Both science and art are often needed in securing the diagnosis of various forms of systemic vasculitis but I believe never more so than when applied to vasculitis of the central nervous system (CNS). The reasons for this include: 1. Lack of a correlative blood test of high positive (i.e. ANCA, cryoglobulins) or negative (i.e. acute phase reactants) predictive value. 2. Lack of a high probability clinical finding to anchor pre-test probability (i.e. inflammatory purpura, mononeuropathy). 3. Low specificity of available neurodiagnostic studies (i.e. MR imaging, direct or indirect angiography). 4. Relatively inaccessible sites for biopsy and limited tissue sampling when performed. Based on these limitations I will briefly review the changing basis of the rational diagnostic approach to CNS vasculitis.

**Diagnostic reasoning as a clinical science**

Efficient and accurate diagnosis is critical to optimal patient care. In the field of vasculitis, both probabilistic as well as causal and rule-based approaches have been advocated, all enhanced by new pathophysiologic insights and evidence-based support for the use of increasingly sophisticated diagnostic tests [1]. For the clinician, it is challenging to apply these related, but often alternative, approaches and thus we make extensive use of short-cuts or rules of thumb known as heuristics. In the clinical setting these heuristics are indispensable as they reduce the need to ask a large number of questions and order unnecessary and often invasive tests; they allow the clinician to perform with efficiency and accuracy. Expert clinicians often employ extremely strong diagnostic approaches such as ‘pattern recognition’ or ‘thin slicing’; however, these techniques are not without potential error especially when applied to diseases outside the expert’s comfort zone. The field of cognitive science and diagnostic reasoning has been recently reviewed [2].

**Diagnostic approach - Vasculitis of the CNS**

While there are no validated diagnostic or classification criteria for primary angiitis of the CNS (PACNS) there has been great progress in the diagnostic approach to vasculitis of the CNS largely driven by refinement and progress in application of the ‘working diagnostic criteria’ proposed 25 years ago [3]. The criteria themselves retain face validity, requiring an unexplained neurologic deficit after a vigorous diagnostic evaluation, evidence of vascular pathology by biopsy or neuroimaging and rigorous exclusion of mimics. Reflections on these criteria suggest that each has been altered by factors such as a general more vigorous diagnostic approach to CNS disease, improved and previously undeveloped diagnostic tools (e.g. vascular wall imaging, routine use of PCR for microbiologic diagnosis, etc.) and elucidation of numerous mimics not recognized at the time of publication (antibody mediated autoinflammatory diseases of the CNS [4], hereditary syndromes such as CADASIL and CRV, new infections such as prion disease and hepatitis C and many others [5,6]. These changes have been recently summarized [7].

**Heuristics and vasculitis of the CNS**

In this brief review, I propose seven heuristics that represent an admixture of evidence-based recommendations and experience based techniques for problem solving when approaching a patient with suspected vasculitis of the CNS. Clearly some of these rules of thumb are more supported by clinical data than others but clinicians do not have the luxury of not engaging in clinical settings where evidence is not conclusive.

**Heuristic 1. There is no specific clinical finding or set of findings of sufficient pre-test probability to secure a diagnosis of PACNS**

CNS vasculitis can affect virtually any anatomic area of the CNS including supra and infratentorial structures including cranial nerves and spinal cord. In addition its onset can be fulminate or insidious and its course relapsing or progressive. The review by Salvarani and colleagues [8] of 101 patients serves to emphasize the protean manifestations of CNS vasculitis noting that headache, cognitive dysfunction, paresis, stroke and visual dysfunction are the most common findings. Despite these limitations, I offer three clinical scenarios where PACNS should always be considered. First in the evaluation of a patient with multiple strokes in multiple vascular territories experienced over time. Second in the patient with both focal (i.e. stroke, paresis) and diffuse vascular territories experienced over time. Third in any patient presenting with a chronic aseptic meningitis-type presentation. In each scenario PACNS warrants serious consideration in terms of heightened pre-test probability.

