Differentiation between neurosarcoidosis and primary central nervous system vasculitis based on demographic, cerebrospinal and imaging features

D. Saygin[1], S. Jones[2], P. Sundaram[3], L.H. Calabrese[4], W. Messner[5], J.O. Tavee[6], R.A. Hajj-Ali[4]

[1]*Department of Internal Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA;*
[2]*Department of Neuroradiology, Cleveland Clinic, Cleveland, OH;*
[3]*Department of Diagnostic Radiology, University Hospitals Parma Medical Center, OH;*
[4]*Department of Rheumatology, Cleveland Clinic, Cleveland, OH;*
[5]*Department of Quantitative Health Sciences, Cleveland Clinic, Cleveland, OH;*
[6]*Department of Neurology, Northwestern University,Feinberg School of Medicine, Chicago, IL, USA.*

Didem Saygin, MD
Stephen Jones, MD
Priya Sundaram, MD
Leonard H. Calabrese, MD
William Messner, MS
Jinny O. Tavee, MD
Rula A. Hajj-Ali, MD

Please address correspondence to:
Rula A. Hajj-Ali,
Cleveland Clinic,
Orthopaedic and Rheumatologic Institute,
9500 Euclid Avenue, Desk A50,
Cleveland, OH 44195, USA:
E-mail: hajjalr@ccf.org

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ABSTRACT

Objective. *Neurosarcoidosis (NS) and primary angiitis of the central nervous system (PACNS) are inflammatory diseases affecting central nervous system, with overlapping clinical and pathological characteristics. Distinguishing these diseases is important given distinct therapeutic implications. In this study, we aimed to compare demographic, CSF and MRI characteristics between these two conditions.*

Methods. *All the clinical, CSF and laboratory characteristics at the time of presentation were retrieved from electronic medical records. Brain and/or spinal cord MRI performed near the time of presentation were blindly evaluated by two neuroradiologists. Data regarding involvement of pachy- and leptomeninges, basal meninges, cranial nerves, cerebral grey and white matter, and spinal cord were recorded for each patient.*

Results. *78 patients with PACNS and 25 patients with NS were included in the study. Mean age of patients was 43.7 (±16.7) and 43.6 (±12.5) in PACNS and NS, respectively. African-American race was found to be associated with the diagnosis of NS rather than PACNS. Patients with PACNS had higher frequency of cerebral involvement, while patients with NS demonstrated more frequent spinal cord, basal meningeal and cranial nerve involvements.*

Conclusion. *These findings suggest that MRI can be an efficient tool in distinguishing PACNS from NS. A follow-up study with a larger sample size would be required to validate our results.*

Introduction

Primary angiitis of the central nervous system (PACNS) is a rare, idiopathic, autoimmune disease affecting small-to-medium-sized vessels in the brain and/or spinal cord without evidence of systemic vasculitis (1). Calabrese and Mallek proposed diagnostic criteria for PACNS in 1988, which was presence of either classic angiographic or histopathologic evidence of vasculitis without evidence of any other condition that could otherwise explain the findings (2). This criterion was later revised by Birnbaum and Hellman due to non-specificity of angiogram results (3). Diagnosis of PACNS was considered "definite" when there is histopathologic evidence of vasculitis and "probable" when both cerebral angiogram and cerebrospinal fluid (CSF) results are highly suggestive of PACNS in the absence of tissue confirmation. Diagnosis of PACNS requires exclusion of other diseases that can affect CNS such as reversible cerebral vasoconstriction syndrome, cerebral atherosclerosis, neurosarcoidosis, Susac syndrome, Moyamoya disease, fibromuscular dysplasia, systemic vasculitides such as polyarteritis nodosa, Behçet's disease, granulomatosis with polyangiitis (Wegener), and autoimmune diseases such as systemic lupus erythematosus, scleroderma, Sjögren's syndrome. Among these diseases, neurosarcoidosis holds a special importance due to several overlapping clinical, imaging and pathologic features and differences in therapeutic strategies with PACNS.

