Imaging the Vasculitides

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KEYWORDS

• Neuroimaging • Computerized tomography • Magnetic resonance imaging
• Single-photon emission tomography • Positron emission tomography
• Cerebral angiography

KEY POINTS

- Neuroimaging plays a vital role in the diagnosis of primary and secondary vasculitic disorders.
- There are a multiplicity of neuroimaging options available to accurately describe the underlying clinical deficits of involved cases.
- Noninvasive neuroimaging modalities provide less risk and when interdigitated, form the basis for a more conclusive understanding of the disease process.
- There are instances in which invasive cerebral angiography may be needed to image the intricate and at times, small involved vessels.
- Neuroradiologists should be included in the multidisciplinary team of physicians caring for patients with vasculitides and in research to provide more sensitive and safe modalities for the accurate diagnosis thereof.

INTRODUCTION

Vasculitis is a term used to describe a diverse spectrum of diseases characterized by inflammation of the blood vessels that may progress to ischemic injury of the central nervous system (CNS) resulting in a myriad of focal and generalized neurologic symptoms. The injury is usually secondary to mural changes resulting in vessel stenosis or occlusion. Endothelial inflammation promotes intraluminal coagulation and thrombosis.[1] Perivascular inflammatory changes and edema contribute to the pathologic picture. Arterial and venous components may be involved separately or together and dural sinuses may be affected. Generalized inflammatory processes may produce a secondary encephalitis or myelitis. The radiological aspects of CNS vasculitis have evolved in the past decade.[2] No one single imaging modality is sufficient or

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preeminent; a combination of studies is typically required for a confident diagnosis of CNS vasculitis.

OVERVIEW AND CLASSIFICATION

With an estimated worldwide incidence of 20 per million for eosinophilic granulomatosis with polyangiitis (EGPA), also known as Churg-Strauss syndrome, 10 per million for granulomatosis with polyangiitis (GPA) or Wegener granulomatosis, 2.6 per million for Takayasu arteritis (TAK), and 0.9 per million for polyarteritis nodosa (PAN),[3,4] and only a fraction of patients presenting with CNS involvement, it is important for clinicians to be familiar with the clinical and neuroradiologic presentations of the vasculitides. This is especially important in young and middle-aged adults in whom the prevalence of atherosclerotic disease is low.[5–9]

The historical aspects of the classification of the vasculitides are reviewed elsewhere in this issue. To illustrate the clinical importance placed on the radiologic manifestations of the PAN group of primary systemic vasculitides, the narrative should begin with Citron and colleagues[10] who described multiorgan arteritis of the CNS in a highly publicized report of 14 Los Angeles multidrug abusers with a common denominator of intravenous methamphetamine abuse by all but 2 patients, and exclusively by 1. Acute vessel lesions included fibrinoid necrosis of the media and intima with infiltration of polymorphonuclear cells, eosinophils, lymphocytes, and histiocytes, followed by vascular elastic and vascular smooth muscle destruction resulting in lesions considered typical for PAN. Substantiation of necrotizing arteritis was present in only 4 of the 14 patients. Citron and Peters[11] responded to the criticism from Baden[12] that he had not observed a causal relation between drug abuse and necrotizing arteritis at the Office of Chief Medical Examiner of New York City for the past one-half century among thousands of autopsied drug abusers, with the countering opinion that evidence of aneurysms noted in 13 of the 14 patients was ample proof of arteritis.

The contribution of angiography to the designation of CNS vasculitis commenced with the identification of angiographic beading and a sausagelike appearance of cerebral vessels at sites of presumed arteritis first in 1964 by Hinck and coworkers[13] in giant cell arteritis (GCA). In 1983, Cupps and colleagues[14] established the utility of cerebral angiography in the diagnosis of histologically proven isolated angiitis or primary angiitis of the CNS (PACNS). As giant cells and epithelioid cells usually found at postmortem examination in such patients were an inconsistent finding in a meningeal and brain biopsy and therefore considered unnecessary for antemortem diagnosis, Moore and Cupps[15] considered angiography necessary for the diagnosis of PACNS. This prevailing opinion was shared by Calabrese and Mallek,[16] who proposed criteria for the diagnosis of PACNS, and Hajj-Ali and Calabrese[17] who later separated PACNS from the reversible cerebral vasoconstrictive syndrome (RCVS), characterized instead by transient nonvasculitic narrowing of intracranial vessels.

