Illustrative Teaching Cases

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Inflammatory Cerebral Amyloid Angiopathy, Amyloid-β–Related Angiitis, and Primary Angiitis of the Central Nervous System

Similarities and Differences

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Cerebral amyloid angiopathy (CAA) results from deposition of amyloid-β fibrils in the wall of the small and medium-sized blood vessels, mostly arteries of the leptomeninges and cerebral cortex. Disruption of amyloid-β-laden vessels, occasionally with fibrinoid necrosis, leads to perivascular leakage. Vascular rupture causes lobar microbleeds or hematomas and high-convexity subarachnoid hemorrhages. The accumulation of amyloid-β causes vessel lumen obliteration, thereby leading to ischemic leukoencephalopathy and cerebral infarction. Varying amounts of perivascular inflammation may be present, involving multinucleated giant cells in the most severe cases. However, frank vasculitic vascular inflammation may be present, involving multinucleated giant cells in the most severe cases.1 However, frank vasculitic destruction of the vessel wall such as is found in amyloid-β–related angiitis (ABRA) and primary angiitis of the central nervous system (PACNS) is absent in the inflammatory form of CAA (I-CAA). There is substantial clinical overlap in the phenotypes of I-CAA, ABRA, and PACNS. A proper diagnosis of these 3 conditions is necessary because their individual treatment differs. Through 3 cases, we summarize similarities and differences between I-CAA, ABRA, and PACNS.

Case 1

A 52-year-old woman complained about limb paresthesias lasting 3 days. She reported cognitive decline and fatigue lasting 3 months, a relentless headache that had lasted for a year, in addition to episodic migraine and tension-type headaches. Past medical history was unremarkable, except for active cigarette smoking. Physical and neurological examination was normal. Brain magnetic resonance imaging (MRI) showed nonspecific lobar, white matter, nonenhancing hyperintensities on T2-weighted sequences. No treatment was initiated in the absence of a specific diagnosis. Blood tests, including inflammatory and prothrombotic work-up, cardiac ultrasound, Holter monitoring, digital subtraction cerebral angiography, and cerebrospinal fluid (CSF) analysis were normal. She remained stable clinically. Three months later, repeat brain MRI revealed new lobar T2-hyperintensities (Figure 1A) and several lobar microbleeds on gradient-echo sequences. CNS biopsy revealed extensive amyloid-β deposits in the wall of small leptomeningeal and cortical arteries, occlusion of some small vessels, and perivascular cortical microhemorrhages but no vascular or perivascular leukocytic infiltration (Figure 1A). Genetic testing revealed apoE ε4/ε4 genotype and I-CAA was diagnosed. Positron emission tomography using 11C-Pittsburg compound B confirmed diffuse amyloid-β deposition (Figure 2). The patient responded clinically and radiologically to a 12-week course of corticosteroids. In 7 years of follow-up, she experienced 3 episodes of recurrent headaches associated with new lobar T2-hyperintensities in different locations, which responded to the same treatment. Asymptomatic T2-hyperintensities shown on MRI repeated between recurrent clinical episodes were not treated and regressed spontaneously.

Case 2

A 50-year-old man presented with psychomotor slowing, disinhibition, 2 weeks of persistent headaches, and subtle right hemiparesis. Brain MRI showed right temporal and insular T2-hyperintensities and a fine leptomeningeal enhancement with gadolinium. CSF analysis documented mild lymphocytic pleocytosis, with negative cultures and stains. Herpetic encephalitis was initially suspected. Acyclovir and intravenous corticosteroids were initiated but discontinued after 4 weeks, when the results of polymerase chain reaction testing for herpes viruses came back negative. The patient had improved clinically and radiologically. He was discharged with a presumptive diagnosis of viral encephalitis. One month later, he had visual hallucinations, psychotic ideations, and
relapsing headaches. Repeat MRI showed recurrent temporal hyperintensities (Figure 1B). MR angiography revealed irregular stenosis of the right middle cerebral artery. Repeat CSF analysis documented increased aseptic inflammation (leukocytes: 13×10⁶/L; proteins: 1.24 g/L). Investigations excluded systemic malignancies, infections, and autoimmune conditions. A temporal lobe biopsy showed vessel wall damage with marked T-cell infiltration and granulomas, and some parenchymal lymphocytic infiltration (Figure 1B). Marked amyloid-β deposition was found to colocalize with the vasculitis. Infectious pathogens were not found. ABRA was therefore diagnosed. The patient was treated with corticosteroids and cyclophosphamide, which was later substituted by azathioprine to complete 3.5 years of treatment. At his last follow-up visit, 6 years after presentation, mild cognitive impairment persisted. He had no relapse.