**Heuristic 2. A lumbar puncture is the key laboratory test in the evaluation of PACNS and should only be omitted in the presence of risk from CNS mass effect**

No evaluation of suspected CNS vasculitis is complete without sampling of the cerebral spinal fluid; a lumbar puncture should be performed unless medically contraindicated. The test is of high specificity, often demonstrating mild to moderate elevations of protein and lymphocytic pleocytosis on over 90% [8]. The CSF analysis serves two primary purposes. As a test of high sensitivity, it serves to help rule out the diagnosis of PACNS (i.e. high negative predictive value) as well as being central to detecting the must rule outs of infection and malignancy.
Contemporary clinicians have witnessed major advances in neurodiagnostics that seemed inconceivable a generation ago. Studies that evaluate the cerebral parenchyma including CT, MRI (with diffusion weighted sequences and gadolinium enhancement) as well as studies reflective of biologic activity including MR spectroscopy and FDG PET (Zuccoli, 2011) have added increasing sensitivity to abnormalities. Thus these imaging studies now have high negative predicative value (SNOUT: Sensitivity rules OUT disease) but at a cost of low specificity thus compromising their positive predicative value (low SPIN: Specificity rules disease IN) [9]. Of course rules such as SPIN and SNOUT, while appealing, are subject to their own forms of bias [10]. Despite such limitations, in the large case series of Salvarani and colleagues MRI was abnormal in 97% thus suggesting that PACNS is unlikely in the setting of a normal study [8].

**Heuristic 4. There is NO angiographic study of 100% specificity for the diagnosis of CNS vasculitis**

Angiography by direct (i.e. conventional) or indirect MRA or CTA can demonstrate abnormalities of the vascular lumen [11]; more recently direct vascular wall imaging [12,13] has added to our ability to detect intracerebral vascular pathology. Despite such progress the technique has limited sensitivity in small vessel disease because of limitations in special and temporal resolution. Biopsy positive, angiogram negative patients are well documented [14]. More critical is the fact that the ‘classic’ findings in CNS vasculitis (narrowing, post-stenotic dilatation, “beading” particularly when found in multiple vascular beds) has not been demonstrated to be highly specific [6]. Expert readers often comment on the significance of smooth segmental narrowing being characteristic of spasm and irregular irregularities being more characteristic of inflammation; these comments are of interest but uncodified in terms of specificity. The clinical caveat for angiography is that even with the presence of a ‘high probability’ angiogram a meticulous search for mimics including spastic, degenerative, and secondary infectious and neoplastic processes is indicated.

**Heuristic 5. Brain biopsy is underutilized and is a valuable but imperfect diagnostic tool**

Brain biopsy is a formidable procedure and clearly poses a high barrier for immediate acquisition of diagnostic information. Alternatively it is the only direct diagnostic technique capable of securing clinical information to minimize the ‘irreducible uncertainty’ that leaves clinicians vulnerable to diagnostic failure. The technique itself, performed by the open or stereotactic route, has been reported to have sensitivity in the range of 50–75% [15,16]. A decision-making process based solely on sensitivity could logically lead to the conclusion that the technique should not be overly relied upon since a false negative rate of 25–50% provides insufficient negative predictive value to influence therapy. An alternative view based on data from biopsy series that have examined specificity (i.e. the frequency of a non-diagnostic study in the absence of CNS vasculitis) document that biopsy frequently detects alternative diagnoses in a high percentage of cases [17]. Thus brain biopsy has both strong positive and negative predictive value and is capable of detecting the must rule outs of CNS vasculitis.

**Heuristic 6. While all alternative possibilities (i.e. diagnoses) in Bayesian reasoning are treated equally, all diagnoses are not clinically equal**

Probabilistic approaches to diagnosis are driven by largely Bayesian-type reasoning. Such approaches require knowledge of test sensitivity and specificity and analyze diagnostic possibilities based on interpreting clinical data and tests using formal instruments such as likelihood ratios to assess such probabilities quantitatively [1]. A caveat not expressed quantitatively in this approach is that all diagnostic possibilities are not clinically equal. For example a diagnostic error confusing PACNS with sarcoidosis of the CNS may have few immediate consequences; however, the misinterpretation of infection with M. tuberculosis for PACNS can be catastrophic. In addition to infections, malignancy, especially CNS lymphoma and intravascular B cell lymphoma, deserve special attention as these conditions can exactly mimic PACNS clinically and in neuroimaging and misdiagnosis will result in under treatment. Thus the must rule outs of infection and malignancy always warrant special attention.

