



HAL
open science

Comparison of patients with biopsy positive and negative primary angiitis of the central nervous system

Ahmad Nehme, Caroline Arquizan, Alexis Régent, Clothilde Isabel, Nelly Dequatre, Benoît Guillon, Jean Capron, Olivier Detante, Sylvain Lanthier, Alexandre Y Poppe, et al.

► To cite this version:

Ahmad Nehme, Caroline Arquizan, Alexis Régent, Clothilde Isabel, Nelly Dequatre, et al.. Comparison of patients with biopsy positive and negative primary angiitis of the central nervous system. *Rheumatology*, 2023, 63 (7), pp.1973-1979. 10.1093/rheumatology/kead542 . hal-04897937

HAL Id: hal-04897937

<https://hal.science/hal-04897937v1>

Submitted on 20 Jan 2025

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Comparison of patients with biopsy positive and negative primary angiitis of the central nervous system

Ahmad Nehme, MD-MSc¹, Caroline Arquizan, MD², Alexis Régent, MD-PhD³, Clothilde Isabel, MD⁴, Nelly Dequatre, MD⁵, Benoit Guillon, MD⁶, Jean Capron, MD⁷, Olivier Detante, MD-PhD⁸, Sylvain Lanthier, MD-OD⁹, Alexandre Y. Poppe, MD¹⁰, Grégoire Boulouis MD-PhD¹¹, Sophie Godard, MD¹², Benjamin Terrier MD-PhD³, Christian Pagnoux, MD-MPH¹³, Achille Aouba, MD-PhD¹⁴, Emmanuel Touzé, MD-PhD¹, Hubert de Boysson, MD-PhD¹⁴ and the Cohort of Patients with PACNS study group

Running title: Biopsy in PACNS

¹Université Caen-Normandie, Neurology, CHU Caen-Normandie, Caen, France

²Neurology, CHU de Montpellier, Montpellier, France

³Internal Medicine, Université Paris-Cité, Hôpital Cochin, AP-HP, Paris, France

⁴Neurology, GHU Paris, Paris, France

⁵Neurology, CHU Lille, Lille, France

⁶Neurology, CHU Nantes, Nantes, France

⁷Neurology, Hôpital Saint-Antoine, AP-HP, Paris, France

⁸Université Grenoble Alpes, INSERM, U1216, Neurology, CHU Grenoble Alpes, Grenoble Institute Neurosciences, Grenoble, France

⁹Neurology, Hôpital du Sacré-cœur de Montréal, Quebec, Canada

¹⁰Neurology, Centre hospitalier de l'Université de Montréal, Quebec, Canada

¹¹Radiology, CHU Tours, Tours, France

¹²Neurology, CHU Angers, Angers, France

¹³Vasculitis clinic, Mount Sinai Hospital, University of Toronto, Ontario, Canada

¹⁴Université Caen-Normandie, Internal Medicine, CHU Caen-Normandie, Caen, France

Title count : 103

Abstract count: 248

Word count: 2545

Tables: 3

References : 26

Correspondance:

Ahmad Nehme, Neurology, CHU Caen-Normandie, Avenue de la Côte de Nacre, 14000 Caen, France

nehme-a@chu-caen.fr

Phone : 02 31 06 31 86

Fax : 02 31 06 51 16

ORCID iD: 0000-0002-7700-6799

Abstract

Objective

There is limited evidence on when to obtain a central nervous system (CNS) biopsy in suspected primary angiitis of the central nervous system (PACNS).

Methods

From the multicenter retrospective Cohort of Patients with Primary Vasculitis of the CNS (COVAC), we included adults with PACNS based on a positive CNS biopsy or otherwise unexplained intracranial stenoses with additional findings supportive of vasculitis. Baseline findings were compared between patients with a positive and negative biopsy using logistic regression models.

Results

200 patients with PACNS were included, among which a biopsy was obtained in 100 (50%) and was positive in 61 (31%). Patients with a positive biopsy were more frequently female (OR 2.90, 95% CI 1.25-7.10, $p=0.01$) and more often presented with seizures (OR 8.31, 95% CI 2.77-33.04, $p<0.001$) or cognitive impairment (OR 2.58, 95% CI 1.11-6.10, $p=0.03$). On imaging, biopsy positive patients more often had non-ischemic parenchymal or leptomeningeal gadolinium enhancement (OR 52.80, 95% CI 15.72-233.06, $p<0.001$) or ≥ 1 cerebral microbleed (OR 8.08, 95% CI 3.03-25.13, $p<0.001$), and less often had ≥ 1 acute brain infarct (OR 0.02, 95% CI 0.004-0.08, $p<0.001$). In the multivariable model, non-ischemic parenchymal or leptomeningeal gadolinium enhancement (aOR 8.27, 95% CI 1.78-38.46), $p<0.01$) and absence of ≥ 1 acute brain infarct (aOR 0.13, 95% CI 0.03-0.65, $p=0.01$) were significantly associated with a positive biopsy.

