Giant cell arteritis: epidemiology, diagnosis, prognosis

Abstract. Giant cell arteritis (GCA) is the most common systemic vasculitis affecting large vessels in subjects over 50 years old. This disease is associated with an increased risk of other inflammatory diseases and vascular conditions. Many studies and guidelines focus on solving GCA-associated problems. The aim of this paper is to perform an analytical review, systematic generalization and discussion of evidence on various epidemiological GCA aspects, modern approaches and methods of its diagnosis as well as risk factors of unfavorable prognosis.

Keywords: giant cell arteritis; large vessel vasculitis; epidemiology; diagnosis; prognosis

Introduction

Among the primary systemic vasculitides associated with a range of vascular disorders, conditions affecting large vessels – giant cell arteritis (GCA) and Takayasu arteritis (TA) – are considered the most common. Both trigger granulomatous lesions of the aorta and/or its principle branches; however, they are distinguished by the onset age: for GCA it occurs after 50 while for a considerably rarer TA – at a younger age. According to the definition revised at the International Chapel Hill Consensus Conference (2012), GCA usually affects the aorta and/or its major branches, with a predilection for the carotid and vertebral arteries and their branches [1]; however, many experts emphasize numerous instances of temporal arterial involvement, especially accompanied by polymyalgia rheumatica (PMR) [2].

GCA is thus defined as an arteritis, often granulomatous and affecting aorta and/or its principal branches, predominantly carotid and vertebral arterial ones, in people over 50 [1]. Relevance of GCA’s diagnostic and prognostic aspects studying is related to underappreciated prevalence of the disease and its contribution into mortality, development of blindness, atherosclerosis and other age-related inflammatory conditions [3-8]. Despite the growing amount of relevant clinical studies and guidelines developed by the national and international societies — among them the British Society for Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR) (BSR/BHPR, 2010) [9], the French Study Group for Large Vessel Vasculitis (GEFA, 2015) [10], and the European League Against Rheumatism (EULAR, 2018) [2] — recognition of GCA remains “a very difficult clinical task” (T. Beketova et al., 2016) [11], especially taking into consideration the probability of any medium-size artery affection, including intracranial, coronary and lower limb ones [12-18].

In 2018, R. Watanabe et al. compared functional profiles of inflammatory macrophages in the vessel walls in patients with GCA and coronary artery disease (CAD) [19]. Earlier, M. Sigl et al. (2014) explained ischemic symptoms in some patients with peripheral artery disease (PAD) by GCA presence; they also referred to GCA as a risk factor (RF) of worse results of interventions (bypass surgery and angioplasty) and to identifying of this large vessel vasculitis (LVV) as “a challenge for all physicians caring for patients with PAD” [7]. According to D. Lavire et al. (2014), GCA needs to be searched for whenever there is a stroke [20].

A large number of epidemiological evidence on GCA was collected while examining a representative sample of the US Caucasian population residing in Olmsted County, Minnesota, most of them having the Northern European roots [15, 21-23]. Some priorities in the field of GCA studying belong to the Mayo Clinic, Minnesota,
The US population is known to have an increased lifetime risk of developing inflammatory rheumatic diseases — both women (every 1 in 12) and men (every 1 in 20). It mainly concerns the risk of rheumatoid arthritis and PMR (3.6% and 2.4% in women, 1.7% for both in men, respectively). GCA affecting temporal arteries is likely to occur in 1.0% of women and 0.5% of men [25].

Earlier referred to as a temporal arteritis, GCA (or Horton’s disease) is considered the most common systemic vasculitis in the individuals over 50 years of age [4, 17-18, 26] or, more generally, in adults [13, 16]. GCA’s principal epidemiological indices are rather varied: they are high in the West, especially in the Northern Europe, Scandinavia, Great Britain, among the Caucasian population, and quite low in Asia and Africa [6, 27-28]. These discrepancies could be attributed in part to the imperfect nomenclature, diagnostic methodology, and factual data registering. This vasculitis (combined with PMR) has a code of М31.5 in the 10th revision of the International Classification of Diseases. According to the statistics, GCA prevalence is 10-35 per 100,000 people over 50 in the USA, Denmark, Norway, Finland, and Sweden. Women suffer on GCA 1.5-6 times more often than men [8, 18, 22, 24]. A number of GCA prevalence indices were obtained through cross-sectional studies of diagnostic imaging tests [15].

Thus, GCA incidence varies from 1.6 to 32.8 per 100,000 people over 50 [15]: in the Northern Europe reaching 15-33 [23, 29], in Germany — 3.5 [18, 30], in the UK — 10, and its peak (74 per 100,000) occurring in women of 70-79 years [31]. According to E. Genda et al. (2018), in Tunisia, GCA is more common in men than in women [27].

GCA is very often associated with PMR manifesting itself through proximal pain, stiffness and restricted active mobility in shoulders and hips and being “surprisingly responsive” to GC-therapy. There are some other conditions whose risk is increased in case of GCA or high cumulative GC doses (Table 1) [31].

Visual impairments are of a paramount importance to GCA, and they manifest themselves through headache, diplopia or a sudden unilateral transient blindness (amaurosis fugax). All of them are rooted in a vasculitis affecting a.ophthalmica and its branches [1]. Ischemic optic neuropathy (ION, i.e. n.opticus ischemia) is revealed by means of a special ophthalmological examination, along with a decreased visual acuity, visual field defect, relative afferent papillary defect, and central retinal arterial occlusion [9]. The ION’s epidemiological parameters were studied within frameworks of the Rochester Epidemiology Study, a major observational study of Olmsted County cohort suffering from GCA diagnosed in 1950-2009. The study results showed this complication to develop in 6.9 % patients with GCA, and in 85% of cases lead to irreversible blindness. The frequency of arterial occlusions turned out as follows: a. centralis retinae — 1.6%, a. cilioretinalis — 0.4%. Incidence of GCA-associated ION is 1.3 per 100,000 people over 50, and in 20% of cases irreversible vision loss occurs without the preceding vasculitis symptoms [21]. In terms of GCA-associated ION

Table 1. Giant cell arteritis’ frequent clinical associations (according to H. Petri et al., 2015 [31])

<table>
<thead>
<tr>
<th>Condition, symptom</th>
<th>RR (95% CI) under GCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polymyalgia rheumatica</td>
<td>14.9 (11.9–18.7)</td>
</tr>
<tr>
<td>Visual disturbances</td>
<td>4.6 (2.7–7.8)</td>
</tr>
<tr>
<td>Oral and/or esophageal thrush</td>
<td>3.7 (2.2–6.0)</td>
</tr>
<tr>
<td>Facial pain</td>
<td>3.3 (2.1–5.3)</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>2.9 (2.3–3.7)</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>2.6 (1.6–4.1)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>2.5 (1.6–3.9)</td>
</tr>
</tbody>
</table>

Notes: GCA — giant cell arteritis, CI – confidence interval, RR – relative risk.
predictors, the British guidelines (BSR/BHPR, 2010) refer to jaw claudication, diplopia, and temporal artery abnormalities [9].

