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Cyclophosphamide for Suspected Primary Angiitis of the Central Nervous System in a Patient with Human Immunodeficiency Virus: A Case Report

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ABSTRACT

Introduction: Central nervous system (CNS) vasculitis is rare, including in human immunodeficiency virus (HIV), occurring in less than 1% of patients. Systemic vasculitis affecting the CNS is termed secondary CNS vasculitis, whereas primary CNS vasculitis, referred to as primary angiitis of the CNS (PACNS) refers to an extremely rare disease specifically confined to the CNS. Only some cases of PACNS in HIV patients have been reported in literature.
Case Report: We report a case of a 46-year-old female with HIV who developed probable primary CNS vasculitis, which was treated with intravenous cyclophosphamide and glucocorticoids for both induction and maintenance. A systematic literature review regarding PACNS and its therapeutic management is presented in this report. There were no clinical trials for PACNS. Based on the American Academy of Neurology (AAN) classes of evidence for therapeutic effectiveness, most data is of intermediate or weak strength.
Conclusion: This case highlights diagnostic and clinical features of PACNS and provides an overview of the current literature regarding pharmacotherapy. Further case reports and additional studies are needed.

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Keywords: Primary angiitis, PACNS, HIV, Cyclophosphamide, Primary CNS vasculitis

How to cite this article

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INTRODUCTION

Primary angiitis of the CNS (PACNS), also referred to as primary CNS vasculitis (PCNSV), CNS vasculitis, and previously, cerebral or primary granulomatous angiitis, is an extremely rare but serious disease with an incidence of 2.4 cases per one million person-years [1–3]. PACNS, unlike other vasculitides, is confined to the CNS. HIV is associated with various systemic vasculitides, from small to large vessel, immune-mediated to infectious. However, PACNS is less common than any systemic vasculitis in both the general population as well as in patients with HIV [4]. After an extensive literature review only a few case reports of PACNS in HIV patients have been identified [5, 6]. Further, in view of diagnostic advances and updated classification, it is uncertain if these cases represent true PACNS [7].

PACNS remains a diagnostic challenge as presentation varies from patient to patient and can range from strokes to chronic headaches. It occurs with the same frequency in men and women with a median age of 50 years and may occur in both adult and pediatric patients [8, 9]. However, the presentation and treatment in pediatric patients differs from that of adults [2, 8]. Therefore, this review is limited to adult patients with PACNS.

The disease is characterized by inflammatory infiltrates composed of lymphocytes, together with necrosis limited to the medium and small vessels of the CNS. The Calabrese diagnostic criteria were developed over 20 years ago, however, MRI scan and pathology are the best diagnostic tools as clinical findings are non-specific and blood tests are usually normal [10]. Recently, subtypes of PACNS have been identified; however, classification remains a challenge [11]. Morbidity and mortality are associated with cerebral infarctions and involvement of large vessels. The prognosis has improved since 1983, when Cupps et al. reported success using a combination of cyclophosphamide and glucocorticoids [12].

Today, treatment includes glucocorticoids and cyclophosphamide, as it remains difficult to predict which patients would do well with glucocorticoid monotherapy [3, 12]. Cyclophosphamide has been shown to improve survival [12]. The optimal duration of treatment is unknown for this off-label use. Outcome is variable with some patients fully recovering and others experiencing permanent neurological damage. Toxicities associated with cyclophosphamide include urothelial toxicity such as cystitis, hematuria, bladder cancer, and infertility. Glucocorticoid toxicity includes bone loss, osteoporosis, diabetes mellitus, and Cushing 's syndrome.

In patients intolerant to cyclophosphamide or those who respond poorly to the drug, rituximab has been used [2, 13]. Some patients receive weekly intramuscular methotrexate maintenance therapy. Other alternatives include azathioprine, chlorambucil, tocilizumab, cyclosporine, aspirin, tumor necrosis factors (infliximab and etanercept), and mycophenolate mofetil [1, 14–16].

We report a case of probable PACNS in a patient with HIV treated successfully with cyclophosphamide and pulse corticosteroids. Additionally, we conducted a systematic literature review for PACNS and evaluated the strength of the evidence using modified American Academy of Neurology (AAN) classes of evidence for therapeutic effectiveness criteria [17].

