Case report

Clinical management issues in vasculitis. Angiographically defined angiitis of the central nervous system: Diagnostic and therapeutic dilemmas

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ABSTRACT

A case of acute neurologic deficit accompanied by a cerebral angiogram consistent with CNS vasculitis is presented. The differential diagnosis and diagnostic decision process generated in this type of evaluation is illustrated.

Introduction

A 43-year-old woman is referred to the rheumatologist for further evaluation and possible escalation of treatment of CNS vasculitis defined by the angiogram displayed below (Fig. 1). In brief the patient is 43-year-old woman who was previously healthy and developed the gradual onset of a severe headache over a 6-hour period. The pain was intense and was nearly relieved by lying flat, but was excruciating with head elevation over 20 degrees.

The patient was hospitalized the next day and underwent CT and MRI examinations of the head which were normal. A lumbar puncture was performed and revealed 3 WBCs, normal protein, no xanthochromia and a normal opening pressure. Her physical examination and neurologic examinations were normal. A cerebral angiogram was performed and was thought to display some subtle areas of luminal narrowing, but was considered equivocal. General chemistries including acute phase reactants, ANA, rheumatoid factor and hypercoaguability studies were normal. The patient's headache was treated symptomatically and improved.

Four days later the headache returned and a repeat MRI now showed a new 4 mm focus of signal abnormality in the cerebellum (Fig.2). A repeat angiogram (Fig.1) was performed which showed dramatic changes with multiple areas of vascular narrowing in multiple vascular beds, consistent with vasculitis. The patient was placed on high dose prednisone (60 mg daily orally) and verapamil (80 mg BID orally) and her headache again improved. She is seeking further opinions on both the accuracy of her underlying diagnosis, whether or not escalation of therapy is warranted (i.e. addition of cyclophosphamide), and how her condition should be followed up.

Discussion

The clinical problem of angiographic diagnosis

The angiogram is indeed consistent with vasculitis within the central nervous system. Unlike vasculitis in peripheral (i.e. visceral) vessels, which frequently demonstrate microaneurysm formation, this is unusual in the CNS. The more common and characteristic findings are those of alternating areas of vascular narrowing with or without post-stenotic dilatation in multiple vascular beds (1). Unfortunately this finding is neither highly sensitive for CNS vasculitis, since many forms, such as granulomatous vasculitis of the CNS, characteristically involve small caliber vessels more often than not associated with a normal angiogram. Furthermore, even a high probability angiogram such as this suffers from lack of specificity as demonstrated by Duna *et al*. (2), being indistinguishable from the effects of other vascular insults including atherosclerosis, infection, intravascular clot or tumor and spasm. In summary the clinician must be aware that there is no totally pathognomonic angiographic picture of CNS vasculitis and thus any diagnosis of CNS vasculitis made on the basis of angiography alone (i.e., without supporting biopsy evidence) must be a clinical-angiographic diagnosis.

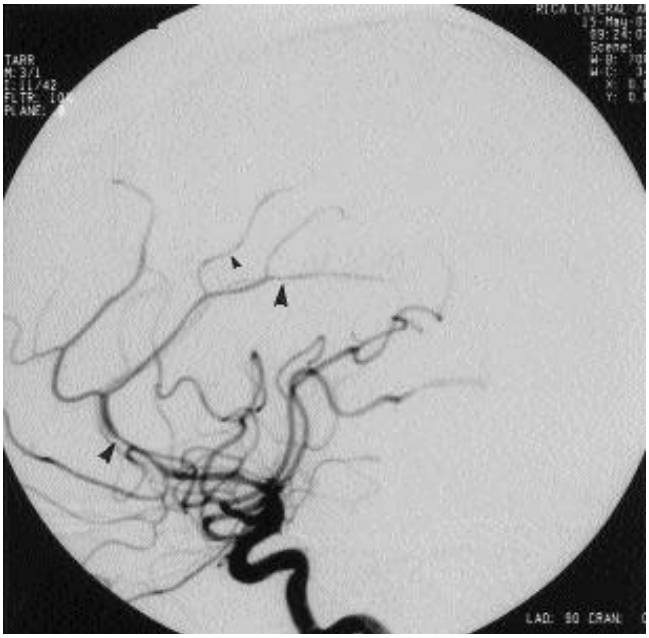

Fig. 1. Cerebral angiogram performed approximately 1 week into the illness demonstrating multiple areas of arterial narrowing (arrows indicate representative areas of narrowing).