The age-related nature is a basic but not universally accepted feature distinguishing GCA from TA. It is of great importance in terms of cardiac and cerebrovascular complications (stroke, myocardial infarction, vessel aneurysms, etc.), crucial lower limb ischemia, as well as of diagnostic difficulties. In particular, in patients over 60, GCA causes 17-24% of cases of fever of unknown origin and/or significant increase of erythrocyte sedimentation rate (ESR) [32]; this fact may be taken into account in differential diagnosis in the elderly. However, GCA is known to develop even with no acute phase indices present [9, 15].

As to GCA contribution to the global burden of disease, in 2009, increased mortality within the first 5 years following the GCA diagnosis was proved by the Utah Population Database analysis [5]. The study results based on the national register of GCA patients with their diagnosis verified by the temporal artery biopsy (TAB) showed an “insignificant” increase of early (2 years following the onset) and late (over 10 years after the onset) mortality levels in 2015: the relative risk (RR) being 1.17 and 1.22, respectively. The link of increased mortality risk 2 years after GCA onset and cardiovascular complications (namely, aortal aneurysm) was also proved [3]. In 2017, those data and results of another study were defined as heterogeneous by evidence of the highest quality — the Cochrane review and meta-analysis (C. L. Hill et al.). The pooled analysis of 17 primary studies found in the main databases of evidence-based medicine (EBM) — Cochrane Library, Medline, and EMBASE — did not prove GCA influence upon mortality level [33].

Analysis of the evidence on epidemiology of GCA-related large vessel complications reveals their heterogeneity. The priority of their description belongs to J. M. Evans et al. (1995) [34]. Complications’ profile and predictors, increased risks of both early aortic dissection and related death were outlined by D. M. Nuenninghoff et al. (2003) [23, 29]. Results of the prospective study of Olmsted County cohort suffering from GCA diagnosed in 1950-2009 revealed large vessels' aneurysms and stenosis in 27% of patients, every one in 5 (18%) had aortic aneurysm and/or dissection, while every one in 8 (13%) had a stenosis. Aneurysms were likely to occur in combination with hyperlipidemia and coronary heart disease (CHD), while stenosis — with cranial symptoms (headache, jaw claudication, scalp tenderness) and increased ESR. Frequency of thoracic aortic aneurysm amounted to 11%, its dissection — 5%. Annual incidence of aortic aneurysm in GCA achieved 18,7‰, of thoracic aortic aneurysm — 8,2‰, abdominal aortic aneurysm — 10,1‰, thoracic aortic dissection — 5,4‰, abdominal aortic dissection — 0,6‰ [23].

In general, the risk of aortic aneurysm development and dissection under GCA is increased 2.0-17.3 times compared to general population [23, 34-36].

D. M. Nuenninghoff et al. (2003) revealed stenosing lesions of neck vessels in 9% of GCA cases, of subclavian, axillary and brachial arteries — in 6%, of iliac and femoral arteries — in 0,6% [23]. Earlier, J. M. Evans et al. (1995) diagnosed upper limb arterial stenosis in 18-21%, cerebral arterial stenosis in 7% [34].

Having examined the cohort of large vessel GCA (LV-GCA) patients a decade after that, in 2013, T. A. Kermani et al. from Mayo Clinic, Minnesota, found a similar prevalence of stenoses and aneurysms — 20-25% [37]. E. L. Matteson et al. (2016) revealed the frequency of GCA-related aortic aneurysm to be 9,6% and proved that from the point of vasculitis’ diagnosis making it takes on average 5,8 years to reveal this complication, while the aortic regurgitation develops in 33,3% of cases, aortic dissection and related death occur in 44,4% of cases [38]. However, the mortality in LV-GCA does not differ from the one in the general US population [37].

Speaking on frequency and predictors of structural vascular complications in patients with GCA, that have never undergone systematic imaging, let’s look at the Cochrane review and meta-analysis of S. L. Mackie et al. (2014). In this cohort, thoracic aortic aneurysm was found in 2-8% of cases, while aneurysm dissection and rupture — in 1 and 6%, respectively. In three primary studies, it was shown that male sex might be a RF for thoracic aortic aneurysm development and dissection under GCA. Based on these studies’ outcomes, experts emphasized the importance of estimation of RR for the above mentioned complications at different GCA stages [35].

In 2015, J. C. Robson et al. [36] published results of analysis of the UK General Practice Research Database’s national register. It was a comparative study of aortic aneurysm frequency in 6999 patients with GCA and 41994 without GCA. The GCA- and non-GCA patients were of a comparable age, sex and residence. By means of a competing risk model a two-fold increase of aortic aneurysm development was proved for GCA, the adjusted hazard ratio (HR) being 1.92 (95% confident interval (CI) 1.52-2.41). Based on the calculated HR (with 95% CI), the significant predictors of aortic aneurysm were determined: being a current smoker (3.37; 2.61-4.37) or an ex-smoker (2.64; 2.03-3.43), presence of cardiovascular disease (1.98; 1.50-2.63), previous antihypertensive therapy (1.57; 1.23-2.01); however, with diabetes mellitus (DM) aortic aneurysm’s HR is 0.32 (0.19-0.56). In GCA patients, among the significant predictors of aortic aneurysm there are ongoing smoking (3.79; 2.20-6.53) or a history of one (2.20; 1.22-3.98), male sex (2.10; 1.38-3.19), antihypertensive drugs taking (1.62; 1.00-2.61); history of DM brings aortic aneurysm’s HR to 0.19 (0.05-0.77). The authors confirmed that, along with male sex,
age and smoking, GCA is aortic aneurysm’s RF (risk is
twofold increased), and recommended to take it into ac-
count while planning the screening programs. The pro-
tective effect of DM in the development of GCA-related
aortic aneurysms was concluded based on lower risk cal-
culated [36].

As for mortality structure under GCA, we did not
found relevant evidence in any available information
sources. Speaking on GCA-related cerebrovascular com-
lications, ischemic vertebrobasilar strokes were proved to
be predominant (73-100% of cases, isolated or dissemi-
nated sites) [4, 20]. In 2014, D. Lavriere et al. found a
significant predominance of this complication in males
and pointed out headache as its predictor [39].

Taking into consideration 28 publications describing
stroke in GCA patients, R. S. Alsolaimani et al. (2016)
suggested an intracranial subtype of this vasculitis with a
100% mortality in case of absent treatment [40].

The results of recent case-control study (H. de Boysson
et al., 2017) demonstrated a link between GCA-associat-
ed stroke with preceding symptoms of n.opticus ischemia
and a less active inflammation. Frequency of stroke at
the point of GCA-diagnosis or a month after the vascu-
litis treatment initiating was 16.7%, 3/4 of all sites were
vertebrobasilar. The patients with stroke were older than
the ones without stroke (78 and 74 years) and experienced
ischemic symptoms more often (63 and 25%) though ane-
mia rarely (59 and 79%). It is worthy of note that inflam-
mination was also less active in patients with stroke: their
ESR (68 and 80 mm/h) and C-reactive protein (CRP) (61
and 91 mg/l) were lower. For GCA, multifactorial analysis
including smoking status, arterial hypertension, DM and
hypercholesterolemia showed the best stroke predictors
to be the decreasing acuity of vision (RR 5,0) and absence
of anemia [4].