CASE REPORT

A 46-year-old female was admitted for headache, vertigo, and an altered mental state. For several days prior to presentation, she developed increasing confusion and forgetfulness. She showed anterograde amnesia and was not oriented to day or time. Her past medical history included type 2 diabetes mellitus, HIV, hypertension, depression, and vertigo. Her home medications were metformin 500 mg twice daily, insulin glargine 10 units SQ nightly at bedtime, benazepril 20 mg once daily, amlodipine 10 mg once daily, escitalopram 10 mg once daily, atorvastatin 20 mg once daily, dolutegravir 50 mg once daily, lamivudine-abacavir 300 mg/600 mg once daily, and sulfamethoxazole-trimethoprim 800 mg/160 mg once daily. She also had a tooth extraction and a cold several days prior to the onset of her presenting symptoms. Her social history was positive for former illicit substance abuse. In the emergency department, she received acetaminophen 650 mg and meclizine 25 mg for symptom management. Her initial coagulation studies, complete blood count, and chemistries were unremarkable except for mild hyperglycemia (118 mg/dL, N 74–106), hyperbilirubinemia (2.4 mg/dL, N 0.2–1.3), and an ESR of 48 mm/hr (N 0–24). The patient's CD4 count was 1026 cells/mm^3, hemoglobin A_1C was 7.8, and vitamin B_{12} and TSH were within normal limits. At this time the patient's weight was 93 kg. Her initial neurologic evaluation was non-focal apart from altered mentation. She was admitted while a broad infectious and inflammatory workup commenced.

A non-contrast computed tomography (CT) scan of the head revealed a right occipital hypodensity with minimal mass effect on the adjacent brain parenchyma and no evidence of midline shift, most consistent with subacute infarct, and was otherwise unremarkable appearing.

Subsequent brain magnetic resonance imaging (MRI) scan with and without contrast revealed acute infarcts in multiple vascular territories, including infarcts in the right middle cerebral artery distribution, left paramedian pons, bilateral occipital lobes, as well as punctate infarcts in the posterior left frontal lobe (Figures 1 and 2). Vascular imaging revealed severe proximal basilar artery stenosis, bilateral distal vertebral artery stenosis, and moderate bilateral internal carotid artery cavernous stenosis. A lumbar puncture was performed and a cerebrospinal fluid (CSF) analysis was unrevealing apart from lymphocytosis. Though a broad infectious workup was negative, her clinical status worsened, and she was started on cyclophosphamide for presumed CNS vasculitis. Subsequent MRI scan revealed new infarcts in the inferior right cerebellum in the distribution of the right posterior inferior cerebellar artery, as well as in the splenium of the corpus callosum, expansion of infarcts in the right paramedian pons and corpus callosum, and hemorrhagic conversion of the right occipital infarct.

A conventional angiogram was consistent with vasculitis, and even though a brain biopsy was performed, it did not capture a representative area of inflammation that was seen on MRI. While tissue diagnosis is considered the gold standard, repeat biopsy was not pursued, as the risks did not outweigh the benefits given the clinical context, high pretest probability, and her response to treatment. Therefore, she was diagnosed with probable PACNS based on her fulminant course with multiple successive strokes in the

setting of lymphocytic CSF pleocytosis, conventional angiogram consistent with vasculitis, and absence of systemic vasculitis. Furthermore, she was stabilized after prolonged course of high dose steroids with additional pulse dose cyclophosphamide. Additionally, her HIV was controlled, with a CD4 count of 1026 cells/mm^3, and she was kept on daily pneumocystis jiroveci prophylaxis with sulfamethoxazole-trimethoprim.

At the time of submission of this report, the patient had received three cycles of cyclophosphamide therapy. During the first cycle the patient received intravenous cyclophosphamide 1000 mg after hydration with 0.9% NS, and premedication with ondansetron 16 mg IVPB for nausea. The patient was started on prednisone 80 mg once daily at the start of cyclophosphamide therapy, which was continued upon discharge. Approximately four weeks later, the patient was admitted again for the second cycle of the same regimen. An MRI scan during this admission showed stable infarcts compared to baseline. The patient received the same premedication and intravenous hydration as in cycle one. Approximately four weeks after the second cycle, the patient was admitted for cycle three, consisting of the same regimen as before. At this time she was deemed to be neurologically stable and responding well to treatment.

