tissue IL-17 production was suppressed and the frequency of peripheral Th17 cells normalized after initiation of corticosteroid treatment. This paralleled not only the reversion of the typical symptoms of GCA, but also the development of plasma IL-1β and IL-6 levels, which were shown to promote Th17 cell differentiation. At the same time, it is known that IL-17 can induce macrophages and other cell types to produce pro-inflammatory cytokines. Together, these data suggest that IL-17 could be responsible for many of the acute manifestations, particularly the constitutional symptoms, of GCA.

3.4. Macrophages

It is also thought that IFNγ is a major factor in the activation of macrophages in GCA lesions, although there is only limited evidence for this [37]. Macrophages constitute the actual effector cells in GCA. It has been shown that they are the major source of a variety of cytokines in arteritic lesions, including IL-1β, IL-6, TNFα, transforming growth factor (TGF)β and IL-32 [38,44–47]. Transcript and protein levels of these cytokines have been shown to be significantly overexpressed in temporal artery specimens from GCA patients compared to non-arteritic controls, particularly in the media near the internal elastic lamina [44–46].

The precise role of these pro-inflammatory cytokines in GCA largely remains to be elucidated. However, in particular IL-6 plays a central role in the induction of an acute phase response, which is pronounced in GCA, and tissue transcript levels of IL-1β and IL-6 correlated with a strong systemic inflammatory response [48]. In addition, IL-6 mRNA and protein levels in GCA lesions as well as circulating levels of IL-6 were inversely associated with the occurrence of disease-related ischemic events [44]. This is in keeping with other studies showing an inverse association between a strong systemic or laboratory inflammatory response and ischemic complications [49–51]. In addition, a negative correlation between tissue angiogenesis and ischemic events has been reported [52]. In vitro and ex vivo, IL-6 was demonstrated to be a potent inducer of angiogenesis, suggesting that this could constitute a compensatory mechanism for ischemia—thereby providing a possible explanation for the inverse correlation between IL-6 expression and ischemic events [44]. Of course, this does not refer to the neoangiogenesis occurring in the intima and media of GCA lesions, but to the potential to form collateral vessels. It remains to be established whether tissue angiogenic activity as measured by the formation of neovessels in the intima and media correlates with the ability to form collaterals. The importance of IL-6 in the pathogenesis of GCA is further demonstrated by case reports of successful treatment of GCA patients with IL-6 blockade [53,54].

Lesional macrophages are also the major producers of metalloproteinases (MMPs), which are known to be upregulated by proinflammatory cytokines, in particular IL-1β and TNFα. The full system required for the activation and regulation of MMP-2 and MMP-9 has been demonstrated to be present and active in GCA lesions [47,55,56]. These two MMPs are capable of degrading elastin, and are therefore implicated in the destruction of the internal elastic lamina, which in turn facilitates the migration of medial myofibroblasts into the media, where their proliferation causes intimal hyperplasia and luminal obstruction. Macrophages in GCA lesions also overexpress platelet-derived growth factor (PDGF)-A and -B [57], which can potently stimulate migration and proliferation of temporal artery-derived myointimal cells [58]. Expression of these growth factors correlated with the degree of intimal hyperplasia, which in turn was associated with the presence of ischemic complications [57]. There are, however, data suggesting that they may also play a role in tissue repair [40]. Macrophages and giant cells in GCA lesions were also identified as major sources of VEGF, and transcript levels of this growth factor correlated with the degree of neovascularization [42]. Importantly, neovessels particularly at the intima–media junction have been shown to be the major site of constitutive and inducible adhesion molecule expression in GCA [59]. Therefore, angiogenesis is likely to be crucial for the recruitment of leukocytes into the media and intima. In addition, macrophages in GCA lesion are sources of reactive oxygen species and reactive nitrogen intermediates, which have been implicated in the apoptosis of vascular smooth muscle cells [60,61].

In addition to tissue-infiltrating macrophages, the majority of circulating CD68+ monocytes of GCA patients is also activated and produces IL-6 and IL-1β mRNA and protein [62]. This systemic activation of monocytes was also observed in PMR patients, suggesting that it is independent of vascular inflammation. Of note, circulating IL-6 levels promptly respond to corticosteroid therapy, but rebound quickly after short-term withdrawal of corticosteroids even after months of therapy. They can remain elevated despite normalization of acute phase reactants, and may represent a better marker of disease activity compared to ESR or CRP [63], although it remains unclear whether patients with persistently elevated IL-6 would benefit from more aggressive corticosteroid treatment.

