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Concordance of angiography and cerebral biopsy results for suspected primary central nervous system vasculitis: A multi-center retrospective review

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ABSTRACT

Objective: Primary CNS Vasculitis (PCNSV) is a rare disease that is often challenging to diagnose. Cerebral angiography and biopsy have been utilized in the diagnostic workup for several decades but limited literature reports on the concordance of findings of angiography and biopsy. The primary objective of this work was to examine how cerebral angiography corresponded with biopsy findings in patients with suspected PCNSV.

Patients and methods: A total of 128 patients who underwent workup for PCNSV between years 2005–2016 were identified by query of existing neurological surgery and angiography databases at University Hospitals Cleveland Medical Center (UHCMC) and the Cleveland Clinic Foundation (CCF). The primary outcome was to examine the concordance of results between angiography and cerebral biopsy. Secondary outcomes included examining concordance between results of biopsy and other commonly performed tests for diagnosis of PCNSV including Magnetic Resonance Imaging (MRI), cerebrospinal fluid white blood cell count (CSF WBC), Erythrocyte Sedimentation Rate (ESR), C-reactive protein (CRP).

Results: 128 patients underwent cerebral biopsy for diagnosis of suspected PCNSV. 93 (73%) of these patients also underwent angiography. Of the 34 patients with positive biopsy findings, only 5 also had positive angiography. Positive angiography was not found to be correlated with positive biopsy in our analysis. The only test that was significantly associated with biopsy proven vasculitis was increased CSF WBC count ($P = 0.0114$).

Conclusions: PCNSV is a rare disease and often requires multiple tests or procedures to obtain definitive diagnosis. These results suggest that cerebral angiography findings are not associated with biopsy findings and should be used cautiously in the diagnostic work-up of PCNSV.

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1. Introduction

Primary CNS Vasculitis (PCNSV), also known as Primary Angiitis of the Central Nervous System (PACNS), refers to inflammation of small and medium vessels of the central nervous system (CNS) in the absence of systemic disease [1]. PCNSV can lead to progressive neurological dysfunction and is often a challenge to diagnose due to the range of presenting symptoms.

In 1988, Calabrese and Mallek proposed diagnostic criteria for PCNSV that included (1) clinical findings of an unexplained neurologic deficit, (2) presence of classic angiographic or histopathological features of vasculitis, and (3) no evidence of systemic vasculitis [2]. Due to the invasive nature of cerebral biopsy, angiography is preferred by some clinicians in order to establish a diagnosis. However, in the decades since the diagnostic criteria were set forth, there has been little consensus on what constitutes an angiogram diagnostic of PCNSV [3].

Furthermore, angiographic changes suggestive of vasculitis may be seen in patients due to diseases that mimic vasculitis, such as reversible cerebral vasoconstriction syndrome (RCVS), Moya Moya disease, systemic vasculitis, and stroke [4]. In 2009, Birnbaum et al. suggested an update to these criteria to prevent misdiagnosis of patients with RCVS [5]. In particular, they suggested that definite diagnosis of PCNSV can be obtained only with tissue biopsy and that only a probable diagnosis of PCNSV can be established due to angiographic findings [5].

In this study, we investigated the concordance between the results of digital subtraction angiography (DSA) and cerebral biopsy. The concordance between biopsy results and the results of magnetic resonance imaging (MRI), cerebrospinal fluid **white**blood cell count (CSF WBC), Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP) were secondary outcomes in our analysis.

2. Patients and methods

2.1. Patient identification

Institutional review board (IRB) approval for this retrospective review was obtained at University Hospitals Cleveland Medical Center (UHCMC) and the Cleveland Clinic Foundation (CCF). Patients were identified by query of neurosurgical and angiographic databases at each institution. A retrospective chart review was conducted on all patients who received cerebral biopsy for evaluation of clinically suspected PCNSV from 1986 to 2006 at CCF and between the years 2005–2016 at UHCMC. Patients with a history or evidence of systemic autoimmune disease were excluded from the study.

2.2. Clinical data collection

A standard data collection form for all findings was completed for patients who underwent biopsy for suspected CNS vasculitis. Demographics and medical comorbidities were recorded.

Results of ESR, CRP, CSF WBC, MRI/MRA, DSA, and cerebral biopsy were recorded. All tests were recorded in binary form. Abnormal values for ESR, CRP, and CSF WBC were defined as follows: ≥ 20 mm/h, ≥ 1 mg/L, and ≥ 5 WBC/hpf, respectively. These were in accordance with the normal ranges used at UHCMC. Positive MRI/MRA was defined by a finalized radiographic report demonstrating either evidence of abnormalities suggestive of vasculitis such as ischemic or hemorrhagic changes affecting vascular territories of variable size or a report where vasculitis could not be excluded.

Positive DSA results were based on the radiologist reading of the angiogram and was defined as evidence of isolated multiple cerebral artery segmental narrowing, as well as other abnormalities suggestive of vasculitis or where the radiologist deemed that PCNSV could not be excluded. Positive cerebral biopsy was defined by histopathological report showing evidence of transmural inflammation of small or medium-sized blood vessels of meninges and/or parenchyma, predominantly lymphocytic inflammatory infiltrate, or fibrinoid necrosis of the vessel wall with or without granulomatous features. In all cases, biopsy included a sample of the cortical surface and adjacent leptomeninges. Biopsies were sampled from regions of the brain that demonstrated abnormalities on imaging in all cases.