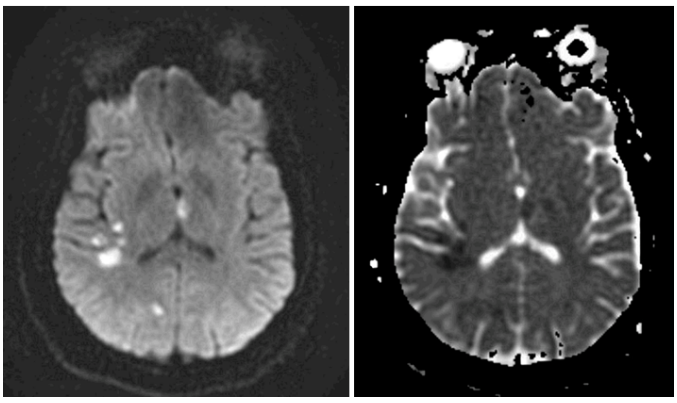

Figure 1: MRI brain diffusion imaging (DWI left, ADC on right) revealing diffusion-positive strokes in multiple vascular territories.

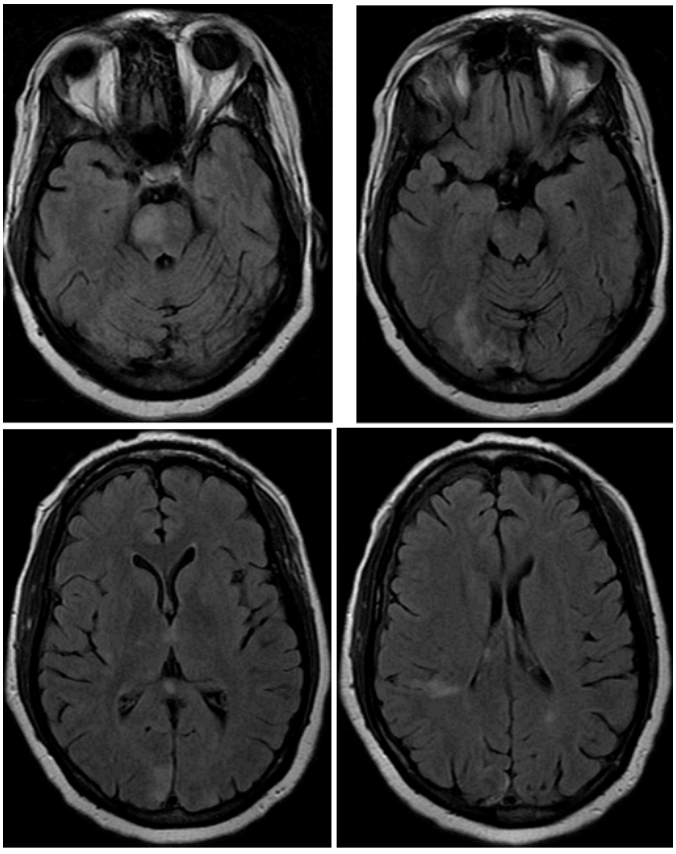

Figure 2: MRI brain (axial FLAIR slices) revealing multiple areas of hyperintensity.

DISCUSSION

Central nervous system vasculitis can be classified as primary or secondary [3, 18, 19]. It is primary when there is no other involvement than the CNS and secondary when it occurs with other inflammatory or systemic conditions such as connective tissue diseases, autoimmune or infectious diseases such as polyarteritis nodosa, systemic lupus erythematosus, varicella zoster, and HIV [9, 18]. The precise causes and pathogenesis of PACNS are unknown.

Our patient was HIV positive but had no evidence of systemic vasculitis or systemic symptoms such as fever, weight loss, or malaise. Furthermore, there was no alternative etiology to PACNS. HIV itself can cause vasculitis, though this occurs as a consequence of opportunistic infections such as cytomegalovirus, meningitis, and mycobacterium avium [4, 9]. The vasculitis is thought to be mainly the result of an immune response. A pathogenic mechanism in HIV may be interaction of T cell mediated cells, superantigens, adhesion molecules, immune complexes, cytokines, and growth factors [4, 20].

