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Clinical phenotypes of Cerebral Amyloid Angiopathy

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Abstract

The term Cerebral Amyloid Angiopathy (CAA) is used to describe the pathological changes occurring in cerebral blood vessels, both leptomeningeal and cortical that result from the deposition of amyloid proteins. This CNS vasculopathy is associated with a spectrum of clinical phenotypes that include both ischemic and hemorrhagic presentations. Dementia, cognitive impairment and transient neurological symptoms or signs are also being increasingly recognized as part of the CAA clinical spectrum.

This review covers the clinical, pathological and neuroimaging aspects of CAA.

Keywords: Cerebral Amyloid Angiopathy; Clinical presentations; AD; Dementia; MRI; Stroke

1. Introduction

Cerebral Amyloid Angiopathy is defined by the deposition of amyloid proteins within leptomeningeal and cortical arteries, arterioles, capillaries, and rarely veins. The term amyloid refers to any amorphous, eosinophilic, extracellular protein deposit with specific staining characteristics, such as Congo red binding and birefringence with polarized light (Fig. 1) [1,2]. There are a number of different proteins that can deposit as amyloid in human CAA (Table 1).

In sporadic and most of the hereditary forms of CAA the amyloid includes β-amyloid peptides 1–40 and 1–42 which aggregate within vessel walls, occasionally spreading and depositing in the surrounding neuropil or within the glia limitans when capillaries are involved (Fig. 2) [1–3]. The composition of the vascular amyloid deposits differs from senile plaques (SP) of Alzheimer's Disease (AD) by having an increased Aβ 40/42 ratio, which seems to shift the amyloid deposition from the parenchyma to the vascular wall [4,5].

CAA occurs within a heterogeneous group of hereditary and sporadic diseases. Hereditary forms account for the minority of the CAA cases but have more pleomorphic phenotypes (Table 1). Sporadic CAA increases dramatically with age, rarely being present before the age of 50, and increasing in prevalence to more than 50% in people over age 90 [3,6]. Data from autopsy series have confirmed age as being a significant risk factor in a variety of different populations [7–9]. Though CAA is frequently presumed to be asymptomatic, it is now increasingly recognized to present with a spectrum of clinical presentations.

2. Historical overview

The histological vascular abnormalities recognizable as vascular amyloid deposition were first described by Gustav Oppenheim, in the brain parenchyma adjacent to hyalinized capillary walls in 6 of 14 autopsied brains of individuals with dementia and the pathology of AD [10]. In 1938, Scholz published the first article in which the primary focus was the

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vascular abnormality now recognizable as CAA. He detected this abnormality in the brains of 15 of 104 unselected autopsies, and he suggested it to be a disease related to aging [10].

Although it has been nearly a century since the first pathological descriptions of CAA, knowledge of its link with intracerebral hemorrhage was recognized only in 1960, when Neumann [11] reported on a 45-year old woman with severe Cerebral Amyloid Angiopathy who had 2 symptomatic lobar hemorrhages and multiple small asymptomatic lobar petechial hemorrhages (PH). After this description further interest followed when it was appreciated that there was CAA underlying a significant proportion of cerebral hemorrhages occurring in non-hypertensive individuals [11,12]. Following these seminal descriptions, there has been an emerging clinical and neuroimaging interest in both sporadic and hereditary cases in the correlations with this pathology.

3. The clinical spectrum of sporadic CAA

The different clinical presentations that are recognized to be associated with CAA may be divided syndromically into stroke; transient neurological events including TIAs, seizures, and migrainous phenomena; cognitive impairment and dementia [1,3].