2.3. Statistical analysis

The primary goal of this study is to examine concordance between cerebral angiography and biopsy findings in patients with suspected vasculitis. First, summary statistics of demographic variables, comorbidity indices, and some physiologic markers were used to describe the study sample. Continuous and categorical variables were summarized with mean (standard deviation) and frequency (percent), respectively. Descriptive statistics were also used to analyze the symptoms, number, and results of diagnostic tests. To compare the effectiveness of laboratory tests results with the biopsy results, standard test statistics such as chi-squared, and two-sided Fisher's exact tests (as appropriate) were used. For this exploratory study with a moderate sample size (n = 128), a p-value less than 0.05 was set for statistical significance. All analyses were performed using SAS (version 9.4, The SAS Institute, Cary, NC).

3. Results

A total of 128 patients who met inclusion criteria were identified. 95 patients were from the Cleveland Clinic and 33 patients were from UHCMC. There were a total of 50 males and 78 females. The mean age of the study population was 49.8 years. The vast majority of the patients were Caucasian (n = 91, 96%) and 26 (27%) were current or former smokers. Demographic information is presented in Table 1.

Presenting symptoms are detailed in Table 2. The most common presenting symptom was headache (55%), followed by mental status change (54%). Of these symptoms, the most common symptom associated with positive biopsy was seizure (44%), followed by mental status change (30%), and focal neurological deficit (30%).

Results of diagnostic tests are outlined in Table 3. There was not a large variation in the number of tests performed for workup. The most commonly performed diagnostic test was MRI/MRA (n = 125, 98%), followed by CSF WBC count (n = 113, 88%) and ESR (n = 105, 82%). Angiography was performed in 73% of patients. Of the tests examined, CRP was the least commonly performed (n = 90, 70%). In the entirety of the study cohort, MRI was the most likely to be positive for

Table 1
Demographics and comorbidities.

Variable	Number of Patients (%)
Age	49.8 (15.9)*
Institution	
UHCMC	33 (26%)
CCF	95 (74%)
Gender	
Male	50 (39%)
Female	78 (61%)
Race†	
Caucasian	91 (96%)
African American	2 (2%)
Asian	1 (1%)
Hispanic	1 (1%)
Diabetes Mellitus	25 (20%)
Coronary Artery Disease	7 (5.4%)
Hyperlipidemia	19 (14.8%)
Hypertension	46 (35.9%)
Smoker†	26 (27%)
Migraines†	17 (18%)

* Mean (standard deviation).
† Denominator is 95 patients from CCF cohort.

Table 2
Presenting symptoms (Total patients = 128).

Presenting Symptom	Number of patients (%)	Patients with positive biopsy	P-value
Headache	70 (55%)	20 (29%)	0.7156
Mental Status Change	69 (54%)	21 (30%)	0.3832
Seizure	27 (21%)	12 (44%)	0.03375
Focal Neurological Deficit	57 (45%)	17 (30%)	0.5841

Table 3
Comparison of diagnostic test results to biopsy results.

Variable (n)	Biopsy (128)		X^2	P-value
	Negative (94)	Positive (34)		
MRI (125)				0.5115
Negative	11 (12.09%)	2 (5.88%)		
Positive	80 (87.91%)	32 (94.12%)		
ANGIO (93)			13.52	0.0002
Negative	24 (34.29%)	18 (78.26%)		
Positive	46 (65.71%)	5 (21.74%)		
ESR (105)			1.1509	0.2834
Negative	36 (45.57%)	15 (57.69%)		
Positive	43 (54.43%)	11 (42.31%)		
CRP (90)			3.0587	0.0803
Negative	35 (51.47%)	16 (72.73%)		
Positive	33 (48.53%)	6 (27.27%)		
CSF WBC (113)			6.4062	0.0114
Negative	50 (60.24 %)	10 (33.33%)		
Positive	33 (39.76%)	20 (66.67%)		

abnormalities associated with PCNSV (90%) followed by angiography (55%). CRP was the least likely to be positive (n = 39/113, 43%).

Results of association between the diagnostic tests and cerebral biopsy are presented in Table 3. Positive DSA findings were not associated with positive cerebral biopsy. Of the 23 patients who underwent DSA and had a positive biopsy, only 5 patients (21.74%) had a positive angiogram. Conversely, of the 70 patients with an angiogram and a negative biopsy, 46 had a positive angiogram (65.71%). There was a significant association between positive angiography and negative biopsy (p = 0.0002). Of the tests interrogated for their association with biopsy results, the only test found to be significantly associated with positive biopsy was CSF WBC count (p = 0.0114) (Table 3).

4. Discussion

This is the largest study to date to investigate the association of conventional tests with cerebral biopsy for the diagnosis of PCNSV. Positive CSF WBC count was the only test found to be significantly associated with positive biopsy results. MRI was the most commonly performed test in our series and was also most likely to be positive (90%) regardless of biopsy result, a finding corroborated in literature [6].

