Cerebral Amyloid Angiopathy Presenting as a Mass Lesion

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A rare clinical presentation of cerebral amyloid angiopathy is reported. Our patient presented with the clinical and radiological signs of a right frontal mass lesion suggesting a brain tumor, and a biopsy provided the diagnosis of cerebral amyloid angiopathy. A brief review of the pathology and clinical features of cerebral amyloid angiopathy is presented. (Stroke 1987;18:234-239)

Primary cerebral amyloidosis is characterized by deposition of amyloid within the cerebral tissue (e.g., core of neuritic plaques and core of plaques in spongiform encephalopathies) and the cerebral and meningeal blood vessel walls (amyloid or congophilic angiopathy) in the absence of systemic amyloidosis. Primary cerebral amyloidosis has been associated with normal brain aging changes and with multiple neurological disturbances including dementia of the Alzheimer's type, cerebral infarction, arteriovenous malformations, radiation necrosis, progressive demyelinating syndrome, chronic vasculitis, dementia pugilistica, hereditary ataxia, hereditary cerebral hemorrhage, and spontaneous cerebral hemorrhage in the elderly normotensive patient. We recently treated a patient with primary cerebral amyloidosis that presented with the clinical picture of an intracerebral mass lesion not related to a hemorrhage. This is a most unusual clinical presentation of primary cerebral amyloidosis, which may be relevant to the proposed etiologies of this disease.

Subjects and Methods

A 55-year-old, right-handed Jamaican housewife was admitted to the Toronto Western Hospital in April 1985 after a generalized seizure with loss of consciousness for 2 minutes and incontinence of urine. There was a transient postictal confusional period that lasted for 20 minutes, resolving completely. Six months prior to admission, the patient had had a convulsive episode, falling to the floor after losing consciousness. On that occasion, the neurological examination was reported as normal but a computerized tomography (CT) scan of the head showed a right frontal hypodense lesion with minimal mass effect, interpreted as a cerebral contusion secondary to a hemorrhage. This is a most unusual clinical presentation of primary cerebral amyloidosis, which may be relevant to the proposed etiologies of this disease.

In 1983, the patient had a liver biopsy that showed chronic hepatitis and cirrhotic changes. Antibodies to hepatitis B virus surface antigen were positive with a negative serology for cytomegalovirus, Epstein-Barr virus, and toxoplasmosis. She admitted to a moderate ethanol intake. She was normotensive and had no family history of neurological illness.

On admission, examination revealed only a mild pyramidal weakness in the left lower extremity with symmetrical and normal myotatic reflexes. The mental status, speech, cranial nerves, gait, and sensory examination were normal. There was no evidence of increased intracranial pressure. The rest of the neurological examination was unremarkable.

Hematological testing showed a microcytic hypochromic anemia, but serum iron, bone marrow biopsy, and renal function were reported as normal. Further laboratory investigation showed no evidence of myeloproliferative, immunologic, or infectious disorders with the exception of a nonsignificant positive antinuclear antibody test (1:100 dil) and a slight increase in the polyclonal IgM serum levels.

No evidence of systemic amyloidosis was found in a gingival biopsy. The EEG showed frequent epileptiform abnormalities arising from the right frontal-temporal region with an irregular slowing in this area, interpreted as consistent with the recent seizure or a structural lesion. A brain CT scan showed a large, ill-defined, hypodense nonenhancing lesion in the right frontal lobe producing minimal local mass effect on the frontal horn of the right lateral ventricle without shift of the midline (Figure 1). There were no signs of previous infarction or hemorrhage throughout the brain parenchyma.

The history of seizures of recent onset in an adult with mild left leg weakness and a CT scan showing a right frontal hypodense lesion suggested the diagnosis of a tumor, such as a low-grade glioma. Two weeks after admission, the patient had a right frontal craniotomy for biopsy; intraoperative ultrasonography was unsuccessful at demonstrating the lesion. The frontal lobe cortex and white matter showed no gross abnormality; particularly, there was no evidence of swollen gyri, granular cortical atrophy, or changes in color or consistency of the brain parenchyma consistent with a
FIGURE 1. Enhanced CT scan showing irregular, hypodense lesion in the right frontal lobe (left) producing mild mass effect on the right frontal horn (right).

recent or old hemorrhage or an ischemic infarction. A plug of cortex in the frontal association area, 3 cm in diameter and extending well into white matter, was resected for biopsy. The patient had an uneventful recovery and was discharged on phenytoin. A follow-up assessment four months after the brain biopsy showed only a mild weakness of the left extensor hallucis longus, and a CT scan showed persistence of the hypodense lesion, although with obvious reduction in its size and resolution of the mass effect.