By 1990, Hunder and colleagues[18] on behalf of the American College of Rheumatology (ACR) noted that the goal in classification was to identify sets of sensitive criteria that recognized a high proportion of patients with a particular form of vasculitis, while specifically excluding a high proportion of those with other diseases. Although highly specific and sensitive classification criteria might prove useful in the depiction of patients for epidemiologic studies and therapeutic trials, such criteria might not necessarily include the full spectrum of manifestations of a particular vasculitic disease, which was instead the role of formal diagnostic criteria. Lie[19] noted that although a definitive diagnosis of vasculitis almost invariably required histologic documentation, the interpretation of a diagnostic tissue sample was subject to variables as diverse as

the pathologist's experience, tissue selection, sample size, chronologic age of the disease, and any prior treatment at the time of the biopsy. The angiographic appearance of aneurysms or occlusions of visceral arteries not due to arteriosclerosis, fibromuscular dysplasia, or other noninflammatory causes, were useful in the classification of PAN[20] with a sensitivity of 73.5% and specificity of 89.2%. The angiographic features of narrowing, aneurysm, or occlusion of the aorta or its primary branches, were useful criteria for the classification of TAK[21] with sensitivities and specificities of 85.5% and 81.2%, 20.3% and 95.9%, and 51.6% and 86.1%, respectively. In the same 1990 volume of the journal, *Arthritis and Rheumatism*, the ACR Subcommittee on Classification of Vasculitis noted no diagnostic features of angiography useful in the classification criteria of EGPA, GPA, hypersensitivity vasculitis, immunoglobulin A vasculitis (IgAV) and GCA.[22–26]

Jennette and colleagues[27] held 2 Chapel Hill Consensus Conferences (CHCCs) beginning in 1994 with a 2012 revision,[28] establishing the nomenclature or nosology of systemic vasculitides. However, different from the ACR Subcommittee on Classification of Vasculitis,[18] Jennette and colleagues[27,28] incorporated prevailing knowledge about etiology, pathogenesis, pathology, demographics, and clinical manifestations, and used a model of the predominant caliber of involved vessel that delineated the 3 major categories of systemic vasculitis including large-size vessel vasculitis (LVV), medium-size vessel vasculitis (MVV), and small-sized vessel vasculitis (SVV) types, adding further distinctions as to the structural and functional characteristics of particular vascular beds, as well as the known biochemical and functional properties that rendered them susceptible to vasculitic injury. With approximately 26 recognized vasculitides in the 2012 revised CHCC, many of which demonstrate overlap in affected involved arteries, coupled with advances in the neuroradiologic techniques for discerning CNS involvement, there has been heightened interest in imaging the cerebral vasculature.

Küker[29] differentiated the entities of extracranial LVV and intracranial MVV and SVV, noting that vasculitic involvement of the internal carotid (ICA), common carotid (CCA), M1 and A1 segments of the middle (MCA) and anterior cerebral arteries (ACA), intracranial vertebral and basilar arteries, and P1 segment of the posterior cerebral artery (PCA), generally regarded as intracranial LVV, would instead be considered systemic MVV by 2012 Revised CHCC nomenclature.[28] Moreover, vasculitic involvement along arterial vessels distal to the MCA bifurcation, as well as communicating vessels such as the anterior and posterior communicating arteries, were still considered MVV systemically although intracranial. They may not be demonstrable along with intracranial LVV by MRI, magnetic resonance angiography (MRA), or computed tomographic angiography (CTA), and may require conventional angiography (CA) for luminal irregularity to be visualized.

The smallest muscular arteries and arterioles in the brain parenchyma, as well as the capillaries and proximal venules, all considered intracranial SVV by their lumen size, corresponded to a caliber of 200 to 500 μm or less,[30,31] and were considered beneath the resolution of invasive and noninvasive neuroimaging, requiring tissue biopsy to diagnose vasculitic involvement. The radiologic findings of nonvasculitic inflammatory vasculopathies, such as systemic lupus erythematosus (SLE), and other noninflammatory vasculopathies, such as RCVS (**Fig. 1**), cerebral atherosclerosis, and spontaneous dissection may mimic PACNS (**Fig. 2**).

NEURORADIOLOGIC APPROACH TO CENTRAL NERVOUS SYSTEM VASCULITIS

Küker[29] described 3 steps in the diagnostic evaluation of CNS vasculitis beginning with the demonstration of brain lesions by T_2-weighted and diffusion-weighted and