Interpretation

Baseline clinical and radiological characteristics differed between biopsy positive and negative PACNS. These results may help physicians individualize the decision to obtain a CNS biopsy in suspected PACNS.

Keywords

Primary angiitis of the central nervous system, biopsy, cerebral vasculitis

Key messages

Biopsy positive PACNS more often presented with parenchymal or leptomeningeal enhancement.

Biopsy negative PACNS more often presented with acute brain infarcts.

Parenchymal samples were more often diagnostic of PACNS than leptomeningeal samples, particularly in purely lymphocytic PACNS.

Introduction

The definitive diagnosis of central nervous system (CNS) vasculitis requires a positive CNS biopsy. (1, 2) In the absence of a positive biopsy, CNS vasculitis is supported by evidence of CNS vascular disease (e.g., intracranial stenoses, brain infarcts) and markers of CNS inflammation (e.g., inflammatory cerebrospinal fluid [CSF], non-ischemic parenchymal or leptomeningeal gadolinium enhancement, concentric vessel wall enhancement). (3) Physicians disagree on which findings should motivate a CNS biopsy and obtain the latter in only a minority of patients with suspected primary angiitis of the CNS (PACNS). (4)

Clinical and radiological characteristics differ between biopsy positive and imaging based PACNS. (5) In previous studies, seizures, cognitive impairment and non-ischemic parenchymal or leptomeningeal gadolinium enhancement were more frequent in biopsy positive PACNS, while acute brain infarcts were more frequent in imaging based PACNS. (6-9) However, since not all patients with imaging based PACNS were biopsied, it remains unknown whether these differences result from selection bias or whether they reflect the existence of PACNS subgroups in which the yield of a CNS biopsy may vary. Identifying findings that are associated with a positive biopsy in PACNS may help clinicians individualize the decision to obtain a CNS biopsy. In this study, the primary objective was to identify which clinical and radiological characteristics were associated with a positive biopsy in PACNS. The secondary objective was to compare PACNS histological subtypes.

Methods

This study complies with the Declaration and Helsinki and the study protocol was approved by the CHU Caen-Normandie institutional review board (#3786), without requirement for written informed consent. In France, patients were informed of their inclusion and had the

right to request exclusion of their data. Local review board approval was obtained when required by individual sites.

Population

Adults with PACNS were enrolled from the multicenter retrospective COVAC cohort, initiated in 2010. (10, 11) The cohort's inclusion criteria were refined to require 1a) vessel wall inflammation on CNS biopsy or 1b) ≥ 1 otherwise unexplained intracranial stenosis with $\geq 1/4$ additional finding supportive of vasculitis (inflammatory CSF, concentric vessel wall enhancement, non-ischemic parenchymal or leptomeningeal gadolinium enhancement, or rapidly progressive and persistent stenoses) and 2) no secondary etiology of CNS vasculitis (e.g., CNS infection, autoimmune connective tissue disease, systemic vasculitis, sarcoidosis, inflammatory bowel disease, active cancer). To allow comparison with previous PACNS cohorts, we included patients with amyloid-beta related angiitis (ABRA), a subtype of cerebral amyloid angiopathy-related inflammation where cerebral vasculitis colocalizes with vascular amyloid-beta deposits. (12-14) Patients with isolated perivascular inflammation were not considered to have a positive biopsy. (15) No patient had complete reversal of intracranial stenoses on follow-up imaging, excluding reversible cerebral vasoconstriction syndrome. (16, 17) The likelihood of including patients with intracranial atherosclerosis that mimicked PACNS was reduced by evaluating the vascular risk factor profile, extracranial atherosclerosis, end organ damage (e.g., hypertension or diabetes related retinopathy), arterial calcifications, and the response to immunosuppressant drugs. One patient with biopsy positive vasculitis isolated to the spinal cord was excluded due to the different clinicoradiological presentations of brain and spinal cord vasculitis.

For the last update, site investigators identified cases diagnosed from 2010-2022 using locally available methods (archives, data warehouse, list of individual physician's diagnoses).

The principal investigators (AN, HdB) reviewed each file to validate the diagnosis. A third investigator (ET) was consulted in case of disagreement.

