

AFTERIMAGES

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Primary Central Nervous System Angiitis, Amyloid Angiopathy, and Alzheimer's Pathology Presenting with Balint's Syndrome

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Abstract. We report a patient who presented with Balint's syndrome as a manifestation of primary central nervous system angiitis. Clinical findings included simultanagnosia, optic ataxia, and optic apraxia. Pathologic evaluation demonstrated amyloid angiopathy and Alzheimer's plaques. The presence of primary central nervous system angiitis along with amyloid angiopathy and Alzheimer's plaques may not be coincidental. Angiitis may be a foreign body reaction to A4 amyloid deposition. (*Surv Ophthalmol* 49:454–459, 2004. © 2004 Elsevier Inc. All rights reserved.)

Key words. amyloid angiopathy • Balint's syndrome • Gerstmann's syndrome • granulomatous angiitis • primary angiitis of the central nervous system

Balint's syndrome is a cortical visual disturbance characterized by the triad of simultanagnosia, optic ataxia, and ocular apraxia. These symptoms may be seen alone or in combination. Simultanagnosia, perhaps the most distinctive element, is also the one most often seen in isolation.¹⁰ Although the patient is able to identify the individual components of a visual stimulus, there is an inability to integrate these components into a cohesive picture. The cause is likely to be bilateral visual inattention, as it is often associated with absent blink to threat.¹⁰ Optic ataxia, also known as visual misreaching, is the inability to reach for an object of regard. Although defined as ataxia, there is no cerebellar involvement, but rather, a disruption of visual connections to the motor cortex.¹⁰ Ocular apraxia consists of impaired sac-

cares. Patients cannot voluntarily generate saccadic movements from one target to another but involuntary saccades are intact.

The usual etiology of Balint's syndrome is bilateral parieto-occipital damage. The causes are numerous and include multifocal infarcts (either watershed or embolic), vasculitis, progressive multifocal leukoencephalopathy, Alzheimer's disease, Creutzfeldt-Jakob disease, and other degenerative processes. It is important to try to elicit the characteristic findings on neuro-ophthalmologic examination, as patients are unable to describe their difficulties, and in fact may appear functionally blind. We present a patient with Balint's syndrome as a manifestation of granulomatous angiitis of the central nervous system. The patient was also found to have cerebral amyloid

angiopathy and Alzheimer's type neuritic plaques, which were likely part of the same pathologic process.

Case Report

An 81-year-old right-handed woman presented in July 2001 with a subacute change in mental status. Approximately 1 month prior to admission, her family noted intermittent disorientation and confusion. Two weeks prior to admission, she developed gait unsteadiness and had a fall resulting in head trauma. The patient complained of visual difficulties described as "spots before my eyes" and "fuzzy vision." She had difficulty turning on the bathroom faucet, using the washing machine, and finding the door handle.

Her past medical history was significant for Lyme disease. In January 2001, she developed an erythema chronica migrans rash and was treated with doxycycline. Her serum Lyme IgG and PCR returned positive, and she was then treated with intravenous cefuroxime for one month. In February 2001, she was diagnosed with breast cancer and underwent a lumpectomy and radiation therapy (March–July 2001). Axillary lymph nodes were negative for tumor.

On examination, she was confused and only oriented to the hospital. She was perseverative with decreased attention. She had difficulty with complex commands and calculations. She had intermittent right–left confusion, finger anomia, left-sided neglect, and agraphia. When asked to write her name, she was unable to put her pen to paper.

Neuro-ophthalmologic examination revealed visual acuities of 20/100 OD and 20/40 OS and bilateral inferior altitudinal defects. Pupils were normal without an afferent pupillary defect, and fundi were normal. She was unable to reach for the examiner's thumb, consistent with optic ataxia. Ocular apraxia was demonstrated as she was unable to generate voluntary saccades between the examiner's thumb and nose. Simultanagnosia was elicited when the patient was asked to describe a picture in a magazine of a dinner party. She was able to identify a woman with a child in the picture, but was not able to describe what was happening in the scene. The remainder of her examination was significant for mild symmetric weakness with brisk reflexes and a bilateral Babinski sign. Her gait was ataxic and wide-based.

Magnetic resonance imaging revealed extensive areas of signal abnormalities in bilateral parieto-occipital regions (Figs. 1A and B). There was diffuse nodular leptomeningeal enhancement particularly within the right parieto-occipital region (Fig. 1C). The diffusion-weighted MRI also revealed abnormalities in that region, and to a lesser extent in the left parieto-occipital region, suggesting ischemia (Fig.