3.1. Stroke

3.1.1. Lobar cerebral hemorrhage

The most recognized clinical presentation of CAA and the basis for the clinical criteria set by the Boston group [13,14], is lobar cerebral hemorrhage which is frequently recurrent [2,3,15]. Indeed, the antemortem diagnosis of CAA is most often established around this presentation [13,15,16]. CAA-related lobar hemorrhages usually affect normotensive individuals over age 55. They account for 5–20% of all spontaneous (non-traumatic) cerebral hemorrhages in elderly subjects [17,18]. The CAA lobar hematoma typically involves the cortical–subcortical regions and can extend from the cortex to the subarachnoid space or less commonly, to the ventricles. Recurrent and multiple hemorrhages are a feature of CAA-related lobar hemorrhage in patients who survive the initial bleed [1,3]. The localization of CAA-related hemorrhage follows the localization of CAA in the cerebral cortex and cortico–subcortical or lobar regions [1–3,15]. Despite the high prevalence of CAA in the occipital cortex, CAA-related hemorrhages have been shown to be more evenly distributed [1,3], with a slight predominance of occipital and frontal cortices [15]. Patients present with cortical dysfunction that correlates to the extent and location of lesions, typically preceded or coincident with a headache, vomiting and nuchal rigidity [19]. CAA is typically absent in regions characteristic of hypertensive hemorrhages (deep brain regions and cerebellum) (Fig. 3). The presence of petechial hemorrhages in a cortical/subcortical location detected by low signal on gradient-recalled-echo (GRE) MRI sequences with T2*-weighting further supports the diagnosis of CAA (Fig. 2) [13]. This low signal is caused by deposited iron products (Fig. 4) [20]. These small cortical–subcortical petechial hemorrhages correlate well with the pathological diagnosis of CAA [13,20]. From the diagnostic standpoint gradient echo MRI has emerged as the most important diagnostic aid for CAA identification during life. The lack of other accurate and accessible biomarkers has otherwise limited knowledge of early detection, characterization of the different clinical presentations of CAA and the potential impact on the patients' neurological status.

Fibrinoid necrosis and aneurysm formation are both implicated in the in the pathogenesis of vessel rupture [1–3]. Possession of the apoE ε2 and 4 alleles has been associated with both fibrinoid necrosis and concentric splitting ("double-barrel" appearance) of the blood-vessel walls (Fig. 5) [21]. It is, therefore, not unexpected that patients with CAA-related hemorrhages and the 2/4 genotype (i.e, with both "risk" alleles) have early and recurrent lobar hemorrhages [21–23]. Nevertheless, at present apoE genotyping does not have a recommended place in the clinical setting for this problem.

There is an emerging question regarding the risks of hemorrhagic complications of thrombolytic agents (e.g. tissue plasminogen activator — rtPA) in patients with CAA. Thrombolysis-related intracerebral hemorrhage in patients with myocardial infarction has similar risk factors and the hematoma features as sporadic CAA related hemorrhages [24]. On the other hand, in a small series of patients

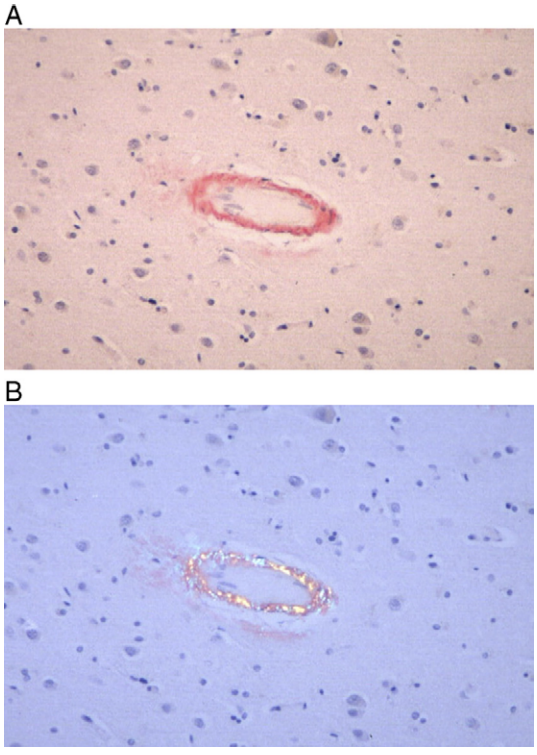

Fig. 1. CAA in sporadic case of Alzheimer's Disease. (A) Congo-red positive material in vessel wall, (B) confirmed as amyloid by showing apple-green birefringence when viewed with polarized light.