The gold standard for the diagnosis of both PACNS and neurosarcoidosis (NS) is tissue biopsy, which often shows granulomatous inflammatory infiltration in both diseases. Clinical presentations and angiographic findings are highly non-specific and not successful in distinguishing these diseases from each other. Both diseases respond to corticosteroids well, which is used as the first-line treatment. Recently, tumour necrosis factor (TNF) inhibitors, especially infliximab have

shown significant benefits in cases of NS; however, there is insufficient data for their efficacy in PACNS and the current recommendation does not support their use in PACNS (4-8). Therefore, distinguishing these diseases earlier would be important giving the distinct therapeutic implications.

In our study, we aimed to describe and compare the demographic, cerebrospinal and magnetic resonance imaging (MRI) characteristics of patients with NS and PACNS to enhance our diagnostic approach, which can lead to more accurate decisions about appropriate treatment strategy.

Methods

This study was approved by Cleveland Clinic institutional review board and conducted in accordance with the declaration of Helsinki. Patients with PACNS were included if they had a biopsy consistent with vasculitis or positive angiography and inflammatory cerebrospinal fluid pattern. Further, diagnosis of PACNS should have been agreed upon by 2 rheumatologists in the department. NS patients were included if they had a positive brain or extra-neural biopsy result.

Demographic characteristics, cerebrospinal fluid findings, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) levels at the time of presentation were retrieved from electronic medical charts. Brain and/or spinal cord MRI performed near the time of presentation were blindly evaluated by two neuroradiologists. Data regarding involvement of pachy- and leptomeninges, brainstem, basal cistern, pituitary sella, hypothalamus, cranial nerves, cerebral grey and white matter and spinal cord were recorded for each patient. For each of these sites, presence, localisation (cerebral lobes, brainstem, cerebellum, tentorium, falx cerebri), and laterality of involvement (uni- *vs*. bilateral) were recorded. Involvement was further defined as abnormal enhancement, signal intensity abnormality or others. Additionally, the presence of ventriculomegaly, mass effect, and parenchymal haemorrhage were recorded. For the comparisons on the basis of diagnosis, comparison of numerical variables between groups was performed using either ANOVA or the Kruskal-Wallis rank-sum test, the latter was employed for variables with highly skewed distributions or possible outliers. Categorical variables were compared between groups using either Pearson's chi-squared or Fisher's exact tests, as appropriate. All statistical analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC). All testing was two-sided and considered significant at the 5% level.

Table I. Characteristics of patients with PACNS and NS.

	PACNS (N=78)	NS (N=25)	*p*-value
Age at presentation	43.7 ± 16.7	43.6 ± 12.5	0.9
Gender (Male/Female)	40/38	17/8	0.1
Race (Caucasian/African American)	73/2	16/8	<.0001
CSF Glucose (mg/dl)	66.5 ± 21.3	70.6 ± 39.8	0.6
CSF Protein (mg/dl)	59 (37.73)	92.5 (41.7,171.2)	0.07
CSF RBC	6.5 (0.34)	6 (1,11987)	0.2
CSF Neutrophils	1 (1.6)	61 (2,83.5)	0.004
CSF Lymph%	85.5 (58.5, 93.2)	87 (18,93)	0.4
CSF Mono%	8 (3.5,16.2)	4.5 (2,7.5)	0.1
CSF Total nucleated cell count	8.5 (1.33)	30 (12,90)	0.04
ACE/Angiotensin Blood	25.1 ± 19.7	27.3 ± 23	0.8
C-Reactive protein level	0.7 (0.2,4.9)	0.3 (0.15,2,8)	0.3
IL-2 receptor levels	641 (394.5,1377.5)	647 (304,1085)	0.8
ESR	15 (5, 29.5)	8 (5,22)	0.6

PACNS: primary angiitis of central nervous system; NS: neurosarcoidosis; CSF: cerebrospinal fluid; ESR: erythrocyte sedimentation rate.
Values presented as mean ± SD, median (P25, P75), or N (column %).