Variables

The first author extracted variables at baseline (prior to treatment) from patient charts, CNS imaging, and biopsy reports. Cognitive impairment was defined as any reported cognitive dysfunction. The CSF was considered inflammatory when white blood cells were $> 10/\text{mm}^3$ or proteins > 0.70 g/L. Imaging variables were defined as per the Standards for Reporting Vascular Changes on Neuroimaging criteria. (18) Acute brain infarcts were considered small if they measured ≤ 2 cm on diffusion weighted-imaging. A tumor-like lesion was defined as a single or multiple non-ischemic edematous lesion(s) with mass effect on adjacent parenchymal or ventricular structures. Pathologists at the participating sites were contacted to stain positive biopsies for amyloid-beta if this was not previously performed.

Statistics

Baseline characteristics were compared using Chi-square or Fisher's exact tests for categorical variables and Student's *t*- or Mann-Whitney-U tests for continuous variables. Patients with a positive and negative biopsy were compared using Firth's biased-reduced univariable logistic regression models. (19) After excluding significant multicollinearity (variance inflation factor > 5), complete case multivariable Firth's biased-reduced logistic regression was performed including variables that reached a p-value < 0.10 in univariable analyses. In two sensitivity analyses, we excluded patients with ABRA and restricted patients with a negative biopsy to those with inflammatory CSF. In an additional analysis, under the missing at random hypothesis, we performed multiple imputations with chained equations for missing covariables in all patients and biopsy results in unbiopsied patients. We generated 50 datasets in a model

that included demographics, clinical and radiological characteristics, and biopsy results. The results of logistic regressions after multiple imputation were pooled using Rubin's rules. In secondary analyses, we compared granulomatous (granulomas in the vessel wall, with or without lymphocytes) and purely lymphocytic PACNS (lymphocytes in the vessel wall, without granulomas). A p-value < 0.05 was considered statistically significant. Analyses were performed using RStudio (version 4.2.0).

Results

Among the 200 patients with PACNS included in the cohort, 83 (42%) were female, with a mean (SD) age of 48 (14) years. A CNS biopsy was obtained in 100 (50%) patients, more often in the presence of seizures ($p<0.001$), cognitive impairment ($p<0.001$), non-ischemic parenchymal or leptomeningeal gadolinium enhancement ($p<0.001$), ≥ 1 cerebral microbleed ($p<0.001$), a tumor-like lesion ($p<0.001$), no acute brain infarct ($p<0.001$) and intracerebral hemorrhage ($p=0.04$) (Supplementary Table S1). A digital subtraction angiogram (DSA) was obtained in 133 (67%) patients.

Among the 100 patients that underwent a CNS biopsy, the latter was positive in 61 (61%). On CT- or MR-angiogram, ≥ 1 intracranial stenosis was present in 2 (3%) patients with a positive biopsy and 34 (87%) patients with a negative biopsy. A DSA was obtained in 34 (56%) patients with a positive biopsy and 30 (77%) patients with a negative biopsy. The latter identified ≥ 1 intracranial stenosis in 5 (15%) patients with a positive biopsy and all patients with a negative biopsy.

Compared to patients with a negative biopsy, patients with a positive biopsy were more frequently female (OR 2.90, 95% CI 1.25-7.10, $p=0.01$) and more often presented with seizures (OR 8.31, 95% CI 2.77-33.04, $p<0.001$) or cognitive impairment (OR 2.58, 95% CI 1.11-6.10, $p=0.03$). On CNS imaging, patients with a positive biopsy more often had non-ischemic

parenchymal or leptomeningeal gadolinium enhancement (OR 52.80, 95% CI 15.72-233.06, $p < 0.001$) or ≥ 1 cerebral microbleed (OR 8.08, 95% CI 3.03-25.13, $p < 0.001$), and less often had ≥ 1 acute brain infarct (OR 0.02, 95% CI 0.004-0.08, $p < 0.001$) (Table 1). In multivariable analyses, non-ischemic parenchymal or leptomeningeal gadolinium enhancement (aOR 8.27, 95% CI 1.78-38.46, $p < 0.01$) and absence of ≥ 1 acute brain infarct (aOR 0.13, 95% CI 0.03-0.65, $p = 0.01$) were significantly associated with a positive biopsy (Table 2). These results were directionally unchanged in the two sensitivity analyses, as well as after imputing missing covariables and biopsy results (Supplementary Tables S2-S4).

When present, acute brain infarcts were more often exclusively small in patients with a positive (14/15 [93%]) versus a negative biopsy (23/38 [61%], $p = 0.02$). The median (IQR) delay between the onset of symptoms and the biopsy was 162 (57-429) days in patients with a positive biopsy and 239 (64-593) days in patients with a negative biopsy ($p = 0.45$).

