Diagnostic strategies in vasculitis affecting the central nervous system

LEONARD H. CALABRESE, DO

Vasculitis affecting the central nervous system (CNS) represents a heterogeneous group of inflammatory diseases arising from a variety of neurologic insults including autoimmune diseases, infection, drug exposure, radiation, and malignancies. It can be broadly classified into two major categories, namely, primary, referring to those patients with vasculitis isolated primarily to the brain, cord, and their leptomeninges occurring in the absence of recognizable triggers or conditions, and secondary, referring to where such associated conditions or co-factors are apparent.

Unlike most other clinical areas of vasculitis, the diagnosis, treatment, and investigation of CNS syndromes is hampered by a variety of factors dissimilar to those encountered in vasculitis affecting many other end organs. These include the inability to readily obtain tissue for biopsy confirmation and the extremely limited amounts obtained even when successful biopsy is attempted. In addition, most diagnostic strategies center on non-invasive neuroimaging techniques of undefined sensitivity and specificity. Further complicating the management of this disease are difficulties surrounding assessment of disease activity. In CNS vasculitis, even when the diagnosis appears secure, the assessment of disease activity is complex and limited by the lack of dynamic change observed in CNS dysfunction due to ischemic injury and the uncertainties surrounding the clinical significance of serial neuroimaging investigations. Despite these limitations, progress has been made in the clinical approach to CNS angiitis, which will be summarized in this report.

DIAGNOSTIC MODALITIES

Test operating characteristics

The use and interpretation of any diagnostic test, ranging from findings obtained on physical examination to specific laboratory tests or radiologic investigations or even biopsy procedures are influenced by several factors. These include test sensitivity, specificity, and, most importantly, the clinician's estimate of the likelihood of disease at the time of testing, or pre-test probability. While a discussion of these variables is beyond the scope of this presentation, they have been the subject of several reviews.[1,2] Several summary points are important to keep in mind when discussing diagnostic strategies.

Test sensitivity is the operating characteristic most readily calculated and is expressed as the frequency of a positive test in the presence of a given disorder. Derivation of test sensitivity implies that a gold standard of diagnosis exists for a given disease and has been validated. Such gold standards are more readily available for certain forms of vasculitis, such as renal or pulmonary disease, which are more accessible to detailed and routine pathologic analysis than vasculitis of the CNS. In CNS vasculitis, clinicians are often forced to rely on indirect tests such as the cerebral angiogram, which is of poorly defined specificity.[3] In general, tests of high sensitivity are most valuable at ruling out the presence of disease. This has been referred to by the acronym SNOUT[1] (high sensitivity rules OUT the diagnosis).

Data on specificity is often more difficult to obtain and must be derived from analysis of test results on a well-characterized population of patients without the disease in question. Preferably, such nondiseased "controls" include patients with conditions that closely mimic the disease in question. For example, relevant data on specificity for ANCA testing come not from healthy subjects but rather from patient populations with relevant mimics such as chronic granulomatous diseases, diffuse pulmonary diseases, and other forms of glomerulonephritis.[4] In general, tests of high specificity are of their greatest diagnostic value in ruling in a given diagnosis and may be remembered by the SPIN rule[1] (ie, high specificity rules IN the diagnosis).

More than the mere awareness of test sensitivity and specificity, we clinicians are interested in how the results of a given test changes our minds, from what we thought the likelihood of a given disease was before we order the test (pre-test probability) to what we think afterward (post-test probability). Post-test probability can be calculated through a variety of techniques, all factoring in knowledge of sensitivity, specificity, and assessment of pre-test probability. Methods of calculation include the direct use of Bayes' theorem[2] or more conveniently through nor-

From the Department of Rheumatic and Immunologic Diseases, The Cleveland Clinic Foundation.
Address correspondence to L.H.C., R.J. Fasenmyer Chair of Clinical Immunology, Vice Chairman Department of Rheumatic and Immunologic Diseases, The Cleveland Clinic Foundation, Desk A50, 9500 Euclid Ave., Cleveland, OH 44195. E-mail: Calabrl@ccf.org

mograms derived from Bayes' theorem.[1] The more recent popularization of likelihood ratios[1] has allowed us to utilize Bayes' theorem to accommodate multiple levels of probability for tests with other than bivariate results.