Results

Seventy-eight patients with PACNS and 25 patients with NS fulfilled the criteria described above and had demographics and CSF data available at the time of the presentation. MRI data was available only for 12 patients with NS and 34 patients with PACNS. All the NS patients were diagnosed with biopsy of the brain and/or extraneural tissue. Sixteen out of 25 NS patients (64%) had lung involvement. Seven patients (28%) had NS with no other identifiable organ involvement. Fifty-six out of 78 PACNS patients (72%) were diagnosed by biopsy. The remaining patients with PACNS (n=22) were diagnosed with abnormal CSF and angiography findings with negative biopsy result in 7 patients and no biopsy in 15 patients.

Demographics

The average age of patients was comparable with 43.7 (±16.7, range: 5–80) and 43.6 (±12.5, range: 25–63) in PACNS and NS patients, respectively. Males were affected more commonly than females in both groups (male/female: 40/38 in PACNS and 17/8 in NS). African-American patients tended to be diagnosed with NS (2 out of 75 in PACNS *vs*. 8 out of 24 in NS; $p<0.001$).

Laboratory findings

Fifteen out of 25 NS patients had CSF analysis. Twenty out of 25 NS patients had plasma ACE levels, 19 had soluble IL-2 receptor, 11 had CRP, and 11 had ESR documented.

Thirty-eight out of 78 patients with PACNS had CSF analysis. 15 out of 78 patients with PACNS had plasma ACE levels, 9 had soluble IL-2 receptor, 27 had CRP, and 29 had ESR documented. Average CSF glucose levels, red blood cell lymphocyte and monocyte counts were similar between PACNS and NS patients (Table 1). CSF neutrophil count, total nucleated cell count and protein levels were higher in patients with NS compared to PACNS (p: 0.004, 0.04, and 0.07, respectively). Blood ACE/angiotensin levels, ESR, CRP, and IL-2 receptor were comparable between PACNS and NS patients (Table I).

Radiologic findings

Pachy- and leptomeningeal involvement was observed similarly in NS and PACNS patients (p: 0.6 and 0.5).