Our source analysis demonstrated that in 2014-2016
P. Ungprasert and other Mayo Clinic researchers pub-
lished a number of cohort studies’ systematic reviews
and meta-analyses evaluating risks of main non-infect-
ious diseases developing with GCA (Table 2) [41-45].
As a result, they proved: a significantly increased risk
of stroke development in GCA [41], an increased risk
of PAD development in GCA [43], as well as an in-
creased risk of malignancy in GCA/PMR (“a low but
statistically significant”, and the risk was higher in the
first 6-12 month after the estimation of GCA diagno-
sis: RR 2,16, 95% CI 1,85-2,53) [44]. Heterogeneity of
the primary studies did not allow to confirm influence
of GCA on CAD development [42]. One meta-analysis
also prompted a hypothesis of GCA’s protective effect in
relation to DM development [45].

As for epidemiological evidence of GCA association
with malignancy and DM, they are heterogenous. Ac-

cording to L. Li et al. (2017), the British GCA patients
have an increased risk of development of all vascular com-
plications (aortal aneurysm, venous thromboembolism,
PAD, stroke, myocardial infarction), as well as of DM
type 2 and depression, though not cancer, compared to
non-GCA patients [46].

Thus, from the perspective of evidence-based approach,
early GCA diagnosis is essential due to the following in-
creased risks: of aortic aneurysm-related death, as well as
of ION and ischemic stroke development. It is blindness
that is considered “the most feared complication of GCA”
[16]. However, the importance of targeted GCA revealing
is not mentioned in the recent international guidelines on
PAD and ischemic stroke management as well.

Speaking on the problems concerning diagnosis and
prognosis in GCA and another large vessel vasculitis
(LVV) — TA, we should mention that our analysis of the
recent papers shows a rising scientific interest to the fol-
lowing issues:
- revising and systematization of LVV’s clinical mani-
festations and subgroups, determining their pathogenic
basis and prognostic value;
- describing LVV’s genetic heterogeneity and cytokine
profile (taking into account the absence of any specific
immunological marker);
- evaluating diagnostic potential (analytical param-
eters) of the imaging tests — ultrasound (namely color
doppler ultrasound), magnetic resonance imaging (MRI),
computed tomography (CT), positron emission tomog-

**Table 2. Risk of some non-infectious diseases development in giant cell arteritis**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Number of studies/participants</th>
<th>Combined hazard ratio (95% CI)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>8/17 919</td>
<td>1.4 (1.27–1.56)</td>
<td>[41]</td>
</tr>
<tr>
<td>CAD</td>
<td>6/10 868</td>
<td>1.51 (0.88–2.61)</td>
<td>[42]</td>
</tr>
<tr>
<td>PAD</td>
<td>4/9789</td>
<td>1.88 (1.04–3.41)</td>
<td>[43]</td>
</tr>
<tr>
<td>Cancer</td>
<td>6 (patients with CA/PMR)</td>
<td>1.14 (1.05–1.22)</td>
<td>[44]</td>
</tr>
<tr>
<td>DM</td>
<td>5/903</td>
<td>0.74 (0.57–0.97)</td>
<td>[45]</td>
</tr>
</tbody>
</table>

Notes: GCA — giant cell arteritis, CAD — coronary artery disease, PAD — peripheral artery disease, PMR — polymyalgia rheumatica, DM — diabetes mellitus.
Clinical judgment on suggested GCA involves an “overall assessment” by the expert clinicians and “rapid, staggering, dramatic clinical improvement” and decreasing of CRP due to GC treatment [16, 49]. In 2002, for instance, S. M. Levine et al. listed among the “classic GCA manifestations” headache, jaw claudication, PMR and vision symptoms, pointing out a high (40%) frequency of a “wide range of occult manifestations”, including those caused by the large vessels damage [16]. At the same time, G. W. Smetana et al. offered a distinction between two GCA subtypes: 1) classic or cranial involving superficial carotid arterial branches — with a prevailing of “inflammatory type” (>90% of cases) and a possibility of “ischemic type” (4%); 2) generalized, or ‘Takayasu-like’ (Table 4) [51]. Since that time, usage of LV-GCA category did become common but not generally accepted; the same is true for the suggested GCA classification. For instance, M. Koster et al. (2018) note a GCA’s “overlapping phenotypes” (isolated classic cranial GCA, isolated extra-cranial/LV-GCA, compounded, etc.) as well as involvement of large vessels in the majority of cases (80-83 %), based on the histology and imaging tests’ results. LV-GCA thus refers to an “aortitis or arteritis of the primary aortal branches proved by the imaging techniques” [15].

As to the GCA cranial symptoms, it’s worthy of noting that their detection in people over 50 is the key reason for clinical suspicion underlying diagnosis. Thus, BSR/BHPR (2010) encourage physicians to pay attention to the following features: “abrupt-onset headache (usually unilateral in the temporal area), scalp tenderness, jaw and tongue claudication, vision symptoms (including diplopia), constitutional symptoms, polymyalgic symptoms, limb claudication” [9]. The EULAR guidelines (2018) interpret cranial symptoms of GCA as headache, vision symptoms, jaw claudication, swelling and/or tenderness of temporal arteries [3].

The results of our analysis of the papers devoted to clinical features GCA in various ethnic groups do not allow to exclude influence of selection bias. For instance, it is the cranial symptoms that prevail in the recent description of GCA in the Africans: headache is present in 91.7%...
of cases, temporal arterial abnormalities in 85.4%, “severe ischemic signs” in 80.2%; frequency of constitutional symptoms achieves 75%, PMR — 56.3%, large vessel manifestations are not mentioned [27]. At the same time, whenever the LV-GCA is in the Europeans revealed, their clinical picture description is full of upper limb ischemia while PMR and cranial ischemia symptoms are either omitted altogether or mentioned as often as while describing the classical GCA [49-50].

As is shown by Table 4, the ratio of occurrence of cranial and extra-cranial (or large-vessel) subtypes of GCA is not defined exactly. Our source analysis allows to explain it with heterogeneity of the described cohorts and primary studies, i.e. using different imaging techniques to diagnose vascular abnormalities, their combinations and term of their use, comparison with TAB results, etc.

An important aspect of GCA diagnosis is finding distinguishing features of its main subtypes. Frequency of common GCA symptoms is presented in Table 5.

According to F. Muratore et al. (2015), LV-GCA is far more often than cranial GCA associated with both blood pressure discrepancy and pulse difference in upper extremities [50]. Although the cranial symptoms were earlier considered a key feature distinguishing GCA subtypes [49], frequency of temporal tenderness and intermittent vision loss is no smaller in LV-GCA than in classical Horton’s disease, with barely any difference in the ESR. Compared to the cranial GCA, LV-GCA is characterized by an early onset (68.2 vs 75.4 yrs), closer association with PMR (26 vs 15%), more frequent recurrences and a higher GC cumulative dose, though less frequent vision loss [50]. Referring to some previous studies [10, 49-50], M. Koster et al. (2018) wrote: “LV-GCA may have a stronger female predominance, younger age of disease onset, longer time to diagnosis and lower inflammatory markers than cranial GCA” [15].