1D). An EEG revealed diffuse slowing. A lumbar puncture revealed 16 white blood cells (84% lymphocytes and 16% monocytes), 68 red blood cells, a protein of 192, and a glucose of 56. The CSF cultures, Lyme PCR, and cytology were all negative. Two more lumbar punctures were performed with similar findings and negative cytologies. A metastatic work-up was negative. Serologies were all unremarkable.

The patient became progressively more obtunded over the next two weeks. A brain biopsy was performed to rule out a neoplastic process. The final pathologic diagnosis was granulomatous angiitis. There was an infiltration of non-caseating granulomas and eosinophils occluding the vessels, with destruction of the vessel walls (Figs. 2A and B). The process extended into the leptomeninges. Silver stain was negative for spirochetes but revealed neuritic plaques (Fig. 2C). There was also evidence of amyloid angiopathy on congo red stain (Fig. 2D). The patient was started on intravenous corticosteroids, which were gradually tapered. Her mental status improved significantly. She was, however, left with residual deficits including the Balint's syndrome. This localized to the bilateral parieto-occipital lesions, which likely represented completed infarctions.

Discussion

We report a patient with granulomatous angiitis in association with amyloid angiopathy and Alzheimer's type neuritic plaques who developed a Balint's syndrome. The patient also had elements of Gerstmann's syndrome, with right–left confusion, acalculia, agraphia, and finger agnosia. The patient's confusing array of recent ailments, including Lyme disease and breast cancer, prompted a brain biopsy that established the diagnosis of primary angiitis of the central nervous system. Although unexpected, the diagnosis may have been suggested by her encephalopathy associated with focal cortical deficits.

Primary angiitis of the CNS (PACNS), also known as granulomatous angiitis, is a vasculitis restricted to the brain and spinal cord. Diagnosis may be elusive, as it is one of the rare vasculitides without systemic manifestations. Lymphocytes, macrophages, and giant cells infiltrate small- and medium-sized vessels, resulting in vessel wall destruction. Diffuse involvement of the leptomeninges is typical so it is not surprising that patients often present with a chronic progressive encephalopathy. Multifocal deficits may accrue as multiple bilateral infarctions ensue.¹⁴ Hemorrhage may also occur secondary to infarction, vessel wall necrosis, or aneurysm rupture.⁹ The differential diagnosis includes secondary CNS vasculitides including those related to infection, malignancy, connective tissue disorders, and sarcoid.² Other vasculitic