4. Presentation

Temporal arteritis is the most typical presentation of GCA, consisting of a broad spectrum of clinical and laboratory abnormalities that are attributable to ischemia on one hand and systemic inflammation on the other hand (see also Table 2). Common ischemic complications include headache, scalp tenderness, and jaw claudication. Frequent manifestations of systemic inflammation are PMR as well as fatigue, general malaise, fever (generally ~38 °C, but occasionally reaching 40 °C), anorexia, weight loss, and night sweats. This is accompanied by elevated acute phase reactants in >90% of patients, although very different cut-off points have been used in various studies. Other laboratory disturbances include liver enzyme abnormalities, thrombocytosis, and generally mild normocytic normochromic anemia, each occurring in between one third and one half of all patients [4,10,64,65].

The most dreaded ischemic complication is visual loss. Visual manifestations usually are among the presenting symptoms or develop shortly after the diagnosis in ~30% of patients and range from transient diplopia and amaurosis fugax to sudden unilateral or bilateral partial or complete visual loss, (see also Table 2). Permanent visual loss affects ~15% of patients. In particular amaurosis fugax is an ominous warning sign of impending permanent visual loss, although loss of sight can also occur without premonitory signs. Once visual loss is established, it is almost always permanent, but it can be prevented by early intervention. Therefore, GCA represents a medical, particularly an ophthalmological, emergency. In the vast majority of cases, loss of vision is due to arteritic anterior ischemic optic neuropathy (AAION), which is almost always caused by narrowing or occlusion of the posterior ciliary arteries. Funduscopy in early AAION reveals slight pallor and edema of the optic disk, scattered cotton–wool spots and small hemorrhages, but by the second day after onset of visual loss the disk becomes chalky white in the majority of patients [66]. Visual field testing generally shows marked constriction of the visual field. Of note, a chalky white disk is also one of the most helpful characteristics in distinguishing AAION from non-arteritic AION [67]. Loss of sight can also stem from central retinal artery occlusion, retrobulbar optic neuritis, or posterior ischemic optic neuritis.

Other rare ischemic manifestations include cerebrovascular accidents (transient ischemic attacks and strokes) and myocardial infarctions. For example, ~2–4% of GCA patients experience strokes—frequently in the vertebrobasilar territory—between the onset of symptoms and 4 weeks after initiation of corticosteroid therapy [51,68]. Other neurological manifestations include peripheral mononeuropathies and polyneuropathies in up to 14% of GCA patients [9,69], most commonly involving the median nerve, followed by the brachial plexus.

Predictors of cranial ischemic events in general and visual loss in particular are transient ischemic manifestations, especially amaurosis fugax and possibly jaw claudication [70–72]. In addition, an inverse association has been observed between clinical or laboratory indicators of a strong initial inflammatory response and the occurrence of ischemic manifestations, including permanent visual loss [44,49,51,70].

Various subtypes of temporal arteritis have been described, including an “occult” variant with ocular manifestations in the absence of systemic signs and symptoms [67], and a “silent” variant characterized by pronounced systemic symptoms and the absence of typical cranial manifestations [10,73]. Patients with silent GCA often present with fever of unknown origin. Most importantly, GCA is a truly systemic disease that can involve large vessels outside the cranium, particularly the aorta and its primary branches. The findings of recent imaging studies suggest large vessels are involved in at least 50% and possibly close to 100% of GCA patients at diagnosis, although they frequently remain asymptomatic [74,75]. In 20–80% of GCA patients with symptomatic large-vessel involvement, signs and symptoms of upper and/or lower extremity vasculitis are among the presenting manifestations and precede the diagnosis of GCA by up to 12 months [1,2,76,77]. Importantly, patients with large-vessel GCA frequently do not exhibit the typical manifestations of cranial GCA, such as headaches, scalp tenderness, temporal artery abnormalities, and possibly visual symptoms [1,77–79]. However, PMR and constitutional symptoms are seen with similar frequency at

Table 2
Manifestations of GCA at presentation.

