Hemorrhagic primary CNS angiitis and vasoconstrictive drug exposure

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Abstract

Background: Primary angiitis of the CNS (PACNS) typically manifests with accumulating neurologic deficits from ischemic strokes. Intracerebral hemorrhage (ICH) is an uncommon complication. There is limited knowledge about the risk factors and features of hemorrhagic PACNS. **Methods:** We identified 49 patients (20 biopsy-proven) with PACNS diagnosed at our hospital from 1993 to 2015. We compared the features of hemorrhagic and nonhemorrhagic PACNS and analyzed the hemorrhagic PACNS cases in detail. **Results:** The mean age was 51 ± 15 years; 13 patients were men. Five patients had ICH (mean age 52 ± 14 years; 4 men) including 4 where ICH was the first manifestation of PACNS.

All ICH patients reported recent exposure to sympathomimetic drugs (e.g., diet pills, nasal decongestants). Patients with ICH had higher rates of headache (100% vs 43%, $p = 0.022$), especially thunderclap headache (60% vs 0%, $p = 0.001$), and eosinophilic vascular infiltrates on brain biopsy (50% vs 9%, $p = 0.084$). In all ICH patients, brain MRI showed lobar hemorrhages with concurrent punctate diffusion-restricted lesions, suggesting an acute inflammatory process. Four received a short course of immunosuppressive therapy. All patients showed complete clinical resolution or significant improvement within weeks. **Conclusions:** In this study, hemorrhagic PACNS was exclusively associated with sympathomimetic drug exposure. The high rate of thunderclap headache, lobar hemorrhages, and the self-limited clinical course suggests a shared mechanism between hemorrhagic PACNS and the reversible cerebral vasoconstriction syndrome (RCVS), a PACNS mimic. This RCVS-PACNS overlap syndrome may result from sympathomimetic drug-induced prolonged distal vasoconstriction, culminating in inflammation. *Neurol Clin Pract* 2017;7:26-34

Over the last decade, several studies have characterized primary angiitis of the CNS (PACNS) as an inflammatory disorder of unknown etiology resulting in progressive cognitive and focal neurologic deficits, heterogeneous pathologic and neuroimaging features, and a variable response to immunosuppressive treatment.¹⁻⁴ The reversible cerebral vasoconstriction syndrome (RCVS)⁵⁻⁷ has been recognized as the most

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important mimic of PACNS that can be definitively distinguished by the presence of recurrent thunderclap headaches or other features.⁴ Brain hemorrhages can occur in both entities.^{8–10} In patients with RCVS, hemorrhages usually occur at onset and have been attributed to ischemic-reperfusion injury from the dynamic arterial caliber changes. The mechanism of hemorrhage in PACNS is related to necrotizing arterial wall damage; however, the timing of hemorrhage, risk factors, and clinical outcome are not adequately understood. In this study, we compared hemorrhagic and nonhemorrhagic PACNS and probed mechanisms. We show that hemorrhagic PACNS accounts for only 10% of all PACNS cases. Its occurrence as the first manifestation of PACNS is rare and invariably associated with exposure to sympathomimetic drugs; such cases may indicate a mechanistic overlap between PACNS and RCVS.

