Editorial

Primary Angiitis of the Central Nervous System: the Penumbra of Vasculitis

Despite remarkable progress in our understanding of many forms of systemic inflammatory vascular disease, vasculitis affecting the central nervous system (CNS) remains largely an enigma. Clearly limiting our ability to better understand these relatively obscure forms of arteritis are a number of factors that continue to be difficult to overcome. Among these are a lack of: clinical signs and symptoms of high specificity, efficient noninvasive diagnostic tests, relevant animal models, extremely limited biologic materials for pathophysiologic investigation, longterm followup of large numbers of patients, and controlled therapeutic trials.

Despite such limitations, vasculitis of the CNS in general and primary angiitis of the CNS (PACNS) in particular have become the subject of increasing interest to clinicians driven in large part by increased awareness, coupled to our growing sophistication and aggressive use of neurodiagnostic modalities.

The modern history of PACNS began about 40 years ago with initial descriptions of a form of arteritis limited to the brain and its overlying meninges, with granulomatous pathology and a chronic and progressive and uniformly fatal course[1]. Even today these case reports serve as a seminal example of what is now referred to as granulomatous angiitis of the central nervous system or GACNS. The disorder remained little other than a curiosity, considered to be genuinely rare and uniformly fatal, until the early 1980s, when enthusiasm for early recognition of the disease increased following successful reports of therapy with a combination of glucocorticoids and cyclophosphamide[2]. By 1988, 46 cases had been described worldwide and preliminary diagnostic criteria were proposed[3]. These criteria included (1) an unexplained neurologic deficit despite aggressive diagnostic evaluation; (2) a high probability angiogram for arteritis and/or histopathologic evidence of arteritis confined to the CNS; and (3) exclusion of all those disorders capable of mimicking the angiographic findings or associated with vascular inflammation of the CNS.

Throughout the 1980s a trend was noted for the majority of newly reported cases to be based solely on angiography without supporting histology, and by the early 1990s we and others[4,5] began to appreciate a shift in clinical patterns within the PACNS literature. Newly appreciated was a subset of patients, diagnosed angiographically, appearing to have a more benign course and perhaps requiring less therapy. In 1995 a subset of PACNS was proposed and designated benign angiopathy of the central nervous system (BACNS)[6]. These patients were believed to represent that group of angiographically documented cases with a relatively benign course, first hinted at from earlier reviews of the literature[4,5]. Today most appreciate PACNS as a highly heterogeneous group of vasculitides limited to the CNS, of which two subsets appear deserving of nosologic distinction, namely GACNS and BACNS. Unfortunately this classification of PACNS into discrete subsets is limited: the majority of cases fulfilling the originally proposed diagnostic criteria fail to fit either of these subsets, and there are no validated criteria for either diagnosis, merely clinical descriptions[7].

The pessimistic view of PACNS as an inexorable and untreatable disorder has now given way to the belief that, when promptly diagnosed, prognosis is actually quite good. Hajj Ali and colleagues[8] recently performed the first longitudinal followup study on 41 patients with the disorder followed at a single institution for a mean period of 4 years. Utilizing the Barthel Index, a scale for assessing post-stroke morbidity, and a specially devised cognitive disability scale designed to pick up more subtle degrees of neurocognitive dysfunction, they found that mortality from all causes was only 10% and that 80% were left with mild or no disability. Importantly, a subset of patients (patients with BACNS) was prospectively identified as having good prognosis and successfully treated with a brief course of glucocorticoids (less than 6 months), with an excellent outcome.

Based upon these preliminary observations, it would appear highly desirable to devise and validate diagnostic and classification criteria allowing clinicians to identify patients who are candidates for less intense therapy. If accomplished, this would provide a strong rationale for the

See Primary angiitis of the central nervous system in children, *page 616.*

design of multicenter randomized controlled clinical trials. Even though this is still a rare disease, novel strategies have recently been proposed to study equally rare conditions utilizing a web based data information system[9]. Such a system is now being actively developed at the Cleveland Clinic to serve as a pilot.

In this issue of *The Journal* an important series of pediatric patients with PACNS is reported. This represents the first sizable series of pediatric patients with PACNS[10]. While only 5 in number, this doubles the reported experience with this entity in children.