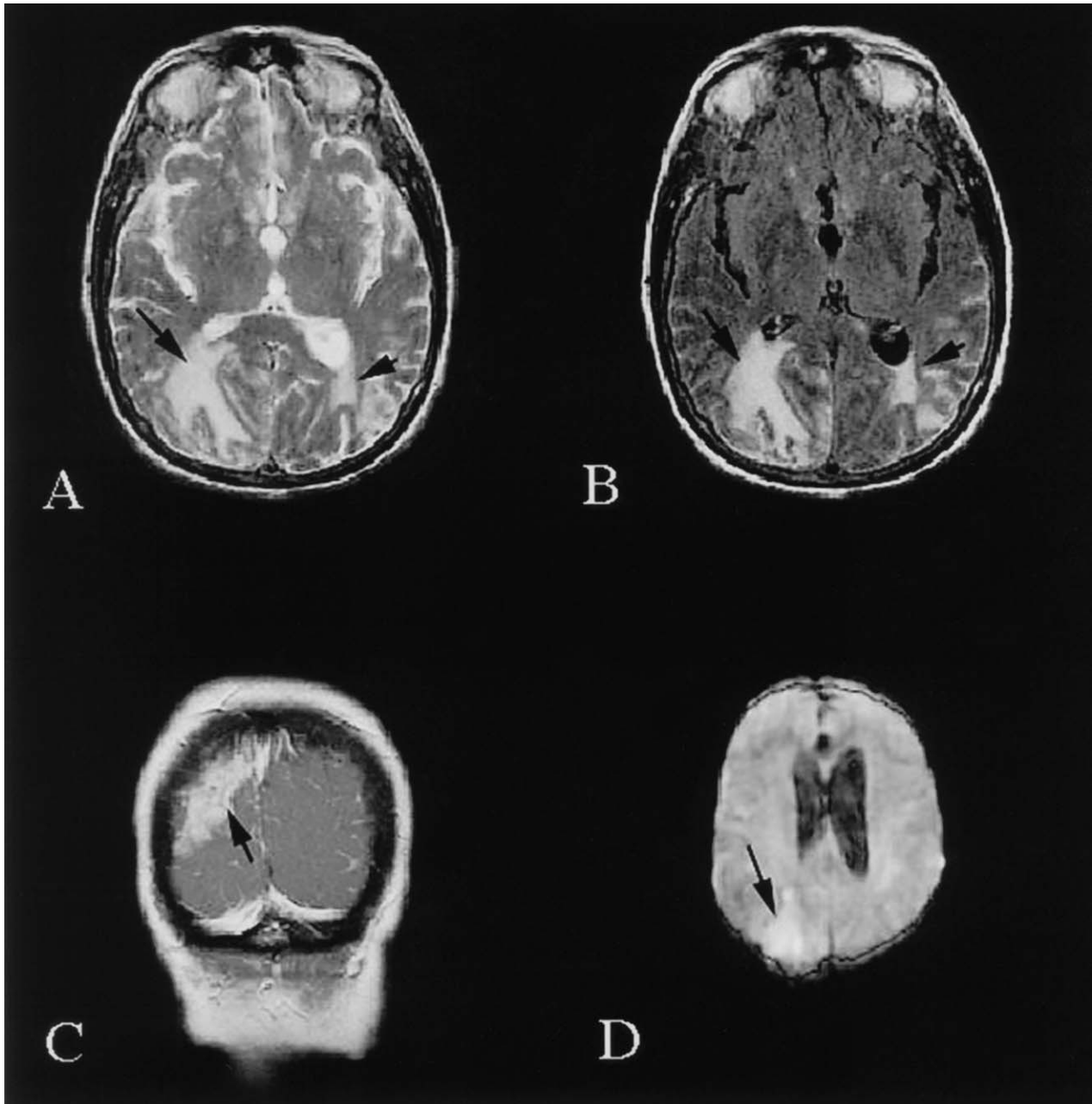


Fig. 1. Initial images. *A:* Axial T2-weighted image shows abnormal signal in bilateral parieto-occipital lobes, greater on the right than left (arrows). *B:* Axial FLAIR image further delineating the extent of bilateral parieto-occipital lesions (arrow). *C:* Coronal T1-gadolinium study demonstrating nodular leptomeningeal enhancement in the lesion (arrow). *D:* Diffusion-weighted MRI shows bright signal in the right parieto-occipital region, suggesting ischemic changes (arrow).

mimics such as emboli, hypercoagulable states, dissection, and radiation vasculopathy may also present some diagnostic confusion.²

Supportive tests include MRI, functional MR imaging, conventional angiogram, and biopsy. MRI findings of primary CNS angitis may include mass lesions, diffuse periventricular abnormalities, enhancing arteries, or overt infarction.¹¹ Unfortunately, these findings may be seen in many other diseases, so invasive testing is required to establish the diagnosis.

Yuh et al have suggested that functional MR imaging, including perfusion and diffusion-weighted MRI may eventually play an important role in the diagnosis of PACNS.¹⁶ These techniques may be more sensitive in detecting the subtle early ischemic changes that conventional MR imaging may miss, by demonstrating the pathologic damage at the microvascular level.

Review of the literature suggests that conventional angiography alone is neither sensitive nor specific