Secondary CNS vasculitis such as infections (e.g. neurosyphilis), systemic vasculitis, and connective tissue disease should be ruled out in cases of suspected PACNS. Our patient did not have clinical or laboratory evidence of such processes, e.g. the anemia, thrombocytopenia, elevated liver enzymes, and low complement typically associated with systemic vasculitis [21]. Infectious causes of vasculitis were ruled out prior to placing the patient on cyclophosphamide, which is immunosuppressive.

Diagnostic criteria for PACNS were suggested in 1987 by Calabrese and Mallek [21]. The differential diagnosis is broad and includes reversible cerebral vasoconstriction syndromes and systemic vasculitis [10, 22]. Reversible vasoconstriction syndrome may be associated with medications, hypertension, eclampsia or the postpartum period, and is the most common mimicker of PACNS. Other mimickers are listed in Table 1 [3, 21, 22–26].

Our patient presented with cognitive impairment and headache, which constitute the two most common

presenting symptoms, however, they are non-specific and made diagnosis difficult. Focal neurological deficits a common presenting symptom due to acute ischemic events, were absent on initial presentation. Subsequent cerebrovascular imaging was consistent with cerebral vasculitis. Clinical features of PACNS are listed in Table 2 [3, 10, 24, 25, 27–29].

Our patient had involvement of the vertebral and basilar arteries, a feature commonly reported with CNS vasculitis [15]. Multiple ischemic infarctions visible on MRI, which occur in 53% of patients, and intracranial hemorrhages which occur in 9% of cases, were found in our patient as well [1, 3]. Hemorrhage is caused by vasculitis-induced blood vessel weakening or aneurysm formation [24]. Thus, our patient can be included in the most ominous subset of patients, i.e., rapidly progressive PACNS.

A literature search was performed to retrieve all publications describing medications used to treat PACNS. The search was conducted in PubMed (1966–March 2016), EMBASE (1980–2016), Ovid and the Cochrane Library, and Google Scholar using the search terms “primary angiitis”, “primary vasculitis”, “PACNS”, “PCNSV”, and “primary cerebral or granulomatous vasculitis”. No language or date restrictions were considered. The FDA website was utilized for identification and review of the latest prescribing information [30]. Included were randomized controlled trials, cohort and case control studies, professional guidelines or recommendations, case reports, case series, and studies conducted on small numbers of patients. Preclinical and chemical screening studies, review articles (other than Meta-analysis or systematic reviews), letters to the editor, editorials, and commentaries were excluded. For each article identified, a second search was conducted both in the databases above as well as by reviewing the bibliography to locate additional articles. We included all reports of patients more than or equal to 18-year-old.

To identify the strength of the evidence regarding treatment for PACNS and evaluate evidence quality, a modified AAN level of evidence classification for therapeutic intervention was employed [17] using a three-tiered system (i.e., strong, intermediate, weak). Strong evidence involved prospective randomized controlled trials or prospective matched group cohort studies directly relevant or inclusion in a Guideline. Intermediate evidence involved conflicting data in randomized clinical trials or cohort studies, case-control studies, evidence in the form of small or pilot trials or case series, or consensus recommendation in the absence of relevant clinical trials and better evidence than case reports. Weak evidence involved isolated or anecdotal case reports, expert opinion or where strong or intermediate evidence failed to include dosages, relapse details, or patient outcomes.

Excluded was secondary vasculitis use or narrative review articles or where the only available literature regarding the use pertained to pre-clinical studies.