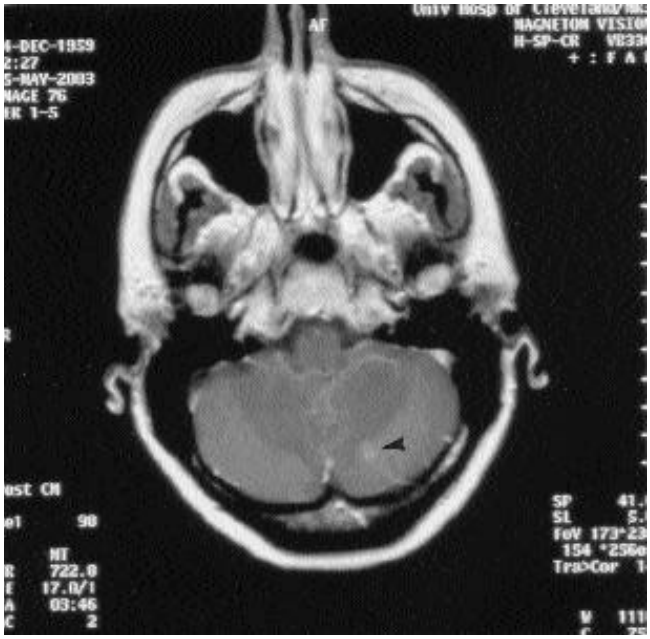

Fig. 2. Arrow points to area of increased signal in the cerebellum on MRI 6 days into the illness. The lesion was not present on initial MRI.

Sorting out the angiographic differential diagnosis

Table I lists the common etiologies known to be associated with a high probability angiogram for CNS vasculitis. Unfortunately the list is much longer and includes a wide variety of rare disorders, both genetic and acquired (3). The first consideration is whether or not this patient actually has vasculitis and thus whether the angiogram represents a 'true positive'. CNS vasculitis is generally divided into the secondary and primary forms (4). Most forms of secondary vasculitis within the CNS, particularly those associated with systemic vasculitic or connective tissue disorders, can generally be suspected on the basis of a clear history and physical examination. The acute onset, absence of constitutional signs and symptoms, lack of evidence for any peripheral target organ involvement and normal laboratory screening assays make secondary vasculitis unlikely in the present case. Primary CNS vasculitis (PACNS) is always a diagnostic challenge, but most forms of histologically defined CNS vasculitis, in particular vasculitis of the granulomatous variety, are associated with a far more chronic course and inflammatory findings in the cerebral spinal fluid. Nevertheless PACNS is difficult to exclude in the present case.

Table I. Common etiologies for a high probability angiogram as seen in cerebral angiits

Cerebral angiitis
Primary form (i.e., PACNS)
Secondary forms
Infections
Intravascular clot
In situ secondary to hypercoaguability
Embolic origin
Intravascular neoplasm
Atherosclerosis
Reversible vasoconstriction (i.e., spasm)

Infections are an extremely important cause of vascular inflammation, resulting from either angioinvasive organisms inducing direct vascular damage or the effects of the host's immune response upon the vessel wall (3). Again the paucity of constitutional features and the normal CSF make most forms of infection unlikely. Intravascular clot from either an underlying systemic hypercoaguability state or from emboli is always a strong consideration as an etiology for stroke (either single or multiple) and abnormal angiogram. While the current angiogram with its appearance of multiple areas of long smooth tapering may not strongly suggest an intraluminal clot, there are no clearly defined parameters of angiographic interpretation in terms of sensitivity, specificity and predictive value to allow us to discard this possibility at the present time. The normal hypercoaguable screen, including anticardiolipin antibody determination as well as the lack of a previous history of clots, is reasonably reassuring. The patient clearly needs to have a transesophageal echocardiogram to rule out a central source of emboli. The procedure was done and was normal. Atherosclerosis can mimic the angiographic findings of vasculitis within the CNS, but the absence of traditional cardiovascular risk factors, the patient's age and the absence of extra-cranial disease make this highly unlikely.

