Imaging in Large Vessel Vasculitides
Bildgebende Diagnostik der Großgefäßvaskulitiden

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Key words
blood vessels, vascular, giant cell arteritis, Takayasu’s arteritis, large vessel vasculitis, MR angiography

received 15.11.2018
accepted 02.04.2019

Bibliography
DOI https://doi.org/10.1055/a-0896-2833
Published online: 2019
Fortschr Röntgenstr © Georg Thieme Verlag KG, Stuttgart · New York
ISSN 1438-9029

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ZUSAMMENFASSUNG

Methode Diese Übersichtsarbeit stellt die wichtigsten bildgebenden Verfahren und einige typische Bildbefunde der beiden Hauptformen der Großgefäßvaskulitiden – der Riesenzellarteritis und der Takayasu-Arteritis – vor, unter spezieller Berücksichtigung der jüngst veröffentlichten EULAR (The European League Against Rheumatism)-Empfehlungen über die Rolle der Bildgebung bei Patienten mit suspendierten Großgefäßvaskulitiden.


Kernaussagen:
- Die Bildgebung wird für die Diagnostik von Großgefäßvaskulitiden als erste, präferierte Ergänzung zur klinischen und laborchemischen Untersuchung empfohlen.
- Radiologische Verfahren sind für die Diagnostik einer Riesenzellarteritis eine sinnvolle, nicht-bzw. geringinvasive Alternative/Ergänzung zur Temporalarterienbiopsie.
- Die jüngsten EULAR-Leitlinien empfehlen die farbkodierte Duplexsonografie als Diagnostikum der ersten Wahl im Falle einer suspendierten Riesenzellarteritis mit der Magnetresonanztomografie als gleichwertige Alternative im Falle uneindeutiger Befunde in der Sonografie und die Magnetresonanztomografie als präferierte bildgebende Modalität zur Detektion einer Takayasu-Arteritis.

ABSTRACT
Background Large vessel vasculitides comprise primary vasculitides of large and medium-sized arteries with various clinical, laboratory and radiological presentations. Imaging has become increasingly important in the diagnosis and monitoring of large vessel vasculitides. It complements clinical and laboratory examination and displays vasculitic changes of large extra- and intracranial arteries with relatively good diagnostic reliability and a low level of invasiveness.

Method This review presents the most important imaging modalities and some typical imaging findings in the context of the two main forms of large vessel vasculitis, giant cell arteritis and Takayasu’s arteritis, with special regard to the recently launched EULAR (The European League Against Rheumatism)
Results and Conclusion Color-coded duplex sonography (CCDS), magnetic resonance imaging (MRI), computed tomography (CT), and 18F-fluorodeoxyglucose positron emission tomography are today’s common imaging methods in large vessel vasculitides representing a reasonable and less invasive alternative or at least a good complement to temporal artery biopsy. Today’s EULAR guidelines recommend an imaging test as the first complementary method to clinical examination with CCDS as the preferred diagnostic test in suspected giant cell arteritis, MRI as the equivalent alternative in the case of inconclusive results, and MRI as the first choice in suspected Takayasu’s arteritis.

Introduction
This review outlines today’s imaging options in the diagnosis and therapy monitoring of large vessel vasculitides (LVV), a group of primary vasculitides, characterized by autoimmune-mediated granulomatous inflammatory processes of large and medium-sized blood vessels, with the aorta and its major branches as predilection sites [1]. The two major forms of large vessel vasculitis are giant cell (temporal) arteritis (GCA) and Takayasu’s arteritis (TA) [2].

Large vessel vasculitides
GCA and TA differ mainly in terms of clinical symptoms, anatomical location of the affected vessels and involvement pattern, as well as epidemiological conditions. While GCA is a disease of the elderly, often associated with polymyalgia rheumatica, with a disease onset at usually 50 years and older, TA mostly affects younger people under the age of 50 years [1, 3].

In both entities the aorta and its major branches are affected. While the supra-aortic vessels such as the subclavian, carotid, axillary, and the superficial cranial arteries, in particular the superficial temporal and occipital artery show typical signs of inflammation in GCA, typically with a segmental involvement pattern [4–6], TA predominantly affects the aortic arch and its major branches from the carotid to the external iliac artery, including the pulmonary artery [1, 7].