Each variation of Bayes' theorem starts with assessment of pre-test probability, which is derived from a synthesis of the clinician's findings (ie, clinical exam, history, available lab, awareness of prevalence and epidemiologic features of a given disease, and experience).[2] Pre-test probability can vary greatly depending on the skill and seasoning of the clinician, and thus some tests may be of far more value in the hands of certain clinicians.

After considering the operating characteristics of a given test and factors influencing pre-test probability, several additional questions must be answered before deciding on a given diagnostic strategy. These include:

Is the diagnostic test available, affordable, precise, and accurate in our hands?

Is the pre-test probability we have derived clinically sensible?

Will the post-test probability we arrive at influence our clinical decision-making and help our patient?

With these issues in mind, we will briefly consider major categories of diagnostic testing in CNS vasculitis.

Laboratory tests

There is no laboratory test of sufficient sensitivity or specificity to rule out or diagnose any form of primary or secondary CNS vasculitis. Since in most instances the diagnosis of CNS vasculitis hinges on a combination of either a positive biopsy or a high-probability vascular imaging study such as angiography while excluding all those conditions capable of mimicking findings, laboratory testing is largely relegated to detecting the myriad of mimicking conditions.[4] These, in general, include infections, malignancies, hypercoagulable and embolic states, and other inflammatory diseases. Lumbar puncture is an invariant part of the work-up for CNS vasculitis based on its value for ruling out infectious and malignant mimickers. Unfortunately, markers sensitive in other conditions such as the presence of elevated acute-phase reactants in systemic necrotizing vasculitis are frequently normal in CNS vasculitis, leaving the clinician unable to rule out CNS vasculitis with any single or combination of laboratory tests.

Neuroimaging

The development of progressively more-sophisticated neuroimaging techniques (ie, computerized tomography, magnetic resonance imaging, single-photon-emission tomography, etc.) have greatly improved our ability to diagnose unexplained CNS ischemic syndromes. While there are no such tests with specificity high enough to secure a diagnosis of CNS vasculitis, these modalities may be extremely useful when applied in stepwise fashion while keeping in mind their limitations. In general, MRI is more sensitive than CT and should be the initial study of choice when approaching a patient with unexplained ischemia except when cerebral hemorrhage is suspected. In terms of test sensitivity, the data vary depending upon the series examining the question and what is the gold standard utilized for the final diagnosis of CNS vasculitis. In the recent series of Pomper et al[6] where all patients were angiographically defined, the MRI had a sensitivity of 100%, whereas in the similar angiographically documented series of Hajj-Ali et al[7] the sensitivity was 77%. In our experience with biopsy-proven cases, the sensitivity of MRI approaches 100%. Findings on MRI examination are variable, but the most specific findings are found on serial examination where multiple foci of ischemia are detected in varying anatomic locations and distributed over time.[5,9] Both gray and white matter can be affected in supratentorial and infratentorial distributions. Modifications of MRI technology such as the inclusion of diffusion and FLAIR sequences will probably increase sensitivity but not specificity of the technique. Combining neuroimaging with lumbar puncture appears to increase the overall sensitivity, and thus a normal MRI and lumbar puncture have a high negative predicative value (ie, SNOUT) and should serve to rule out the disorder except in rare cases.

In patients with the granulomatous variant of primary angiitis of the CNS (PACNS), enhancement of the leptomeninges is occasionally observed and may serve to increase the sensitivity of biopsy. Less well appreciated is the fact that 15% of PACNS patients may present with mass-like lesions and thus should be approached as suspected infection or tumor.[5] More specialized studies such as SPECT and PET scanning may increase sensitivity but are in no way specific for the diseases and should not be used to secure the diagnosis.