	[150]	[7]	[8]	[9]	[10]	[15]	[4][a]
	1981–2004	1996–2005	(14 years)	1986–2003	1977–2002	1983–2004	
	N = 240	N = 70	N = 75	N = 96	175	102	
Manifestation	Lugo, Spain	Otago, New Zealand	Barcelona, Spain	Tunisia	Limoges, France	Riyadh, Saudi Arabia	
Visual overall	23.3			34			0.37 (0.30–0.44)
Amaurosis fugax		10	8	5	19.4		
Diplopia				1			0.09 (0.07–0.13)
Permanent visual loss	12.9	14.3	10.6	11	12.6		
Jaw claudication	40.8	24.3	45	41	39.4	8.8	0.34 (0.29–0.41)
Abnormal temporal artery	72.9		81	85	60.3	17.6	0.65 (0.54–0.74)
Headache	86.4	67.1	80	92	77.1	38	Any 0.76 (0.72–0.79) Temporal 0.52 (0.36–0.67)
Scalp tenderness	33.8	22.9	48	40	51.8	27	0.31 (0.20–0.44)
Fever	9.5	12.9	48	56	54.9	4.9	0.42 (0.33–0.52)
Constitutional symptoms overall	60.8			75	71.2		
Malaise		17.1					
Anorexia		14.3					0.35 (0.23–0.48)
Weight loss		12.9	57	64	51.2	3.9	0.43 (0.35–0.53)
PMR	40	31.4	42.6	56	26.9		0.34 (0.28–0.41)
Elevated ESR		95.7 >20 mm/h		100	93.5 >50 mm/h		0.96 (0.93–0.97) >50 .83 (0.75–0.90)
Elevated CRP				100 (34 tested)	95.1 > 15		
Anemia		2.9			64.1 (20% severe)		0.44 (0.34–0.54)

[a] This column represents a sensitivity analysis of up to 35 studies, with sensitivity being defined as the proportion of patients exhibiting a particular symptom.

presentation. The most common manifestation of upper and/or lower extremity vasculitis itself is unilateral or bilateral upper and/or lower extremity claudication [1,77,79,80]. Digital ischemia and Raynaud's phenomenon may also be present in upper extremity vasculitis, while ischemia, ulcers and gangrene are additional manifestations when the lower extremities are involved. Physical findings consist of decreased or absent pulse in the affected extremity and arterial bruit.

Aortic involvement is most often clinically silent or may manifest only as a systemic inflammatory syndrome, including fever of unknown origin [81,82]. It often goes undetected until an aneurysm is discovered during routine chest radiography or until catastrophic complications occur. Actually, it is not uncommon for giant cell aortitis to be diagnosed only when an autopsy is performed in patients who died from aortic rupture or when a surgical specimen removed at the time of aneurysm repair is biopsied [76,83,84]. There also have been a number of reports of patients dying from aortic dissection shortly after the diagnosis of GCA [76,83,85,86]. This indicates that aortic involvement can be not only an early, but also the first, manifestation of GCA. Indeed, systemic screening has revealed the presence of aortitis in more than half of all GCA patients at diagnosis [74]. If aortitis is symptomatic, patients may complain of back pain, abdominal pain, or dyspnea, depending on the aortic branch involved [80]. An aortic insufficiency murmur may also be detectable.

5. Diagnosis

5.1. Biopsy

A biopsy of an artery showing the typical histological features (inflammatory infiltrate in at least the adventitia and media of the arterial wall with fragmentation of the elastic lamina with or without giant cells) provides the most definite evidence of GCA. Because of its easy accessibility and frequent involvement, the temporal artery is chosen as the biopsy site. A unilateral biopsy is performed on the side with the most prominent symptoms. Some clinicians recommend to immediately analyze frozen sections of the first biopsy and to directly proceed with a biopsy on the contralateral side if this analysis yields negative results. However, the additional diagnostic yield is generally deemed to be too low to justify routinely obtaining bilateral biopsy specimens, although it may add valuable information in selected cases [87,88]. The recommended length of the biopsy sample is between 1 and 2 cm [87,88], but recent data indicate that a threshold length of 0.5 cm (after formalin fixation) is associated with increased diagnostic yield [89].