Table 1
Genetic, clinical, radiological and pathological data from hereditary forms of CAA

Hereditary CAA	Gene/ mutation	Amyloid Protein	Age of onset	Clinical Phenotype	Neuroradiological phenotype	Pathological phenotype
Hereditary cerebral hemorrhage with amyloidosis-Dutch type [30,54–58]	APP E693Q mutation	Aβ	39–76	Lobar brain hemorrhages; dementia in survivors; epilepsy in survivors.	Lobar hemorrhages; PHs in the gray-white matter junction in T2*MRI; infarcts; diffuse white matter damage.	CAA affects cerebral and cerebellar meningeal arteries and cerebro-cortical arterioles. CAA is more severe occipitally; Diffuse plaques; Hemorrhages and infarcts.
Hereditary CAA - Iowa type [31,59]	APP D694N mutation	Aβ	60–70	Progressive aphasia/ dementia; Lobar brain hemorrhage (in Spanish kindred).	Occipital gyriform calcification and l eukoencephalopathy. Cortical PHs in T2*MRI.	Extensive CAA; Calcified deposits in vessel walls; Diffuse plaques; NFTs; Cortical infarcts and hemorrhages.
Hereditary CAA - Flemish type [60–62]	APP A692G mutation	Aβ	41–61	Amnesic syndrome/ dementia; Lobar brain hemorrhage.	Cortical central atrophy; white matter lesions; Lobar brain hemorrhages.	Extensive CAA large amyloid core SP cerebral and cerebellar and NFTs.
Hereditary CAA - Italian kindred [63,64]	APP E693K mutation	Aβ	50s	Lobar brain hemorrhages.	NA	Extensive CAA.
Hereditary cerebral hemorrhage with amyloidosis-Icelandic type [2,65]	CystC Leu68Gln	Acys	20–50	Lobar brain hemorrhages; cognitive impairment or dementia in survivors.	NA	Extensive CAA within small arteries and arterioles of leptomeninges, cerebral cortex, basal ganglia, brainstem, and cerebellum.
Familial amyloid polyneuropathy/ meningo-vascular amyloidoses [66–71]	TTR Asp18Gly or Val30Gly or Tyr69His	ATTR	36–53	Dementia, ataxia, and spasticity. Dementia, seizures, ataxia, hemiparesis, and decreased vision. Subarachnoid hemorrhage.	Symmetric calcification of the cortex; MRI contrast enhancement at the surface of the cortex. Superficial siderosis.	TTR-amyloid deposits predominated in cerebrospinal leptomeningeal vessels and in subpial and subependymal regions. Brain parenchyma is not involved.
Familial amyloidoses Finnish type [72]	GEL G654A or G654T	AGel	30	Dementia, ataxia, neuropsychiatric features; corneal lattice dystrophy, cranial and peripheral neuropathy	White matter lesions in postmortem MRI.	Minor cortical CAA, white matter AGel angiopathy and myelin loss; major spinal angiopathy.
Prion disease with cerebral amyloid angiopathy [73]	PRNP Y145Stop	APrP	38	Dementia, extrapyramidal signs, ataxia and spastic paraparesis.	Late cerebral atrophy and ventricular dilatation.	Extensive CAA in leptomeningeal and parenchymal vessels, NFTs in cortex. Severe gliosis and neuronal loss.
Familial British dementia [2,53]	BRI2 Mutation in stop codon	ABRi	40–60	Dementia; spasticity; ataxia; rare Lobar brain hemorrhages.	Frontal and occipital white matter lesions; lesion in the corpus callosum. No evidence of hemorrhages.	Extensive CAA affecting vessels in the leptomeninges and both gray and white matter; abundant amyloid plaques and severe neurofibrillary degeneration.
Familial Danish dementia [74,75]	BRI2 decamer duplication in codon 265–266	ADan	30	Cataracts; deafness; dementia; spasticity; ataxia; rare strokes.	White matter lesions.	Extensive CAA in cerebral vessels, choroid plexus, cerebellum, spinal cord, and retina; plaques and neurofibrillary tangles; ischemic lesions in white matter. Uniform diffuse atrophy .
Familial Alzheimer's Disease and Down Syndrome [76–81]	PS1 PS2; APP	Aβ	Variable	Dementia; Lobar brain hemorrhages and spastic paraparesis	Variable	Variable CAA.

the presence of petechial hemorrhages on gradient echo imaging was reported to not substantially increase the risk of either symptomatic or asymptomatic brain hemorrhage following IV rtPA administered between 3 and 6 h after stroke onset [25]. More prospective data is required in order to clarify the risk of hemorrhagic complications with the use