LVV may be associated with considerable morbidity and mortality. Early diagnosis and adequate therapy are essential for preventing these complications. The seriousness of the most common complications in GCA and TA is particularly due to the involved vessels’ vicinity and relevance in terms of blood supply to the brain and its associated structures. Cerebrovascular involvement and damage is a well-known complication in TA and is controversially discussed in GCA [8–10]. Irreversible vision loss as a result of anterior ischemic optic neuropathy (AION) in the case of GCA, stenosis and occlusion of large arteries with the consequence of ischemic (brain) injuries as well as aortic aneurysms and dissections in the case of TA belong to the most severe sequelae of vasculitic vessel changes [11–13].

Diagnosis of large vessel vasculitides
Identifying patients with LVV might be a challenge as they often present with nonspecific clinical symptoms and systemic inflammatory constellation of laboratory values. To date, the classification criteria for GCA of the American College of Rheumatology (ACR) include various clinical aspects and histopathological findings of the superficial temporal artery, but no imaging features [14, 15]. Temporal artery biopsy is still considered the “gold standard” in diagnosing the cranial form of GCA [14, 16, 17].

Due to rapid technological progress and its low invasiveness yet good diagnostic reliability, imaging has gained in importance in the diagnosis and monitoring of LVV. Today, imaging is the preferred complementary method to clinical examination as a reliable noninvasive alternative to temporal artery biopsy [18].

Imaging modalities and imaging findings in LVV
The most common imaging modalities in the context of LVV are color-coded duplex sonography (CCDS), computed tomography/CT angiography (CTA), magnetic-resonance imaging/angiography (MRI/MRA), and 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) [19, 20]. Table 1 summarizes the imaging modalities used in the context of LVV and the respective typical imaging findings. For further technical details, we refer to the recently published EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice [18].

Key Points:
- Imaging is a noninvasive diagnostic test for diagnosing and monitoring large vessel vasculitides and is recommended nowadays as the first complementary method to clinical examination.
- Imaging is a reasonable alternative or at least a good complement to temporal artery biopsy in the case of suspected giant cell arteritis.
- Today’s EULAR guidelines recommend CCDS as the preferred diagnostic test in suspected giant cell arteritis, with MRI as an equivalent alternative in the case of inconclusive results, and MRI as the first choice in suspected Takayasu’s arteritis.

Citation Format
Guggenberger K et al. Imaging in Large

With CCDS, the vessel's lumen as well as the vascular wall anatomy and the directly surrounding tissue may be assessed. For visualization of small arteries, particularly the superficial cranial arteries, a high-frequency linear transducer with a B-mode frequency of at least 10 MHz, optimally > 15 MHz should be used [18, 21]. For sonographic imaging of the extracranial supra-aortic arteries, a high-frequency linear transducer with a B-mode frequency of at least 10 MHz, optimally =/> 15 MHz should be used [18].

Atherosclerotic plaques, in contrast to vasculitic stenosis, usually do not cause significant changes in the Doppler spectrum or in the vascular wall thickness. Consequently, ultrasound is not very sensitive in the detection of these changes [22]. The detection of stenosis and occlusion of the affected vessel usually requires a Doppler examination, especially when atherosclerotic plaques with adjacent necrotic areas are present.