Procedural risk often drives diagnostic algorithms and many clinicians choose angiography as an early diagnostic test due to the relatively lower procedural risk compared to cerebral biopsy [7–9]. Angiography provides information regarding the contours of cerebral vessels, however, it does not give any definitive indication of the underlying etiology. Changes in vessel contour can be due to several etiologies including infection, atherosclerosis, and fibromuscular dysplasia, among others [10]. Kadkhodayan et al. investigated the sensitivity and specificity of conventional angiography in 38 patients and reported that 14 had findings characteristic of PCNSV on angiography, however, of these 14 patients, none had a positive biopsy for PCNSV [4].

These results are concordant with our findings that positive results on cerebral angiography were not associated with positive histopathological findings. A disproportionate number of patients with positive angiogram (46/51, 90%) did not have positive cerebral biopsy. Unexpectedly, we found there to be a significant association between negative angiogram and positive biopsy (p = 0.0002). This mismatch is startling and highlights the fact that taken on its own, angiography may not be abnormal in the case of patients with PCNSV. A comparison of DSA findings of patients with RCVS and PCNSV found that while all RCVS patients had abnormal angiography results, only 56% of patients with PCNSV had evidence of abnormality [11].

However, DSA may not be the only way to separate RCVS and PCNSV since advances in MRI technology have enabled visualization of patterns that were previously not apparent. A study of 60 patients found that patients with PCNSV most often demonstrated multi-territorial, bilateral, distal acute stroke lesions in small or medium artery distributions [12]. Another study compared patients with PCNSV and RCVS and that found patients with PCNSV demonstrated concentric wall enhancement and thickening while patients with RCVS demonstrated negligible enhancement and uniform wall thickening [13]. As a result of these technological advances, while DSA is often useful in distinguishing RCVS from PCNSV, it may not be the only way of differentiating between RCVS and PCNSV and that MRA, a less invasive technique, may prove more beneficial.

Furthermore, if angiography is negative it does not necessarily rule out PCNSV. Salvarani et al. reported results for 8 patients who had normal angiography but had findings suggestive of vasculitis on cerebral biopsy [14]. All 8 patients responded to treatment suggesting that this cohort of patients had PCNSV that affected vessels below the resolution of conventional angiography and thus could not be detected. As a result, if a patient with suspected PCNSV has a negative angiogram, diagnostic testing should still include cerebral biopsy.

Cerebral biopsy is limited by the fact that false-negative results have been known to occur [15]. However, in a systematic literature review of diagnostic tests for PCNSV, McVerry et al. reported that false-negative biopsies, as determined by autopsy, occurred predominantly in patients who did not have other imaging such as brain MRI as part of the clinical investigation [15]. In our study, cerebral biopsy was guided by cerebral imaging, most often by MRI. Furthermore, including both brain and adjacent leptomeningeal tissue also increases tissue yield for biopsy, [16] which was the case in our study.

These findings lead us to conclude that angiography has a limited role in the diagnosis of PCNSV. Cerebral and leptomeningeal biopsy remain the **gold**standard for diagnosis of cerebral vasculitic disease [4,17,18]. Even though biopsy is the most invasive diagnostic tool for PCNSV, the risk of biopsy must be weighed against the risk of treatment with long-term immunosuppressive therapy [19]. In our series, 73% of patients with a cerebral biopsy had also undergone angiography, suggesting that biopsy is eventually performed to clarify diagnosis. Due to the low sensitivity of angiography reported previously in the literature, using angiography as a less invasive diagnostic tool does not ultimately preclude the need for biopsy [2,20].

4.1. Limitations

This work is a retrospective chart review and, as such, is subject to misclassification bias and incomplete data. Our analysis included more women with 50 males and 78 females. This may be due to selection bias since we reviewed the charts of all patients that received a biopsy for suspected PCNSV and more women received a cerebral biopsy. However, there was no significant difference in the rates of positive biopsy findings between men and women (24% vs. 28%, p = 0.6).

Furthermore, our results are limited by the frequency of the tests performed. Not every patient underwent every diagnostic test examined. For example, only 73% of the patients received an angiogram in addition to biopsy. Due to missing tests, we are wary of making any claims regarding the sensitivity and specificity of any test and are only able to comment on association between the results. In addition,

because of the retrospective nature of the study, we were unable to make any assertions regarding the role of angiography in determining the site of biopsy. Due to the lack of clear consensus criteria for positive angiography findings for PCNSV, future studies should examine associations between individual angiography findings [21] and results of cerebral biopsy to determine if specific findings are better associated with biopsy results.

5. Conclusion

PCNSV is difficult to diagnose with several tests available for diagnostic workup. In our study, positive cerebral angiography was not significantly associated with positive histopathologic diagnosis of PCNSV. Angiography exposes patients to seemingly unnecessary risk and it does not appear to provide additional diagnostic information.

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Declaration of Competing Interest

The authors of this manuscript do not have any disclosures or conflict of interest.

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