Distribution of the major arteries affected by LV-GCA was studied by F. Muratore et al. (2015) by means of X-ray imaging techniques. The results showed that in most cases (93%) abnormalities concerned the left subclavian artery. Other vascular damage distribution was as follows: right subclavian artery — 72%, left axillary artery — 66%, right axillary artery — 54%, abdominal aorta — 48%, descending aorta — 44%, innominate — 43%, left common carotid artery — 42%, aortic arch — 41% [50].

The most frequent involvement of subclavian arteries was also proved by means of ultrasound — in GCA patients without cranial symptoms, usually women of a younger age. In half of those cases (52%) TAB tests were negative [49, 55].

Opinions on the TAB value for GCA diagnosis have been recently changed. In 2002, speaking on the early vasculitis recognition, S. M. Levine et al. noticed that the imaging techniques (such as color doppler ultrasound, CT- and MRI-angiography, PET) do not replace TAB as “gold standard for GCA verification” [16]. Later on, taking into account the frequency of false negative TAB results [56], researchers started to pay even more attention to the alternative diagnostic tests, and this trend reflects in the 2018 EULAR guidelines [2]. However, in a number of countries, namely the UK (BSR/BHR, 2010) and France (GEFA, 2015), TAB is prescribed whenever there is a GCA suspicion [9-10].

Table 4. Frequency of manifestations of the main subtypes of giant cell arteritis

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>GCA and its frequency, sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasculitis of cranial/temporal arteries</td>
<td>Classical cranial GCA (cranial-GCA, c-GCA) is the most common [7, 37, 49-50, 52]</td>
</tr>
<tr>
<td>Vasculitis of thoracic or femoral arteries</td>
<td>Large vessel GCA (LV-GCA, extra-cranial GCA) accounts for 15-36% of cases [7, 16, 37, 49-50, 52-53], according to other sources – for 60-73% [54]</td>
</tr>
</tbody>
</table>

Note: GCA — giant cell arteritis.

Table 5. Frequency of some symptoms of giant cell arteritis in its main subtypes (according to F. Muratore et al., 2015 [50])

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With LV-GCA</td>
</tr>
<tr>
<td>Pulse differences on the right and left hands</td>
<td>60</td>
</tr>
<tr>
<td>Blood pressure discrepancy in upper extremities</td>
<td>&gt; 52</td>
</tr>
<tr>
<td>Upper extremities claudication</td>
<td>50</td>
</tr>
<tr>
<td>Bruits</td>
<td>40</td>
</tr>
<tr>
<td>Pedal arterial pulse difference</td>
<td>15</td>
</tr>
<tr>
<td>Claudicatio intermittens</td>
<td>10</td>
</tr>
<tr>
<td>Aortic regurgitation murmur</td>
<td>7–8</td>
</tr>
</tbody>
</table>

Notes: GCA — giant cell arteritis, LV-GCA — large-vessel giant cell arteritis.
Specific histological findings in the biopsy specimens with artery taken from patients with classic GCA are described in Table 3. Fibrinoid necrosis is known to be absent in this vasculitis; however, the GCA feature is a granulomatous inflammation with giant cells on the border of intima/media or (more often) a panarteritis with mononuclear or lymphocytic infiltration. The TAB is considered positive if these changes are detected; nevertheless, even in those patients with clinical signs of temporal arteritis TAB is positive only in 85% of cases. For the large vessel GCA, the TAB test sensitivity does not exceed 60% [50, 55, 57-58].

There is a number of important clinical-histological GCA associations established nowadays. Having examined 888 biopsy specimens from GCA patients, A. Cavazza et al. (2014) confirmed many false negative TAB results: only 39.9% of samples were positive. Based on this study, a histological range of GCA temporal arteritis was described and 4 categories of diseases were singled out: 1) small vessel vasculitis (SVV, 9% of biopsy specimens); 2) vasa vasorum vasculitis (VVV, 6.5%); 3) inflammation limited to adventitia (ILA, 7%); 4) transmural inflammation (TMI, 77.5%). In case of TMI, infiltrations are found between media and adventitia. They are composed of T-cells and macrophages (more rarely of plasmocytes), and contain giant cells (in 75%) or laminar necroses and calcifications (in 15-20%). Compared to SVV and VVV, TMI is associated with more pronounced cranial symptoms, acute phase markers and clinical signs of systemic inflammation, more frequent halo-sign on color doppler ultrasound of temporal arteries and less frequent GC-therapy at the biopsy time. While ILA manifestations are closer to TMI, ILA patients experience headache far more rarely, along with temporal artery abnormalities and ultrasound halo-sign [57].

According to the BSR/BHPR (2010) and GEFA (2015) guidelines, the TAB test in suspected GCA should be performed by an experienced surgeon. For this purpose, a unilateral biopsy is enough; however, the size of artery’s fragment for examining multiple sections should be no smaller than 1 cm [9-10].

The issue of GC influence on TAB and other diagnostic tests results is of paramount clinical importance. According to Mayo Clinic studies (E. L. Matteson, 2017), giant cells disappear after one week of GC therapy; however, other histological signs of arteritis persist for weeks, months or even years. Furthermore, patients on GC may present such “atypical” TAB results as “minor inflammation”, “treated arteritis”, etc. [38]. The UK experts notice the probability of revealing of GCA histological signs during 2-6 weeks of GC therapy [9].

Recurrences. Symptoms of GCA requiring treatment recur in most patients during the first 2 years of the disease and with the use of maintenance doses of GC (prednisolone <10 mg daily). 47-51% of patients present the preceding PMR symptoms, 31-42% — cranial ones, but every one in 5 (18%) has prevailing constitutional signs. Such relapses were studied in the Spanish and Italian medical centers’ cohorts by M.A. Alba (2014) and G. Restuccia (2016-2017) et al. They estimated the principal RFs of GCA recurrences as following: the required cumulative GC dose and duration of switch to the maintenance dose [59-61].

G. Restuccia et al. consider the GCA recurrence almost certain in case of ≥38°C fever at the onset and advanced inflammatory infiltration of vascular walls ascertained by the TAB test; anemia also promotes the relapses [60]. M.A. Alba et al. register a higher frequency of GCA recurrences with osteoporosis than without it (65 vs 32%) [59].

According to L. Martinez-Lado et al. (2011), in the Spanish cohort of GCA patients the frequency of relapses in the first year of the disease is 40.8%. The most frequently recognized symptoms are headache (52%) and PMR (30%), and “the best predictor of relapses” is anemia at the GCA onset [62].

At the Chilean medical center, the relapses in the first year of the disease were observed in 50% of patients, for first 2 years – in 68%, for first 5 years – in 79%. According to C. Labarca et al. (2016), RFs of GCA recurrences are the female sex, arterial hypertension and DM [63].

The RFs for favorable prognosis in GCA are also identified: G. Restuccia et al. (2017) consider both achieving of long-term remission (i.e. complete clinical remission with no ascertained increase of inflammatory markers for a year) and decreasing of risk of relapses to be more likely if there is no PMR or anemia at the disease onset [61].