Table 1: PACNS- The Great Masquerader- Conditions Mimicking PACNS

Infections Associated With CNS Vasculitis	
Viral (Human immunodeficiency virus, varicella-zoster, cytomegalovirus)	*Mycoplasma pneumoniae*
Hepatitis	*Borrelia burgdorferi*
Bacterial endocarditis	*Mycobacterium tuberculosis*
Acute bacterial meningitis	*Rickettsia* spp. (Rocky Mountain spotted fever, typhus)
Bartonella spp.	Fungal infections (aspergillosis, coccidiomycosis, candidiasis)
Subarachnoid cysticercosis	Neurosyphilis
Systemic Vasculitides	
Lymphoma (especially Hodgkin’s disease)	Kawasaki disease
Polyarteritis nodosa	Giant cell arteritis
Henoch-Schonlein purpura	Takayasu’s arteritis
Wegener’s granulomatosis	Churg-Strauss syndrome
Antineutrophil cytoplasmic antibody-associated vasculitis	Behçet disease
Hypocomplementemic urticarial vasculitis	
Connective Tissue Diseases	
Neuropsychiatric lupus	Mixed connective tissue disease
Rheumatoid arthritis	Dermatomyositis
Sjogren’s syndrome	Storage diseases
Inflammatory bowel disease	Systemic lupus erythromatosis
Sarcoidosis	Cogan syndrome
Morphea or linear scleroderma	
Miscellaneous	
Drug-induced cerebral vasculitis—thiouracil, allopurinol, minocycline, penicillamine, carbamazepine, phenytoin, methotrexate, isotrentino, heroin, cyclosporine, sympathomimetics such as cocaine, ergotamine, ephedrine, amphetamine, oxymetazoline, phenylpropanolamine)	Graft versus host disease

Moyamoya syndrome	Sneddon syndrome
Reversible posterior leukoencephalopathy syndrome	MELAS (Mitochondrial encephalomyopathy, lactic acidosis, stroke)
Degos disease	Amyloid angiopathy
Fabry's disease	Pseudoxanthoma elasticum
Lipohyalinosis	Postpartum angiopathy
Atypical multiple sclerosis	Optic neuritis
Call—Fleming syndrome	CADASIL
Migrainous vasospasm	Susac syndrome
Whipple's disease	CNS malignancy-related angiitis
Rasmussen encephalitis	Hodgkin's and non-Hodgkin's lymphoma
Radiation vasculopathy	Intracranial dissection
Fibromuscular dysplasia	N-methyl-o-aspartate receptor-mediated encephalitis

Table 2: Clinical and Diagnostic Characteristics of PACNS

Signs & Symptoms, Lab and Imaging Findings	Percentage	Our Patient
Headache	63	+
Cognitive Impairment	50	+
Hemiparesis	44	-
Stroke	40	+
Aphasia	28	-
Transient ischemic attacks	28	-
Ataxia	19	-
Seizures	16	-
Dysarthria	15	-
Blurred or decreased visual acuity	11	-
Intracranial hemorrhage	<10%	+
Amnesic syndrome	<10%	+
Lymphomonocytic pleocytosis	>90%	+
Brain biopsy evidence	75%	+
Mass lesions	15%	-
Spinal cord involvement	5%	-
Elevated ESR	<25%	+
Abnormal brain CT	50-60%	+
Abnormal MRI	75%	+

Table 3: Published Clinical Research of PACNS in Adults

Drug	Results	Strength of Evidence	Reference
N = 163 patients G alone- IV M 1 g (3–17 pulses, median 5), then P 60 mg/day (median) for 0.4–107 mo (median 9 mo) N Therapy 72 P + C 2 C 51 C PO 150 mg/day (1–33 mo) 23 C IV 1000 mg/mo (1–17 mo) Azathioprine 100 mg/day (range 100–150 mg/day) for 0.4–76 mo (median 11 mo) + P (6 patients) Mycophenolate 2,000 mg/day (median) + P (3 patients) Rituximab 2 injections (1 patient)	Favorable response 85% P alone; 80% C + P C + P; increased mortality rate 27% of patients relapsed Relapse less frequent in patients treated with C + P versus P alone (OR 2.9) Higher disability scores and poor response to treatment associated with increasing age at time of diagnosis (OR 1.44), cerebral infarctions (OR 3.74), large vessel involvement (OR 6.14)	-Intermediate evidence - Cohort study (retrospective) (mostly same patients as cohort below- study extension)	Salvarani 2015
N = 101 patients (over 21 years old period) 97 G -25- 1 g M -72- 60 mg P daily 49- I -46 C PO 150 mg/day or IV 1 g/m² -3 azathioprine	Favorable response 81%- G alone 85% - G + I Relapses occurred in 25%	-Intermediate evidence -Retrospective chart review (could not conclude if necessary as group may have initially had more severe disease)	Salvarani 2007

