

WHAT IS YOUR CALL?

Cognitive decline in an older physician

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Competing interests:

Gregory Day is the recipient of a Future Leaders in Dementia award, including support for travel (Pfizer Canada). Simon Carette is a collaborator on a grant from the National Institutes of Health in his role as Site Principal Investigator of the Vasculitis Clinical Research Consortium. David Tang-Wai holds a grant with the Weston Foundation, and is a collaborator on grants from the Canadian Institutes of Health Research, Alzheimer Society of Canada, Parkinson Society Canada and the Michael J. Fox Foundation.

This article has been peer reviewed.

The authors have obtained patient consent.

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CMAJ 2015. DOI:10.1503/
cmaj.140589

A 78-year-old right-handed physician with hypertension and dyslipidemia presented to the emergency department with progressive memory impairment and acute onset of left-sided weakness. His only medication was daily low-dose acetylsalicylic acid. His family reported that cognitive difficulties began four months before presentation, when he was noted to be physically and cognitively slower, and suddenly “forgot” how to electronically document patient encounters. Over the following four weeks, geographic disorientation in familiar surroundings and dressing apraxia developed. He began to repeat questions and misplace possessions. He retired from clinical practice and ceased driving. He was assessed by his primary care physician two weeks before presentation to the emergency department: normal performance on the Mini-Mental State Examination (29/30) and shuffling gait were documented.

He was admitted to the general medicine service for further evaluation. Physical examination showed stable vitals. The patient was alert, with fluent speech, but was disoriented to place. A left facial droop, hemiparesis and pronator drift were noted. Nonenhanced computed tomography (CT) of the brain and screening blood tests, including fasting glucose and lipids, were normal.

Neurology consultation was obtained the following day. The patient’s score on the Mini-Mental State Examination had decreased to 21/30, with deficits in executive function and memory. Evaluation with the Montreal Cognitive Assessment yielded a final score of 6/30, with prominent deficits in all domains except for naming. On neurologic examination, the patient had left-sided hyperreflexia with flexor plantar responses, cogwheel rigidity at the left wrist, asymmetric bradykinesia and shuffling, “magnetic” gait. The left facial droop and hemiparesis, documented hours before, had resolved, but the pronator drift persisted.

What is the most likely cause of the patient’s symptoms and signs?

- Alzheimer dementia
- Right-sided vascular infarction(s)
- Multi-infarct (vascular) dementia

- Primary central nervous system vasculitis (also known as primary angiitis of the central nervous system)
- Other (rare) causes of rapidly progressive dementia (e.g., Creutzfeldt–Jakob disease, limbic encephalitis)

Right hemispheric cortical and subcortical lesions were suspected based on the history of visuospatial disorientation, dressing apraxia and the clinical examination confirming left-sided pyramidal and extrapyramidal findings. However, the impairment of language observed on cognitive testing raised the possibility of left-sided involvement. Although the subacute timing of presentation and the step-wise accrual of deficits were compatible with multi-infarct dementia, no infarction was identified on brain CT, decreasing the likelihood of large or medium vessel infarction. The fluctuation in neurologic signs noted between presentation and reassessment within 24 hours raised the possibility of transient interruptions in cerebral blood flow, which may be seen in conditions characterized primarily by vascular inflammation. In the absence of systemic symptoms and signs of connective tissue disease to suggest systemic vasculitis, vasculitis limited to the central nervous system was proposed as the most plausible diagnosis (d).

What is the next investigation?

- Computed tomography of the brain with angiography
- Magnetic resonance imaging (MRI) of the brain with angiography
- Digital subtraction cerebral (conventional catheter-guided) angiography
- Cerebrospinal fluid analysis
- Measurement of serum markers of connective tissue disease

Urgent MRI of the brain with angiography was requested (b), not only to detect small areas of infarction or hemorrhage that likely were overlooked on imaging with nonenhanced CT, but also to evaluate for large- or medium-vessel changes. Consistent with clinical predictions,

MRI (Figure 1) showed scattered T_2 and fluid-attenuated inversion recovery hyperintensities throughout the right hemisphere. Multiple lesions showed restricted diffusion and enhancement with gadolinium, consistent with acute or subacute ischemic infarcts. Low signal on susceptibility-weighted images overlying the surface of the right cerebral hemisphere was concerning for subarachnoid hemorrhage. Angiography showed normal-calibre intra- and extracranial vessels of the head and neck.