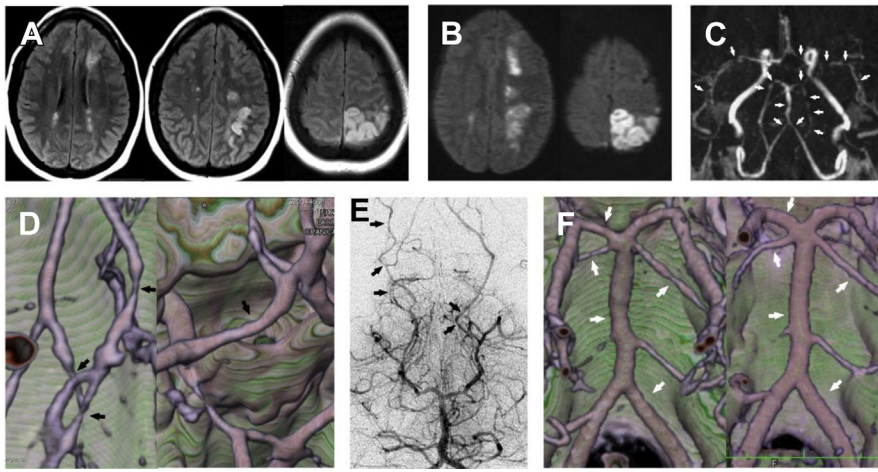

Fig. 1. RCVS. (*A*) MRI FLAIR imaging on presentation demonstrates multifocal abnormal hyperintense signal within the bilateral hemispheric white matter, more prominent in the parietal and occipital lobes where it extends to the cortex. (*B*) T_2-diffusion imaging demonstrates restricted diffusion consistent with acute ischemia. The white matter distribution within the left hemisphere straddles the anterior, middle, and posterior cerebral vascular territories, a "watershed" distribution. (*C*) MRA at admission demonstrates short-segment multifocal narrowing within the distal bilateral vertebral arteries, the basilar artery, and bilateral middle and posterior cerebral vasculature (*white arrows*). (*D*) CTA demonstrates moderate narrowing within the right PCA P2 segment and a more severe narrowing distally within the P3 parieto-occipital segment (*left, black arrows*). Mild narrowing is present within the ACA A1 segment (*right, black arrow*). (*E*) CA confirms multifocal narrowing within the bilateral posterior cerebral arteries (*black arrows*). (*F*) Follow-up CTA (at presentation on the left, 5 months' follow-up on the right) reveals complete resolution of the original findings (*white arrows*). (*Courtesy of* Adam Davis, MD New York, NY.)

perfusion-weighted MRI, followed by the delineation of underlying vascular pathology by 1.5-T MRA to study the entire course of the carotid and vertebral arteries, as well as the circle of Willis. Time-of-flight (TOF) MRA sequences permit detection of more subtle stenoses and improve spatial resolution, as well as mural thickness in basal brain arteries with MRA source images; moreover, MRI may discern mural enhancement. Conventional angiography with digital subtraction (DSA) is used to evaluate medium-sized and small brain vessels and the status of cerebral hemodynamics and assessment of brain perfusion.

Gomes[32] divided available neuroimaging studies into 3 groups, including the brain parenchyma, vessel lumen, and vessel wall. Parenchymal findings, although least specific, were necessary to detect the presence of disease as well as to follow progression and remission status. Vessel lumen and wall abnormalities, although highly suggestive for systemic vasculitis when present, were considered nonspecific and insensitive in the diagnosis of intracranial SVV.

Parenchymal Imaging

The MRI findings of CNS vasculitis have been previously described,[33–36] the commonest of which are T_2/fluid-attenuated inversion recovery (FLAIR) hyperintense lesions secondary to ischemia distributed throughout subcortical and deep white matter, the deep gray nuclei, and the cortices. The MCA territory is the commonest involved