Thus, for GCA, both disease onset characteristics and comorbidity profile look prognostically important. The topical aspect of prediction of GCA outcomes (risk of death, complications, recurrences, and achieving of long-term remission) is evaluating the influence of immunosuppressive and target biologic therapy. Both studying the effects and use of tocilizumab, ustekinumab and abataceptum seem to be especially promising [15].

It’s worthy of noting that LV-GCA is the one causing most difficulties on the terminological and diagnostic dimension. For patients evaluated for GCA without predominant cranial symptoms, differential diagnosis circle may include the following diseases: 1) rheumatologic: primary systemic vasculitides (Takayasu arteritis, Behçet disease, polyarteritis nodosa, ANCA-associated ones) and secondary vasculitides (in rheumatoid arthritis, systemic lupus erythematosus, spondyloarthritides), IgG4-related disease, retroperitoneal fibrosis, idiopathic aortitis; 2) infectious: endocarditis, syphilis, Herper zoster, Epstein-Barr virus, cytomegalovirus); 3) haematological: amyloidosis, multiple myeloma, Erdheim-Chester disease; 4) atherosclerotic disease [15].
When the LV-GCA subtype was recognized and as common ascertained, a hypothesis of Takayasu arteritis and Horton’s disease continuity and unity (i.e. a single LVV) was raised. However, having studied the genetic, immunological and clinical aspects of TA and GCA, the scientists could not confirm it [50, 54-55, 64-66].

In particular, K. Maksimovicz-McKinnon et al. (2009) suggested a role of both selection bias and bias on imaging techniques use in patients with the above mentioned vasculitides. They performed a retrospective data analysis of 144 GCA and TA patients, predominantly females (82 and 91% respectively) and the Caucasians (95 and 88%). As a result, in GCA were confirmed a higher frequency of classical cranial symptoms and significantly lower use of imaging techniques to examine large vessels (62 vs 100%); however, the affecting of at least one arterial segment was revealed in 3/4 of cases [54].

The single LVV hypothesis was disproved by the “detailed phenotyping” of 45 GCA and TA patients performed by S. Futura et al. (2015). GCA was more often associated with headache and long-term stenosing changes of subclavian and carotid arteries, higher levels of ESR and CRP and lower frequency of relapses (60 vs 22%). Vasculitides were to be distinguished according to the type of subclavian and carotid arterial damage [67].

The same year, T. A. Kermani et al. received a different set of data: prevailing aneurysmatic changes of thoracic aorta in GCA (100 vs 19% in TA) and stenosing ones in TA (81% vs 0% in GCA). To disprove the single LVV hypothesis, it was noted that TA was mainly associated with a frequent damage to thoracic and femoral arteries, brachiocephalic trunk, carotid, mesenterial, left renal arteries and BP discrepancy in upper extremities [64].

The results of studying clinical and laboratory features as well as use of imaging tests to diagnose the vascular damages in GCA and TA are summarized in Table 6. It’s worthy of noting that TA is very rare (incidence 0.5-3 per 1 million people), mainly occurs in Asia, and even there the distribution of vascular damages is not homogeneous: the Japanese and Korean patients more often have their aortal arch damaged, the Indian and Thai patients (as well as the European and Tunisian ones) more often have their abdominal aorta damaged [27-28].

As Table 6 shows, imaging techniques allowed detecting a high frequency of aortitis in GCA — up to 65% [54]. While recognizing aortitis as a common feature of GCA, experts note varying frequency of its detection with different tests: up to 40% with histological studies (however, clinical symptoms of aortitis are present twice as rarely), 20-65% with CT (for 4 weeks after the suggested GCA, there are aortic wall thickening of various length revealed; later, detected are the structural damages of aorta and its branches, such as ectasia, dilatation, aneurysm, stenosis, and occlusion), 83% with PET [48, 68-72]. These results obtained in 1995-2014 confirmed the necessity of using imaging techniques to diagnose LV-GCA [73-75].

Signs of inflammation of the aorta (aortitis) and its primary branches detected by various imaging modalities are described in Table 7: when CT- or MRI-angiography are used, they account for circumferential wall thickening, contrast enhancement, stenosing/occlusion and/or dilatation/aneurysm (the latter sign may also be revealed by a conventional angiography); when 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) is used, there is homogeneous wall hypermetabolism detected; when color doppler ultrasonography — hypoechoic wall thickening (halo-sign) [15].

The Mayo Clinic experience described by T. A. Kermani, E. L. Matteson et al. in 2013-2016 [37, 38] confirms the necessity of CT- or MRI-angiography to detect the damage to thoracic aorta and its branches in patients “with a strong clinical suspicion on GCA” and negative TAB tests, as these imaging techniques help detect signs of vasculitis in 1/3 of cases. The authors have suggested an algorithm for monitoring aortic aneurysm in GCA. Initial screening includes both chest X-ray and abdominal ultrasound; echocardiography should be performed every 1-3 years; CT- or MRI-angiography are considered methods of choice while dealing with extracranial GCA. If the screening result is positive (i.e. aortic dilatation or aneurysm detected), the relevant guidelines on aortal aneurysm management should be followed with control examinations every 6-12 months. With negative screening, imaging tests are to be repeated every 5 years [27, 28].

It is worthwhile to notice, that CT and MRI screenings for GCA-aortitis complications are also recommended by the French GEFA group (2015) with intervals of 2 to 5 years and only if there are no contraindications to a possible surgery on aorta [10], and by the EULAR (2018) along with ultrasonography and individual approach to both screening test choice and inter-screening interval determination [2].

The new diagnostic algorithm for evaluating patients with suspected GCA proposed by M.J. Koster et al. (2018) is presented in Fig 1. [15].

Relevance of PET diagnostic potential studying in GCA is explained by both a great contribution of this vasculitis into a range of possible reasons for fever of unknown origin in the elderly and a frequent association of GCA/PMR and malignancy [32, 39]. In the recent years, namely PET/CT (i.e. FDG-PET combined with low-dose CT without contrast enhancement — in order to obtain anatomical correlations and PET data correction) has often been using to detect aortoarteritis in GCA [26, 76]. Importance of PET/CT for elderly patients “with non-specific complaints” and significantly elevated ESR was emphasized by K. D. Lensen et al. (2013): “PET/CT may be of potential value in the diagnostic work-up of patients with elevated ESR if routine evaluation reveals no...”
diagnosis. In particular, large-vessel vasculitis appears to be a common finding. A normal PET/CT scan in these patients suggests that it is safe to follow a wait-and-see policy” [32].

Approach to PET/CT use at the Mayo clinic is in line with the suggestion of S. Prieto-Gonzalez et al. (2014) to prefer PET/CT over CT- and MRI-angiography “only in specific cases”: when there is a suspected malignancy or “unclear diagnosis”. In cases of suspected LV-GCA, the primary analytical parameters of PET/CT as diagnostic test are: sensitivity of 80%, specificity of 79% [27-28, 71].

PET sensitivity and specificity for vascular damage detection in GCA, according to M. D. Stellingwerff et al. (2015), amounts to 89.5 and 97.7% respectively [26]. The evidence base for accuracy of PET is presented in Table 6.