A positive temporal artery biopsy result is not 100% specific for GCA [90]. Its sensitivity ranges from ~70% to >90%, which underscores that a negative biopsy does not exclude the diagnosis of GCA and some patients must be diagnosed with GCA on clinical grounds alone in the absence of histological evidence [1,6,10,91–94]. Biopsy confirmation of GCA is thought to be important for preventing unnecessary corticosteroid therapy over prolonged periods in patients who do not actually have the disease. However, the need for a biopsy should be carefully considered since biopsy results do not always have a major impact on patient management in clinical practice [95,96].

The focal and segmental nature of the inflammation, resulting in so-called skip lesions [97] is often claimed to explain negative biopsy results in patients with a clinical diagnosis of GCA, but actually is likely to account for only a small percentage of cases [98]. Steroid treatment for 1 or even 2 weeks before the temporal artery biopsy is performed has little effect on the positivity rate, although the histology becomes less typical with longer corticosteroid treatment [99,100]. It should be remembered that GCA does not invariably involve the temporal artery or even cranial arteries. For example, a considerable portion (30–40%) of patients with large-vessel involvement have negative temporal artery biopsy results [1,77], and it is becoming increasingly evident that subclinical large-vessel involvement is much more frequent than previously appreciated [74,75].

5.2. Clinical and laboratory parameters in the diagnosis of GCA

Because the biopsy is not entirely specific and <90% sensitive, the diagnosis of GCA must remain clinical. There are no official diagnostic criteria. Only classification criteria designed to distinguish patients with GCA from patients with other vasculitides have been published [90] (See Table 3). Their use as diagnostic criteria is inappropriate. Two large analyses provide some guidance on the diagnostic value

of the typical signs of symptoms of GCA [4,101]. They underscore that many of the common manifestations of GCA, including constitutional symptoms, PMR, headache, and even the presence of any visual disturbance, are non-specific. Nonetheless, diplopia was associated with a significantly increased positive likelihood ratio (LR, 3.4 and 1.99), but is reported by only ~10% of patients. Jaw claudication is associated with a high LR (>4), but also is not very sensitive, affecting only 30–40% of patients. Temporal artery abnormalities, in particular beading and prominence, are detected with higher frequency and also significantly increased the likelihood of GCA (4.6 and 3.08, respectively), while the absence of any temporal artery abnormality decreased it [4,101]. Importantly, thrombocytosis carried the highest positive LR 5.98 [101] (it was not included in the earlier study) [4]. This agrees with the results of a large U.S. population-based analysis, which found CRP levels > 2.45 mg/dL and platelet counts > 400,000 to be the strongest laboratory predictors of a positive temporal artery biopsy, whereas ESR was not significant in models already including CRP and platelet count [64]. CRP levels have been shown to be more sensitive than ESR, while the combination of the two gives the highest specificity [102].

5.3. Differential diagnosis

The systemic symptoms of GCA are non-specific and require careful differential diagnosis, which includes infections, malignancies and a variety of other vasculitides. In rare cases, Wegener's granulomatosis, polyarteritis nodosa, and microscopic polyangiitis can affect the temporal artery, but exhibit different histopathology. Involvement of respiratory tract, kidney, or skin and the presence of antineutrophil cytoplasmic antibodies are other characteristics that allow differentiation of these vasculitides from GCA. Takayasu's arteritis commonly affects the aorta and its primary branches, but it can be distinguished demographically, since it affects people younger than 40 years, whereas GCA is rarely seen in people aged less than 50 years. Note also that rheumatoid arthritis can occasionally present with pain and stiffness in the pelvic girdle and shoulders resembling the primary manifestation of PMR.