Vasculitis was more frequently diagnosed on parenchymal than leptomeningeal samples (55/97 [57%] versus 16/62 [26%], $p < 0.001$). In patients with leptomeningeal enhancement, vasculitis was present in 8/15 (53%) leptomeningeal and 18/22 (82%) parenchymal samples. In patients with parenchymal enhancement, vasculitis was present in 10/21 (48%) leptomeningeal and 43/49 (88%) parenchymal samples.

Histological subtypes were purely lymphocytic in 35 (57%), granulomatous in 25 (41%) and necrotizing in 1 (2%). Fifty-seven (93%) positive biopsies were stained for amyloid-beta, revealing ABRA in 9 patients (15%). Among the four patients without amyloid staining, all had lymphocytic PACNS, three were aged less than 40 years old, and one was 42 years old with no hemorrhagic manifestations on brain MRI. Compared to purely lymphocytic PACNS, granulomatous PACNS was associated with headaches (OR 4.40, 95% CI 1.47-14.96, $p < 0.01$), inflammatory CSF (OR 4.66, 95% CI 1.36-20.10, $p = 0.01$), acute subarachnoid hemorrhage (OR 11.17, 95% CI 2.24-111.09, $p < 0.01$), ≥ 1 cerebral microbleed (OR 3.21, 95% CI 1.08-10.45, $p = 0.04$) and ≥ 1 intracranial stenosis on DSA (OR 7.24, 95% CI 1.12-80.64, $p = 0.04$). No patients

with purely lymphocytic PACNS had ABRA. Vasculitis was more frequently diagnosed on parenchymal than leptomeningeal samples in purely lymphocytic PACNS ($p < 0.001$) but not in granulomatous PACNS ($p = 0.29$) (Table 3). After excluding patients with ABRA, granulomatous PACNS remained significantly associated with headaches (Supplementary Table S5).

Discussion

In a large cohort of patients with PACNS, of which 50% were biopsied, the baseline presentation differed between patients with a positive and negative biopsy. Patients with a positive biopsy more often had cognitive impairment, seizures, non-ischemic parenchymal or leptomeningeal gadolinium enhancement, and cerebral microbleeds. Intracranial stenoses and acute brain infarcts were absent at baseline in 89% and 75% of patients with a positive biopsy, respectively. In patients with acute brain infarcts and intracranial stenoses, the diagnosis of vasculitis was supported by markers of CNS inflammation, such as inflammatory CSF and/or concentric vessel wall enhancement.

Limited evidence exists on when to obtain a CNS biopsy in suspected PACNS. A positive biopsy increases diagnostic certainty, which can support the decision to introduce or escalate immunosuppressive treatments. A CNS biopsy can also reveal an alternative diagnosis in up to 39% of patients with suspected PACNS. (20, 21) In a single center series, serious complications occurred after a CNS biopsy in 4% of patients with suspected PACNS. (21) Because of its reported low diagnostic yield, clinicians may encounter difficulties justifying a CNS biopsy to patients or their colleagues. The median time between symptom onset and a CNS biopsy was relatively long, which may have reflected the subacute course of the disease, the delay in recognizing the indication for a biopsy, or difficulties in obtaining a biopsy.

Previous studies have suggested that biopsies may be negative in PACNS due to irregular involvement of intracranial vessels or to sampling of normal brain areas. (22, 23) In addition, the differences between biopsy positive and negative PACNS may reflect the size of the

involved vessels. (24) In our study, biopsy positive PACNS was associated with markers of small vessel involvement, such as non-ischemic parenchymal or leptomeningeal gadolinium enhancement and cerebral microbleeds. Biopsy negative PACNS was associated with intracranial stenoses and acute brain infarcts, which are more often secondary to involvement of proximal intracranial vessels that are not usually sampled in a CNS biopsy. When present in patients with a positive biopsy, acute brain infarcts were exclusively small in 93% of cases, which further supports that markers of small vessel involvement are associated with biopsy positive PACNS. The CSF was non-inflammatory in 33% of patients with a positive biopsy, which suggests that CSF results should not be used in isolation to exclude patients from a CNS biopsy.