Table 3: *(Continued)*

N= 52 - G (all but 1)- 7 as monotherapy (M for 3 pulses 250–1000 mg, then P 1 mg/kg for 23 mo - 44 (85%) C (Pulse IV 0.6–0.7 g/m² Q2–4 wks for 3 pulses, then monthly for up to 12 pulses) - 43 C+ G; 1 C alone - Rituximab- 1 pt 375 mg/m² weekly for 4 infusions (for C refractory disease) - Azathioprine- after C induction- 22 pts; 2 mg/kg/day -Methotrexate- 1 pt after induction -Mycophenolate- 1pt after induction	Favorable response 32/49 pts (65) Relapse 13/49 (27%) Death 3 (6%) Rituximab effective for C refractory disease Patients receiving methotrexate or mycophenolate remained free of disease Neurological damage persisted for 82% of pts	Intermediate evidence Cohort study	De Boysson 2014
M + C IV; 12 mo therapy (no dosages provided)	Initial response to M followed by relapse at 3 weeks	Weak evidence Case report	Rosenberg 2013
C IV + M (twice only-patient lost to follow-up) (dosages not provided)	Beneficial effect; no relapse at 2 mo	Weak evidence Case report	Bajij 2015
N=4; C + G		Weak evidence Case reports (4)	Cupps 1983
Rituximab (2 IV doses of 1 g 2 weeks apart) + P (60 mg/day); P continued for 8 mo- lowered to 20 mg/day; maintenance therapy with methotrexate IM 15 mg weekly for 5 mo + P 10 mg/day	No relapses at 13 mo Methotrexate discontinued because of nausea and vomiting	Weak evidence Case report	Salvarani 2014
TNF blockers- patients resistant to G + C Infliximab 5 mg/kg single infusion Etanercept 50 mg/week (for 20 mo); then 25 mg once weekly (for 8 mo)	Rapid/effective improvement Etanercept arrested relapse No relapses at 34 and 60 mo	Weak evidence Case reports (2)	Salvarani 2008
N= 15 No dosages reported. 8 patients on G, 2 patients also on C (others not reported)	1 patient on C+G improved after 4 mo 1 patient on C+G died after 2 weeks 5 improved; 3 with residual effects such as cortical blindness and confusion	Weak evidence Case series	Lie 1992

C = cyclophosphamide
P= prednisone PO
M= methylprednisolone IV
G= glucocorticoids
I= immunosuppressants

Most of the medications have only intermediate or weak evidence consisting of several small retrospective cohort studies and case reports (Table 3). The vast majority of literature pertains to systemic or secondary vasculitis with PACNS treatment recommendations derived from systemic vasculitis. No clinical trials in PACNS have been conducted. There is one cohort of 101 patients and a second cohort that extends the follow-up and includes some additional patients (N=163) [1, 2]. These cohorts constitute intermediate evidence. All other literature retrieved regarding PACNS pharmacotherapy pertains to weak evidence.

Cyclophosphamide and glucocorticoids remain the standard of care. Cytotoxic agents have been used for CNS vasculitis for decades based on therapeutic protocols in systemic vasculitides, anecdotal reports and cohort studies with favorable results [12]. The use of cyclophosphamide was first described in 1978 for use in secondary vasculitis [31]. The mechanism appears to be autoantibody suppression. However, no clinical trials have been conducted and it is unknown whether cyclophosphamide is the most effective and least toxic cytotoxic agent.

There is controversy regarding whether to administer glucocorticoids as monotherapy or to add cyclophosphamide. In 163 patients with PACNS, a favorable response was observed in 80% of patients treated with prednisone and cyclophosphamide versus 85% in patients treated with prednisone alone [2]. Prednisone alone was associated with more frequent relapses but relapses were not associated with rapid therapy withdrawal. It was noted that cerebral infarcts were associated with poor treatment responses. Predominant involvement of medium-sized vessels, as in our patient, may be less likely to respond to glucocorticoid monotherapy [25]. In addition to the presence of cerebral infarcts, large vessel involvement, focal neurological deficits and cognitive impairment are associated with increased mortality [1].

Prednisone should be initiated as soon as the diagnosis of PACNS is made at a single or divided dose of 1 mg/kg/day orally. If the patient does not respond promptly, cyclophosphamide should be added. In life-threatening or severe/progressive cases and/or for disease flares, pulse parenteral methylprednisolone at 1 g for three days may be used but no evidence exists this is more effective than oral prednisone [3].