METHODS

Patients with PACNS were identified from 3 sources as described previously⁴: (1) personal cases from 1998–2015; (2) patients with diagnostic brain biopsy or autopsy, 2002–2015; and (3) discharge ICD-9 diagnostic code 437.4 (cerebral vasculitis) from 1993 onwards. Hospital records of all patients were reviewed in detail. We excluded patients diagnosed with systemic vasculitis (e.g., systemic lupus erythematosus), infective arteritis (e.g., varicella-zoster, Lyme, tuberculosis, syphilis, cryptococcus), moyamoya disease, intravascular lymphoma, cerebral vasospasm from aneurysmal subarachnoid hemorrhage, and RCVS. The final sample of 49 patients included 20 patients (41%) with pathologically proven PACNS and an additional 25 patients (51%) who fulfilled the diagnostic criteria proposed for PACNS,¹¹ namely (1) presence of an unexplained neurologic deficit after thorough clinical and laboratory evaluation; (2) documentation by cerebral angiography or tissue examination of an arteritic process within the CNS; and (3) no evidence of a systemic vasculitis or any other condition to which the angiographic or pathologic features could be secondary. Of these 25 patients, 16 had inflammatory CSF findings and 9 were diagnosed only on basis of abnormal angiography, which can be inaccurate; however, their inclusion was justified by the progressive clinical evolution over several months, consistent with PACNS. The final 4 patients (8%) fulfilled PACNS criteria (1) and (3) but not (2). They were included on the basis of abnormal CSF results, a clinical course highly consistent with PACNS, and multiple neurologic expert opinions providing consensus about the diagnosis.

Hospital records were reviewed to extract information on demographics, triggers, medical history, neurologic deficits, clinical course, and diagnostic test results. We analyzed the initial and follow-up MRI and cerebral angiograms performed during admission. Since our goal was to identify hemorrhagic presentations of PACNS, postdischarge scans were not analyzed. We recorded the lesion type as infarction or hemorrhage (parenchymal, subarachnoid, or subdural). Features such as leptomeningeal enhancement and white matter lesions were noted. We classified infarctions according to their number, location, and affected arterial territory. Parenchymal hemorrhages were classified according to location (lobar, deep, or cerebellar). Hemorrhagic presentation of PACNS was defined as the presence of any intracranial hemorrhage on the initial brain imaging study.

For statistical analysis, Mann-Whitney *U* and Fisher exact tests were used as appropriate. A value of $p < 0.05$ was considered statistically significant.

Standard protocol approvals, registrations, and patient consents

This retrospective study was approved by our hospital's Human Research Committee.

RESULTS

The mean age of the cohort was 51 ± 15 years (range 24–80, 13 men). Five patients (10%) had hemorrhagic PACNS (mean age 52 ± 14 years, 4 men). As shown in the table, patients with and without hemorrhage showed no differences in demographics and risk factors such as

Table Comparison of primary angiitis of the CNS with and without intracerebral hemorrhage

Feature	Hemorrhage (n = 5)	No hemorrhage (n = 44)	p Value
Age, y	52 ± 14	51 ± 15	0.917
Female	20	27	0.599
Headache	100	43	0.022
Thunderclap headache	60	0	0.001
Vasoconstrictive drugs	100	25	0.002
Serotonergic antidepressants	0	20	0.345
Sympathomimetic agents	100	7	0.001
Illicit agents	20	7	0.359
History of hypertension	20	25	0.644
Admission blood pressure >140/90 mm Hg	40	25	0.598
Systolic	160 ± 48	137 ± 27	0.097
Diastolic	99 ± 38	78 ± 16	0.023
Antiplatelet agents	60	23	0.109
Anticoagulant agents	20	5	0.281
Biopsy performed	80	73	0.599
Biopsy-proven cases	75	39	0.325
Eosinophils in brain biopsy (if done)	50	9	0.084
CSF examination performed	80	91	0.430
CSF abnormal ^a	40	52	0.480
Catheter angiogram performed	60	73	0.445
Catheter angiogram abnormal	40	55	0.655
MRI performed	100	100	—
Multiple disseminated infarct	80	61	
Multiple infarct and diffuse T2 lesions	0	23	
Isolated diffuse T2 lesions	0	4.5	0.001
Vasculitic mass lesion	0	7	
Isolated leptomeningeal vasculitis	0	4.5	
Length of stay, d	20 ± 10	20 ± 15	0.981
Glucocorticoid treatment	60	91	0.107
Cyclophosphamide treatment	40	61	0.325
Modified Rankin Scale score 0-3	80	75	0.644
Modified Rankin Scale score 4-6	20	25	

Values are mean ± SD or %.