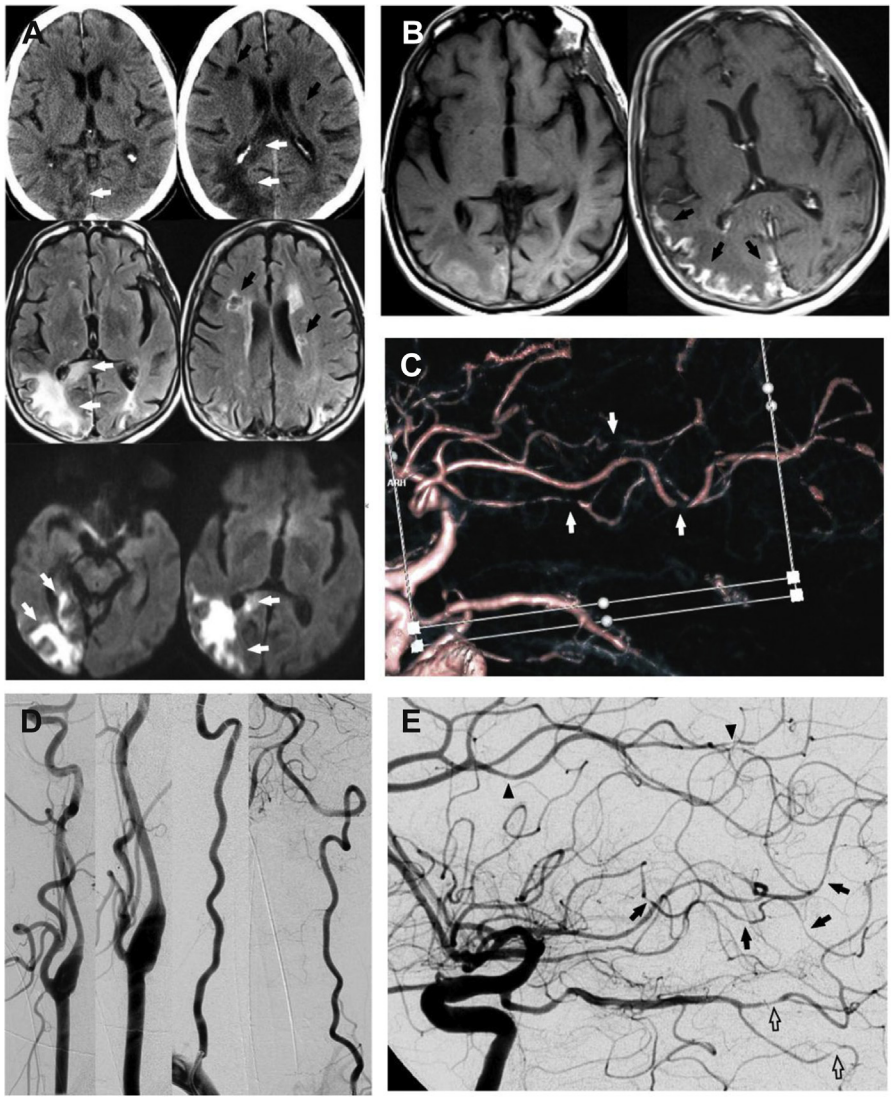

Fig. 2. PACNS. (*A*) Noncontrast CT (*top*) demonstrates multifocal regions of low attenuation. Those in the right frontal subcortical white matter and left basal ganglia (*black arrows*) are sharply defined, without mass effect and likely reflect old infarctions. Both the cortex and underlying white matter of the right occipital lobe are involved, as is the right splenium of the corpus callosum (*white arrows*). In these locations, the margins are more ill-defined and there is subtle mass effect characterized by sulcal and ventricular effacement, suggesting acute ischemia in the right PCA territory. MRI FLAIR imaging (*middle*) demonstrates central low and peripheral high signal intensity within the frontal and periventricular white matter lesions (*black arrows*) consistent with chronic encephalomalacia from old infarctions. The FLAIR hyperintense signal within the right occipital lobe is more confluent and extends to the posterior temporal lobe and splenium, involving both cortex and white matter (*white arrows*) and better delineates the extent of the acute infarct. DWI (*bottom*) demonstrates restricted diffusion consistent with acute ischemia. (*B*) T_1-weighted imaging before and after gadolinium demonstrates extensive leptomeningeal enhancement along

in CNS vasculitis.[37,38] Diffusion-weighted imaging (DWI) helps to distinguish acute, subacute, and chronic ischemia and is thus mandatory. Lesions are frequently bilateral and of differing ages. Involvement of multiple vascular territories or lesions within a frankly nonvascular territorial distribution may be clues to the diagnosis of CNS vasculitis, although they also can be seen in association with thrombophilic and cardiogenic multiple embolic process that produce ischemia. Ischemic lesions are present in up to one-half of patients with PACNS.[35] Nonspecific white matter changes, which may be the only finding in symptomatic patients,[39,40] are unlikely findings of atherosclerotic hypertensive disease in young patients, yet sometimes difficult to distinguish from CNS demyelinating disease.

Intraparenchymal and subarachnoid hemorrhages may be presenting or associated radiographic features of CNS vasculitis,[41] although they occur less commonly than ischemic lesions so noted in up to 40% of patients with PACNS as compared with hemorrhage that occurred in only 4% to 12% of patients.[42–44] There is uncertainty regarding the significance of microscopic hemorrhage in patients with CNS vasculitis. T_2-weighted gradient-echo MRI, which depicts chronic blood or hemosiderin products as regions with marked signal intensity loss (susceptibility effect), was useful in demonstrating multiple silent petechial hemorrhages scattered throughout both cerebral hemispheres located in cortical-subcortical regions in a patient with stereotypic tingling spells in the right hand followed by acute mutism due to histological-proven PACNS. Brain computed tomography (CT) showed a small hematoma in the left parietal lobe and 1.5-T T_1-weighted, turbo spin-echo T_2-weighted, and FLAIR brain MRI demonstrated acute hemorrhage in the left parietal lobe as well as subacute hemorrhage in the right frontal lobe.[42] However, T_2-weighted gradient-echo images showed multiple small hemorrhages scattered throughout the cerebral hemispheres located in the cortical-subcortical regions sparing the basal ganglia, thalamus, and brain stem. Conversely, neither large nor small silent cortical hemorrhages were found among 25 patients with intracranial vasculitis using T_2*-weighed MRI.[45]

Leptomeningeal enhancement by MRI was noted in up to 9% of patients with PACNS,[34,44] often in association with cognitive disturbances, normal MRA and conventional or catheter angiography (CA), granulomatous angiitis histopathology and small-vessel involvement.[44]

Delayed perfusion and reduced cerebral blood volume may be seen on brain CT and MRI in patients with cerebral vasculitis.[34,45,46] Magnetic resonance spectroscopy reveals elevated glutamate and glutamine levels and reduced N-acetyl aspartate (NAA) content in cerebral vasculitis,[46,47] and absence of a choline peak.[46–48]