In addition to controversy over whether to add C, controversy also exists as to whether cyclophosphamide should be given as continuous oral therapy or intravenous pulse therapy and no trials have been conducted to answer this question. The goal of pulse therapy is to minimize cyclophosphamide exposure. In systemic vasculitis trials, intravenous cyclophosphamide was as effective and produced less leucopenia than oral cyclophosphamide in inducing remission [31, 32]. Relapse rates were not reported in either study [31, 32]. In another study, a higher relapse rate was observed with IV pulse use and adverse effects were more frequent with continuous oral cyclophosphamide [33]. However, that study investigated relatively short courses of treatment. There is some evidence that prolonged treatment with low-dose pulse cyclophosphamide for 18–24 months may reduce the rate of relapse [34]. Again, all these studies are in systemic vasculitis, not PACNS.

The pulse dose is monthly infusions of 15 mg/kg or 500 to 1000 mg/m^2 [24, 35]. The median oral dose of cyclophosphamide has been reported to be 150 mg/day with a range of 75–150 mg/day for a median duration of seven months with a range of 1–33 months [2]. An oral dosage of 2 mg/kg/day is frequently used. While the results of those trials are inconclusive, in other vasculitides, oral cyclophosphamide was successful when given for 3–6 months. Dosages should be adjusted for age and renal dysfunction [3].

Cyclophosphamide may result in life-threatening infections, cancer (particularly of the bladder or secondary lymphomas), hemorrhagic cystitis, and infertility. Bladder toxicity and myelodysplastic syndrome greatly increase with cumulative doses > 30 g [35]. Carcinoma of the renal pelvis was reported in a patient receiving long-term cyclophosphamide for cerebral vasculitis [36]. Immunosuppression from cyclophosphamide can result in serious, sometimes fatal infections and the degree of neutropenia correlates with reduced resistance to infections. Patients should receive pneumocystis prophylaxis with oral sulfamethoxazole/trimethoprim. Other supportive therapy includes antiemetics and normal saline hydration. While plasmapheresis is ineffective, intravenous immunoglobulin (IVIG) has been successful in some refractory patients [37].

While glucocorticoids remain the standard of care for remission, in patients unable to take cyclophosphamide, rituximab at a dose of 1 gm for two doses administered two weeks apart has been used. A double blind randomized trial in systemic vasculitis comparing rituximab to cyclophosphamide, found rituximab non-inferior to cyclophosphamide for remission induction and more effective for inducing remission of relapsing disease (67% versus 42%, p=0.01) [38].

After induction, many advocate switching to a low risk immunosuppressant to minimize cyclophosphamide exposure [3, 24, 29, 39]. The induction-maintenance strategy has been used in secondary vasculitis using azathioprine at 1–2 mg/kg/day [40]. In a recent study, azathioprine was used in 25% of patients for maintenance therapy, following cyclophosphamide induction. However, in PACNS a treatment course for 12–18 months, preferably 18, is used in most patients assuming relapses do not mandate prolonged therapy [3, 21]. Some continue maintenance therapy for 2–3 years [22]. Other agents include methotrexate at 20–25 mg/week, or mycophenolate mofetil at 1–2 g/day once remission has been obtained [3]. Comparison of methotrexate and azathioprine in patients with systemic vasculitis have not shown either to be superior, however, methotrexate does not penetrate the CNS well [29]. Methotrexate dosage should be reduced in patients with severe renal impairment [41].

In treatment-resistant cases, tumor necrosis factor α blockers (e.g. infliximab 5 mg/kg or etanercept 50 mg/week) and mycophenolate mofetil (2 g/day) have been used. A relapse rate of approximately 25% may occur with serial MRI scan or MRA follow-up at 4th–6th week and at 3rd–4th month intervals thereafter [3, 16, 25].

CONCLUSION

Primary angiitis of the central nervous system is a rare but serious disease that presents both diagnostic and therapeutic challenges. Favorable neurological outcome is a realistic goal. Knowledge regarding the epidemiology, pathogenesis, diagnosis and management continues to evolve. Optimal management remains uncertain. Pulse cyclophosphamide treatment and identification of patients to initially receive immunosuppressant therapy and alternatives require further investigation.

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Author Contributions

Martha M. Rumore – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Samantha Su – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Jake Pellinen – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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