Table 1

<table>
<thead>
<tr>
<th>Imaging Modality</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Typical Findings in Large Vessel Vasculitides</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCDS GCA: Sensitivity 77%, Specificity 96% with clinical diagnosis of GCA as the reference standard [43]</td>
<td>&gt; Good availability</td>
<td>&gt; Operator-dependent</td>
<td>&gt; Hypoechogetic, non-compressible &quot;halo&quot; sign</td>
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<td></td>
<td>&gt; Fast, reliable, non-invasive</td>
<td>&gt; Limited by anatomical location</td>
<td>&gt; Facultative alterations of the flow velocity profile</td>
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<td></td>
<td>&gt; High resolution</td>
<td>&gt; Especially thoracic aorta and proximal supra-aortic branches</td>
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<td></td>
<td>&gt; No radiation</td>
<td>&gt; Limited information on inflammatory activity</td>
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<td></td>
<td>&gt; No nephrotoxic contrast agents</td>
<td>&gt; Dynamic examination (flow measurement)</td>
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<td>&gt; Low costs</td>
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<td>&gt; High frequency linear transducer with a minimum frequency of at least 10 MHz, optimally &gt; 15 MHz should be used [18, 21]. For sonographic imaging of the extracranial supra-aortic arteries, a high-frequency linear transducer with a B-mode frequency of at least 10 MHz, optimally =/&gt; 15 MHz should be used [18].</td>
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<td>&gt; Assessment of morphologic changes and inflammatory activity, especially the vessel's lumen and wall and the surrounding tissue</td>
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<tr>
<td>CT/CTA GCA: Sensitivity 73%, Specificity 78% with clinical diagnosis as the reference standard [44] TA: Sensitivity 100%, Specificity 100% with conventional angiography as the reference standard [45]</td>
<td>&gt; Good availability</td>
<td>&gt; Radiation exposure</td>
<td>&gt; Mural thickening and enhancement</td>
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<td></td>
<td>&gt; Fast, reliable, non-invasive</td>
<td>&gt; Nephrotoxic contrast agents</td>
<td>&gt; Late contrast uptake</td>
</tr>
<tr>
<td></td>
<td>&gt; High resolution</td>
<td></td>
<td>&gt; Vascular stenosis/occlusion/ectasia</td>
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<td></td>
<td>&gt; Wide scan range</td>
<td></td>
<td>&gt; Surrounding edema/tissue reaction</td>
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<td></td>
<td>&gt; Relative high specificity, good differential diagnosis</td>
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<tr>
<td></td>
<td>&gt; Assessment of morphologic changes and inflammatory activity, especially the vessel's lumen and wall and the surrounding tissue</td>
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<td>MRI/MRA GCA: Sensitivity 73%, Specificity 88% with clinical diagnosis of GCA as the reference standard [43] TA: Sensitivity 100%, Specificity 100% with conventional angiography as the reference standard [46]</td>
<td>&gt; High resolution</td>
<td>&gt; Limited availability</td>
<td>&gt; Mural thickening and enhancement</td>
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<td></td>
<td>&gt; Wide scan range</td>
<td>&gt; Time-consuming</td>
<td>&gt; Vascular stenosis/occlusion/ectasia</td>
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<tr>
<td></td>
<td>&gt; Technical flexibility</td>
<td>&gt; Dependent on patients' compliance</td>
<td>&gt; Surrounding edema/tissue reaction</td>
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<td></td>
<td>&gt; Functional/dynamic imaging</td>
<td>&gt; Expensive</td>
<td>&gt; Sequelae, e.g. infarction, necrosis, bleeding</td>
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<td></td>
<td>&gt; High sensitivity and specificity, good differential diagnosis</td>
<td>&gt; No standardized reading</td>
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<td></td>
<td>&gt; Assessment of morphologic changes and inflammatory activity</td>
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<td>FDG-PET Extracranial GCA: Sensitivity 67 - 77%, Specificity 66 - 100% with temporal artery biopsy/clinical diagnosis as the reference standard [44, 47]</td>
<td>&gt; High resolution</td>
<td>&gt; Limited availability</td>
<td>&gt; Mural thickening and tracer uptake</td>
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<td></td>
<td>&gt; Wide scan range</td>
<td>&gt; Expensive</td>
<td>&gt; Vascular stenosis/occlusion/ectasia</td>
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<td></td>
<td>&gt; Assessment of morphologic changes and inflammatory activity, especially the vessel's lumen and wall and the surrounding tissue</td>
<td>&gt; Radiation exposure</td>
<td>&gt; Surrounding edema/tissue reaction</td>
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<td>&gt; Relative low sensitivity</td>
<td>&gt; Mural thickening and tracer uptake</td>
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<tr>
<td>Conventional Angiography</td>
<td>&gt; High sensitivity in luminal changes, especially in small vessels</td>
<td>&gt; Limited availability</td>
<td>&gt; Vascular stenosis/occlusion/ectasia</td>
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<td></td>
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<td>&gt; Expensive</td>
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<td>&gt; Radiation exposure</td>
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<td>&gt; Operator-dependent</td>
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<td>&gt; No information on vessels' wall and surrounding tissue</td>
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</table>

CCDS

With CCDS, the vessel's lumen as well as the vascular wall anatomy and the directly surrounding tissue may be assessed. For visualization of small arteries, particularly the superficial cranial arteries, a high-frequency linear transducer with a B-mode frequency of at least 10 MHz, optimally > 15 MHz should be used [18, 21]. For sonographic imaging of the extracranial supra-aortic and extremity arteries, linear probes with a minimum frequency of 5 MHz, optimally > 8 MHz (7 – 15 MHz [18]) are preferably applied. For the assessment of large vessels, especially the abdominal aorta and its visceral branches as well as the iliac arteries, a curved array probe with a lower frequency (usually 3.5 – 5 MHz) is usually required.