Angiography

In the evaluation process of CNS vasculitis, cerebral angiography is both the most powerful and poorly understood diagnostic modality. Its power is derived from the fact that it is frequently and justifiably used as a gold standard for diagnosis. Its limitations derive from its lack of quantitative and qualitative codification and the fact that most clinicians and neuroradiologists fail to appreciate its low level of specificity. A comprehensive classification of cerebral arteritis from the angiographic perspective was published nearly three decades ago by Ferris and Levine,[8] and little has been added in terms of furthering the technique's diagnostic accuracy beyond these qualitative descriptions or patterns that neuroradiologists apply to their reading. More recent reviews[5,7,9] continue to emphasize patterns characteristic of vasculitis, including alternating areas of stenosis and ectasia (ie, beading). These types of changes may be seen in multiple vessels in multiple vascular beds but also may be limited to a single vessel. Other angiographic abnormalities described in CNS vasculitis include absence or cut off of one or more vessels and may be entirely normal in up to 40% of biopsy-proven cases.[10]

Our informal assessment and experience with this technique suggest that, in terms of diagnostic specificity, the highest level is associated with beading in multiple vessels in multiple vascular beds (ie, high probability), whereas similar findings in a single vessel or bed is intermediate in terms of specificity. All other findings includ-

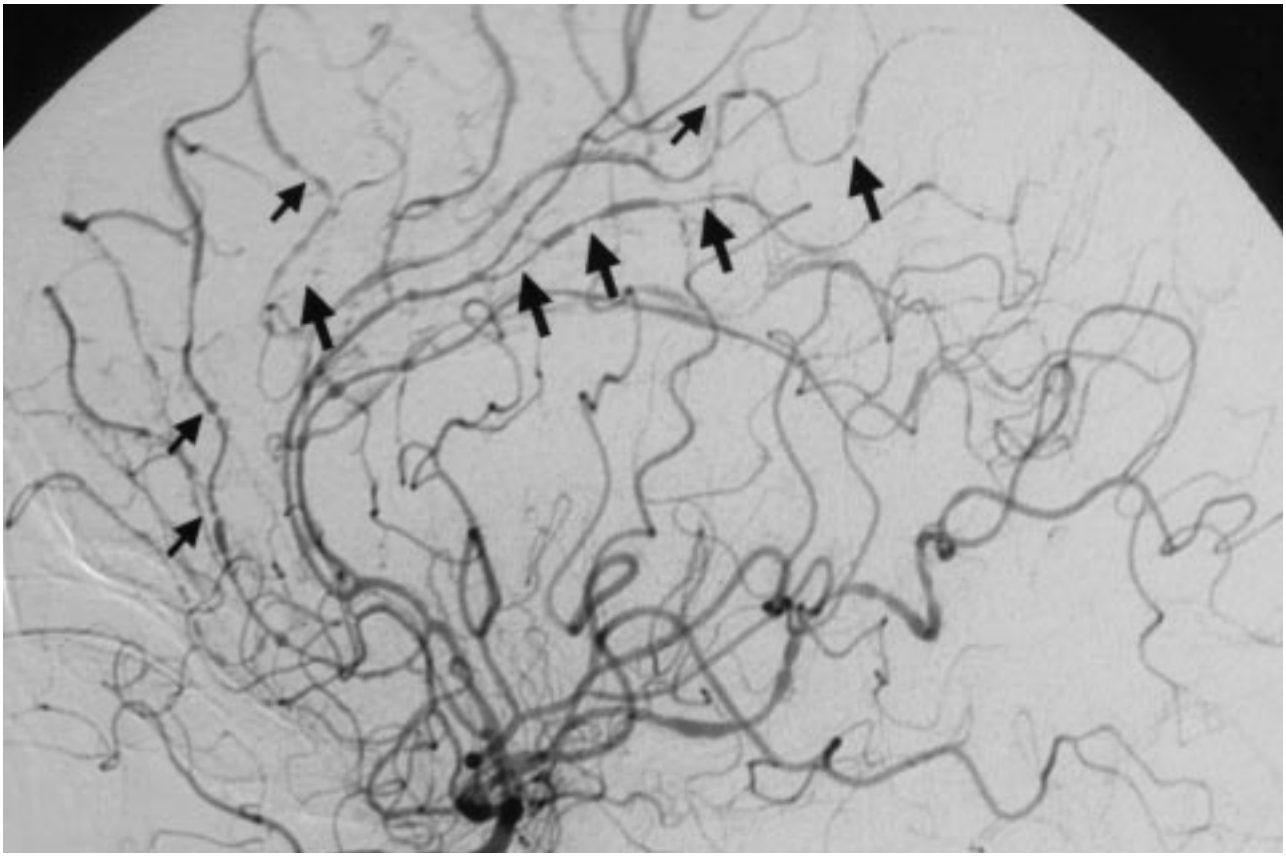

Figure 1. Typical angiographic findings in a patient with biopsy-proven CNS vasculitis. Arrows point to areas of alternating stenosis and ectasia.

ing simple vessel cut off, luminal irregularity in a single vessel or bed (ie, nonbeaded), or an entirely normal angiogram would be low probability. Even when using these conventions, Duna and Calabrese[3] found that the specificity of a high-probability angiogram in a small series of patients with suspected CNS vasculitis was only 26%. With such low specificity, the cerebral angiogram can only secure the diagnosis of CNS vasculitis when the pretest probability is extremely high, implying that all appropriate exclusions[5] have been ruled out and there is a compatible clinical picture.

Lastly, although invasive it has been demonstrated that cerebral angiography is a safe technique[11] and can be performed serially to follow disease activity when necessary.[6,12]

Biopsy