5.4. Imaging techniques in the diagnosis of GCA

5.4.1. Imaging techniques in the diagnosis of temporal arteritis

Complications of the temporal artery biopsy procedure are rare (~0.5%), but include facial nerve injury, eyebrow drooping, skin necrosis, infection, and stroke. In addition, some patients may refuse to undergo this invasive procedure. Over the last years, simultaneous color Doppler and duplex ultrasonography of temporal arteries of GCA patients has emerged as a valid alternative. It typically reveals a dark hypoechoic circumferential wall thickening around the artery lumen, the so-called “halo sign”, which disappears after 2–3 weeks of therapy [103]. The results of two recent meta-analyses indicate that in the hands of experienced ultrasonographers using industry-wide standards for Doppler measurements, a unilateral halo sign has a specificity of 89–91% and a sensitivity of 69–75% for the diagnosis of GCA (depending on the diagnostic standard used for comparison) [104,105]. The presence of a bilateral halo sign improves specificity to 100%, but reduces the sensitivity to 43% [104]. As a result, it has been recommended to include color Doppler ultrasonography as a diagnostic criterion for GCA and to reserve temporal artery biopsies for patients with negative ultrasonography results. In clinical practice, ultrasonography of the temporal artery has already been shown to be as well accepted and equally effective as biopsy results in guiding the treatment of patients [106]. A major drawback or ultrasonography is its operator dependency. High-resolution magnetic resonance imaging (MRI) has been reported to have very similar diagnostic power as ultrasonography [107], but more data are needed before it can be recommended as a diagnostic tool in GCA.

Table 3
Traditional format criteria for the classification of giant cell arteritis [90].

- Age ≥ 50 years
- New onset of or new type of localized pain in the head
- Temporal artery tenderness to palpation or decreased pulsation, unrelated to arteriosclerosis of cervical arteries
- ESR ≥ 50 mm/h (Westergren method)
- Biopsy specimen with artery showing vasculitis characterized by a predominance of mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cells.

When compared to patients with other forms of vasculitis, the presence of at least 3 of the following 5 criteria was associated with a sensitivity of 93.5% and a specificity of 91.2%.

5.4.2. Diagnosis of large-vessel GCA

The diagnosis of large-vessel GCA generally cannot be established by biopsy, but requires imaging techniques. Angiography used to be the reference standard, but a variety of imaging techniques are increasingly taking the place of this invasive procedure with high radiation exposure. These include computed tomography (CT), CT angiography, MRI, and MR angiography (MRA). Ultrasonography can also be used for examining large-vessel involvement, but does not allow evaluation of thoracic arteries [78,108]. High-resolution, and particularly high-field (3 T), MRI can be complemented by MRA to detect extracranial/large-vessel involvement during the same examination as for the cranial involvement. However, there are still insufficient data to evaluate its diagnostic performance [74,75]. 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) can detect vasculitis in earlier stages than angiography and has emerged as a promising diagnostic tool in extracranial GCA, with a sensitivity of ~0.8 and specificity of ~0.89 [109]. Particularly in patients with atypical presentation of GCA, e.g., weight loss, fever, malaise, arm claudication, and a negative temporal artery biopsy, FDG-PET is invaluable and should be the diagnostic technique of choice [110,111]. However, PET has several limitations, including the lack of a standard method for quantifying FDG uptake and its unsuitability for examination of the temporal or other cranial arteries.

6. Treatment and clinical course

6.1. Treatment and course of cranial GCA

High-dose glucocorticosteroids are the only first line effective therapy for GCA, and treatment should be started as soon as the diagnoses has been established and, when there is a strong clinical suspicion of GCA, even before the biopsy results are available, early diagnosis is critical. The optimal dosage has not been determined, but it is customary to start with 40–60 mg/d, some advocate as much as 1 mg/kg/d [87,112]. The typical manifestations of GCA respond very rapidly to corticosteroid therapy, with fever, headache, and PMR symptoms typically resolving within hours to days, whereas some ischemic complications such as jaw claudication take considerably longer. The inflammatory response returns to normal within 2–4 weeks.

Early treatment is particularly important in patients with actual or threatened visual loss because it may avert further deterioration in visual acuity, prevent the involvement of the other eye, and may even allow some visual improvement [71,113]. However, in most cases visual loss that has already occurred at the time that steroid therapy is started is not reversed, and further visual deterioration or loss of vision loss in a previously unaffected eye can occur, particularly during the first week after initiation of steroid therapy [66,114–116]. While there have been reports of improvements in visual acuity after corticosteroid therapy, such partial recovery is rarely accompanied by amelioration in visual field [113,114]. This suggests that it may stem from patients learning to view eccentrically rather than a representing a real improvement in visual function. A strong predictor of

threatened visual loss is the occurrence of transient ischemic visual manifestations, in particular amaurosis fugax [49,70,71]. Conversely, numerous studies show an inverse association between a strong initial inflammatory response (either clinical or laboratory or both) and the risk of ischemic complications [49–51,70]. Patients with actual or threatened visual ischemic complications are often treated with i.v. pulse methylprednisolone, usually 1 g/d for three days, even though evidence for the effectiveness of this approach is limited to some observational studies [117,118] and not confirmed in others [115].