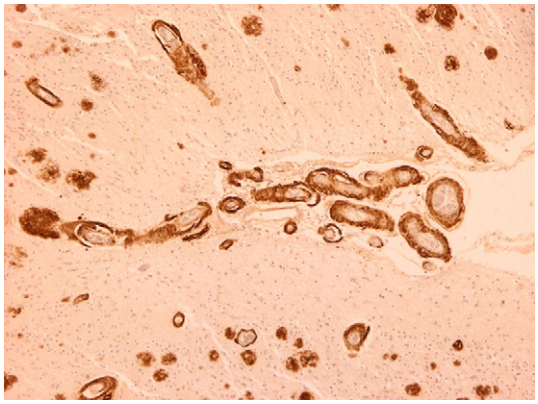

Fig. 2. Sporadic case of Alzheimer's Disease. A-beta Immunohistochemistry demonstrating A-beta protein deposition in the walls of leptomeningeal and parenchymal vessels (CAA) and in senile plaques.

of thrombolysis in patients with CAA. There are currently no recommendations to guide antithrombotic or fibrinolytic treatment based on the detection of cerebral petechial hemorrhages on MRI [24,26].

3.1.2. Ischemic infarctions

Manifestations of cerebral ischemia should be considered within the clinical spectrum of CAA. CAA related ischemic infarcts are more often located in the cerebral cortex, with lesions that have been described as 'cortical lacunes'. These cortically based lesions may present as TIAs or minor strokes in elderly CAA patients [12,27]. CAA with ischemic infarctions are observed in patients, with both hereditary and, less frequently, sporadic forms of CAA [12,28–31].

In tissue biopsies of patients with a history of recent cerebral or cerebellar infarctions, CAA was found in 13% of cases, compared to 3.7% of controls, OR 3.8 (95% confidence-interval 1.3–10.9) [32].

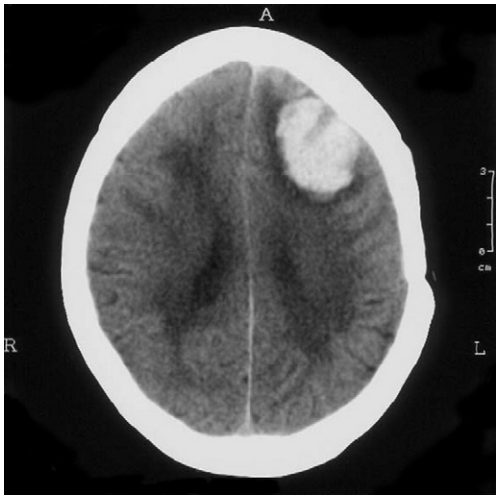

Fig. 3. CT scan of a biopsy proven CAA patient that presented with a stroke syndrome. Acute left frontal lobe hemorrhage. Peri-ventricular white matter hyperdensity.

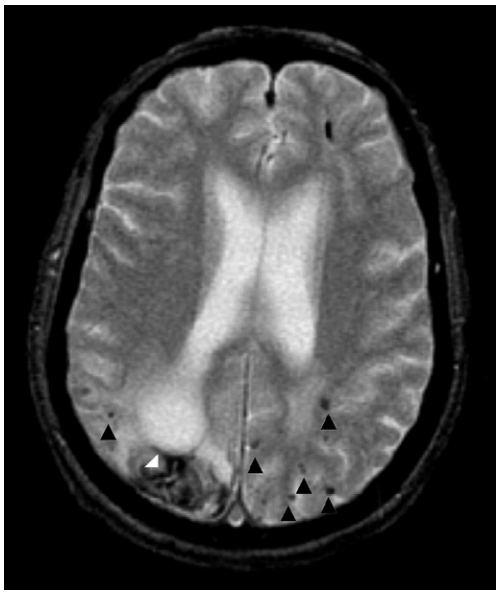

Fig. 4. Axial T2*GRE MR with T2*-weighting image of sporadic CAA case. Multiple petechial cortical hemorrhages (black arrowheads) and a major lobar brain hemorrhage (white arrowhead).

The pathogenic mechanisms underlying ischemic lesions related to CAA remains uncertain. Whether it is through vascular stenosis or obstruction, or whether it results from a dynamic change in the vessel physiology or both, is presently debated [33,34].