A tentative diagnosis of small-vessel vasculitis was made, integrating the findings on MRI (multifocal ischemia with atraumatic subarachnoid hemorrhage and normal-appearing large- and medium-sized vessels). Erythrocyte sedimentation rate (64 [normal ≤ 6] mm/h) and C-reactive protein (178 [normal ≤ 0.8] mg/L) were elevated. Systemic markers of connective tissue disease (e.g., rheumatoid factor, antinuclear antibody) were normal. Cerebrospinal fluid analysis showed a normal glucose level, with a protein level of 0.64 (normal 0.15–0.45) g/L, 23 (normal 0) $\times 10^6$ /L red blood cells and 1 (normal ≤ 5) $\times 10^6$ /L leukocytes. Cytology and immunohistochemistry confirmed T cell predominance, compatible with chronic inflammation. A right temporal artery biopsy was normal, excluding temporal arteritis.

Without an alternative explanation for the patient's progressive deficits, a right frontal leptomeningeal and cortical biopsy was obtained. Findings were consistent with primary central nervous system vasculitis (Figure 2). Immunosuppression was started with intravenous methylprednisolone (1 g daily for five days), and maintained with oral prednisone (60 mg daily) and cyclophosphamide (100 mg daily). Antiplatelet therapy with low-dose acetylsalicylic acid was continued.

Five weeks after the initial presentation, the patient was discharged from hospital with a score of 3 on the modified Rankin Scale.¹ Clinical follow-up at 5, 7, 15 and 18 months showed gradual improvement in overall cognitive abilities with persistent impairment of delayed verbal recall. By five months, he had an improved score of 2 on the modified Rankin Scale. By 18 months, the neurologic examination was normal and his score on the Mini-Mental State Examination was 27/30; functional performance as assessed by the modified Rankin Scale was unchanged. Cyclophosphamide was used for a total of six months before being replaced by azathioprine.

Discussion

Multi-infarct or mixed dementia (implying mixed vascular and Alzheimer disease pathology) is the most likely diagnosis when older patients with

vascular risk factors present with neurologic deficits and stepwise cognitive decline. In such cases, admission to hospital allows for rapid assessment and management of vascular risk factors, with the goal of preventing further ischemic injury and facilitating rehabilitation.² Admission also provides an opportunity for prospective evaluation of atypical features, including lack of response to appropriate management, which may provide clues toward an uncommon diagnosis.

Primary central nervous system vasculitis is a rare inflammatory disease that usually presents with progressive neurologic decline and diffuse neurologic deficits. Incidence peaks at 50 years of age, although cases across all age groups are described.^{3,4} Diagnostic criteria have been proposed (Box 1),⁵ but application is limited by variations in clinical presentation, lack of specific noninvasive testing and reluctance to obtain central nervous system tissue for histopathological analysis. As this case illustrates, rare diseases may present in common ways, and should be considered in patients who fail to respond to appropriate treatments. Without invasive sampling of brain parenchyma and leptomeninges, the diagnosis of primary central nervous system