Image resolution of 0.1 mm for superficial arteries can be achieved with modern ultrasound transducers [21]. A hypoechogetic, non-compressible halo sign around inflamed vessels is the typical finding in vasculitides, in the case of giant cell arteritis especially around the superficial temporal artery [22]. Sometimes, alternations of the Doppler spectrum, as well as stenosis or even occlusion of the affected vessel's lumen may occur. Atherosclerotic plaques, in contrast to vasculitic stenosis, usually...
have a more heterogeneous, eccentric and irregular nature. Measurement of the intima-media thickness was demonstrated to have a relatively high predictive value and can reliably distinguish vasculitic from normal arteries in suspected GCA [23]. Contrast-enhanced ultrasound may depict further information about the vessel wall. Contrast uptake of the vessel wall can visualize hyperemia and hypervascularization, typical features of an ongoing inflammatory process [24].

MRI/MRA
In both GCA and TA, the involvement patterns are variable and may include the coronary, carotid, external iliac, as well as the superficial cranial and the intracranial arteries. Therefore, imaging should include the potentially affected vasculature to capture the entire disease extent. MR imaging has a relatively wide scan range and is suitable for the assessment of the vessel’s lumen and wall of large body vessels, and extracranial superficial cranial arteries, particularly the superficial temporal and occipital arteries [25, 26]. Furthermore, intracranial arteries as well as the surrounding tissue and any complications can be assessed simultaneously.

MR vessel wall imaging requires suppression of the signal arising from the luminal blood or from other surrounding structures, such as the brain parenchyma or cerebrospinal fluid in the case of intracranial arteries in order to clearly differentiate the vessel wall [27]. A contrast-enhanced, fat-suppressed, high-resolution black blood T1-weighted spin echo sequence is the most valuable sequence for detecting mural inflammatory changes in superficial cranial arteries in GCA.

MR angiography, especially TOF (time-of-flight) angiography in the case of assessment of the intracranial arteries and contrast-enhanced time-resolved TWIST (time-resolved angiography with interleaved stochastic trajectories) angiography in the case of assessment of the large body vessels, are helpful to evaluate the lumen diameter, detect any vessel stenosis or occlusion and blood flow alterations. However, they are not suitable for the visualization of specific vasculitic changes as they do not delineate the vessel walls.

Navigated fat-suppressed T1w-3D black-blood MRI with peripheral pulse unit triggering has been demonstrated to be a reliable tool in the diagnosis of thoracic LLV [28].

Unenhanced T1-weighted, T2-weighted or diffusion-weighted imaging might add important anatomical and functional information and may be helpful in detecting vasculitic complications, such as infarctions or hemorrhage.

Characteristic MRI findings of vasculitis comprise direct and indirect signs [29]. Direct signs of vessel inflammation include mural thickening greater 600 µm and contrast enhancement of the affected vessel [26]. Stenosis or occlusion of the affected vessels may be present. Indirect signs of vasculitides, indicating already incurred complications, include non-arteriosclerotic vascular stenosis and, in the case of brain-supplying arteries, cerebral ischemic infarction or perfusion deficit and intraparenchymatous or subarachnoid hemorrhage [29]. Vascular stenosis caused by inflammation is characterized by circular contrast enhancement and narrowing of the luminal diameter, in contrast to eccentric plaque and stenosis in case of arteriosclerotic changes [29, 30].

CT/CTA
CT is a widely available and fast cross-sectional imaging method able to capture vessels from the skull to the lower limbs in one scan. CT-angiography combined with a parenchymal, venous or portal venous contrast phase allows assessment of the vessels’ lumen in terms of caliber irregularities or stenosis, the vessels’ wall in terms of thickening and contrast enhancement, and assessment of the surrounding tissue [18]. CT is suitable for detecting structural lesions and wall inflammation with a higher resolution and shorter procedural time than MRI, however it entails radiation exposure [31]. Vasculitic vessel wall lesions are usually smoother and more homogeneous than arteriosclerotic lesions. Calcifications are not typical.