3.1.3. Subarachnoid hemorrhage (SAH)

Over age 60, CAA is a rare cause of primary SAH yet it is the most frequent cause of ICH accompanying secondary SAH [35]. The SAH source may be intraparenchymal with hemorrhage extending into the subarachnoid space or from leptomeningeal vessels leaking into the subarachnoid space. Further studies are still needed to clarify this issue [36].

There have been descriptions of localized SAH or superficial siderosis over cortical *sulci* in patients that presented with transient neurological symptoms, in patients

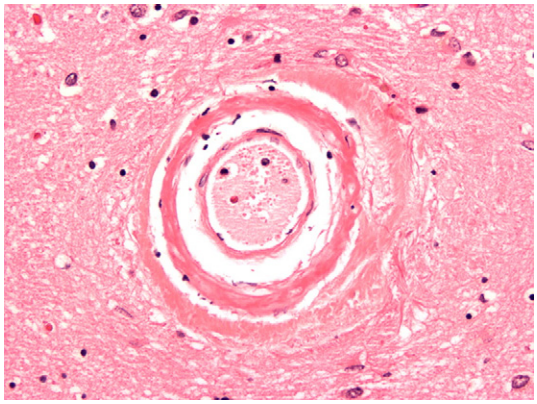

Fig. 5. Double barrel appearance of CAA of an amyloid-laden vessel in a case of sporadic CAA.

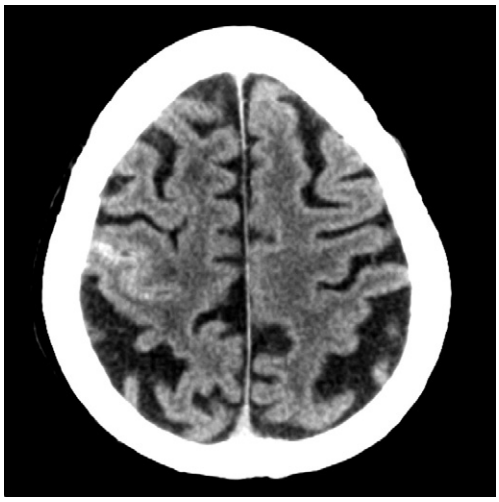

Fig. 6. CT Scan of a probable CAA patient that presented with left sensitive seizures and post-ictal left hemiparesis, showing a right perirolandic subarachnoid hemorrhage.

demonstrated to have had CAA (Figs. 6 and 7) [37,38]. The extensive involvement of the meningo-cortical vessels by the amyloid deposits and its rupture underlies the SAH and related clinical manifestations that can be recognized in CAA.

3.2. Transient focal neurological symptoms and signs (TFNSS)

TFNSS can include different phenomena such as focal seizures with or without Todd's paralysis, focal deficits (TIAs) or positive visual symptoms similar to migrainous auras. Most of the published cases describe brief stereotypic phenomena that sometimes preceded major hemorrhagic events. A favorable response to antiepileptic drugs supports an epileptic mechanism for some TFNSS [38].

There have been no systematic studies elucidating these phenomena in patients with CAA with only case reports in the literature [27,37,38]. The transitory nature of the clinical symptoms and signs, coupled with the absence of a clear CAA biomarker make clinical–pathological correlation difficult to establish. Underlying the TFNSS different pathologies have been described including: petechial cortical hemorrhages [38], subpial–subarachnoid hemorrhages [37] or ischemic lesions ("cortical lacunes") (Figs. 4, 6 and 7) [27].

3.3. Cognitive impairment and dementia

The relationship of CAA with cognitive impairment and dementia has been well recognized. There is an inverse correlation between CAA presence and cognitive function that has been reported in both case series [39] as well as in the population based studies. In the MRC study, severe CAA was identified in 36.5% of individuals with dementia compared to 7% without dementia, OR 7.7 (95% CI, 3.3 to 20.4) [7]. CAA is present in >80% of AD case-series [8,17]. In the Honolulu-Asia Aging Study (HAAS), the comorbid presence of CAA with AD was associated with significantly worse cognitive test performance [40]. CAA can cause both mild cognitive impairment and full blown dementia, in sporadic and hereditary cases [41].