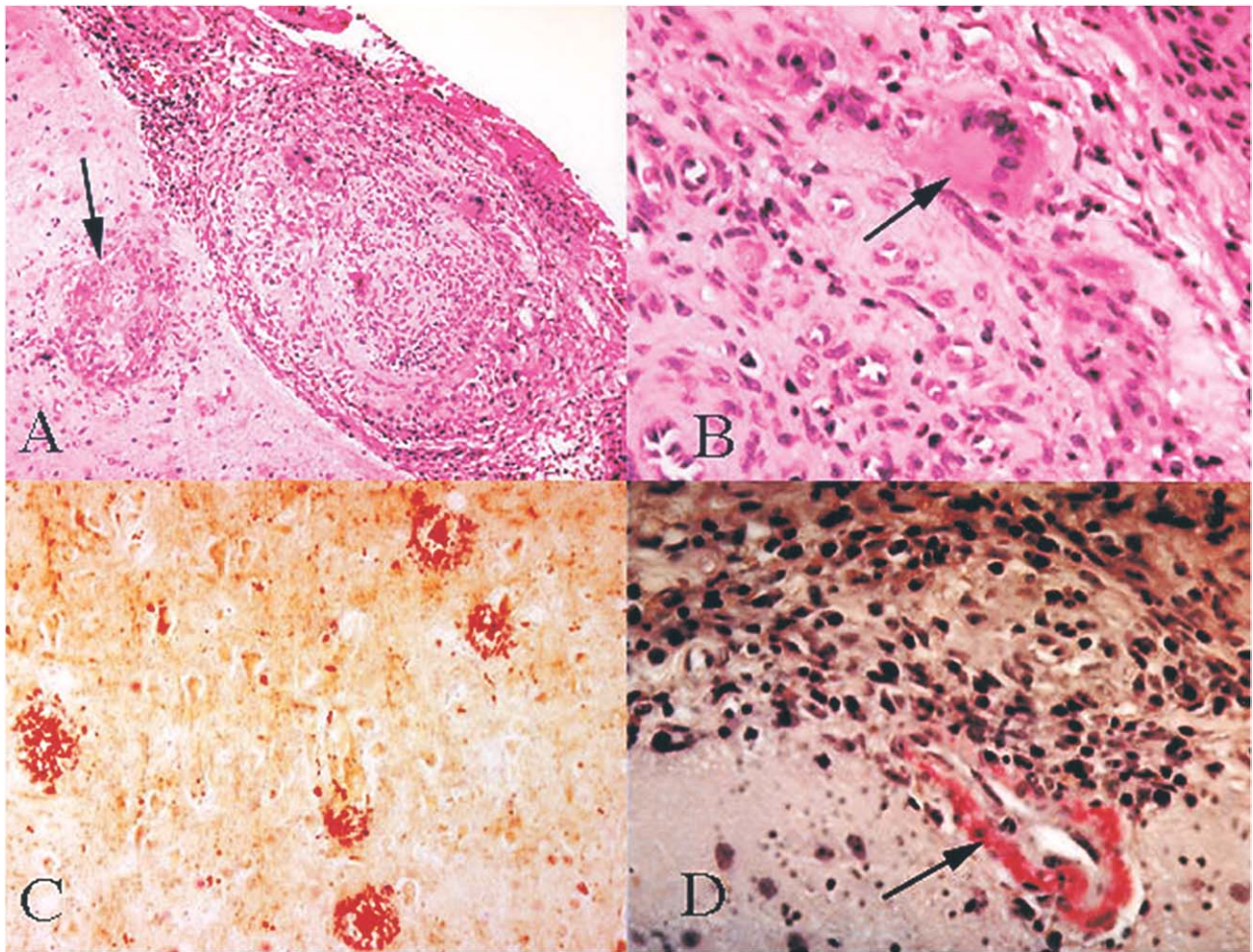


Fig. 2. Afterimages. A: Low-power H&E stain (10 \times) demonstrates diffuse inflammation in the leptomeninges with infiltration of lymphocytes, eosinophils, and macrophages. In addition, one can see destruction of a parenchymal vessel (arrow). B: High-power H&E stain (40 \times) demonstrating a multinucleated giant cell (arrow). C: Multiple neuritic plaques are seen on this silver stain. D: Congo red stain demonstrating the presence of amyloid within a vessel wall (arrow).

enough to always establish the diagnosis of primary CNS angiitis. Calabrese et al reported a series in which 39% of histologically confirmed cases of PACNS had completely normal angiograms.³ The classic angiographic features of vasculitis were seen in only 25% of PACNS cases.³ Another series by Chu et al⁴ reported a higher sensitivity for angiography of 78%. The specificity of angiography in that series was only 14%, whereas for biopsy it was 100%.⁴

Given these disturbing statistics, a normal catheter angiogram certainly does not exclude the diagnosis of angiitis, and biopsy is required. In one study, Alrawi et al found that diagnostic testing (MRI, lumbar puncture, and conventional angiogram) was unreliable in predicting the diagnosis of PACNS.¹ In that series, of 61 patients that were biopsied, 36% were diagnosed with PACNS, 39% had alternative diagnoses, and 25% were non-diagnostic.¹ Thus, a specific diagnosis was obtained in 75% of the cases that were

biopsied. Of the patients with biopsy-proven PACNS, 84% had prior angiograms that were normal, demonstrating the necessity of biopsy for patients with normal angiograms.¹