Targeting a radiological abnormal area may increase the diagnostic yield. In a study from the Mayo Clinic PACNS cohort, all of the positive biopsies were targeted to a radiologically abnormal area. (23) The results of our study support targeting areas of parenchymal or leptomeningeal enhancement, as the latter were the strongest predictors of a positive CNS biopsy. All CNS biopsies should include parenchymal samples, as the latter were more often diagnostic of vasculitis irrespective of the enhancement pattern. When comparing histological subtypes, the higher yield of parenchymal samples was only identified in purely lymphocytic PACNS. Amyloid-beta related angiitis was associated with granulomatous vasculitis and is more likely to affect the leptomeninges, which possibly explains why the yield of leptomeningeal samples was higher in granulomatous than purely lymphocytic PACNS. (25)

In addition, the baseline presentation varied according to the histological subtype. Granulomatous PACNS more often presented with hemorrhagic imaging findings, reflecting its association with ABRA. (25) Biopsies should particularly be analyzed for amyloid-beta deposits in patients with headaches, microbleeds, and acute subarachnoid hemorrhage. The sensitivity analysis excluding patients with ABRA supported that differences between biopsy positive and negative PACNS were not explained by patients with ABRA. Most differences between histological subtypes were no longer significant after excluding patients with ABRA, although headaches remained more frequent in amyloid negative granulomatous PACNS. Further studies

comparing ABRA and amyloid negative biopsy positive PACNS are necessary to determine if ABRA should continue to be classified as a subgroup of PACNS.

The differences between patients with a positive and negative biopsy are consistent with a previous report of 45 biopsied patients with PACNS. (23) Unlike the Mayo Clinic cohort, purely lymphocytic PACNS was more common than granulomatous PACNS. (13) This difference may be due to the lower proportion of patients with ABRA in our study, as clinicoradiological criteria for the diagnosis of cerebral amyloid angiopathy-related inflammation may have decreased the number of patients with ABRA undergoing a biopsy in recent years. (26)

Strengths of this study include its multicenter recruitment and sample size. The number of biopsied patients was double that of the previous study on this topic. (23) While not all patients were biopsied, the potential for selection bias was reduced by restricting the primary analysis to patients that underwent a CNS biopsy and by using multiple imputation models to predict biopsy results in unbiopsied patients, increasing the robustness of our findings.

Limitations of this study include its retrospective design and that biopsies could not be centrally reviewed. Concentric vessel wall enhancement has not been validated for the diagnosis of CNS vasculitis. Inherent to all studies on PACNS, the diagnosis remained unproven in patients without a positive biopsy. Importantly, patients with intracranial atherosclerosis can present with isolated involvement of intracranial arteries, no arterial calcifications, mildly inflammatory CSF and concentric vessel wall enhancement. We cannot rule out that some included patients had intracranial atherosclerosis mimicking PACNS. However, the inclusion criteria were narrower than previous studies and the files were reviewed by the principal investigators, which reduced the likelihood of including mimics of PACNS. Chart review did not allow us to always determine whether the biopsy was blind or targeted to a radiological lesion. Clinical and imaging variables were evaluated at baseline but can vary with disease evolution (e.g., intracranial stenoses and acute brain infarcts can be absent at baseline but appear during follow-up in patients with PACNS). (7) The study population was not compared to patients with

suspected PACNS for whom CNS biopsy revealed an alternative diagnosis, as the cohort does not include this population. Since CNS biopsies can reveal alternate diagnoses in patients with suspected PACNS (e.g., lymphoma, infection, encephalitis), the findings of this study require validation in a cohort of patients with undifferentiated disease undergoing a biopsy for suspected PACNS. Patients with suspected PACNS and no intracranial stenoses require a biopsy to confirm the diagnosis of PACNS. However, our results suggest that a biopsy is unlikely to be positive in patients with suspected PACNS who present at baseline with large acute brain infarcts, intracranial stenoses and no gadolinium enhancing lesions.

In summary, baseline clinical and radiological characteristics differed between patients with biopsy positive and negative PACNS. These results may help physicians individualize the decision to obtain a CNS biopsy in suspected PACNS.

Data availability statement:

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

Funding:

This work was supported by a training grant from the Fonds de Recherche du Québec en Santé (FRQ-S).

Acknowledgments:

CHU Montpellier/Montpellier: Xavier Ayrignac. CHU Lille/Lille: Hélène Zéphir. CHU Nantes/Nantes: Antoine Néel. Hôpital Saint-Antoine/Paris: Arsène Mekinian. Centre Hospitalier de l'Université de Montréal/Montréal: Laurent Létourneau-Guillon. Hospices Civils de Lyon/Lyon: Laurent Derex, Mathieu Gerfaud-Valentin. CHRU Strasbourg/Strasbourg: Véronique Quénardelle, Laurent Daniel Kremer. CHU Toulouse/Toulouse: Cédric Gollion. Hôpital Foch/Suresnes: David Weisenburger. Hôpital Pitié-Salpêtrière/Paris: Matthieu Vautier. Hôpitaux