Finally the possibility that this angiogram represents arterial spasm or more properly reversible segmental vasoconstriction needs to be considered. Similar clinical angiographic patterns (sudden onset of headache and diffuse angiographic changes) have been described in many settings, including patients exposed to sympathomimetic drugs

Table II. Most common disorders associated with angiographic evidence of cerebral vasoconstriction.

Complex headaches
Thunderclap headaches
Post exertional headaches or sex headaches
Post partum angiopathy
Severe hypertension
Post carotid endarterectomy
After administration of serotonergic, sympathomimetic or illicit drugs
Benign angiopathy of the central nervous system

and drugs of abuse (i.e. cocaine) (5), in the post partum period (6), after carotid endarterectomy (7), after sexual intercourse (8), after exertion (8), with severe hypertension and with a history of migraine (9) (Table II).

The most common form of headache described in association with such angiographic changes is the thunderclap headache, which is described as severe and explosive headache with peak intensity reaching crescendo within 30 seconds of its onset – sudden and unexpected as a "clap of thunder" (10). These headaches should always prompt an evaluation for subarachnoid hemorrhage but when none is found patients are often treated symptomatically and discharged. Unfortunately these headaches may recur over a 7- to 14-day period and result, as in this case, with a delayed stroke. Angiographic abnormalities such as these do not occur with classic migraine even when accompanied by stroke (11).

Finally the entity of benign angiitis of the CNS should be entertained (12). This is a recently described nosologic entity defined by similar clinical, angiographic and CSF findings but is not associated with any of the other conditions in Table II. As in this case, the clinical features are not those of the thunderclap, exertional or sex headache variety, nor any of the other disorders listed. The key features of benign angiopathy of the central nervous system (BACNS) are outlined in Table III. In BACNS, the term 'benign' has been employed because it originally was viewed as a more favorable form of CNS vasculitis than the granulomatous variant with which it was once commonly confused. The term 'angiopathy' was applied since the underlying pathologic basis for it has until recently remained unclear. It is now know to be a disease of reversible vasoconstriction or spasm, and not arterial inflammation. Evidence in support of the vasoconstrictive mechanism in BACNS comes from its similarity to those conditions referred to above where secondary vasoconstriciton has been clearly implicated (i.e., post-partum, sympathomimetic drug-induced, hypertensive etc.) and the recent demonstration that in BACNS the lesions are rapidly reversible (12).

How can vasoconstriction be recognized and clinically diagnosed in such settings? First, it requires a high degree of suspicion. The presence of any one of the associated disorders in Table II should always prompt serious consideration that a high probability angiogram reflects spasm and not arteritis in the CNS. Furthermore, the other clinical features of BACNS should always be present (Table III). The female predominance is helpful, but these conditions may also occur in men (12). The remarkably acute nature of the symptoms, as in this case, and the normal lumbar puncture combined with the dramatic angiographic evolution within less than one week's time are also supporting. Finally, it can not be stressed enough that the most essential element for proving the presence of underlying vasoconstriction is to demonstrate dynamic change (i.e., improvement) in the underlying cerebral blood flow with therapy (or at times with observation alone) (12).

The importance of this strategy requiring demonstration of dynamic change can be best understood when considering a patient with widespread cerebral atherosclerosis presenting with the acute onset of a focal neurologic event, with or without headache. Most patients with this condition would have a normal lumbar puncture and not uncommonly a few will undergo cerebral angiography which may be interpreted as 'high probability' for vasculitis. In light of the criteria in Table III, could this case presumably represent BACNS or one of its variants ? While most such patients can be sorted out on the basis of other findings (i.e., cardiovascular risk profile, extra-cranial atherosclerosis, etc.) the only definitive evidence for this not being BACNS would be the failure to demonstrate improved blood flow on re-study regardless of what therapy was administered.

Table III. Essential features of benign angiopathy of the central nervous system (BACNS).