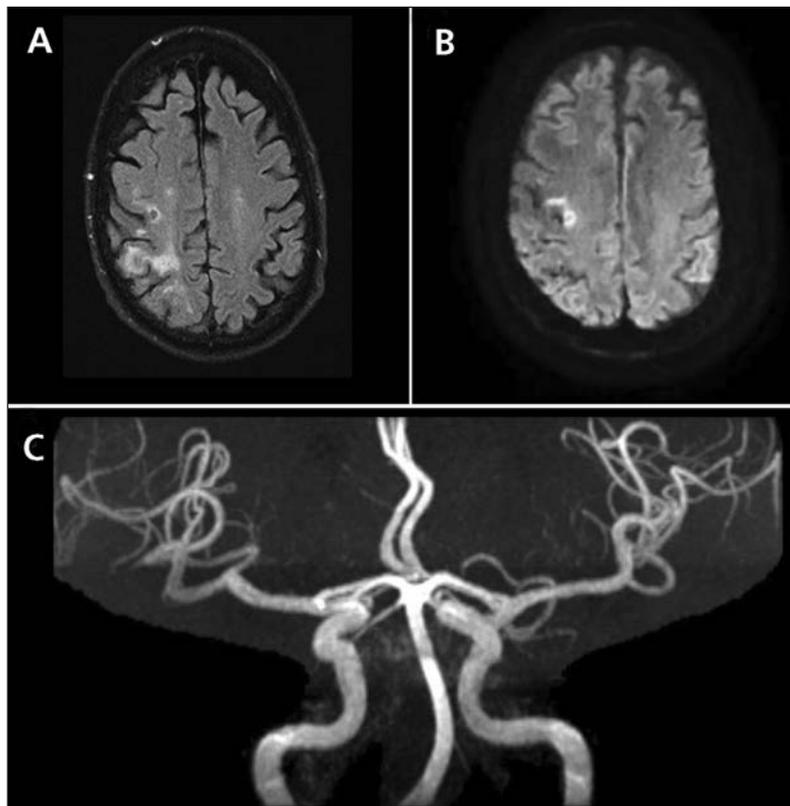


Figure 1: Magnetic resonance imaging of the brain in a 78-year-old man with cognitive decline. (A) Fluid-attenuated inversion recovery sequence showing multiple hyperintense lesions in right frontal and parietal cortices (temporal lobes not shown). (B) Diffusion-weighted imaging showing multiple areas of restricted diffusion. (C) Normal magnetic resonance angiography of the circle of Willis.

vasculitis may have been overlooked in this case, jeopardizing the patient's outcome.

Diagnosing primary central nervous system vasculitis

The onset of primary central nervous system vasculitis may be acute, with rapid progression, but it is more frequently insidious and progressive, developing over weeks (as in this patient), or even longer. Making the diagnosis requires a thorough history and physical examination to detect neurologic symptoms and signs not otherwise explained. In the largest retrospective case series reported to date, headache, encephalopathy and persistent neurologic deficits were most commonly noted, occurring in 81%, 69% and 51% of 131 patients.³ Spinal cord involvement may occur in as many as 15% of cases.⁶ Systemic symptoms (i.e., fever, weight loss, skin changes), however, are not typically observed, and serum measures of acute inflammation are often normal.³ Accordingly, the presence of prominent systemic features may sug-

Box 1: Criteria for the diagnosis of primary central nervous system vasculitis⁵

- Existence of an acquired neurologic deficit that remains unexplained despite thorough investigation.
- Demonstration of classic angiographic or histopathologic features of angiitis within the central nervous system.
- No evidence of systemic vasculitis or any other disorder that could account for angiographic or pathologic disease features.