Universitaires de Marseille/Marseille: Stéphanie Machado, Adil Maarouf. CHRU Nancy/Nancy: Lisa Humbertjean. CHU Rennes/Rennes: Stéphane Vannier. Hôpital Bicêtre/Paris: Christian Denier. CHU Nice/Nice: Barbara Casolla, Saskia Bresch, Michael Levraut. Hôpital Henri-Mondor/Créteil: Hassan Hosseini. CHU Liège/Liège: Nicolas Lambert. Hôpital Sainte-Anne/Toulon: Marie Subreville. Hôpital Bichat/Paris: Thomas Papo. CHU Bordeaux/Bordeaux: Igor Sibon. Hôpital Lariboisière/Paris: Chloé Comarmond-Ortoli, Mikael Mazighi. CH Luxembourg/Luxembourg: Philippe Kerschen. CH Perpignan/Perpignan: Denis Sablot. CHRU Tours/Tours: Marie Gaudron, Alexandra Audemard-Verger. CH Le Mans/Le Mans: Fabienne Closs-Prophette. CH Métropole-Savoie/Chambéry: Jérémie Papassin. Hôpital du Scorff/Lorient: Laure Daelman. Hôpital Saint-Joseph/Paris: Mathieu Zuber. Fondation Rotschild/Paris: Michael Obadia. CH Versailles/Versailles: Fernando Pico. CH La Rochelle/La Rochelle: Paul Cantagrel. CH Saint-Nazaire/Saint-Nazaire: Julie Graveleau. CHU Clermont-Ferrand: Louis Poncet-Megemont. CH Emile Durkheim: Thomas Ancel.

Authorship contributions:

A.N, H.dB, C.P and E.T contributed to the conceptualization and methodology of the study. A.N and H.dB conducted the formal analysis and wrote the original draft. All authors contributed to the data curation and reviewing/editing of the manuscript.

Conflicts of interest:

The authors declare no conflict of interest.

References

1. Birnbaum J, Hellmann DB. Primary angiitis of the central nervous system. *Arch Neurol* 2009;66(6):704-9.
2. Parisi JE, Moore PM. The role of biopsy in vasculitis of the central nervous system. *Semin Neurol* 1994;14(4):341-8.
3. Nehme A, Boulanger M, Aouba A, Pagnoux C, Zuber M, Touzé E, et al. Diagnostic and therapeutic approach to adult central nervous system vasculitis. *Rev Neurol (Paris)* 2022;178(10):1041-1054.
4. Nehme A, Lanthier S, Boulanger M, Aouba A, Cacoub P, Jayne D, et al. Diagnosis and management of adult primary angiitis of the central nervous system: an international survey on current practices. *J Neurol* 2023;270(4):1989-1998.
5. Beuker C, Strunk D, Rawal R, Schmidt-Pogoda A, Werring N, Milles L, et al. Primary Angiitis of the CNS: A Systematic Review and Meta-analysis. *Neurol Neuroimmunol Neuroinflamm* 2021;8(6).
6. de Boysson H, Boulouis G, Aouba A, Bienvenu B, Guillevin L, Zuber M, et al. Adult primary angiitis of the central nervous system: isolated small-vessel vasculitis represents distinct disease pattern. *Rheumatology (Oxford)* 2017;56(3):439-44.
7. Schuster S, Bachmann H, Thom V, Kaufmann-Buehler AK, Matschke J, Siemonsen S, et al. Subtypes of primary angiitis of the CNS identified by MRI patterns reflect the size of affected vessels. *J Neurol Neurosurg Psychiatry* 2017;88(9):749-55.
8. Salvarani C, Brown RD, Jr., Calamia KT, Christianson TJ, Huston J, 3rd, Meschia JF, et al. Angiography-negative primary central nervous system vasculitis: a syndrome involving small cerebral vessels. *Medicine (Baltimore)* 2008;87(5):264-71.
9. Boulouis G, de Boysson H, Zuber M, Guillevin L, Meary E, Costalat V, et al. Primary Angiitis of the Central Nervous System: Magnetic Resonance Imaging Spectrum of Parenchymal, Meningeal, and Vascular Lesions at Baseline. *Stroke* 2017;48(5):1248-55.
10. de Boysson H, Zuber M, Naggara O, Neau JP, Gray F, Bousser MG, et al. Primary angiitis of the central nervous system: description of the first fifty-two adults enrolled in the French cohort of patients with primary vasculitis of the central nervous system. *Arthritis Rheumatol* 2014;66(5):1315-26.
11. de Boysson H, Arquizan C, Touzé E, Zuber M, Boulouis G, Naggara O, et al. Treatment and Long-Term Outcomes of Primary Central Nervous System Vasculitis. *Stroke* 2018;49(8):1946-52.
12. Moussaddy A, Levy A, Strbian D, Sundararajan S, Berthelet F, Lanthier S. Inflammatory Cerebral Amyloid Angiopathy, Amyloid- β -Related Angiitis, and Primary Angiitis of the Central Nervous System: Similarities and Differences. *Stroke* 2015;46(9):e210-3.