Biopsy of CNS tissues would logically be considered the ultimate gold standard of diagnosis, but clearly the procedure is limited by several factors. First, while data from other conditions have demonstrated that the procedure can be done with minimal morbidity and mortality,[5] it is highly invasive and carries certain risks. Successful biopsy also requires a willing and experienced neurosurgeon, who may not always be available. When the procedure is performed, the technical aspects must be tailored to the individual patient. For example, in patients with suspected granulomatous angiitis of the CNS, the procedure of choice is open wedge biopsy of the tip of the nondominant temporal lobe with sampling of the overlying leptomeninges.[13] Alternatively, directing the biopsy to an area of leptomeningeal enhancement when present may serve to increase the sensitivity. Even when all the technical limitations have been factored in, CNS vasculitis is notoriously a patchy disease, with data from previous reviews suggesting as many as 25% of biopsies may be falsely negative.[10] Finally, even when vasculitis is seen in sampled tissues, it is imperative to perform special stains and cultures for occult infections that may produce secondary vascular inflammation.

In a recent series[14] of 30 consecutive biopsies for suspected CNS vasculitis performed at a single institution, the false-negative rate of biopsy was 16%, yielding a sensitivity of about 84%, which, we believe, is reasonable. When comparing biopsy to other diagnostic modalities such as MRI and angiography, the predictive value of brain biopsy in this study was 90-100%, versus 37-50% for angiography and 43-72% for MRI. These authors concluded that wedge biopsy of cortical and leptomeningeal tissues is central to the multidisciplinary approach to patients with suspected CNS vasculitis.

Pitfalls

Clearly the greatest pitfall in the diagnosis of CNS angiitis is overreliance on neuroradiography, especially

angiography, without performing the necessary and extensive exclusions of mimicking conditions. Failure to biopsy because of concerns of how to handle regarding false negatives is also a pitfall because it does not consider a) the profound morbidity of long-term high-dose immunosuppression given empirically, and b) the ability of biopsy to detect conditions other than CNS vasculitis that have radically different treatments. Finally, it must be appreciated that no single specialist has the necessary expertise to evaluate and treat all of the potential disorders that may present as suspected CNS vasculitis, and thus a team approach is essential. This team should consist of a physician knowledgeable in the diagnosis and treatment of vasculitis including the use of immunosuppressives, a neurologist with special expertise in cerebrovascular disorders other than vasculitis, a capable neuroradiologist who knows the limitations of his procedures, a neurosurgeon willing to tailor a biopsy for a given patient, and a knowledgeable neuropathologist.

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