Clinical	
	Most common in young women
	Acute onset (hours to days)
	Severe headache and or focal neurologic event
	Normal or near normal CSF analysis
Radiographic	
	High probability angiogram for vasculitis (segmental narrowing, ectasia or beading in multiple vascular beds)
	Reversibility of angiographic abnormalities after therapy
Reversibility	
	Clear demonstration of reversibility by cerebral angiography, trans-cranial Doppler or other neuroimaging technique
Exclusions	
	Other disorders associated with reversible cerebral vasoconstriction

Treatment of reversible cerbral vasoconstriction

The appropriate therapy for cerebral vasoconstriction may vary according to the clinical setting. When associated with hypertension or incriminant drug exposure, treatment of the underlying hypertension or removal of the putative drug is essential. When it occurs in the setting of the other disorders presented in Table II or in its idiopathic form, i.e. BACNS, there are no controlled trials to help guide us, only limited observa-

tional data.

It is interesting that in some cases spontaneous remission has been well documented (10,12), but this strategy is not comforting since it is known that some cases, including the present, go on to delayed infarctions. In the largest series of such cases (n= 16) reported by Hajj-Ali *et al*. (12) glucocorticoids were used in 77% and none for more than 6 months, 85% received calcium channel blockers with or without glucocorticoids, and one patient was untreated. No patient was given cytotoxic drugs and these agents were actually discontinued in 3 who were treated for presumptive 'vasculitis' before their final diagnosis of BACNS.

The calcium channel blocker of choice is unclear for most patients in this series were treated with verapamil. In two recent case reports (13,14) of the successful therapy of reversible segmental cerebral vasoconstriction with severe headache, both resolved following treatment with nimodipine although one patient received adjunctive glucocorticoids and the other magnesium sulfate. What is clear from all of these reports is that if the confidence in the diagnosis is high and the follow-up meticulous, no patient should ever be treated with a cytotoxic agent and the treatment course can be relatively brief.

Appropriate follow-up

As noted above, the essential feature for securing this diagnosis is the demonstration of reversibility of the vascular lesions over a relatively brief period of time (i.e., weeks to a few months). Methods to demonstrate these dynamic changes vary and may be invasive (i.e., repeat cerebral angiography) or non-invasive [i.e., magnetic resonance angiography (MRA) or transcranial Doppler (TCD)]. The timing of follow-up studies is not yet clear, but we do have some limited data to guide us. In the study of Hajj-Ali *et al*. (12) 10 of their 16 patients underwent repeat cerebral angiography, demonstrating total or near total resolution in all within a mean interval of 3 months and as early as 18 days after therapy. When baseline lesions can be demonstrated by MRA, follow-up investigations can be performed earlier and more frequently without the fear of adverse events such a stroke, which may be seen in a small percentage of patients undergoing cerebral angiography.

Finally, TCD offers an excellent non-invasive approach for following cerebral blood flow non-invasively and has been used in several case reports as in the current case (13, 15). This test has excellent reproducibility and accuracy (16), can be repeated frequently and is capable of clearly demonstrating reversibility of large caliber vessel involvement when it involves those at the base of the brain. The technique is limited by technical factors, including the fact that in approximately in 10% of individuals it is impossible to insonate the intra-cerebral vessels due to the lack of an acoustic window. In addition, not all patients with reversible cerebral vasoconstriction will have abnormal flow velocities at presentation, presumably due to the more distal distribution of their disease.

Management of the case

By the time the rheumatologist encountered the present patient, her headaches were dramatically better on prednisone 60 mg per day and verapamil 80 mg BID. Baseline TCDs were still abnormal, however (Table IV), nearly 3 weeks after therapy was initiated. The dose of the calcium channel blocker was gradually increased to 360 mg per day and the prednisone was gradually discontinued over the next 8 weeks, when TCD velocities fell to the normal range. We intend to leave the patient on long-term calcium channel blockers.

Table IV. Transcranial Doppler ultrasonography (TCD) of the middle cerebral arteries during serial TCD examinations (cm/sec).

	Right	Left
Day 23	101**	102**
Day 40	92*	79+
Day 43	76+	60+
Day 56	79+	76+

**Moderately elevated; *borderline elevated; +normal for age

Final diagnosis

Benign angiopathy of the CNS (BACNS).

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