<table>
<thead>
<tr>
<th>Table 6. Comparative characteristic of giant cell arteritis and Takayasu arteritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sign / Characteristic</td>
</tr>
<tr>
<td>With GCA</td>
</tr>
<tr>
<td>--------------------------</td>
</tr>
<tr>
<td>Clinical symptoms</td>
</tr>
<tr>
<td>New headache</td>
</tr>
<tr>
<td>BP discrepancy in upper extremities</td>
</tr>
<tr>
<td>Upper extremity claudication</td>
</tr>
<tr>
<td>Jaw claudication</td>
</tr>
<tr>
<td>Vision impairments</td>
</tr>
<tr>
<td>Diplopia</td>
</tr>
<tr>
<td>Laboratory test results</td>
</tr>
<tr>
<td>ESR and CRP</td>
</tr>
<tr>
<td>Imaging test results</td>
</tr>
<tr>
<td>Damage to at least one segment of a large vessel</td>
</tr>
<tr>
<td>Aortal damage</td>
</tr>
<tr>
<td>Subclavian arterial damage</td>
</tr>
<tr>
<td>Distribution of affected vessels</td>
</tr>
<tr>
<td>Subdiaphragmal</td>
</tr>
<tr>
<td>Thoracic, abdominal aorta, innominate, mesenteric, carotid, left renal arteries</td>
</tr>
<tr>
<td>Prevailing aneurysmatic thoracic aortic damage</td>
</tr>
<tr>
<td>Prevailing stenosing thoracic aortic damage</td>
</tr>
<tr>
<td>Prevailing type of carotid and subclavian arterial damage</td>
</tr>
<tr>
<td>Clinical course and prognosis</td>
</tr>
<tr>
<td>Frequency of relapses</td>
</tr>
</tbody>
</table>

Notes: GCA — giant cell arteritis, TA — Takayasu arteritis, BP – blood pressure, CRP — C-reactive protein, ESR — erythrocyte sedimentation rate.

<table>
<thead>
<tr>
<th>Table 7. Signs of aortitis or aortic primary branches’ arteritis (according to M. Koster et al., 2018 [15])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signs</td>
</tr>
<tr>
<td>-------------------------------------------</td>
</tr>
<tr>
<td>Circumferential wall thickening (≥2 or 3 mm aorta)</td>
</tr>
<tr>
<td>Contrast enhancement</td>
</tr>
<tr>
<td>With gadolinium uptake</td>
</tr>
<tr>
<td>Wall oedema</td>
</tr>
<tr>
<td>Homogeneous wall hypermetabolism</td>
</tr>
<tr>
<td>Vascular stenosis/occlusion and/or dilatation/aneuysm</td>
</tr>
<tr>
<td>Dark, hypoechoic circumferential wall thickening (halo-sign)</td>
</tr>
</tbody>
</table>

Notes: CTA — computed tomography angiography, MRA — magnetic resonance angiography, FDG-PET — ¹⁸F-fluorodeoxyglucose positron emission tomography.
8. Our analysis of the secondary evidence mentioned [76-78] allows to determine, that their sources were controlled studies found in 3 computer databases of EBM (Medline, EMBASE, Cochrane Library) and contained TAB rather than ACR classification criteria as their reference test.

In particular, F. L. Besson et al. (2011) performed a systematic review of 14 and meta-analysis of 6 primary studies of PET accuracy as a diagnostic test for GCA with or without concomitant PMR. The review came up with a result concerning determination of both marker of vasculitis (increased FDG vessel uptake superior to liver uptake) and typical for GCA pattern of FDG uptake by the aorta (smooth linear or intermittent segmented one). Meta-analysis (101 patients with GCA) confirmed effectiveness of PET for GCA diagnosis: positive likelihood ratio was 6.73 (95% CI 3.55-12.77), negative likelihood ratio 0.25 (0.13-0.46), accuracy 0.84 (0.76-0.90). Within the structure of PET positive results in cases of suspected GCA, quota of true results is 84% while quota of false results 16% [77].

PET’s efficacy for confirming suspected LVV was proved by M. Soussan et al. (2015)’s systematic review (21 studies, 413 GCA and TA patients) containing two meta-analyses (GCA: 4 studies, 57 patients; TA: 7 studies, 191 patients). Their results proved even higher accuracy of PET in detecting aortoarteritis under GCA than under TA. Considering the criterion “FDG vessel uptake $\geq$ liver uptake” efficient, experts emphasized the importance of evidence base reinforced, PET’s threshold values determined and their clinical value ascertained [78]. Similar conclusions on PET and FDG-PET were made by Y. H. Lee et al. (2016) using meta-analysis of 8 studies (170 GCA and TA patients) [76].

It’s worth mentioning valuable results of two monocenter studies completed recently in Germany and France. M. D. Stellingwerff et al. (2015) studied PET/CT analytical parameters in a cohort of 18 GCA patients. Their results are:

1) confirmed the highest diagnostic accuracy of PET/CT when FDG vessel uptake prevails over liver uptake (with sensitivity of 83%, specificity of 91%) as well as higher diagnostic accuracy of PET/CT (92%) when there is no GC therapy;

2) while comparing 4 semiquantitative indices of «standardized uptake value» (SUV), i.e. maximized FDG uptake (SUVmax aorta, SUVmax aorta-to-liver ratio, SUVmax aorta-to-superior-caval-vein ratio, SUVmax aorta-to-inferior-caval-vein ratio), the best parameters (sensitivity of 92%, specificity of 69%; when there is no GC therapy – 90 %) were showed by the SUVmax aorta-to-liver ratio;

3) the greatest number of vascular segments with a diffuse pattern of FDG uptake was found in patients who did not receive GC;

4) informative value of CRP level as to result of PET/CT in GCA turned out low [26].
In the second study, D. Laviriere et al. (2016) evaluated analytical parameters of PET and CT-angiography as diagnostic tests for vascular damage in GCA — primarily (sensitivity, specificity) and secondary (positive and negative predictive values — PPV and NPV) ones. The study involved 24 patients with a suspected GCA; based on “clinical judgment, TAB and ACR criteria” diagnosis was made in 15 (62.5%). In patients with negative TAB results, the clinical diagnosis “was considered final if no diagnosis other than GCA was provided at the end of a follow-up period of >6 months”. The frequency of false negative results of different diagnostic tests in GCA turned out as follows: TAB — 60.0%, PET — 30.0%, CT — 26.7%. Results of the study are presented in Table 9. They confirmed usefulness of both PET and CT as tools for GCA diagnosis. Taking into account a higher PPV, the authors concluded that PET “should stand as the best noninvasive technique for GCA diagnosis. Accordingly, a “no biopsy strategy” could be assessed in patients suspected for GCA with a strong FDG uptake in large vessels” [39].

Taking into account a low number of participants and monocenter type of the study, however, it’s worthwhile noticing some revealed important aspects of PET use in GCA:

1) even a short (for 1-5 days) GC therapy decreases sensitivity of PET (as inhibition of inflammation lowers FDG uptake) and increases probability of false negative test’s results;

2) CRP blood level is of informative value as to PET results, as it tends to correlate with FDG uptake (assessed by the mean SUVmax at all the arterial segments), that is in agreement with some previous reports [71] and contradicting others [26];

3) “the main specificity challenge for PET in older patients with GCA is to distinguish between true aortitis and atheroma (FDG uptake being more focal and restricted to aorta in atheroma)”;

4) there is a hypothesis raised on PET value “in diagnosing GCA relapses, evaluating steroid refractory disease or predicting risk of later aortic dilation” [39].