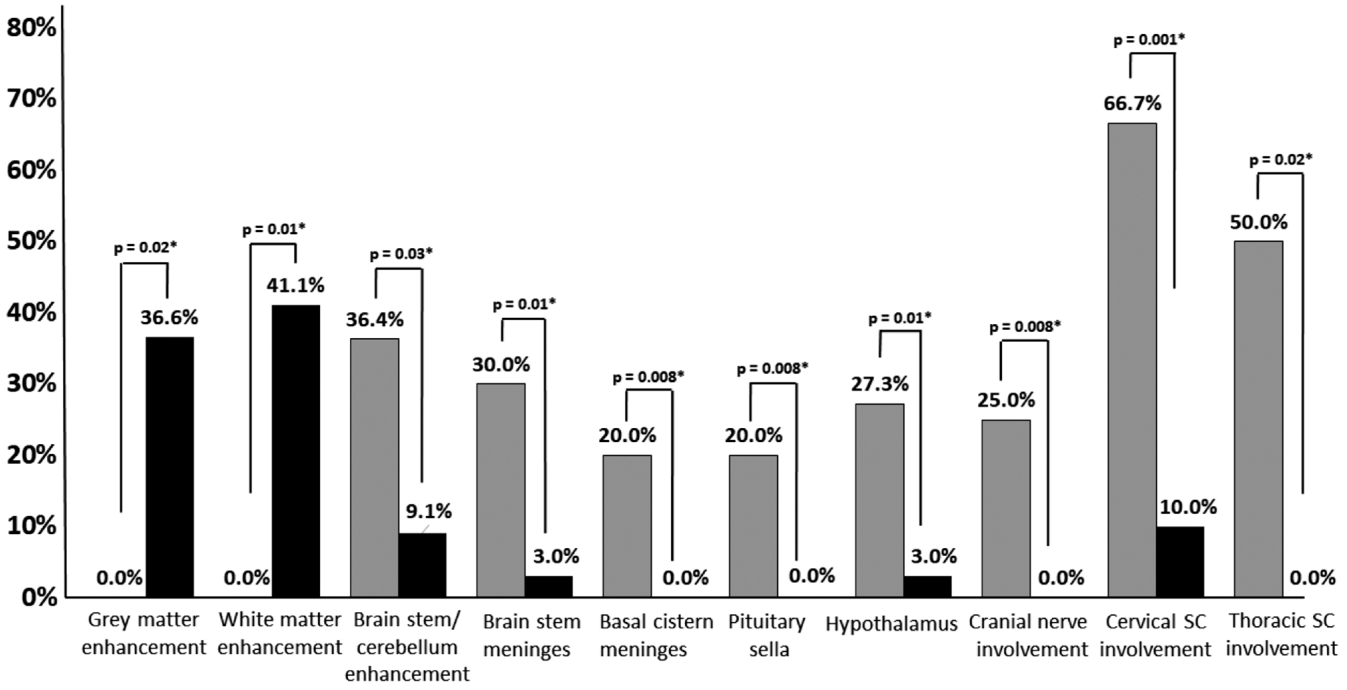

Fig. 1. Comparison of different involvement patterns in brain and spinal cord MRI in patients with PACNS and neurosarcoidosis.

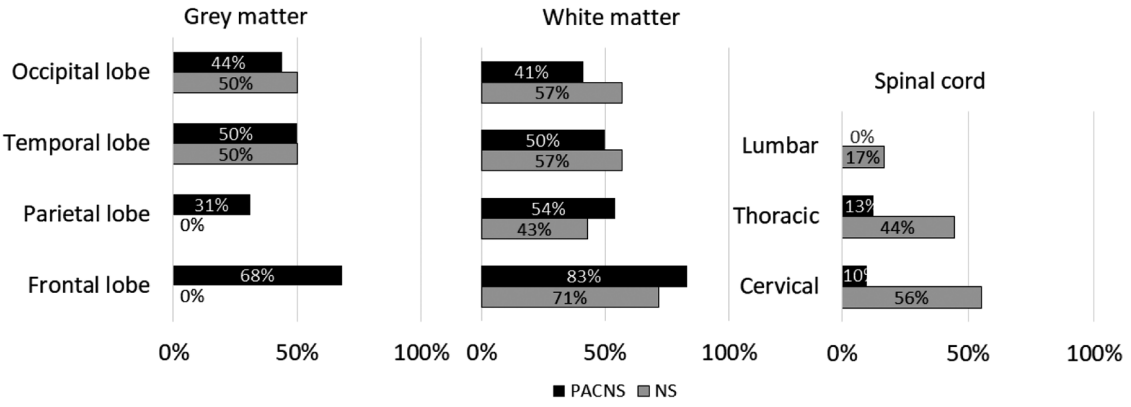

Fig. 2. Distribution of grey matter, white matter and spinal cord involvements in patients with PACNS (black) and neurosarcoidosis (grey).

However, PACNS patients tended to have unilateral pachymeningeal involvement while NS patients had bilateral involvement (p=0.001). Brainstem, basal cistern, pituitary sella turcica, hypothalamus and cranial nerves were affected more commonly in NS compared to PACNS (Fig. 1; p=0.01, 0.008, 0.008, 0.01, and 0.008, respectively).

White and grey matter enhancement and signal intensity abnormality were more commonly observed in patients with PACNS compared to NS (p=0.01, 0.02, 0.03, 0.04, respectively). Frontal, parietal, occipital and temporal lobes were affected similarly in both NS and PACNS (Fig. 2). Frequency of basal ganglial enhancement and abnormal signal intensity was comparable between PACNS and NS patients (p=0.3). Brainstem and/or cerebellar enhancement was seen more commonly in NS (Fig. 1; p=0.03).