High-Resolution MRI

High-resolution MRI (hrMRI), using gadolinium-enhanced fat-saturation T_1 spin-echo techniques, provides useful information of possible inflammatory changes in those with suspected systemic LVV. More recently, the use of vessel wall imaging has increased due to the multiple applications in vivo, such as the differentiation between

the cortical surface of the posterior temporal and occipital lobes. (*C*) CTA demonstrates multifocal vascular narrowing within several branches of the MCA (*white arrows*) with intervening regions of normal-appearing vasculature. At the bottom of the image, vascular narrowing within the PCA (not marked) is present. (*D*, *E*) CA reveals completely normal extracranial vasculature. The ACA (*black arrowheads*), MCA (*black arrows*), and PCA (*black outlined arrows*) demonstrate mild to severe short-segment stenoses. (*Courtesy of* Adam Davis, MD and Tibor Bescke, MD.)

atherosclerosis and vasculitis, the visualization of intracranial dissection, and to determine which aneurysm has ruptured in patients with acute subarachnoid hemorrhage and multiple aneurysms. The arterial wall enhancement in patients with vasculitis is probably related to contrast leakage from the lumen into the arterial wall, given the increased permeability of the endothelium; it is also possible that the presence of dilated neovessels in the wall is responsible for the increased contrast enhancement. It is important to keep in mind that there may be a discordance between the MRI findings and the clinical vasculitis activity.[49]

In 26 patients with TAK and 16 healthy subjects so studied,[50] contrast-enhanced T_1-weighted spin-echo MRI using small fields of view and thin slices showed enhancement of thickened aortic wall compared with myocardium, suggesting active TAK. The degree of disease activity was concordant with laboratory measures of disease activity in 88.5% of patients, including erythrocyte sedimentation rates (ESRs) and C-reactive protein (CRP). The measured signal intensity of the aortic wall relative to that of myocardium during the early phase of contrast-enhanced MRI, which was significantly correlated with serologic markers of inflammation, provided a useful assessment of disease activity in TAK. Notably, T_2-weighted signal intensity changes were less sensitive than enhanced images. In 64 consecutive patients with suspected GCA, Bley and colleagues[51] assessed mural thickness, lumen diameter, and mural contrast-enhancement scores by T_1-weighted spin-echo images with sub-millimeter in-plane spatial resolution. Their findings demonstrated that evaluation of the mural inflammatory MRI signs for diagnosing vasculitis resulted in a sensitivity of 80.6% and a specificity of 97.0%, in comparison to histologic results alone, which demonstrated a sensitivity of 77.8% and specificity of 100%. Some positive MRI results were associated with biopsy-negative histopathology for GCA, presumably due to sampling errors with skip lesions predominating in the tissue biopsy. Among patients with GCA who received treatment with corticosteroids less than 10 days, sensitivity of hrMRI ranged from 81% to 85%, whereas others receiving corticosteroids for more than 10 days demonstrated a sensitivity of 33%. Notwithstanding, hrMRI still should provide sensitive and specific information when neuroimaging is performed within days following the initiation of immunosuppressive treatment. In addition, in GCA, Geiger and colleagues[52] demonstrated how mural contrast enhancement of the ophthalmic arteries could be demonstrated using a 3-T MRI examination and they showed that it is a common finding in patients with GCA with suspicious ophthalmic arteries involvement.

hrMRI findings of intracranial vasculitis include concentric and asymmetric vessel wall thickening, an eccentric or narrowed vessel lumen, and vessel wall enhancement. Enhancement may be limited to the vessel wall or extend to adjacent leptomeninges. For intracranial large vessel disease, direct vascular wall inflammatory wall changes provide greater specificity than indirect luminal imaging findings. The degree and persistence of vessel wall enhancement helped to differentiate PACNS from RCVS because mural enhancement is less prominent in RCVS and resolves in nearly all restudied patients at 3 months while those with PACNS demonstrate an increased vessel wall enhancement that persists for greater than a year.

An additional role of wall imaging MRI is to help selecting the appropriate target for biopsy in cases of suspected vasculitis.

Indirect Vessel Imaging Techniques

Indirect imaging techniques that characterize changes in the vessel lumen leading to ischemia, infarction, and hemorrhage in cerebral vasculitis can be obtained by MRA, CTA, and CA; however, these do not provide direct evidence of the associated

underlying mural and perivascular inflammation. Catheter angiography provides up to 0.2 mm of spatial resolution and 0.5 to 0.25 seconds of temporal resolution in a typical study, exceeding MRA and CTA.[30] The spatial resolution of multidetector CTA, which is dependent on detector row thickness, is approximately 0.4 to 0.75 mm. CA provides detailed information regarding hemodynamics that is generally absent from both CTA and MRA. Dynamic 320-section CTA provides limited hemodynamic information with a temporal resolution of 1 second and a spatial resolution of 0.5 mm.[53] Indices for MRA spatial resolution are even less precise than these other techniques.