FDG-PET
18F-fluorodeoxyglucose positron emission tomography (FDG-PET) provides functional information in terms of metabolic activity and is rather known for its significance in oncology. FDG-PET allows whole-body imaging, thus the assessment of all vascular territories, in one single examination. FDG-PET may deliver valuable information for diagnosis, extent assessment, disease activity and therapy response evaluation. However, it does not clearly delineate the vessel wall. Increased FDG-uptake in the vessel wall indicates hypermetabolism, a typical feature of vasculitis on PET, thus depicting disease activity. In general, visual FDG-uptake of the vessel wall that is higher than the tracer uptake in the liver suggests vasculitic changes in the context of large vessel vasculitides [32]. A characteristic finding in GCA is a linear or segmental pattern of tracer uptake in the aorta and its main branches [33]. However, trace uptake is nonspecific and, as in other imaging methods, differentiation between vasculitic and arteriosclerotic lesions might be a challenge [34].

Conventional angiography
Particularly due to its invasiveness, conventional angiography has lost importance in the context of LVV over the past years and has been replaced mostly by less invasive imaging techniques [18, 35]. Conventional angiography in general is an invasive imaging method allowing very sensitive assessment of the lumen of large and small vessels in terms of stenosis and occlusion, with the additional option of therapeutic intervention in the same procedure. Vasculitic vessel changes of large and medium-sized vessels, in particular vascular stenosis and occlusion or aneurysms sometimes require surgical interventions, especially in symptomatic disease refractory to immunosuppressive medical therapy. Therapeutic options include open surgery or endovascular intervention, with percutaneous transluminal angioplasty, stent insertion, and stent graft placement as possible options [36]. Considering the size of the affected vessels, endovascular therapy is mainly suitable for the treatment of TA lesions, especially of the aorta and the supraaortic branches, the coronary and renal arteries [36]. Endovascular treatment in GCA is rare and is mainly applied in the case of extracranial vessel involvement, in particular balloon angioplasty in the case of stenosis or occlusion of upper or lower limb arteries [37, 38]. There are only a few cases described in the literature.
in which endovascular stenting of the internal carotid artery and the vertebral artery was attempted [39 – 41]. However, the specificity of conventional angiography regarding the diagnosis of vasculitic vessel changes is limited, as it does not depict the vessel walls or surrounding tissue but just the intraluminal flow. Typically, vasculitic stenoses display smooth tapering of the affected segment compared to more clearly delineated arteriosclerotic stenoses (Fig. 1, 2, Table 1).

**EULAR recommendations concerning the use of imaging in the diagnosis and monitoring of patients with large vessel vasculitides**

EULAR (The European League Against Rheumatism) has recently published its first recommendations on the role of imaging in the diagnosis and monitoring of patients with suspected large vessel vasculitides. These recommendations are mainly based on a systematic literature review [43], intended to guide primary, secondary and tertiary care physicians, such as neurologists, ophthalmologists and rheumatologists through diagnosis and monitoring in regard to the application of imaging modalities [18]. Considering the severity of possible complications, early initiation of adequate therapy should be the first priority in the management of large vessel vasculitides. Presuming expertise, adequate equipment, operational procedures and settings, an early imaging examination is considered the preferred complement to clinical criteria in patients with suspected large vessel vasculitides. Presumably, imaging should take place before or as early as possible after the initiation of therapy, as the sensitivity is significantly reduced within a few days of treatment with glucocorticoids [48 – 51]. However, if adequate imaging is not readily available or if the imaging tests are inconclusive, other diagnostic tests should be conducted to clarify the suspected diagnosis or, in the case of...
clinically obvious cases, treatment should be started in spite of an incomplete diagnostic process.

Giant cell arteritis

In the case of suspected predominantly cranial GCA, color-coded duplex sonography (CCDS) of the temporal or/and axillary arteries is recommended as the preferred imaging modality, especially because of its widespread and fast availability, good reliability, and absence of procedural risks such as radiation and cost-efficiency. If CCDS is inconclusive or not available, an alternative is high-resolution MRI. The sensitivity and specificity of CCDS and high-resolution MRI in detecting mural inflammation signs in giant cell arteritis are of comparable value [43, 52].