Once all reversible signs and symptoms have subsided and ESR has returned to normal, usually after 2–4 weeks, corticosteroids should be gradually tapered. Note that tapering should not be in the form of alternate day therapy since this increases the risk of relapses [87]. Treatment duration is highly variable, with a majority of patients being able to discontinue corticosteroids after 1–2 years. Some patients with GCA can quite rapidly taper corticosteroids and achieve permanent remission [119–121]. However, 40–50% of patients experience relapses during corticosteroid tapering and/or recurrences after corticosteroid withdrawal [119,122]. In some patients, the disease takes a relapsing chronic course requiring indefinite treatment with low-dose corticosteroids. Relapses can occur at any time during corticosteroid tapering [121,122], the main clinical manifestations being headaches, PMR, and constitutional symptoms, whereas visual manifestations are rare [8,119]. Relapses are often accompanied by elevated acute phase reactants; anemia and thrombocytosis are additional laboratory findings in a subset of relapsing patients. The results from a small clinical trial indicated that addition of i.v. methylprednisolone at 15 mg/kg/d for 3 days to the regular therapeutic regimen of 40 mg/d allowed more rapid tapering of the glucocorticosteroid dose to $\leq$5 mg/d and was associated with fewer relapses compared to 40 mg/d plus saline [123]. However, this induction therapy did not significantly affect the occurrence of treatment-related adverse events. In another trial, lower dose (240 mg/d) i.v. pulse therapy did not show any steroid-sparing effect [124]. Recurrences of the disease after the complete withdrawal of corticosteroids can occur in 20–30% of patients overall and are seen most commonly during the first year after corticosteroid termination [119,121]. Whether a patient ultimately is able to achieve complete remission does not seem to be influenced by relapses and recurrences [122]. The few predictors of relapses or recurrences that have been identified to date all relate to the inflammatory response at diagnosis and include a higher number of clinical inflammatory parameters [8], ESR [125], and anemia [119].

6.2. Treatment and course of large-vessel GCA

Patients presenting with symptomatic large-vessel GCA with or without typical symptoms of cranial GCA are treated with corticosteroids at the same doses as patients with cranial GCA, although it is currently not known whether they would benefit from higher doses. If involvement of the upper and/or lower extremities occurs after the diagnosis of GCA, it frequently manifests within a few months of initiation of corticosteroid therapy [1,2,79,126]. Thoracic aortic dissection also appears to be an early complication of GCA, occurring after a median of 1.1 years, and in 4 of 30 patients with aortic aneurysm and/or dissection developed in the absence of documented aortic aneurysm [126]. This suggests that corticosteroid doses sufficient to revert the signs and symptoms of temporal arteritis may be inadequate to suppress or prevent vasculitis of the large arteries. However, upper or lower extremity involvement may occur long after corticosteroid withdrawal, and aortic aneurysms also most commonly represent late complications. In a large retrospective study, median time from diagnosis of GCA to diagnosis of thoracic and abdominal aortic aneurysm was 10.9 years and 6.3 years, respectively [126]. Interestingly, unlike thoracic aortic dissection, abdominal aortic dissection was not an early complication, developing a median of 7.6 years after the diagnosis of GCA.

Data on the long-term evolution of large-artery involvement are sparse. The response to corticosteroids is slower than the rapid symptomatic relief experienced by patients with cranial GCA, with claudication and other signs and symptoms taking weeks to months to improve [127]. After a median follow-up of 32 months (range 1–181) 44% of patients with symptomatic upper and/or lower extremity vasculitis experienced complete resolution of clinical signs and marked improvement or healing of lesions seen on imaging, another 44% improved, the remainder worsened [1]. Similarly, the inflammatory lesions detected by ultrasonography in the proximal arm arteries of patients with GCA, some of whom remained asymptomatic, completely resolved in 30% of patients, improved in 53%, remained unchanged in 8%, and worsened in 10% over a mean follow-up of 40 months [127]. However, approximately 25% of patients with upper and/or lower extremity vasculitis related to GCA require revascularization surgery (venous bypass graft, angioplasty, thromboendarteriectomy, or thrombectomy) [1,2]. Limb amputation may be necessary in 5–10% of patients [1,2,76].