13. Salvarani C, Brown RD, Jr., Christianson TJH, Huston J, 3rd, Giannini C, Hunder GG. Long-term remission, relapses and maintenance therapy in adult primary central nervous system vasculitis: A single-center 35-year experience. *Autoimmun Rev* 2020;19(4):102497.
14. Agarwal A, Sharma J, Srivastava MVP, Sharma MC, Bhatia R, Dash D, et al. Primary CNS vasculitis (PCNSV): a cohort study. *Sci Rep* 2022;12(1):13494.
15. Giannini C, Salvarani C, Hunder G, Brown RD. Primary central nervous system vasculitis: pathology and mechanisms. *Acta Neuropathol* 2012;123(6):759-72.
16. de Boysson H, Parienti JJ, Mawet J, Arquizan C, Boulouis G, Burcin C, et al. Primary angiitis of the CNS and reversible cerebral vasoconstriction syndrome: A comparative study. *Neurology* 2018;91(16):e1468-e78.
17. Singhal AB, Topcuoglu MA, Fok JW, Kursun O, Nogueira RG, Frosch MP, et al. Reversible cerebral vasoconstriction syndromes and primary angiitis of the central nervous system: clinical, imaging, and angiographic comparison. *Ann Neurol* 2016;79(6):882-94.
18. Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol* 2013;12(8):822-38.
19. Firth D. Bias Reduction of Maximum Likelihood Estimates. *Biometrika* 1993;80(1):27-38.
20. Alrawi A, Trobe JD, Blaivas M, Musch DC. Brain biopsy in primary angiitis of the central nervous system. *Neurology* 1999;53(4):858-60.
21. Torres J, Loomis C, Cucchiara B, Smith M, Messé S. Diagnostic Yield and Safety of Brain Biopsy for Suspected Primary Central Nervous System Angiitis. *Stroke* 2016;47(8):2127-9.
22. Hajj-Ali RA, Singhal AB, Benseler S, Molloy E, Calabrese LH. Primary angiitis of the CNS. *Lancet Neurol* 2011;10(6):561-72.
23. Miller DV, Salvarani C, Hunder GG, Brown RD, Parisi JE, Christianson TJ, et al. Biopsy findings in primary angiitis of the central nervous system. *Am J Surg Pathol* 2009;33(1):35-43.
24. Salvarani C, Brown RD, Jr., Hunder GG. Adult primary central nervous system vasculitis. *Lancet* 2012;380(9843):767-77.
25. Salvarani C, Hunder GG, Morris JM, Brown RD, Jr., Christianson T, Giannini C. A β -related angiitis: comparison with CAA without inflammation and primary CNS vasculitis. *Neurology* 2013;81(18):1596-603.
26. Auriel E, Charidimou A, Gurol ME, Ni J, Van Etten ES, Martinez-Ramirez S, et al. Validation of Clinicoradiological Criteria for the Diagnosis of Cerebral Amyloid Angiopathy-Related Inflammation. *JAMA Neurol* 2016;73(2):197-202.

Table 1. Comparison at baseline of biopsy positive and negative primary angiitis of the central nervous system

	Biopsy positive (n=61)	Biopsy negative (n=39)	Odds ratio (95% CI)	p-value
Mean (SD) age (years)	47 (16)	49 (13)	0.99 (0.96-1.01)	0.36
Female sex (n, %)	31 (51)	10 (26)	2.90 (1.25-7.10)	0.01
<i>Symptoms (n, %)</i>				
Seizure	27 (44)	3 (8)	8.31 (2.77-33.04)	< 0.001
Cognitive impairment	46 (75)	21 (54)	2.58 (1.11-6.10)	0.03
Headache	36 (59)	25 (64)	0.81 (0.35-1.84)	0.62
<i>Cerebrospinal fluid (n, %)</i>				
White blood cells > 10/mm ³ or proteins > 0.70 g/L	39 (67)	23 (59)	1.42 (0.62-3.28)	0.41
<i>Imaging (n, %)</i>				
≥ 1 acute brain infarct	15 (25)	37 (95)	0.02 (0.004-0.08)	< 0.001
Parenchymal enhancement	48 (81)	3 (9)	36.76 (11.40-155.73)	< 0.001
Leptomeningeal enhancement	21 (36)	2 (6)	7.04 (2.04-36.92)	<0.01
Parenchymal or leptomeningeal enhancement	51 (86)	3 (9)	52.80 (15.72-233.06)	< 0.001
≥ 1 cerebral microbleed	33 (58)	5 (14)	8.08 (3.03-25.13)	< 0.001
≥ 1 intracerebral hemorrhage	8 (13)	2 (5)	2.38 (0.61-13.14)	0.22
Acute subarachnoid hemorrhage	9 (15)	4 (10)	1.43 (0.45-5.21)	0.56