Microscopic Examination

Sections of the brain were embedded in paraffin and stained with hematoxylin and eosin (HE), phosphotungstic acid hematoxylin, Congo red, Gordon and Sweet silver reticulin stain, martius scarlet blue (MSB), and Bielschowsky stain. Immunohistoperoxidase studies were done using rabbit antisera against human serum immunoglobulins (IgA, IgG, IgM) and complement (C3).

The diagnosis of cerebral amyloid angiopathy (CAA) was based on the presence of small arteries and arterioles in the leptomeninges and cerebral cortex showing thickening of their walls due to the hyaline and eosinophilic deposit as seen on HE staining, which were Congo red-positive and displayed the typical "apple-green" birefringence of amyloid with crossed polarized light (dichroism) (Figure 2). Several neuritic (senile) plaques were found in the affected cortex, some showing a small central amyloid core (Figure 3). Only rare neurons contained neurofibrillary tangles. A few of the amyloid-positive cortical vessels showed cuffing by mononuclear cells in addition to having amyloid deposits in their walls (Figure 4). Rare amyloidotic vessels also contained multinucleated giant cells in the perivascular mononuclear cell infiltrate. Congo red staining failed to show any amyloid in the cytoplasm of giant cells. Few vessels showed "plaque-like" amyloid angiopathy. MSB staining failed to reveal fibrin in the walls of the affected vessels, including those with perivascular cuffing. A marked reactive astrogliosis was observed, particularly adjacent to amyloidotic vessels. Portions of the biopsy free of CAA did not show astrogliosis. There was no evidence of neuronal loss or spongiform changes. No microscopic infarctions or evidence of old hemorrhagic foci (such as perivascular hemosiderin-laden macrophages) were found. Immunoperoxidase staining showed a dark brown granular uptake in the amyloid-laden vessels with all the immunoglobulins and the complement tested.

Discussion

Amyloid deposits in the central nervous system (CNS) have been found within neuritic plaques and blood vessel walls. The focus in this paper is on the amyloid found in CAA, which has been reviewed recently and divided into 2 main categories: 1) Congophilic macroangiopathy, where amyloid is confined to the wall of leptomeningeal and perforating cortical
FIGURE 2. Photomicrograph of meningeal and intracortical vessels showing extensive mural amyloid deposition. Congo red stain with (right) and without (left) crossed polarized light. Bar = 100 μm.

arteries and arterioles (congophilic angiopathy of Pantelakis) and 2) Congophilic microangiopathy, where the cortical arterioles and capillaries are affected. Amyloid can infiltrate the perivascular brain parenchyma to produce the so-called plaque-like angiopathy ("Drusige Entartung" of Scholz or "dyshoric angiopathy" of Morel and Wildi. Nevertheless, all this terminology "fails to recognize the disease continuum from extra-to-intra-cortical sites," and does not elucidate the pathogenesis of primary cerebral amyloidosis.

In the literature, the mean age at onset of symptoms of CAA is around 70 years, and there is evidence that the incidence of CAA increases with age. Nevertheless, the degree of severity of the lesion has been found not to be age-dependent. There is no significant sex predilection.

Amyloid deposits occur within the wall of leptomeningeal and cortical arteries, arterioles, and capillaries, and in the adventitia of veins and venules in the cortex. White matter is usually spared except in the subcortical zones. The amyloid deposition occurs within the media and adventitia with fragmentation of the elastica. In leptomeningeal vessels, amyloid deposits are segmental, being more uniform in their deposition in the cortical vessels. In addition, there is a topographic predilection for amyloid deposits in the neocortex, with less involvement or sparing of the vessels of the basal ganglia, cerebellum, and brainstem. Within the neocortex, the occipital (striate cortex) and temporal lobes are the most affected; however, Cosgrove et al found the frontal lobe to be the most heavily involved area in 24 cases of CAA.