^aAbnormal: leukocyte count ≥5 or protein level ≥80 mg/dL.

hypertension or exposure to antiplatelet agents. In all patients, extensive tests for alternate stroke etiology, including blood tests for infections and systemic rheumatologic conditions, proved negative. Several features were associated with hemorrhagic presentation: thunderclap headaches (exclusive to this group), sympathomimetic drug use (100% vs 7%, $p = 0.001$), and eosinophils in brain biopsy specimens. Patients with hemorrhage showed concurrent multiple disseminated acute infarcts but not the other types of lesions associated with PACNS, suggesting an acute vasculitic phenomenon.

While hemorrhagic strokes can occur in PACNS, brain hemorrhage as the first manifestation of PACNS is extraordinary.

Summaries of the 5 patients with hemorrhagic PACNS are presented below, and their imaging and pathology findings in the figure. Of note, 3 had onset with thunderclap headache and 4 had lobar hemorrhages on first presentation. All 5 patients reported exposure to sympathomimetic agents. Four were treated with immunosuppressants, and showed improvement.

PACNS

Patient A Two weeks after initiating daily intranasal oxymetazoline treatment for sinusitis, a 75-year-old man developed gradual-onset severe, persistent headache and recurrent spells of left face and arm spreading numbness and weakness. Admission examination showed normal blood pressure and mild left facial weakness. Brain MRI (figure, A.a–A.c) showed a small right frontal cortical hemorrhage with subarachnoid extension, and leptomeningeal enhancement over the right hemisphere. Head and neck CT angiography showed no vascular abnormality. CSF examination showed 60 leukocytes/mm³ (92% lymphocytes) and proteins 186 mg/dL (normal <60 mg/dL). Serial MRI over 3 months showed accumulating small acute infarcts and persistent leptomeningeal enhancement. Brain biopsy (figure, A.d) showed granulomatous angiitis with eosinophils and necrotizing angiitis but no evidence for amyloid deposition. He was treated with glucocorticoids and had prompt resolution of symptoms. Follow-up MRI showed resolution of the leptomeningeal enhancement and no new infarcts. Glucocorticoids were stopped. He has remained asymptomatic over the last 4 years.

Patient B A 55-year-old man developed a severe thunderclap headache with vertigo, photophobia, and right hemiparesis. His medical history included hypertension, diabetes, elevated body mass index (62.1), gastric bypass surgery, deep vein thrombosis with pulmonary embolism occurring 6 months before presentation, and fusiform dilation of the right vertebral artery detected 4 months before presentation. For 15 years he had consumed numerous over-the-counter diet pills containing ephedra, ma-huang, and amphetamines. He was on amlodipine, benazepril, aspirin, white-willow bark, nonsteroidal analgesics, and warfarin (started after the pulmonary embolism). Admission examination showed blood pressure 120/80 mm Hg, right gaze-evoked nystagmus, and ataxia. Head CT (figure, B.a) showed a right cerebellar hemorrhage. The admission international normalized ratio (INR) was 3.5; he was treated with vitamin K and fresh frozen plasma. Within hours after admission, he became somnolent with new right hemiplegia. Repeat INR was 1.9; head CT showed expansion of the cerebellar hemorrhage with tonsillar herniation. He underwent emergent posterior decompression. After initial recovery in the postoperative period, he suddenly worsened. Repeat INR was 1.2, and imaging (figure, B.b and B.c) showed a new left cerebellar hemorrhage and an acute left pontine infarction. Histopathologic examination of the surgically evacuated tissue (figure, B.d) showed marked multifocal vasocentric inflammatory lesions and features of necrotizing angiitis, and no evidence for amyloid deposition. CSF examination proved negative. He was treated with glucocorticoids and cyclophosphamide. His clinical examination improved progressively but 5 months later he died of urosepsis.