Magnetic resonance angiography

This noninvasive nonionizing indirect vessel wall imaging study does not require intravenous contrast administration for the assessment of intracranial stenoses and vascular occlusions in suspected CNS vasculitis. MRA may overestimate vascular stenosis secondary to diminished signal intensity from vessel tortuosity and slow flow. The more subtle finding of intracranial vessel irregularity is more difficult to assess due to lower spatial resolution. Among 9 arteries from 14 young patients with clinical and radiological suspicion of cerebral vasculitis, the sensitivity for detecting a stenosis by 3-dimensional TOF MRA or DSA varied from 62% to 79% for MRA, and 76% to 94% for DSA. The specificity for detecting a stenosis varied from 83% to 87% for MRA and from 83% to 97% for DSA. Using the criterion of greater than 2 stenoses in 2 or more separate vascular distributions as a true positive criterion for cerebral vasculitis, the false-positive rate for MRA and DSA were comparable.[54] When more than 2 stenoses are noted on MRA, DSA is unlikely to add further diagnostic precision in a given patient with suspected cerebral vasculitis, but yet might be useful when MRA is normal or discloses fewer than 3 stenoses.[54]

Computed tomography angiography

Indirect vessel wall imaging using CTA has been used in TAK, GCA, PAN, and CNS vasculitis. The efficacy of CTA in TAK, a chronic idiopathic LVV that primarily affects large vessels such as the aorta and its major branches, as well as the pulmonary and coronary arteries, is well established.[55] Nonspecific inflammation of involved vessels leads to concentric wall thickening, fibrosis, and thrombus formation. These produce the characteristic neuroradiologic findings of focal stenosis, occlusion, dilatation, and luminal irregularity with a characteristic distribution and severity of involvement. The relative sensitivity and specificity of CTA for TAK was respectively 93% to 95% and 98% to 100%.[56] The salient CTA features of TAK include mural thickening, luminal changes, collateral vessels, and other findings usually with respect to the pulmonary and coronary arteries. In the early stages of TAK, mural inflammatory changes may precede luminal contour changes, an important advantage of CTA as compared with DSA.

CTA is useful in patients with GCA in whom LVV occurs in 25% of patients,[57] especially in those with confirmed biopsy pathology to screen for the presence of stenosis, dissection, and aneurysms, and to assess the extent of arterial involvement or monitor vascular lesions for signs of progression.[58] Intramural leaky microvessels, which give rise to delayed enhancement of the arterial wall, are consistent with, but not specific for inflammatory vasculopathy. Moreover, generally irreversible wall thickening and increased intrawall blood pooling despite immunosuppressant treatment should not be used to assess the inflammatory burden or disease activity.[56] Aneurysm formation along gastrointestinal and renal arteries and other systemic medium-sized vessels so noted on CTA, particularly in the absence

of aortic involvement, are useful neuroradiologic signs of PAN and the differential diagnosis of TAK.[59,60]

An entity considered by some to be part of the GCA spectrum, and often diagnosed with a CTA of the neck, is carotidynia, a clinical entity first described by Fay in 1927, that manifests as unilateral tenderness and pain in the neck at the level of the carotid bifurcation. These 2 clinical signs of carotidynia are not specific, and other causes of neck pain can have the same clinical presentation. It is thought to be caused by perivascular inflammation as suggested by the increase of the ESR or CRP and ipsilateral lymph node enlargement and pharyngeal or laryngeal inflammation. The findings on CT include perivascular infiltration, defined as soft amorphous tissue replacing the fat surrounding the carotid artery. A relationship with GCA has not been demonstrated, however in a series of 47 patients, 8 patients had an autoimmune disease, such as rheumatoid arthritis, SLE, ankylosing spondylarthritis, Graves disease, Sjögren syndrome and Hashimoto thyroiditis.[61] The newly proposed name for the condition is transient perivascular inflammation of the carotid artery (TIPIC) syndrome.

CTA also provides useful assessment of stenotic, dilated, and focally occluded vessels of the circle of Willis and the second-order and third-order branches of the ACA, MCA, and PCA involved by CNS vasculitis. However, the resolution of luminal irregularity is less well appreciated on CTA compared with CA, because the former modality, which is less dynamic, requires the inference of collateral flow and angio-architecture from opacified vessels. The radiation dose penalty, which is slightly greater than a routine head CT, makes CTA suitable as an initial screening modality for CNS vasculitis in adults, but less desirable in children and young adults. CT readily identifies abnormal mural thickening as defined by thickness greater than 1 mm in 93% of patients with clinical evidence of TAK along the ascending aorta, arch of aorta, and descending thoracic aorta.[55] Up to 73% of patients with TAK demonstrate changes within the cervicocerebral vessels, most commonly the arch and descending thoracic aorta, brachiocephalic artery, and common carotid artery where wall thickening varied from 1 mm to 10 mm. Once considered the gold standard for detecting abnormal vasculature, CA may be falsely negative in the early stages of TAK.[47,55] This is an important consideration, as the disease is most effectively treated with immunosuppressive therapy during the earliest phase of the illness; a time when CA may be nondiagnostic. CTA is an excellent option in these circumstances, as it provides not only information regarding luminal abnormalities, including stenosis, occlusion, aneurysmal dilatation, and contour irregularities similar to CA, but direct diagnostic findings, including wall thickening, calcification, and abnormal enhancement.[47,55] Although nonspecific to the cerebrovascular circulation, Yamada and colleagues[56] demonstrated a sensitivity and specificity of 95% and 100%, respectively, for CTA in the diagnosis of TAK, with claims of positive correlation of vessel wall changes to the histopathologic findings.[47] Heterogeneous mural enhancement and an inner concentric low-attenuation ring that enhanced at delayed imaging likewise demonstrated a positive correlation with the acute phase of histopathologic findings of vascularization and intimal swelling in the tunica media.