Mass effect and ventriculomegaly was observed similarly in both PACNS and NS. Even though it did not reach statistical significance, parenchymal haemorrhage was more common in PACNS compared to NS (p=0.07).

Cervical and thoracic spinal cord enhancements were seen almost exclusively in patients with NS (Fig. 2; p=0.01, 0.02, respectively). There was only 1 patient with lumbar spinal cord involvement in NS group and none of the PACNS patients had lumbar spinal cord involvement.

Discussion

PACNS and NS are diseases that have overlapping clinicopathological features, thus difficult to differentiate from each other in the clinical setting. Most common presenting symptoms of both PACNS and NS include headache, stroke, transient ischaemic attack, cognitive changes, and seizure. Histopathologic examination of the affected tissue is granulomatous vasculitis characterised by mononuclear inflammation of the vessel wall with granulomas in PACNS and perivascular inflammatory infiltrate with granulomas in NS.

In this study, we have compared demographic, CSF, laboratory and imaging findings of patients with PACNS and biopsy-proven NS and shown the dif-

ferentiating features of these two conditions to enhance the diagnostic approach of clinicians.

Consistent with previously published cohorts, both PACNS and NS had a slight male predilection as opposed to systemic sarcoidosis with female predilection (9-12). Mean age at the time of presentation was around 44 for patients with both diseases, indicating that age and gender are likely not very helpful for distinguishing these diseases. However, more African-American individuals were affected by NS than PACNS (32% in NS *vs*. 2.5% PACNS) similar to systemic sarcoidosis.

ESR and CRP levels were comparable between PACNS and NS and not elevated in most cases of our cohort. Consistent with our data, ESR and CRP were respectively elevated (>30) in only 7.7-19.8% and 33% in a previously published large cohort of patients with PACNS (9, 10).

CSF findings of our patients with PACNS in this study were consistent with the previously published cohorts with median leukocyte count of 6 cell/ml, protein level of 50-72 mg/dl, and RBC count of 7.5 cell/ml (9, 10). Cerebrospinal fluid glucose level, number of RBCs, neutrophil%, lymphocyte% and monocyte% were comparable between NS and PACNS patients; however, CSF protein levels (59 *vs*. 92.5 mg/dl) and number of total nucleated cells (8.5 *vs*. 17) tended to be higher in NS than PACNS. This finding may be explained by more frequent involvement of basal cisterns and more diffuse involvement of pachymeninges in NS than PACNS in this cohort. Wengert *et al*. showed in his study with 25 patients with NS that patients with diffuse leptomeningeal involvement had higher CSF cell counts and protein levels and lower glucose levels than patients without leptomeningeal involvement (13).

MRI of brain and/or spinal cord provides important, often non-specific information in the diagnostic work-up of a patient with unexplained neurological symptom(s) (14). Blinded review of images by two radiologists in this study showed some valuable distinguishing features between PACNS and NS. One of them is that NS was associated with more bilateral pachymeningeal involvement, brainstem, cerebellum, basal cistern, cranial nerve and spinal cord involvement than PACNS, whereas PACNS was associated with more parenchymal involvement of the white and grey matter than NS. Predilection of NS to brainstem structures and spinal cord may be explained by its tendency to involve perforating arteries, which are mostly anatomically distributed in these parts of CNS (15, 16). Limitations of this study include the small number of patients and retrospective data collection with incomplete data points.

Conclusion

African-American race was found to be associated with the diagnosis of NS rather than PACNS. Patients with PACNS had higher frequency of white and grey matter involvement, whereas patients with NS demonstrated more frequent spinal cord, basal meningeal and cranial nerve involvements. These findings suggest that MRI can be an efficient tool in distinguishing PACNS from NS. A follow-up study with a larger sample size would be required to validate our results.

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