Unfortunately, although biopsy has been considered the gold standard in diagnosing cerebral arteritis, it has certain limitations as well. Calabrese et al found the diagnostic sensitivity of premortem biopsies (compared to autopsy studies) to be 74%.³ Chu et al⁴ reported a relatively higher sensitivity of 83% for biopsy. It has been recommended that both the leptomeninges and the underlying cerebral cortex be sampled for higher sensitivity. In addition, when the suspicion of PACNS remains high and the biopsy is negative, one might consider a repeat biopsy.

Traditionally, PACNS has been viewed as a disease with a relentless, chronic, but fluctuating course.³ Based on limited data, the mainstay of therapy is high dose corticosteroid therapy and cytotoxic agents

such as cyclophosphamide.³ Calabrese et al found that survival in their cohort was enhanced by the use of combination immunosuppressive therapy.³ However, Vollmer et al¹⁴ described a subset of patients with idiopathic granulomatous angiitis of the CNS (IGANS) that may have a more benign course and respond to corticosteroids alone as demonstrated by our patient.

An unusual finding in our patient is the concurrence of primary CNS angiitis, cerebral amyloid angiopathy (CAA), and Alzheimer's plaques. There are several case reports of amyloid angiopathy and angiitis occurring together and it has been suggested that this in itself represents a specific subset of primary CNS angiitis patients.⁵ Fountain and Eberhard reviewed the literature and found that approximately 10% of patients with CNS angiitis also had amyloid angiopathy.⁵ While difficult to establish which is the primary event, one theory proposes that amyloid deposition may be a response to the inflammatory process that occurs in angiitis.⁵ Alternatively, amyloid deposition itself may cause an immune inflammatory response as a foreign body, resulting in the destruction of vessels, and the subsequent development of vasculitis.^{5,6,8,15} In addition, the presence of Alzheimer's plaques may have not been coincidental in our patient, as there may have been a link between all three pathologic processes. Our patient did not have a pre-existing dementia prior to the onset of her symptoms. Another case of angiitis, amyloid angiopathy, and neuritic plaques occurring together has been described.⁷ Amyloid deposition has been clearly associated with Alzheimer's disease, and it has been suggested that these two entities represent the same disease process.^{7,12} The vascular amyloid has been shown to be identical to the amyloid present in senile plaques.¹² In one case some of the giant cells contained congophilic material immunoreactive for the Alzheimer A4 peptide. This supports the hypothesis that the granulomatous angiitis may represent a foreign body reaction to A4 amyloid deposition.⁶ To further support the existence of a correlation between these three entities, there is a unique group of patients with a genetic Dutch form of CAA (HCHWA-D) that show findings of both amyloid angiopathy and Alzheimer's disease.¹³ In this cohort, pathologic examination demonstrates microvascular degenerative and inflammatory changes, some of which are consistent with granulomatous angiitis.¹³

Given the difficulty in diagnosing primary CNS angiitis, biopsy of the meninges and underlying cortex is currently the gold standard for diagnosis. Biopsy must be considered for patients with progressive encephalopathy, multifocal deficits, and normal angiograms, once the possibility of vasculitis has been entertained. Further developments may

eventually lead to the use of non-invasive functional MR imaging in the diagnosis of PACNS. The mainstay for treatment is aggressive immunosuppression, with high dose corticosteroids and, if progression continues, chemotherapeutic agents, such as cyclophosphamide. Our case demonstrates that the triad of primary CNS angiitis, cerebral amyloid angiopathy, and Alzheimer's plaques may represent a unique subset of CNS angiitis patients. The underlying immune mechanism is uncertain, but an inflammatory response to foreign body deposition of A4 amyloid protein has been proposed.

Method of Literature Search

A MEDLINE search was performed for the period 1966 to 2003. Search words used were *granulomatous angiitis of the central nervous system, primary CNS angiitis, primary CNS angiitis and amyloid angiopathy, central nervous system vasculitis and cerebral amyloid angiopathy, cerebral amyloid angiopathy and Alzheimer's disease, and central nervous system vasculitis and Alzheimer's disease*. All articles judged to be of clinical significance were included. Non-English abstracts were excluded.

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