Catheter angiography

Although CA has been the gold standard for diagnosis of cerebral vasculitis, it occupies a less important role compared with MRA and CTA in the initial evaluation of suspected patients. The classic angiographic features of CNS vasculitis are multifocal luminal narrowing, vascular contour irregularity, and vascular dilatations with the appearance of a string of beads often along multiple vessels and in differing vascular

territories, although ectasia and normal luminal diameter also may occur. The affected vessel may demonstrate a smooth or irregular luminal contour and vascular stenosis, which is classically a discrete short segment or elongated. The size of the vessels affected, and the distribution of lesions within each of the vessels varies with the vasculitic etiology and may be a clue to the proximate cause. Extracranial large vessel narrowing and undulation of long segments with variable luminal angiographic involvement occurs in GCA, whereas variable intracranial skull–based and medium cortical vessel involvement occurs in anti-neutrophil cytoplasm antibody–associated vasculitides, SLE, and PACNS. There is no predilection for vessel branch points in PACNS in contrast to atherosclerosis and hypertensive disease.[62] Whereas luminal narrowing along vascular regions of laminar flow disruption and high shear stress, such as the ICA bulb, petro-cavernous junction, and cavernous segments, suggests atherosclerosis, multifocal stenosis and luminal irregularity within the same vessel segment with intervening normal vessel contours, and isolated stenosis within separate vascular territories and otherwise normal vessel contours favors vasculitis. Multiple emboli generally present with more obstructive than stenotic lesions, and tend not to occur as discretely along multiple vascular territories or in tandem along the same vessel in contrast to CNS vasculitis. Angiographic features that favor MVV involvement due to systemic vasculitis and autoimmune disease in contrast to PACNS include abrupt vascular truncation, occlusion, and microaneurysm formation.[63] The collateral circulation should be investigated and quantified by CT and MR perfusion imaging in patients with severe luminal narrowing and vascular occlusion of medium and large vessels, as should abnormal cerebral hemodynamics typified by slow anterograde flow, diminished distal luminal size, and prolonged circulation time. Vascular dissection, which rarely occurs in intracranial vasculitis, is much more common in the extracranial vasculature in GCA.

The sensitivity of CA for PACNS is 40% to 100%,[34,35,38,40,62–66] and the specificity no higher than 37% for CA in the diagnosis of PACNS[67]; however, they may vary depending on the particular clinical, radiographic, and histopathologic definitions used. SVV involvement is typically beneath resolution of CA. Children especially with so-called angiography negative, biopsy positive, small-vessel childhood PACNS,[68] who present with negative angiography and a positive MRI, are generally considered to be candidates for cerebral and leptomeningeal biopsy to confirm the presence of vasculitis.

There is a poor correlation between neuroradiologic findings on MRI and CA in PACNS.[38,63] Whereas two-thirds of lesions detected by MRI showed a CA lesional correlate, 44% of lesions detected by CA were conversely identified on MRI. Of 41 territories involved by MRI in a series of patients with PACNS, CA correlated with 15%, whereas among 50 vascular territories involved by CA, a correlate was found in only 34% of MRI studies.

The risk of transient neurologic injury is 10%, and permanent morbidity occurs in approximately 1% of patients undergoing CA for the evaluation of CNS vasculitis.[69] Intravenous corticosteroids administered before CA may ameliorate the risk of injury and reduce complications.

NUCLEAR MEDICINE IMAGE MODALITIES

PET

Nuclear medicine evaluation of neurovasculitis remains promising but problematic. Conceptually the ability to monitor metabolic activity within the vessel wall should be a good indicator of inflammatory activity. PET with ^{18}Fluorodeoxyglucose (FDG-

PET) has been the best studied radionuclide for this indication, particularly in systemic LVV. One meta-analysis[70] demonstrated a wide variability of diagnostic sensitivity for TAK ranging from 28% to 100%, whereas the range of specificity was 50% to 100%. Fused PET and CT images provide superior anatomic localization and improved sensitivity and specificity of 91% and 89% for TAK. A greater diagnostic sensitivity of 80% and specificity of 89% in those studied by FDG-PET were noted for GCA.[71] Nonetheless, the specificity of FDG-PET is degraded by the presence of atherosclerosis, as active inflammatory plaques may produce false-positive findings.[72] The utility of FDG-PET for monitoring disease activity in these patients may be problematic. Some patients with TAK deemed inactive by clinical criteria may in fact demonstrate biopsy-proven active inflammation.[73] Studies indicate that FDG-PET may be a sensitive and helpful diagnostic study for identifying these patients with subclinical active disease, with 83% of patients with biopsy-proven GCA demonstrating positive FDG-PET studies.[74] The sensitivity and specificity of FDG-PET in the identification of active vasculitic disease compared with clinical signs and laboratory criteria lead to respective rates of 100% and 89%.[75] The fusion of MRI for morphology and volumetric assessment, and FDG-PET for metabolic analysis of the brain, has been used to investigate the autoimmune encephalitides, and may have a role in the investigation of CNS vasculitides.[76]