Informative value of vessel ultrasonography as to confirm GCA diagnosis has been studied by many researchers [7, 14, 23, 52, 55, 65, 73–75, 79–80]. According to W. Schmidt et al. (2008), ultrasound signs of temporal arterial involvement (halo-sigh, stenosis, occlusion) are present in 84% of patients with GCA: 95% of patients with no sign of proximal arteries of upper extremities involvement and 58% of patients with LVV symptoms [55]. Systematic review by S. L. Mackie et al. (2014) showed that frequency of carotid arterial involvement ascertained by color duplex ultrasound amounts to 29–54 % [35].

Comparing the available guidelines in the application of “diagnostic tests of the first line” for confirming suspected GCA, let we note the differences: the French experts (GEFA, 2015) do not consider ultrasound of temporal arteries could replace TAB [10], their British counterparts (BSR/BHPR, 2010) do not mention ultrasound at all, while, according to the EULAR (2018), ultrasound is “the first imaging modality in patients with suspected predominantly cranial GCA” — either as isolated exami-
nation of temporal arteries or in combination with ultrasound of axillary arteries [2]. As for MRI, the EULAR considers it to be an alternative to the ultrasound of temporal arteries, while the GEFA does not recommend it. Both GEFA and EULAR note a low value of ultrasonography for aortitis diagnosis [2, 10].

Simultaneous or consecutive ultrasound of several vessels is a method of improving GCA diagnostic accuracy, i.e. detecting damaged arteries, their distribution, description of abnormalities’ type as well). In 2014, as a result of studying a range of TAB-positive GCA cases, A. P. Diamantopulos et al. determined analytical param-

Table 10. BSR/BHPR guidelines’ (2010) statements on giant cell arteritis diagnosis and monitoring [9]

<table>
<thead>
<tr>
<th>№</th>
<th>Statement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Early recognition and diagnosis of GCA is paramount. Particular attention should be paid to the predictive features of ischaemic neuro-ophthalmic complications (C)</td>
</tr>
<tr>
<td>2</td>
<td>Urgent referral for specialist evaluation is suggested for all patients with GCA. TAB should be considered whenever a diagnosis of GCA is suspected. This should not delay the prompt institution of high-dose GC therapy (C)</td>
</tr>
<tr>
<td>3</td>
<td>Imaging techniques show promise for the diagnosis and monitoring of GCA. However, these do not replace TAB for cranial GCA. Their role in early diagnosis of cranial GCA is an important area of future research (B)</td>
</tr>
<tr>
<td>4</td>
<td>Large vessel GCA should be suspected in patients with prominent systemic symptoms, limb claudication or persistently high-inflammatory markers despite adequate GC therapy. Imaging techniques, such as PET and MRI scanning, should be reserved for the assessment of suspected large-vessel involvement (C)</td>
</tr>
<tr>
<td>5</td>
<td>Monitoring of therapy should be clinical and supported by the measurement of inflammatory markers (C; this is a consensus statement)</td>
</tr>
</tbody>
</table>

Notes: GCA — giant cell arteritis, TAB — temporal artery biopsy, GC – glucocorticosteroid, MRI — magnetic resonance imaging, PET — positron emission tomography.

Table 11. GEFA recommendations’ (2015) statements on giant cell arteritis terminology, nomenclature, classification and diagnosis [10]

<table>
<thead>
<tr>
<th>№</th>
<th>Statement</th>
</tr>
</thead>
</table>
| 1 | Terminology  
1A. It’s possible to use both terms «GCA» and «Horton’s GCA» |
| 2 | Nomenclature and classification  
2A. GCA is an arteritis of aorta and/or its branches in subjects over 50 with clinic-histological signs of cranial arterial involvement or vision impairment.  
2B. ACR classification criteria may be used for research purposes |
| 3 | Clinical diagnosis  
3A. GCA should be suspected first of all in subjects over 50 with abrupt-onset headache, jaw claudication, temporal arteries changes detected on inspection, sudden vision impairments.  
3B. GCA diagnosis should not be based on clinical data only, without an additional examination |
| 4 | TAB  
4A. TAB is necessary for increasing of GCA diagnosis probability. However, its performance should not delay the treatment initiation while its negative results do not exclude presence of GCA.  
4B. GCA diagnosis may be confirmed by detecting of mononuclear infiltrates in the vascular media; additional feature is presence of giant cells in the infiltrates.  
4C. Basic principles are: unilateral biopsy of an arterial fragment of no less than 1 cm and study of multiple section series |
| 5 | Instrumental study of temporal artery  
5A. Imaging of temporal arterial changes by means of ultrasound or MRI does not replace TAB as a first-line diagnostic test.  
5B. Ultrasound of temporal artery should be performed by an experienced specialist.  
5C. MRI of temporal artery is not recommended |
| 6 | Instrumental study of aorta and its branches  
6A. GCA diagnosis confirmation may be promoted by detecting of aortitis or arteritis of aortal branches by means of CT, MRI or PET. However, these methods do not replace TAB as a first-line diagnostic test |
| 7 | Biomarkers  
7A. Laboratory diagnostic tests for GCA should include ESR, CRP or fibrinogen assessment.  
7B. Other markers, besides ESR, CRP or fibrinogen, are not recommended for GCA diagnosis and monitoring |
| 8 | Aortal complication detection  
8A. Screening for aortitis complications with CT or MRI should be performed when GCA diagnosis is made and then every 2-5 years unless a patient has contraindications to a probable surgical intervention on aorta |

Notes: GCA — giant cell arteritis; GC – glucocorticoids; TAB — temporal artery biopsy; CT — computed tomography; MRI — magnetic resonance imaging; PET — positron emission tomography; CRP — C-reactive protein; ESR — erythrocyte sedimentation rate.
eters of **combined color duplex ultrasonography** of temporal, axillary and common carotid arteries (sensitivity of 100%, specificity of 91%) and concluded, that it is possible to use this diagnostic method instead of TAB in routine clinical practice [80]. At the same time, W. Schmidt et al. justified the expediency of **ultrasound monitoring** in GCA using color duplex ultrasound of the upper and lower limb vessels and considering a bilateral echo signal reduction (halo-sign) to be a high-specific vasculitis feature. They noted the importance of the following issues: 1) an “early” performing ultrasound after the initiation of GC therapy (as an inhibition of inflammation lowers test sensitivity); 2) taking into consideration “masking” influence of upper limb arterial GCA on BP measuring results while diagnosing arterial hypertension [65].