Patient C A 44-year-old woman with hypertension and chronic sinusitis developed 3 recurrent thunderclap headaches over a span of 2 days followed by confusion. Admission examination showed blood pressure 130/80 mm Hg and mild left arm weakness. Brain imaging (figure, C.a–C.c) showed a right parietal lobar hemorrhage with subarachnoid

Figure Neuroimaging and brain biopsy findings

Letters (A-E) correspond to patients A-E in the text. Patient A: Brain MRI shows a small right frontal lobar hemorrhage on susceptibility-weighted image (A.a), a small acute ischemic lesion adjacent to the right lateral ventricle on diffusion-weighted image (A.b), and leptomeningeal enhancement overlying the right temporal and occipital lobes on postcontrast T1 image (A.c). Leptomeningeal brain biopsy (A.d) shows granulomatous angiitis with eosinophilic infiltration. Patient B: Head CT (B.a) shows a right cerebellar hemorrhage; brain MRI after posterior surgical decompression shows the residual right cerebellar hemorrhage and a new left cerebellar hemorrhage on susceptibility-weighted image (B.b) as well as a new small acute pontine infarction on diffusion-weighted image (B.c). Histopathologic examination of the surgically evacuated tissue shows granulomatous necrotizing angiitis (B.d). Patient C: Brain MRI shows a right frontal lobar hemorrhage with subarachnoid extension (C.a) and a subacute right corona radiata infarction (C.b) on fluid-attenuated inversion recovery images, as well as scattered acute punctate infarcts on diffusion-weighted image (C.c). Brain biopsy shows showed lymphocytic and eosinophilic angiitis (C.d). Patient D: Brain MRI shows multiple lobar and subcortical hemorrhages on susceptibility-weighted image (D.a) and multiple scattered acute infarcts on diffusion-weighted images (D.b, D.c). Cerebral angiogram shows an irregular notched appearance of the branch arteries (arrows) consistent with arteritis (D.d). Patient E: Brain MRI shows simultaneous acute hemorrhages in right frontal and posterior temporal lobes (E.a) and left temporal lobe (E.b) on susceptibility-weighted images, and multiple scattered acute infarcts on diffusion-weighted image (E.c). Cerebral angiogram shows an irregular notched appearance of the branch arteries (arrows) consistent with arteritis (E.d).

extension, multiple disseminated small acute and subacute infarcts, and small rounded sulcal hyperintensities on fluid-attenuated inversion recovery sequence (dot sign). She had been on daily aspirin and twice-daily phenylpropanolamine for several years. CSF examination was normal. Transfemoral cerebral angiography showed a widespread irregular, notched appearance of distal branch arteries. Brain biopsy showed lymphocytic and eosinophilic infiltration within and around the arterial walls (figure, C.d) and no evidence of amyloid deposition. She improved clinically with glucocorticoid and cyclophosphamide therapy, and was discharged home. Immunosuppressive treatment was stopped after 3 months.

Patient D A 38-year-old man presented with a single thunderclap headache and blurred vision. Admission examination showed blood pressure 204/155 mm Hg, left homonymous hemianopia, and sensory loss. He was on aspirin and over-the-counter nasal decongestants containing pseudoephedrine. Brain MRI (figure, D.a–D.c) showed a 51-milliliter right temporal lobe hemorrhage with disseminated small acute infarcts and chronic microbleeds. CSF examination showed 7 leukocytes/mm³ and protein level 54 mg/dL. Transfemoral cerebral angiography (figure, D.d) showed a widespread irregular, notched appearance of distal branch arteries. An open right frontal brain biopsy showed normal parenchyma and blood vessels. His signs and symptoms improved spontaneously. Serial MRI showed no new lesions. He has remained asymptomatic over the last 4 years.