In 34 patients with aortitis detected by routine CT scan at diagnosis or when the patient became symptomatic, CT scans at 6 months of follow-up showed disappearance of aortitis in 3 (9%), improvement in aortitis in 47%, unchanged in 41%, and deterioration of aortic thoracic aneurysm in 1 [80]. During a median follow-up of 16 months (range 9–120 months), aortic thoracic aneurysm developed in 3 patients overall, aortic abdominal aneurysm in 1, but no dissections occurred. In this and other series, at least 40% of patients with aortic aneurysms require surgery for resection and/or aortic valve replacement or repair [80,84,128]. Dissection of aortic aneurysms also is associated with a dramatic increase in mortality [129].

Patients with GCA were found to face a more than 17-fold higher risk of thoracic aortic aneurysm compared to the general population [130]. They were also 2.4 times more likely to develop isolated abdominal aortic aneurysm, although this failed to reach statistical significance. Population-based studies from Minnesota and northern Spain yielded almost identical incidence for aortic aneurysm and/or aortic dissection, namely 18.7 and 18.9 per 1000 person-years at risk [126,131], although the results of systematic screening for aortic aneurysms suggest that these may be underestimates of the true incidence [128]. The incidence of large-artery stenosis was 13.5 per 1000 person-years at risk [126]. Overall, 27% of patients with GCA develop symptomatic large artery complications during a median follow-up of 7.6 years.

Prognostic factors for the development of extra-aortic large-vessel involvement have not been investigated. The search for predictors of aortic aneurysmal has yielded conflicting results, but in two large retrospective studies, the following risk factors were identified: hypertension at the time of diagnosis, PMR in association with severe abnormalities of laboratory markers of inflammation [131], aortic insufficiency murmur at diagnosis of GCA, and hyperlipidemia or coronary artery disease at any time during follow-up [126]. FDG uptake at diagnosis may be able to predict aortic dilatation late in the course of GCA, but this awaits independent confirmation [110].

6.3. Adverse events of corticosteroid therapy and steroid-sparing adjunctive therapy

At least 50% of GCA patients experience one or more of the adverse events that are commonly associated with corticosteroid therapy [122,132]. These include posterior subcapsular cataract, infections, hypertension, gastrointestinal bleeding, diabetes mellitus and avascular necrosis of the hip. Because corticosteroid therapy also induces osteoporosis, thereby increasing the risk of bone fractures, bone protection measures (calcium, vitamin D and, if necessary, bisphosphonates) are now recommended for all patients undergoing

chronic corticosteroid therapy. Because of the frequent occurrence of corticosteroid-induced adverse events, there have been numerous attempts to identify effective steroid-sparing therapies in patients with GCA. Unfortunately, these have yielded rather disappointing results.

6.3.1. Methotrexate (MTX) and azathioprine (AZA)

A meta-analysis of individual patient data from three studies with conflicting results revealed that MTX allowed a significant reduction in the cumulative dose of corticosteroids (824 mg at 48 weeks and 1015 mg at 72 weeks), but not in the frequency of adverse events, and significantly reduced the risk of a first and second relapse [133]. Note, however, that these effects did not become significant until 48 weeks after initiation of MTX therapy. Also note that MTX was given at doses between 7.5 and 15 mg/week, and it has been suggested that more contemporary doses (20–25 mg/week) should be evaluated in GCA patients [134]. Although AZA also showed a steroid-sparing effect after 52 weeks in the only published trial, the study suffered from a small sample size, the inclusion of PMR and GCA patients, and a high withdrawal rate due to side effects in AZA-treated patients [135].