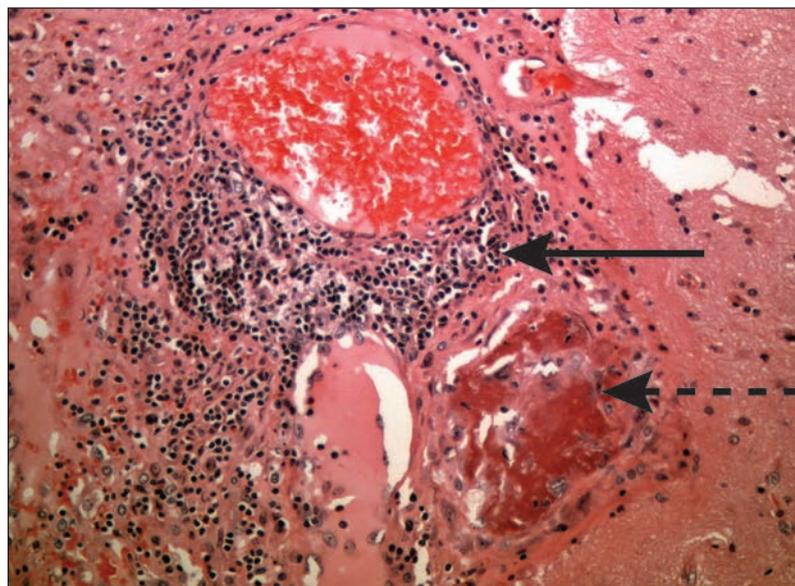


Figure 2: Histological section from a right frontal leptomenigeal and cortical biopsy showing dense lymphocytic infiltration within the media of small leptomenigeal vessels (solid arrow), leading to obliteration of the vessel lumen and focal areas of thrombosis (dashed arrow) (hematoxylin-eosin, original magnification $\times 10$).

gest an alternative explanation for symptoms, including systemic causes of vasculitis that may involve the central nervous system.⁷

When approaching the patient with suspected primary central nervous system vasculitis, brain MRI is the noninvasive screening test of choice. Abnormalities were shown in 97% (87/90) of patients with primary central nervous system vasculitis undergoing MRI in a large multispecialty clinic.⁴ In this series, ischemic infarcts were the most commonly observed finding, detected in 53% (48/90) of patients. Infarcts were typically multifocal (85%) and bilateral (83%), with gadolinium enhancement in 37%. Intracranial hemorrhage and leptomeningeal enhancement were observed in less than 10% of patients.⁴ Abnormalities on cerebrospinal fluid analysis are also expected, with modest lymphocytic pleocytosis ($>20 \times 10^6/L$ leukocytes) and elevated protein reported in 80%–90% of pathologically confirmed cases.⁵ Given the high sensitivity of MRI and cerebrospinal fluid analysis, the absence of abnormalities on these noninvasive studies should alert the clinician to consider alternative clinical diagnoses.⁸ It is important to note, however, that neither MRI nor cerebrospinal fluid analysis are specific for the diagnosis of primary central nervous system vasculitis.

Fulfillment of diagnostic criteria for primary central nervous system vasculitis requires objective demonstration of a vasculitic process within the central nervous system. This may be accomplished through the use of noninvasive MR or CT cerebral angiography, with supportive findings including alternating areas of stenosis and dilatation, which are most commonly described bilaterally.⁴ In the patient with radiologically confirmed changes in cerebral vasculature, it is particularly important to consider reversible cerebrovascular vasoconstriction syndromes. Similar to primary central nervous system vasculitis, reversible cerebrovascular vasoconstriction syndromes are characterized by prolonged vasoconstriction of the cerebral arteries, which may be accompanied by additional neurologic symptoms and signs.⁹ Reversible cerebrovascular vasoconstriction syndromes may be distinguished from primary central nervous system vasculitis by its predilection for younger patients (median age 42 yr);¹⁰ the frequent association with acute-onset, severe (i.e., thunderclap), recurrent headaches; normal cerebrospinal fluid composition; and resolution of vasoconstriction within days or weeks.⁹ When noninvasive investigations remain nonconclusive, conventional catheter-guided angiography may be considered, recognizing that even conventional angiography may not detect changes in vessels less than 500 μm in diameter.¹¹

The limitations of angiography exemplify the importance of invasive biopsy in patients with suspected primary central nervous system vasculitis who have negative results on angiography. Brain biopsy may also be required in patients with known vascular changes to exclude alternative diagnoses (i.e., atherosclerosis, radiation vasculopathy, infection, malignancy, reversible cerebrovascular vasoconstriction syndromes), and to confirm the diagnosis of primary central nervous system vasculitis before committing to long-term immunosuppressive treatment. When possible, open-wedge biopsy should be performed targeting active lesions identified on neuroimaging and encompassing the richly vascularized leptomeninges. This recommendation is especially important in patients with normal angiography,⁵ allowing pathological analysis of small vessels.