Patient E A 47-year-old man with ecstasy abuse and chronic hypertension complicated by retinopathy and nephropathy was admitted with headaches and confusion. Admission blood pressure was 220/122 mm Hg. Brain MRI showed disseminated small acute as well as chronic infarctions and multiple microbleeds in the cerebral and cerebellar hemispheres. He was assumed to have stroke from hypertensive microvascular disease and discharged on an antihypertensive treatment regimen. One year later, he was readmitted with headaches and confusion. The admission blood pressure was 220/129 mm Hg. Brain MRI showed multiple lobar hemorrhages, accumulating chronic small infarcts, new acute infarcts, and stable microbleeds (figure, E.a–E.c). Cerebral angiography showed irregular notched appearance of multiple distal cerebral arteries (figure, E.d). CSF was normal. His clinical examination remained stable and he was discharged.

During the course of the study, we encountered a patient with systemic vasculitis and brain hemorrhages (presumed hemorrhagic cerebral angiitis). Her summary is presented to show that in addition to hemorrhagic PACNS, vasoconstrictive drugs can potentially induce a hemorrhagic systemic vasculitis.

Systemic vasculitis

Patient F A 30-year-old woman with a new diagnosis of skin rash developed sudden, severe (thunderclap) headache, confusion, and visual-spatial deficits after consuming the first 2 doses of phen-fen (a combination of phentermine and fenfluramine) for treatment of obesity. Brain imaging showed a left parieto-occipital infarct with postischemic hemorrhage and multiple disseminated small acute infarcts. CSF examination was normal. Transfemoral cerebral angiography showed no vascular abnormalities. Skin biopsies showed a necrotizing granulomatous vasculitis affecting medium-sized vessels. A follow-up brain MRI showed hemorrhagic transformation of all the prior infarcts, and new ischemic lesions. A stereotactic biopsy of the left occipital lesion showed an organizing infarction. She improved clinically with a short course of glucocorticoid and cyclophosphamide therapy, and was discharged home.

DISCUSSION

Since the 1970s, vasoconstrictive drugs and over-the-counter agents (diet pills, cough and cold remedies, exercise supplements) have been associated with ischemic and hemorrhagic stroke

We propose the existence of a RCVS-PACNS overlap syndrome where intense or prolonged vasoconstriction from sympathomimetic drugs induces vascular inflammation.

from diverse mechanisms including vasoconstriction and necrotizing angiitis.^{12–17} In 2000, the Food and Drug Administration withdrew phenylpropanolamine from the market due to its association with brain hemorrhage. Yet other vasoconstrictive agents remain available and have been associated with stroke.^{18–20} In this single-center study where stringent criteria were used to identify patients with PACNS, exposure to sympathomimetic agents was the only plausible risk factor and was documented in all patients with hemorrhagic PACNS.

We have previously documented similarities between our pathologically proven and unproven PACNS cases,⁴ supporting the accuracy of PACNS diagnosis in the entire cohort. All met the widely used criteria for PACNS.¹¹ Among the 5 cases with hemorrhagic PACNS, 3 were biopsy-proven and 2 had typical features of PACNS⁴ (positive angiography with irregular notched appearance and typical imaging or CSF findings). One patient had prior infarcts and cerebral microbleeds and the others presented with hemorrhage. It was the hemorrhagic stroke that led to the diagnosis of PACNS in all 6 patients. In patient A, symptoms and imaging findings raised the possibility of cerebral amyloid angiopathy-related inflammation (CAA-ri) or β -amyloid-related angiitis (ABRA); however, brain biopsy showed no evidence for amyloid deposition. Patient E had chronic hypertension, which is associated with deep parenchymal hemorrhages (rarely multiple^{21,22}) but not multiple simultaneous lobar hemorrhages.