**Heuristic 7. Failure to respond or progress on cyclophosphamide and glucocorticoids suggests an alternative diagnosis rather than refractory disease**

In my experience the vast majority of cases of PACNS do respond to aggressive therapy if the diagnosis is made promptly and damage is not too extensive. In the face of a patient progressing on appropriate therapy it always prudent to question the diagnosis rather than blindly escalate therapy. This type of error is a variant of what is known as an anchoring heuristic which implies relying overly on our initial impressions. More precisely, the error we most want to avoid is dubbed premature closure when we cling to our initial diagnosis despite mounting evidence of an alternative disorder [18].

**Conclusion**

Collectively these heuristic or experience based short-cuts underpin the complexity of the diagnosis of CNS vasculitis and support that both art and science are required by clinicians faced with limited data sets. Moreover, both diagnosis and care must be highly individualized and generally done through a...
multi-specialty team approach. Adhering to the principles of
diagnostic reasoning by utilizing both intuitive and analytic
approaches will minimize errors and improve patient care.

Disclosure of interest: the author declares that he has no conflicts of interest concerning this article.

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Available online 6 March 2013

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http://dx.doi.org/10.1016/j.rpm.2013.01.036

L37. Reversible cerebral vasocostruction syndrome: Distinction from CNS vasculitis

Reversible cerebral vasocostruction syndromes (RCVS) is characterized by severe headaches with or without other neurological symptoms, and diffuse segmental constriction of cerebral arteries that resolves within three months [1,2]. Cases with RCVS have long been considered and treated as having primary angitis of the central nervous system (PACNS). Calabrese and colleagues recognized that clinicoradiological features in these cases did not exhibit the progressive course of PACNS, but showed prompt normalization of cerebral angiography and clinical recovery, even without immunosuppressive therapy [3]. In 2007, Calabrese and colleagues proposed the name RCVS, together with a set of diagnosis criteria [1]. RCVS is now recognized as a main differential diagnosis of PACNS [4]. The aim of this review is to present the clinicoradiological spectrum of RCVS in order to enable distinction from PACNS.

RCVS is probably not such a rare condition, since the first large series included 67 patients in 3 years time in a single institution [5]. Three large series are published so far from France [6], Taiwan [7,8], and USA [9]. RCVS is most likely still underdiagnosed, particularly in patients with stroke, or in patients with headache as the only clinical symptom. RCVS can occur at any age, but peaks at around 42 years of age and is most common in females [2].

RCVS is attributed to a transient disturbance in the control of cerebral vascular tone with sympathetic overactivity. It may occur spontaneously, but at least half the cases occur after exposure to vasoactive drugs or postpartum [1,2]. Incriminated substances include selective serotonin or mixed adrenaline and serotonin recapture inhibitors, triptans, ergot derivatives, alpha-sympathomimetics (pseudoephedrine, epinephrine or norepinephrine), and most illicit drugs except opium derivates. About 10% of cases in women occur during postpartum, mainly during the first week after delivery, following a normal pregnancy, or a pregnancy complicated by proteinuria or HELLP syndrome [10]. Numerous other precipitants have been described [1,2]. Patients with RCVS frequently have a history of migraine (20–40%), and migraine seems to be a risk factor for haemorrhages in RCVS [6]. There is an overlap between RCVS and the posterior reversible encephalopathy syndrome (PRES) which is also a self-limited syndrome, characterised by headache, confusion, and seizures, and by white matter hyperintensities on MRI with increased ADC [11]. This vasogenic brain oedema usually reverses in a few days and is also attributed to an alteration of arterial tone regulation. RCVS and PRES are frequently associated [2].

The clinical presentation of RCVS is dominated by headache, which is the first symptom in more than 95% of cases and