p-value for univariable Firth's bias-reduced logistic regression

Missing: white blood cells (3), protein level (3), parenchymal enhancement (8), leptomeningeal enhancement (8), ≥ 1 cerebral microbleed (6)

Table 2. Multivariable logistic regression comparing biopsy positive and negative primary angiitis of the central nervous system

	Adjusted odds ratio (95% CI)	p-value
Female sex	4.03 (0.75-21.57)	0.10
Seizures	4.22 (0.68-26.28)	0.12
Cognitive impairment	3.96 (0.68-22.96)	0.13
≥ 1 acute brain infarct	0.13 (0.03-0.65)	0.01
Parenchymal or leptomeningeal gadolinium enhancement	8.27 (1.78-38.46)	< 0.01
≥ 1 cerebral microbleed	4.52 (0.98-20.80)	0.053

p-value for multivariable Firth's bias-reduced logistic regression

Table 3. Comparison at baseline of granulomatous and purely lymphocytic primary angiitis of the central nervous system

	Granulomatous (n=25)	Purely lymphocytic (n=35)	Odds ratio (95% CI)	p-value
Mean (SD) age (years)	50 (16)	44 (15)	1.02 (0.99-1.06)	0.16
Female sex (n, %)	14 (56)	17 (49)	1.33 (0.48-3.72)	0.58
<i>Symptoms (n, %)</i>				
Seizure	9 (36)	17 (49)	0.61 (0.21-1.69)	0.34
Cognitive impairment	19 (76)	26 (74)	1.08 (0.34-3.55)	0.90
Headache	20 (80)	16 (46)	4.40 (1.47-14.96)	<0.01
<i>Cerebrospinal fluid (n, %)</i>				
White blood cells > 10/mm ³ or proteins > 0.70 g/L	20 (87)	19 (56)	4.66 (1.36-20.10)	0.01
<i>Imaging (n, %)</i>				
≥ 1 acute brain infarct	9 (36)	6 (17)	2.61 (0.83-8.74)	0.10
Parenchymal enhancement	20 (80)	28 (85)	0.72 (0.19-2.74)	0.62
Leptomeningeal enhancement	12 (48)	8 (24)	2.78 (0.95-8.56)	0.06
Parenchymal or leptomeningeal enhancement	22 (88)	28 (85)	1.24 (0.30-5.86)	0.77
≥ 1 cerebral microbleed	17 (74)	15 (45)	3.21 (1.08-10.45)	0.04
≥ 1 acute intracerebral hemorrhage	5 (20)	3 (9)	2.49 (0.60-11.78)	0.21
≥ 1 acute lobar intracerebral hemorrhage	4 (16)	2 (6)	2.80 (0.57-17.28)	0.21
Acute subarachnoid hemorrhage	8 (32)	1 (3)	11.17 (2.24-111.09)	< 0.01
Tumor-like lesion	7 (28)	15 (43)	0.54 (0.18-1.54)	0.25
≥ 1 intracranial stenosis (any imaging)	5 (20)	2 (6)	3.60 (0.78-21.54)	0.10
≥ 1 intracranial stenosis (digital subtraction angiogram)	4 (33)	1 (5)	7.24 (1.12-80.64)	0.04
<i>Biopsy (n, %)</i>				
Leptomeningeal vasculitis	11/15 (73)	4/11 (36)	4.26 (0.90-23.14)	0.07
Parenchymal vasculitis	20/23 (87)	34/35 (97)	0.25 (0.02-1.68)	0.16
Amyloid-beta positive	8 (32)	0	30.60 (3.46-4045.08)	< 0.001

p-value for univariable Firth's bias-reduced logistic regression

Missing values: white blood cells (3), protein level (3), parenchymal enhancement (2), leptomeningeal enhancement (2), ≥ 1 cerebral microbleed (4), stenosis (digital subtraction angiogram) (27), amyloid-beta positive (4)