While hemorrhagic strokes can occur in PACNS,^{3,9,23} brain hemorrhage as the first manifestation of PACNS is extraordinary. It has been described in only 2 previous case reports.^{24,25} In a series of 131 patients, 16 (12.2%) developed brain hemorrhage within 3 months after the diagnosis of PACNS was established; however, the number with hemorrhage as the first manifestation was not reported.⁹ Of note, necrotizing vasculitis was documented in 3 of the 4 patients with biopsy-proven hemorrhagic PACNS in that report.⁹ A multicenter cohort study of 51 patients with PACNS found macrohemorrhages in 10 patients (20%) and microbleeds in 4 patients; however, the timing of hemorrhage is not provided.³ Vasoconstrictive drug exposure history was not reported in any of these publications. In our series, sympathomimetic drug exposure was significantly higher in patients with hemorrhage, and pathology showed necrotizing angiitis with eosinophils, suggesting a possible drug reaction. While other mechanisms (hypertension, platelet dysfunction, anticoagulation) may have partly contributed, our data suggest that sympathomimetic drugs induce a necrotizing angiitis that can develop rapidly and culminate in brain hemorrhage, frequently heralding PACNS.

A subtype of PACNS, ABRA, is associated with brain hemorrhages and hemorrhage can rarely be its first manifestation.²⁶ Unlike the frequent mass lesions and white matter changes described in this entity, our patients with drug-induced PACNS had multiple scattered acute infarcts, and 3 had multifocal hemorrhages occurring together or in close proximity. Indeed, multiple simultaneous nontraumatic lobar hemorrhages are a rare phenomenon associated with only a handful of conditions, namely RCVS, acute myeloid leukemia, bacterial endocarditis, cerebral amyloid angiopathy (including ABRA and CAA-ri), ataxia-telangiectasia, cerebral sinovenous thrombosis, acute hemorrhagic leukoencephalitis, brain metastases (e.g., melanoma), cavernous malformations, and Churg-Strauss syndrome. Drug-induced necrotizing PACNS should be added to this list, and a careful history of drug exposure elicited in such patients.

Four patients had thunderclap headache (recurrent in one), and all improved promptly with or without immunosuppressive therapy. These features suggest an alternate diagnosis of RCVS, a condition where up to 40% harbor brain hemorrhages that are frequently present on initial imaging. However, the concurrent small, widely disseminated infarcts that were not restricted to watershed regions, and the irregular, notched appearance of distal arteries, were more consistent with PACNS.⁴ We propose the existence of a RCVS-PACNS overlap syndrome where intense or prolonged vasoconstriction from sympathomimetic drugs induces vascular inflammation. Indeed, a published case of PPA-associated ICH also had thunderclap headache and angiographic changes resembling RCVS, and subsequent brain biopsy showed angiitis.²⁵ The vasoconstriction–vasculitis overlap mechanism has been suggested in another patient with postpartum angiopathy or RCVS.²⁷ These cases represent the rare minority of patients where distinction between RCVS and PACNS remains truly challenging. Interestingly, this syndrome appears to be related to sympathomimetic rather than serotonergic drug use, which is more common in RCVS, suggesting mechanistic differences related to neurotransmitter systems.

Our observations have important clinical implications. First, it is important to elicit a careful history of vasoconstrictive medications and over-the-counter agents in patients with cerebrovascular events, especially when imaging reveals simultaneous infarcts and hemorrhages, or multifocal hemorrhages. If exposure exists, the offending agent should be discontinued and the patient counseled about risks. Immunosuppressive therapy may be beneficial; however, hemorrhagic PACNS appears to be self-limited, so long-term therapy may not be warranted. It remains unclear whether the risk is idiosyncratic, or dependent upon the dose and duration of exposure, and whether there is a risk with re-exposure. Further studies are warranted to evaluate the risk and safety profile of common and often innocuous vasoconstrictive agents.

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AUTHOR CONTRIBUTIONS

Study concept and design: Drs. Topcuoglu and Singhal. Acquisition of data: Drs. Topcuoglu, Jha, Frosch, and Singhal. Analysis and interpretation of data: Drs. Topcuoglu and Singhal. Drafting of the manuscript: Drs. Topcuoglu and Jha, J. George, and Dr. Singhal. Critical revision of the manuscript for important intellectual content: Drs. Topcuoglu, Jha, and Frosch, J. George, and Dr. Singhal. Study supervision: Dr. Singhal.

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