In the case of a positive imaging test and high clinical probability, GCA may be diagnosed without any further testing. In the case of a negative imaging test and low clinical suspicion, GCA may be considered unlikely [18]. In the case of uncertainty after clinical examination and imaging, further steps need to be taken to confirm or exclude GCA. CT and PET are not suitable for assessing inflammation of intracranial arteries. However, CCDS, PET, MRI or CT may be used to assess inflammatory wall and/or luminal changes in extracranial arteries in the framework of GCA.

Temporal artery biopsy is not supposed to be discarded as a diagnostic procedure in GCA in favor of imaging by the new EULAR recommendations. Instead, imaging should be preferred over biopsy as a diagnostic procedure for its low invasiveness, rapid availability of imaging results and its superior evaluation of disease extent and identification of other involved arteries in further locations. This is of importance, since GCA is a systemic disease and most often affects more than a single vessel territory. However, under circumstances in which adequate imaging and expertise are not available, temporal artery biopsy is indicated to confirm clinically suspected GCA. Imaging is redundant, provided that temporal artery biopsy has already been conducted and is positive [18]. A negative biopsy result does not rule out GCA as there might still be unaffected segments of the temporal artery in active vasculitis. In the case of a negative or questionable biopsy, imaging might provide additional information.

Takayasu’s arteritis

In suspected TA, MRI is recommended as the preferred diagnostic test if available to investigate luminal changes and mural inflammation. Alternatively, PET, CT and/or CCDS may be used for the assessment of inflammation processes or luminal changes in patients with TA. However, the value of CCDS in assessing the aorta and some of its branches is limited due to their anatomical location [18].

For long-term monitoring of large vessel vasculitides as well as the assessment of complications and structural damage, MRI/MRA, CTA and/or CCDS may be used. The modality and frequency of repeat scanning should be adjusted to the individual circumstances. However, routine imaging is not provided for patients in clinical and biochemical remission. Conventional angiography is not recommended anymore in the diagnosis and monitoring of large vessel vasculitides [18, 35].
Discussion

The major limitation of imaging in large vessel vasculitides is the significant decrease in the sensitivity of CCDS and MRI after treatment initiation with glucocorticoids [51]. It is reported that the sensitivity of MRI decreases significantly within five days after therapy initiation [53], and the halo sign in CCDS disappears about 14–21 days after initiation of glucocorticoid treatment [54]. However, within several days after treatment initiation, diagnosis through imaging, no matter which modality, may be difficult in some cases [55].

In contrast, temporal artery biopsy seems to be valuable up to 4 weeks after treatment initiation [56].

Furthermore, each modality has its specific constraints. CCDS is an operator-dependent diagnostic test, based on the operator’s subjective evaluation of findings and the lack of reproducibility. The availability of MRI is restricted, its costs are relatively high and the required imaging times may be rather long. CT, PET/CT and conventional angiography are associated with radiation exposure and use of i.v. contrast agents. Conventional angiography has a high sensitivity in detecting vessel stenosis or occlusion with the option of endovascular treatment if needed. However, besides its invasiveness, its comparably low specificity regarding the underlying cause of luminal change is a limiting factor. Conventional angiography only depicts luminal changes occurring in advanced vasculitic disease stages, and it cannot adequately capture early signs of vasculitic disease, in particular vessel wall changes where the luminal diameter is still preserved.

The diagnostic value of the two first-choice modalities in GCA and TA, i.e., CCDS and MRI, is comparable (pooled sensitivity of MRI: 73%; specificity: 88%) [43]. There is not much data on the diagnostic value of CT/CTA in the diagnosis of LVV, a small study indicates a sensitivity of 73% and a specificity of 78% for CTA in diagnosing GCA [31].

Summary

As a result of ongoing technological progress, imaging has gained great importance in the diagnosis and therapy monitoring of large vessel vasculitides. Due to its low invasiveness and high diagnostic reliability, imaging is a reasonable alternative and/or good complement to temporal artery biopsy. There are a variety of possible imaging modalities in the context of large vessel vasculitides, and sometimes different imaging tests can supply complementary information. Today’s EULAR guidelines concerning the diagnosis of large vessel vasculitides recommend an imaging test as the first complementary method to clinical examination with CCDS as the preferred imaging modality in suspected GCA, MRI as an equivalent alternative in the case of inconclusive results, and MRI as the first choice in suspected TA.

Conflict of Interest

The authors declare that they have no conflict of interest.

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