Single-Photon Emission Computed Tomography

Single-photon emission computed tomography (SPECT) uses multiplanar nuclear medicine imaging for the investigation of regional CNS perfusion abnormalities. It provides direct information about the pathophysiology and cerebral metabolism in cerebral vasculitides at the level of capillary endothelium in the blood-brain barrier (BBB) microcirculation beyond the resolution of MRA, CTA, and CA.[77,78]

There are claims of the utility of brain SPECT imaging in the clinical diagnosis and management of cerebral vasculitis associated with SLE,[79,80] Kawasaki disease,[81] IgAV,[82] neurologic Behçet disease,[83] GPA,[84] and brain irradiation.[85,86] Apart from the direct impact of vascular narrowing and occlusion resulting from necrotizing arteritis and vascular infiltration, other explanations for an abnormal brain SPECT include circulating immune complexes on the BBB,[87] and neurotoxic effects of antibodies and brain antigenic targets,[81] glial cell interactions,[86] and pathogenic hypersensitivity responses to brain antigens released during vascular-mediated tissue necrosis.[86]

The results of brain SPECT imaging were described in one patient with histologically verified cerebral vasculitis.[88] This 71-year-old man with later-proven granulomatous angiitis of the brain underwent Tc-99m hexamethylpropyleneamine oxime brain SPECT 3 weeks after onset of CNS disease. There was irregular radiotracer uptake throughout both cerebral hemispheres with scattered multiple areas of hypoperfusion, further demonstrated in surface volumetric images. Postmortem examination showed fibrinoid necrosis, inflammatory cells, mainly lymphocytes, histiocytes, and a few multinucleated giant cells involving medium-to-small meningeal and parenchymal vessels with intramural vascular deposits of amyloid, without systemic vasculitis.

Color Doppler Ultrasonography

Color Doppler ultrasonography and color duplex imaging provide direct imaging and evaluation of superficial arteries and their vessel walls. It has been most extensively studied in systemic LVV, such as GCA and TAK. It provides a high-resolution imaging of the walls of deep-seated vessels as compared with MRI, detecting wall thickness

and edema, the latter of which produces a hypoechoic signal on color Doppler ultrasonography as a halo sign. In a meta-analysis of 998 patients with 17 studies, the sensitivity of the halo sign for biopsy-proven GCA was only 75%, but specificity was 83%. Concentric homogeneous mural thickening, stenosis, and occlusion of the aorta and brachiocephalic branches are typical ultrasonography features of GCA and TAK,[72,89,90] which may be differentiated from atherosclerotic disease by the absence of plaque formation, concentric long segment involvement, and location. Ultrasonography revealed subtle mural changes characterized by a homogeneous, circumferential mid-echoic wall thickening within the subclavian and carotid arteries in the early stages of TAK preceding abnormalities detected by CA,[91] with overall greater wall thickness of the CCA and ICA in the vasculitic vessels compared with controls. The CCA intima-to-medial thickness ratio was increased in patients with TAK compared with normal controls,[92] yielding respective sensitivity and specificity rates of 82% and 70%.

The wall diameters of common, frontal, and parietal division of the superficial temporal artery were significantly greater in patients with GCA than in symptomatic patients without the disease, as well as asymptomatic age-matched controls.[93] A hypoechoic halo surrounding a patent vessel lumen was found in 73% of patients with biopsy-proven vasculitis, but not in symptomatic patients without GCA and asymptomatic controls. The histopathologic finding of mural cellular infiltration did not correlate with a hypoechoic halo albeit attributed to edema. The halo disappeared at a mean of 16 days after effective treatment. Similar findings are present in the occipital arteries,[94] although the sensitivity is less when compared with the superficial temporal arteries. The halo examination is useful for symptomatic patients presenting with nuchal pain, occipital headache, or occipital scalp tenderness, especially when occipital artery involvement may be the only imaging manifestation of the disease.

SUMMARY

The neuroimaging evaluation of vasculitis may seem complex and nonspecific, particularly for PACNS and the primary systemic autoimmune vasculitides. When all imaging modalities, including those that provide parenchymal, luminal, and mural evaluation, are brought to bear on a given patient with suspected vasculitis, the entire constellation of findings typically brings clarity to the situation. When imaging is combined with the clinical and laboratory results, this diagnostic triad becomes more predictable even in the most difficult of clinical cases.

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