<table>
<thead>
<tr>
<th>№</th>
<th>Statement</th>
<th>Level of evidence</th>
<th>Level of agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>In patients with suspected GCA, an early imaging test is recommended to complement the clinical criteria for diagnosing GCA, assuming high expertise and prompt availability of the imaging technique. Imaging should not delay initiation of treatment.</td>
<td>1</td>
<td>9.2 (2.1) 90 % ≥ 8</td>
</tr>
<tr>
<td>2</td>
<td>In patients in whom there is a high clinical suspicion of GCA and a positive imaging test results, the diagnosis of GCA may be made without an additional test (biopsy or further imaging). In patients with a low clinical probability and a negative imaging results, the diagnosis of GCA can be considered unlikely. In all other situations, additional efforts towards a diagnosis are necessary.</td>
<td>2</td>
<td>9.4 (1.0) 90 % ≥ 8</td>
</tr>
<tr>
<td>3</td>
<td>Ultrasound of temporal±axillary arteries is recommended as the first imaging modality in patients with suspected predominantly cranial* GCA. A non-compressible “halo” sign is the ultrasound finding most suggestive of GCA.</td>
<td>1</td>
<td>9.7 (0.6) 100 % ≥ 8</td>
</tr>
<tr>
<td>4</td>
<td>High resolution MR† of cranial arteries* to investigate mural inflammation may be used as an alternative for GCA diagnosis if ultrasound is not available or inconclusive.</td>
<td>2</td>
<td>9.2 (1.1) 90 % ≥ 8</td>
</tr>
<tr>
<td>5</td>
<td>CT† and PET† are not recommended for the assessment of inflammation of cranial arteries.</td>
<td>5</td>
<td>9.5 (1.2) 95 % ≥ 8</td>
</tr>
<tr>
<td>6</td>
<td>Ultrasound, PET, MRI and/or CT may be used for detection of mural inflammation and/or luminal changes in extracranial arteries to support the diagnosis of LV-GCA. Ultrasound is of limited value for assessment of aortitis.</td>
<td>3 (PET and CT) and 5 (MRI and ultrasound)</td>
<td>9.8 (0.6) 100 % ≥ 8</td>
</tr>
<tr>
<td>7</td>
<td>In patients with suspected TA, MRI to investigate mural inflammation and/or luminal changes should be used as the first imaging test to make a diagnosis of TA, assuming high expertise and prompt availability of the imaging technique.</td>
<td>3</td>
<td>9.1 (1.4) 90 % ≥ 8</td>
</tr>
<tr>
<td>8</td>
<td>PET, CT and/or ultrasound may be used as alternative imaging modalities in patients with suspected TA. Ultrasound is of limited value for assessment of thoracic aorta.</td>
<td>3 (КТ) и 5 (ПЭТ и УЗИ)</td>
<td>9.4 (0.8) 100 % ≥ 8</td>
</tr>
<tr>
<td>9</td>
<td>Conventional angiography is not recommended for the diagnosis of GCA or TA as it has been superseded by the previously mentioned imaging modalities.</td>
<td>5</td>
<td>9.8 (0.6) 100 % ≥ 8</td>
</tr>
<tr>
<td>10</td>
<td>In patients with LV (GCA or TA) in whom a flare is suspected, imaging might be helpful to confirm or exclude it. Imaging is not routinely recommended for patients in clinical or biochemical remission.</td>
<td>5</td>
<td>9.4 (0.8) 100 % ≥ 8</td>
</tr>
<tr>
<td>11</td>
<td>In patients with LV (GCA or TA), MRA, CTA and/or ultrasound may be used for long-term monitoring of structural damage, particularly to detect stenosis, occlusion, dilatation and/or aneurysms. The frequency of screening as well as the imaging method should be decided on an individual basis.</td>
<td>5</td>
<td>9.3 (1.2) 95 % ≥ 8</td>
</tr>
<tr>
<td>12</td>
<td>Imaging examinations should be done by a trained specialist using appropriate equipment, operational procedures and settings. The reliability of imaging, which has often been a concern, can be improved by specific training. Suggestions for technical and operational parameters are depicted in box 1.</td>
<td>5</td>
<td>9.8 (0.6) 100 % ≥ 8</td>
</tr>
</tbody>
</table>

Notes: EULAR — European League Against Rheumatism, LVV — large vessel vasculitis, GCA — giant cell arteritis, TA — Takayasu arteritis, CT — computed tomography, CTA — computed tomography angiography, MRA — magnetic resonance angiography, MRI — magnetic resonance imaging, PET — positron emission tomography. *Cranial symptoms of GCA include headache, vision symptoms, jaw claudication, swelling and/or tenderness of temporal arteries. †CT and MRI also refer to specific angiographic techniques such as CTA and MRA, and PET is commonly combined with CT or CTA. ‡Cranial arteries: superficial temporal, occipital and facial, usually all visible in one examination in MRI.
In conclusion, the problem of evidence-based diagnosis of GCA is solved by developing international clinical recommendations. Table 10 presents 5 out of 9 statements of the BSR/BHPR guidelines for the management of GCA (2010) concerning its diagnosis and monitoring [9].

Among 15 topics of French recommendations on GCA management (GEFA, 2015), 8 tackle issues of terminology, nomenclature, classification and diagnosis (Table 11); consensus level of 80% is being reached for all such statements [10]. Table 12 presents all 12 statements of EULAR recommendations (2018) for the use of imaging in LVV in clinical practice [2]; all statements but for 7-8, devoted to TA, concern GCA.

As Table 12 shows, a pivotal aspect of management of patients with suspected LVV is an early use of accessible and expertly performed imaging diagnostic test (in case of a suspected GCA – biopsy or ultrasound of temporal arteries may be combined with ultrasound of axillary arteries; in case of a suspected TA – MR angiography) with no delay of treatment initiation. EULAR does not recommend: 1) conventional angiography as a diagnostic test for LVV; 2) specific angiographic methods (CT and PET) for assessment of cranial arterial inflammation; 3) routine use of imaging when no vasculitis relapse is suspected.

Information analysis of GCA relapse prediction showed a promising determination of such serum biomarker as osteopontin (sOPN), glycoprotein participating in Th1- and Th2-lymphocyte differentiation, tissue inflammation and remodeling. Nowadays, it is sOPN that is considered a GCA activity marker and GCA relapse predictor [81].

Pathogenic mechanisms of GCA’s vascular complications, namely early aortic dilatation, remain an object of studies and discussions. Besides a persistent remaining subclinical mural inflammation, it is attributed to an “early damage of the elastic fibers and muscular layer by inflammation, inefficient vascular repair or remodeling after injury, vascular ageing and/or hemodynamic factors” [82].

Conflicts of interests. Authors declare the absence of any conflicts of interests that might be construed to influence the results or interpretation of their manuscript.

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Гігантоклітинний артеріїт: епідеміологія, діагностика, прогноз

Резюме. Гігантоклітинний артеріїт (ГКА) — найпоширеніший системний васкуліт, що уражує величезні судини у осіб старше 50 років. Захворювання на нього пов’язане з підвищеним ризиком розвитку низки інших запальних хвороб і судинних ускладнень. Розв’язанню основних асоційованих з ГКА проблем присвячено множество зарубежних наукових і рекомендацій. Целью публікації є аналітичний огляд, систематичне узагальнення та обговорення доказів, що стосуються різних аспектів епідеміології ГКА, сучасних підходів і методів його діагностики, а також чинників ризику несприятливого прогнозу. Ключові слова: гігантоклітинний артеріїт; васкуліт великих судин; епідеміологія; діагностика; прогноз

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