All these patients were diagnosed angiographically and none was documented by biopsy. Thus these observations raise the traditional question about diagnostic certainty that permeates the adult literature of histologically unsubstantiated cases. To the authors' credit, a vigorous search for mimicking conditions, especially infections, was performed in each case and none was found. In comparison to adult disease, these cases would appear atypical, with a preponderance of large vessel involvement and angiographically unilateral disease. In addition, in contrast to the favorable outcome reported by Hajj Ali, their series appears to be associated with greater morbidity.

Do these cases represent the same disease seen in adults? Unfortunately, we are unable to tell, given the absence of histology. Based on radiographic grounds and clinical outcome, the cases would appear atypical. Their cases clearly do not represent GACNS and would also be atypical for BACNS in my opinion[7]. The authors chose to secure the diagnosis angiographically because most of the mimicking diseases seen in adults are rare in children and because of the risks of biopsy. They further assert that angiography is the "gold standard of radiographic diagnosis" of CNS vasculitis. While there is an element of truth in both these assertions, the fact remains that angiography alone is not, and never will be, 100% specific for the diagnosis of CNS vasculitis. In the absence of histologic confirmation we will continue to wonder whether cases diagnosed solely on the basis of angiography are equivalent. Studies performed in adults have clearly shown the lack of specificity of angiography[11,12] and the importance of biopsy in diagnostic process. Unfortunately, as the authors point out, biopsy is only 75–80% sensitive and thus nearly a quarter of patients with documented disease will have false negative tests, leaving the clinician with frequent diagnostic uncertainty.

Given that there are no highly efficient tests, noninvasive or invasive, to diagnose PACNS, what is the clinician to do? In adults, I believe in most circumstances, when prolonged therapy with glucocorticoids and cyclophosphamide are considered, biopsy is warranted, even in the presence of a high probability angiogram. As emphasized by Moore[13], biopsy in adults is essential to both secure the underlying diagnosis of vasculitis and to rule out mimicking conditions detectable only by tissue confirmation. For those cases clearly falling within the BACNS category, diagnosis can usually be made solely on the basis of angiography. Whenever the clinical course deviates from the predicted, however, biopsy and even repeat biopsy become essential.

Is the same true for children suspected of PACNS? The answer is unknown. But until we learn more about pathophysiology, our understanding of PACNS will continue to be far from clear. A penumbra is a space of partial illumination, such as in an eclipse, between perfect shadow and full light. Despite significant progress, PACNS remains foursquare in the penumbra awaiting full illumination.

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REFERENCES

1. Cravioto M, Feigin I. Non-infectious granulomatous angiitis with a predeliction for the central nervous system. Neurology 1959; 9:599-609.
2. Cupps TR, Moore PM, Fauci AS. Isolated angiitis of the central nervous system. Am J Med 1983;74:97-106.
3. Calabrese LH, Malek JA. Primary angiitis of the central nervous system. Report of eight new cases, review of the literature and proposal for diagnostic criteria. Medicine 1994;67:20-40.
4. Calabrese LH, Furlan AJ, Gragg LA, et al. Primary angiitis of the central nervous system. Diagnostic criteria and clinical approach. Cleve Clin J Med 1992;59:293-306.
5. Hankey GJ. Isolated angiitis/angiopathy of the central nervous system. Cerebrovasc Dis 1991;1:2-15.
6. Calabrese L, Gragg LA, Furlan AJ. Benign angiopathy: a distinct subset of angiographically defined primary angiitis of the central nervous system. J Rheumatol 1993;20:2046-50.
7. Calabrese LH, Duna FG, Lie JT. Vasculitis in the central nervous system. Arthritis Rheum 1997;40:1189-201.
8. Hajj-Ali RA, Villa-Forte AL, Abou-Chebel A, et al. Long-term outcomes of patients with primary angiitis of the central nervous system [abstract]. Arthritis Rheum 2000;43 Suppl:S162.
9. De Groen PC, Barry JA, Schaller WJ. Applying worldwide web technology to the study of patients with rare diseases. Ann Intern Med 1998;129:107-13.
10. Gallagher T, Shaham B, Reiff A, et al. Primary angiitis of the central nervous system in children: A report of five cases. J Rheumatol 2001;28:616-23.
11. Duna G, Calabrese L. Limitations in the diagnostic modalities in the diagnosis of primary angiitis of the central nervous system. J Rheumatol 1995;22:662-7.
12. Chu CT, Gray L, Goldstein LB, et al. Diagnosis of intracranial vasculitis: A multidisciplinary approach. J Neuropathol Exp Neurol 1998;57:30-40.
13. Moore PM. Vasculitis of the central nervous system. Semin Neurol 1994;14:307-12.