With light microscopy, Congo red stains the fibrillar protein component (the major amyloid protein), while periodic acid-Schiff (PAS) stains glycoproteins (i.e., amyloid P component), and alcian blue stains the glycosaminoglycans (other minor components of the amyloid substance). Cerebral amyloid fluoresces under ultraviolet light when stained with thioflavine-S. Electron microscopy shows that filamentous amyloid fibrils measuring 9–9.5 nm replace the media and adventitia, sparing the endothelial cells. Ishii et al have identified an electron-dense material in the media, possibly representing degenerated smooth muscle cells.

The clinical presentation of CAA has been broadly categorized by Okazaki et al into progressive dementia, vascular syndromes, or both. The severity of CAA in an individual case has been found to correlate positively with the degree of symptomatology. The dementia profile is usually that of the Alzheimer’s type with disorientation and severe memory impairment. The typical vascular syndromes are those of transient ischemic attacks, cerebral infarction, multiple ischemic episodes, or spontaneous intracerebral hemorrhages which, when large, are characteristically superficial and lobar. The superficial location of these cerebral hemorrhages correlates with the anatomic distribution of amyloid-laden vessels; therefore, rupture into the subarachnoid space is also frequent.
ever, large hematomas may rupture into the ventricular system. Multiple intracerebral hemorrhages, separated in both time and place, have been reported.

Spontaneous intracerebral bleeding related to CAA ranges from petechial hemorrhages to massive hematomas; CT and angiographic findings are nonspecific although suggestive of the diagnosis and have been reviewed elsewhere. The reported incidence of CAA as the cause of spontaneous intracerebral hemorrhage varies, and figures from 2% to 16.6% may be found, according to different series. Bleeding has been attributed to weakening of the vessel wall due to amyloid infiltration although secondary miliary aneurysms have been described. Spontaneous or traumatic (including surgical) rupture of affected vessels seems to be the principal cause of hemorrhage.

CAA is frequently associated with hypertensive fibrinoid necrosis, and although the latter may induce or increase the size and extent of the hemorrhage due to CAA, it is not an essential factor. The treatment of patients with lobar hematomas in which CAA is suspected should consist of aggressive medical management of increased intracranial pressure, leaving surgical evacuation as the last resort. The experience of Ishii et al is that CAA is a diffuse process in which recurrent hemorrhage occurs in different parts of the brain. They had great difficulty establishing hemostasis when evacuating these hematomas due to diffuse oozing of blood and, furthermore, they had no death due to cerebral herniation in their series.

Our patient presented after 2 isolated episodes of general tonic-clonic seizures associated with a hypodense lesion in the right frontal lobe. Microscopic find-
ings of the brain biopsy were diagnostic of CAA. Although occasional amyloidotic vessels had a perivascular mononuclear cell infiltrate, extensive examination of the tissue failed to reveal a true vasculitis. Giant cell reaction in CAA has been described in association with giant cell arteritis\(^7,40\) and with isolated angiitis of the CNS,\(^41\) but in the absence of arteritis these changes have been reported in CAA only once before.\(^10\) Nevertheless, giant cells have been described in systemic amyloidosis as a foreign body reaction around perivascular amyloid deposits.\(^42\) Perivascular cuffing by mononuclear cells in association with fibrinoid necrosis of the vessel wall has also been described before.\(^11\)

Recently, Mandybur\(^43\) has used the terminology of CAA-associated vasculopathies to describe different vascular changes that he postulates to be related to or dependent on CAA. Specifically, these changes may be obliterator, hyalining, necrotizing, and/or inflammatory. In relation to the latter, perivascular or, less often, transmural chronic inflammatory infiltrates are described; we believe that our case represents an example of CAA with an associated vasculopathy of the inflammatory type rather than an association of CAA with a CNS vasculitis.

Our patient did not exhibit any clinical, hematological, or serological manifestations of a systemic vasculitic disorder. Furthermore, histological examination of the biopsy specimen did not show evidence of transmural inflammatory infiltrates, nonamyloid hyaline arteriolar degeneration, or fibrinoid necrotizing vascular changes. Similarly, the lack of clinical and histological features of isolated angiitis of the CNS excluded this possibility.

In spite of many investigations seeking the origin of amyloid material in the brain, the pathogenesis of this disease remains obscure. The cumulative evidence points toward different mechanisms involved in the formation and deposition of amyloid within the CNS; local synthesis and deposition of a transported plasma precursor is among the most accepted theories.

**References**

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