Case 3

A 57-year-old wildlife conservation technician had right-sided hemiparesis and expressive aphasia. He reported fatigue and lack of concentration lasting 3 weeks. Because he was exposed to dead animals, an infectious cause was suspected, despite the absence of fever, headaches, or other suggestive signs. Brain MRI showed multifocal white matter T2-hyperintensities and vasogenic edema, without diffusion restriction (Figure 1C). Leptomeningeal and intracerebral gadolinium enhancement was present. CSF analysis showed modest inflammation (leukocytes: 2×10⁶/L; proteins: 0.54 g/L). Extensive analysis of blood and CSF excluded an infectious process. Stereotactic brain biopsy was inconclusive. The patient followed a fluctuating clinicoradiological course, with responses to corticosteroid therapy and recurrences when discontinued. Further investigation by MR angiography identified narrowing of the left distal intracranial carotid and proximal middle cerebral artery. An open brain biopsy showed vessel wall destruction, T-cell predominant infiltration, fibrinoid necrosis, and prominent endothelial cells (Figure 1C). There were no amyloid-β deposits, granulomas, or neoplastic cells. PACNS was diagnosed. The patient was treated for 2 years with corticosteroids combined initially with cyclophosphamide followed by azathioprine. He responded clinically and radiologically, without relapses. Four

Figure 2. Positron emission tomographic scan showing diffuse uptake of 11C-Pittsburgh Compound B in inflammatory cerebral amyloid angiopathy.
years after presentation, residual cognitive decline and mild expressive aphasia persisted.

**Discussion**

Partial overlap exists between the clinical features and investigation results of I-CAA, ABRA, and PACNS. Most I-CAA and ABRA patients are aged ≥50 years, whereas one-half of PACNS patients present before this age. Presenting symptoms indiscriminately consist of different combinations of new-onset headaches, neuropsychiatric manifestations, focal neurological deficits, and epileptic seizures. Hallucinations may be more common in ABRA. Because spinal vessels are spared from amyloid deposits, symptoms of myelopathy are unexpected in I-CAA and ABRA and, therefore, suggest PACNS. Under these 3 conditions, variable degrees of CSF inflammation may be present. Autoantibodies and other blood markers of inflammation are generally absent. Brain MRI commonly shows white matter T2-hyperintensities (Figure 1) and leptomeningeal gadolinium enhancement may be present. However, multiple lobar microbleeds present on gradient-echo sequences are hallmarks of I-CAA. Their association with ABRA remains understudied. Acute infarcts, pseudotumor lesions, and intracerebral gadolinium–enhancing lesions are consistent with ABRA and PACNS. Cerebral angiography is unremarkable in I-CAA, but may show nonspecific vasculitic changes in ABRA and PACNS if medium-sized arteries are involved. The use of high-resolution contrast-enhanced vessel wall MRI may distinguish these changes from nonvasculitic causes. 

CNS biopsy may reveal distinctive histopathologic changes (Figure 3). The amount of amyloid-β deposits and the location and severity of the inflammatory reaction differ between I-CAA, ABRA, and PACNS. By definition, CAA is characterized by vessel wall amyloid deposits. An intense perivascular inflammation with multinucleated giant cells is found in a minority of CAA patients, possibly those with an exaggerated inflammatory response to vascular leakages that occur from amyloid-β laden arteries. ApoE ε4/ε4 genotype or other cofactors not yet identified may potentiate the intense inflammatory response in I-CAA. By contrast, frank vessel wall inflammation is found in ABRA and PACNS, including architectural destruction and infiltration by leukocytes. Multinucleated giant cells forming granulomas, fibrinoid necrosis, or both are variably present. In ABRA, amyloid-β colocalizes with inflammatory changes and can be shown within phagocytes in the vessel wall. This suggests that amyloid-β deposits comprise the main antigen triggering the vasculitic reaction. Conversely, amyloid-β deposits are absent or do not colocalize with the inflammatory changes in PACNS, suggesting that they are incidental findings or innocent bystanders under this condition. Antigens triggering the vasculitic response in PACNS are presumably independent from amyloid-β deposits. I-CAA generally responds clinically and radiologically to short courses of immunosuppressant treatment; however, long-term recurrences are frequent. Superiority of prolonged immunosuppressant treatment, which is recommended in ABRA and PACNS, remains unproven in I-CAA. One way of increasing our knowledge on these conditions is recruiting patients into ongoing trials, such as The INTERnational Study on Primary Angiitis of the CEntral nervous system (INTERSPACE).

**TAKE-HOME POINTS**

- Inflammatory form of cerebral amyloid angiopathy, amyloid-β–related angiitis, and primary angiitis of the central nervous system (CNS) share several clinical features and investigation results.
- The presence of multiple lobar microbleeds on gradient-echo brain magnetic resonance imaging and apoE ε4/ε4 genotype help distinguish inflammatory form of cerebral amyloid angiopathy.
- Amyloid-β–related angiitis and primary angiitis of the central nervous system are clinically similar. Presenting age ≤50 years and myelopathy symptoms suggest primary angiitis of the central nervous system. CNS biopsy may reveal distinctive histopathologic changes.
- Whether amyloid-β–related angiitis and primary angiitis of the central nervous system can be differentiated by gradient-echo magnetic resonance imaging (multiple versus few lobar microbleeds) and positron emission tomography using 11C-Pittsburg compound B (diffuse versus minimal uptake) remains to be investigated.

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References


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