6.3.2. Cytokine blockade

Small randomized controlled trials with different TNF antagonists as adjuvant therapy have yielded conflicting results. Infliximab did not show a glucocorticoid-sparing effect and did not reduce the risk of relapse compared to glucocorticoid monotherapy [136], whereas etanercept was associated with a significantly lower cumulative dose of corticosteroids in people who already suffered from severe steroid-induced adverse effects such as diabetes, osteoporosis or hypertension [137]. The relapse rate was also lower, but the effect did not reach statistical significance due to the small number of subjects. Very promising results have recently been reported in patients treated with tocilizumab, a humanized IL-6 receptor antibody, in addition to conventional corticosteroid therapy. Blockade of IL-6 induced prompt and complete clinical response and allowed rapid tapering of prednisone in all patients reported in the literature to date, including two patients who already suffered from corticosteroid-induced adverse events [54] and some patients who received tocilizumab from the time of diagnosis of GCA [53]. Unfortunately, follow-up was short in all cases. Controlled trials are urgently needed to confirm the beneficial clinical and steroid-sparing effects of IL-6 blockade, and the intention to conduct such a trial was reported in one of the above case series [53].

6.3.3. Aspirin

Thromboembolic events are not thought to play a major role in the ischemic damage in GCA. Nonetheless, the results of retrospective chart reviews suggest that low-dose aspirin significantly reduces the risk of presenting with cranial ischemic complications or developing them during follow-up [138,139], although this was not confirmed in other cohorts [51,140]. There is experimental evidence that aspirin can potently suppress IFNγ transcription and enhance the suppression exerted by dexamethasone in GCA lesions [141]. This suggests that aspirin may have a steroid-sparing effect in GCA. Randomized controlled clinical trials are needed to clarify the usefulness of aspirin in GCA, but low-dose aspirin should be considered for all patients without contraindications [87,112].

6.3.3.1. Mortality. The majority of studies analyzing the all-cause mortality of patients with GCA through the use of either Kaplan Meyer survival curves, life tables, standardized mortality ratios, or case–control design found the survival of GCA patients in various parts of the world to be similar to that of the general population ([6,86,142] and studies summarized in [143]). However, the results from several other investigations indicate that GCA is associated with increased mortality [85,132,143–145]. In two studies from London and Sweden, the mortality risk was significantly increased in women, but not in men [85,145], whereas in a Danish patient population, the excess mortality reached statistical significance in men, but not in women [144]. Especially vascular disorders have been found to cause excess mortality among GCA patients [145], and in one study this was particularly evident during the first few months after diagnosis and was thought to be related to insufficient corticosteroid doses [86]. Others attributed excess early mortality to steroid-related complications, particularly infections [132,142,146]. The majority of studies indicate that patients with GCA do not face an increased risk of cancer overall or specific types of cancer, and mortality from cancer was not increased in a Spanish population-based study [147]. Importantly, patients who develop aortic dissection have a dramatically reduced life expectancy compared to patients without large artery complication (1.1 years vs. 10.9 years) [129].

7. Concluding remarks

Since it is now recognized that clinically silent large-vessel involvement is very common in GCA, it will be important to determine to what extent large-vessel vasculitis or aortitis at diagnosis increases the risk of symptomatic large-vessel involvement during the disease course. It should also be clarified whether such patients would benefit from more aggressive treatment, i.e., initial pulse i.v. methylprednisolone or higher doses of oral corticosteroids or other treatment modalities. The results of the clinical trial evaluating the efficacy of tocilizumab are eagerly awaited. Given the high risk of aortic aneurysms and dissections in GCA and the markedly increased risk of death in patients who develop aortic dissection, it is increasingly recognized that patients should be screened regularly for aortic aneurysms and possibly also for extra-aortic large vessel involvement [75,134]. The major questions—who should be screened, when and how, and should detection of large-vessel involvement alter treatment—remain largely unanswered [134]. A detailed algorithm for the early detection of aneurysms in GCA has been proposed [75], but remains to be validated. At a minimum, patients should have annual chest radiographs to monitor for thoracic aortic aneurysms, screening for abdominal aortic aneurysm also is advisable [75,112,134]. Of note, there are data suggesting that symptomatic stenosis of the arm arteries and aortic aneurysm and/or dissection are almost mutually exclusive [126]. However, more recent studies suggest that aortic involvement is quite frequent in patients with symptomatic extra-aortic large-vessel GCA and vice versa [1,80]. Therefore, screening for further large-vessel involvement may be particularly important in this patient group.

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