Diagnostic histopathological samples demonstrate mononuclear infiltrates within vessel walls, without eosinophils or predominant neutrophilic exudates. Giant cells and granulomata are frequently seen but are not necessary for diagnosis.⁵ A normal biopsy result does not, however, rule out the diagnosis of primary central nervous system vasculitis. False-negative biopsy rates may be as high as 25% in autopsy-confirmed cases, recognizing the patchy distribution of disease and/or inaccessibility of lesions.¹² For these reasons, patients with negative biopsy results who have moderate-to-high pretest probability for primary central nervous system vasculitis should be considered for empiric treatment, with ongoing clinical assessment for response.

More recently, high-resolution MRI evaluating arterial wall characteristics has emerged as a potential noninvasive means of differentiating between primary central nervous system vasculitis and related causes (e.g., reversible cerebrovascular vasoconstriction syndromes).¹³ A prospective study involving greater numbers of patients is required, however, before reconsidering the recommendation for biopsy in patients with suspected primary central nervous system vasculitis.

Treatment of primary central nervous system vasculitis

Patients meeting diagnostic criteria for this condition should receive urgent treatment aimed at reducing central nervous system inflammation. No controlled trials of acute or chronic treatments in primary central nervous system vasculitis are currently available; thus recommendations are based on clinical experience and interpretation of published case series. High-dose (pulse) glucocorticoids are the mainstay of acute treatment. Potent cytotoxic agents are typically reserved for the most severe cases. The utility of biologic thera-

pies (e.g., tissue necrosis factor- α blocking agents) is speculative, with benefit suggested in open-label treatment trials including small numbers of patients with rapidly progressive symptoms and aggressive disease.³ Chronic immunosuppression is critical to disease control and should be provided with antiplatelet agents and aggressive management of vascular risk factors important to secondary stroke prevention (i.e., hypertension, diabetes, dyslipidemia, smoking cessation) in patients presenting with ischemic infarction. Relapses are common, occurring in 25% of patients.^{3,4}

With prompt diagnosis and treatment, the prognosis for primary central nervous system vasculitis remains hopeful: at follow-up, most patients remain minimally disabled (modified Rankin Scale score ≤ 3).^{3,6} Delays in treatment are associated with progressive central nervous system dysfunction and accrual of deficits, which may persist despite treatment. The outcome of untreated disease is death.

Conclusion

This case emphasizes the importance of applying a stepwise approach to the evaluation of patients presenting with cognitive decline. Although the presentation in our patient was suggestive of multi-infarct dementia, the rate of decline, fluctuating course and normal CT of the brain was inconsistent with the diagnosis, raising the suspicion of vasculitis. Invasive testing was used to confirm the diagnosis of primary central nervous system vasculitis and to justify initiation of immunosuppression. In the patient with vascular risk factors and stepwise neurologic decline, it remains critical to exclude common causes of deficits. When deficits remain unexplained, the diagnosis of primary central nervous system vasculitis should be considered and invasive testing pursued.

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Contributors: Gregory Day drafted the manuscript, which all of the authors revised. All of the authors approved the version submitted for publication and agreed to act as guarantors of the work.

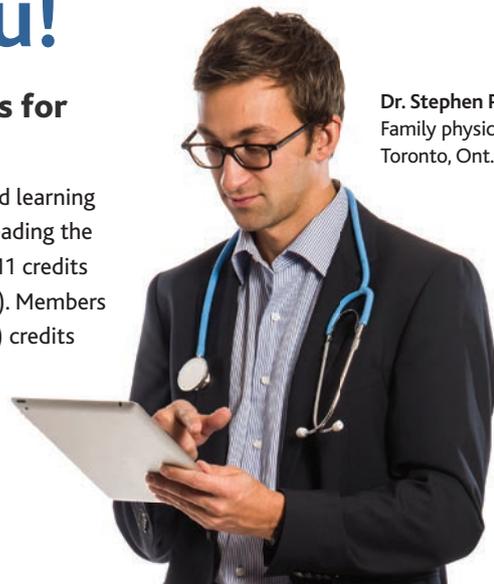
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