Editorial

Primary angiitis of the central nervous system: reflections on 20 years of investigation

L.H. Calabrese

Leonard H. Calabrese, D.O.,
Professor of Medicine,
Cleveland Clinic Lerner College of Medicine of Case Western Reserve University; R.J. Fasenmyer Chair of Clinical Immunology; Theodore F. Classen D.O. Chair of Osteopathic Research and Education; Vice Chairman, Department of Rheumatic and Immunologic Diseases,
9500 Euclid Avenue, Desk A50,
Cleveland, Ohio 44195, USA.
E-mail: calabrl@ccf.org

Received and accepted on March 14, 2009.

Clin Exp Rheumatol 2009: 27 (Suppl. 52): S3-S4.

Competing interests: none declared.

In this issue of *Clinical and Experimental Rheumatology*, Neel and Pagnoux (1) provide a comprehensive review of PACNS including a historical perspective, clinical, radiographic and pathologic features as well as adding insights regarding pathogenesis and thoughts on treatment. It is truly impressive to view the progress in this small field since our initial efforts to define this disorder over two decades ago (2). We then proposed "working" diagnostic criteria, which, while still unvalidated, have served as a standard for most of the studies included in the current review. To remind ourselves, those criteria were intended to provide a basis upon which to slowly build a platform of literature-based research; predictions at that time were that relatively few cases were likely to come from any single institution, and that only by combining experiences were new insights likely to come forth. This prediction has held true and even with large retrospective series from the Mayo Clinic it took nearly three decades to amass 100 cases (3).

Those criteria for diagnosing PACNS are essentially unchanged in their implicit design from their original wording of two decades ago but their interpretation has changed radically. The proposed diagnostic criteria from 1988 (2) were as follows. First, the patient must have a neurologic deficit that remains unexplained after a thorough neurologic evaluation. Second the patient must have either angiographic features compatible with PACNS or a positive biopsy of central nervous system tissue. Finally, the patient must be found not to have any disorder either capable of mimicking the angiographic findings or, alternatively, capable of producing similar pathology. The question should be asked as to what is still the same and what is different?

First, the initial criterion of conjuring this rare diagnosis only in situations where a careful evaluation has failed to uncover alternative etiologies is still reasonable. While the diagnosis of PACNS is being made far more frequently, as noted above, even at the Mayo Clinic less than a handful of cases were confirmed yearly over the past 30 years. What is radically different today however is what currently represents a "thorough neurologic evaluation". Today magnetic resonance imaging is not experimental but routine and standard of care in such evaluations. In addition, cerebral spinal fluid analysis (CSF) is now not only considered essential but molecular screens for occult pathogens (especially viral pathogens) and certain other diagnoses (*i.e.* prion diseases, mitochondrial disorders, etc.) have remarkably increased our palate of unexplained neurologic diseases.

The second criterion requiring actual evidence of vascular disease by angiography and biopsy is also unwavering, but again the technology to accomplish this has advanced. Imaging the intracerebral vasculature can now be done less invasively by several indirect angiographic techniques such as MR and CT with far greater spatial resolution than in years past and thus more patients have vascular imaging given the reluctance to proceed to direct angiography. Despite these advances, direct angiography remains the gold standard for imaging the vascular lumen though as Neel and Pagnoux point out the study is still plagued by low specificity even when detecting "classic" findings. A technological advance in vascular imaging generating significant excitement in the field has been the exploitation of high resolution MR with contrast enhancement capable of defining luminal wall abnormalities including

enhancement (4) similar to those descriptions of arteritis of the aorta and its branches in large vessel disease (5). We have confirmed the utility of this technique and believe further studies of large numbers of well-studied patients are clearly warranted.

Finally, the third criterion of excluding angiographic and pathologic mimics is just as important today as when it was proposed but has become a far more complex process. Many diseases that were mentioned in the current review were either not recognized to present in such a fashion (*i.e*. VZV infection), or were erroneously thought to be angioinflammatory in nature (*i.e*. reversible cerebral vasoconstrictive disease). Some diseases that we now routinely rule out before assigning a diagnosis of PACNS were not known, or perhaps not widely known, in 1988 (*i.e*. mitochondrial disorders, hepatitis C infection, Susac's, etc.) (6). Over time, this list will inevitably expand as well.

What is the rheumatologist to do given this remarkably complex matrix of tests, diagnoses and limitations imposed by the rarity of this disorder in order to be clinically accurate in diagnosis? As we have emphasized in the past, in our experience, PACNS remains one of the consummate diagnostic conundrums in rheumatology and immunology and perhaps in medicine today. Given the issues described above we suggest a team approach for optimal diagnosis and management since no one specialist, no matter how experienced, is expert in all diseases and requisite studies required to manage such patients. Aside from having a clinician such as the rheumatologist to administer and monitor the immunosuppressive therapy, a neurologist with an interest in non atherosclerotic cerbrovascular disease is key. In addition, a neuroradiologist who recognizes the limitations of vascular imaging and is aware of the broad differential diagnostic possibilities is also important. Finally, an aggressive and attentive neurosurgeon, willing to craft an individualized biopsy and a thorough neuropathologist interested in analyzing small samples for all diagnostic possibilities and responsible for distributing and storing vital tissue for essential and future investigations ideally round off this team. Clearly, few centers have such groups assembled. Perhaps most patients with this disease would be better served by having access to such services.

References

1. NEEL A, PAGNOUX C: Primary angiitis of the central nervous system. *Clin Exp Rheumatol* 2009; 27 (Suppl. 52): Sxx-Sxx.
2. CALABRESE LH, MALLEK JA: Primary angiitis of the central nervous system. Report of 8 new cases, review of the literature, and proposal for diagnostic criteria. *Medicine* 1988; 67: 20-39.
3. SALVARANI C, BROWN RD JR, CALAMIA KT *et al*.: Primary central nervous system vasculitis: analysis of 101 patients. *Ann Neurol* 2007; 62: 442-51.
4. KUKER W, GAERTNER S, NAGLE T *et al*.: Vessel wall contrast enhancement: a diagnostic sign of cerebral vasculitis *Cerbrovasc Dis* 2008; 26: 23-9.
5. SO E, FLAMM SD, WHITE RD, SCHVARTZMAN PR, MASCHA E, HOFFMAN GS: Takayasu arteritis: utility and limitations of magnetic resonance imaging in diagnosis and treatment. *Arthritis Rheum* 2002; 46: 1634-42.
6. HAJJ-ALI R, CALABRESE LH: Central nervous sytem vasculitis. *Curr Opin Rheum* 2008; 21: 10-18.