CAA impairs cognitive function through a number of different mechanisms that include: 1. — Ischemic or hemorrhagic lesions which disrupt neuronal circuits or cause strategic lesions [42]; 2. — Interference with cerebrovascular autoregulation in response to blood pressure with resultant ischemia to white matter supplied by Aβ-laden meningocortical arteries [43]; 3. — Lowering the threshold of dementia in a predisposed patient (e.g. AD patient) [40,44] either by neuronal loss associated with the severity of CAA [45] or by functional disturbance of the transport of essential nutrients across the blood–brain barrier as a result of the deposition of Aβ in capillaries [44]. The observed patterns of cognitive impairment are related to the underlying mechanisms and location of vascular injury in CAA. Stepwise decline can occur both with recurrent lobar hemorrhage as well as with recurrent ischemia [1–3]. Though CAA related hemorrhages are known to involve cortical–subcortical regions and spare the structures most usually associated with strategic infarcts (e.g. thalamus and caudate), affected cortical regions (e.g. right parietal) can be, solely responsible for the cognitive decline of patients with CAA [46]. As well, the severity of white matter disease (WMD) and the presence of silent infarction on MRI scan are identified as important risk factors for subsequent cognitive decline and development of dementia [47].

Several studies support the hypothesis that there are links between white matter damage and CAA. There is diffuse white matter damage in hereditary forms of CAA (e.g. Dutch and Iowa) while in sporadic CAA there is often periventricular

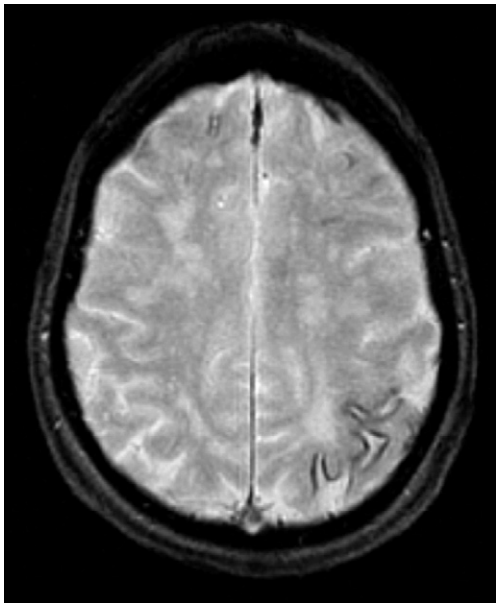

Fig. 7. Axial T2* GRE MR image of autopsy proven sporadic CAA case that experimented transient neurological symptoms (aphasia and right motor deficit). This image shows low signal in a gyriform pattern over the left parietal lobe, attributable to deposited iron products in a superficial meningeal or subpial location.

leukoencephalopathy featuring gliosis, myelin loss, and hyalinization of the blood vessel walls [30,48]. White matter disease is associated with increased cognitive decline in about 20% of the patients, particularly those where it is severe. Patients with WMD have a high incidence of concomitant petechial hemorrhages that can negatively affect their cognitive performance [39]. Though not specifically addressed, it is presumed that the involvement of the subcortical and particularly periventricular white matter, and the concomitant circuit disruption leads to a pattern of cognitive decline where apathy, impaired executive function and psychomotor slowing predominating over impaired episodic memory. On the other hand, when the memory deficit is the dominant presenting feature, over speed of processing, gait and other cognitive domains it is plausible that both parenchymal and vascular amyloid are playing synergistic roles in the process.

3.4. Subacute to rapidly progressive cognitive decline

There are some clinical circumstances, where CAA becomes associated with a more rapidly progressive rate of cognitive decline and dementia. In such instances the Aβ vascular deposits or CAA seem to become associated with a full blown angiitis, where there is a profuse inflammatory response including multinucleated giant cells in vessel walls and where macrophages can be seen to have internalized amyloid [49,50]. There have been a total of 41 cases with such a CAA associated angiitis wherein a rapidly progressive dementia has been the most frequent presentation. Language and praxis are amongst the most frequently affected cognitive domains within these cases while headaches, seizures, hallucinations and confusion have also been reported concomitantly. These case series are likely biased towards the most serious presentations that progressed to autopsy, leaving open to speculation whether there might be more minor clinical symptoms might be seen in CAA patients with lesser inflammatory responses.

The aggressive clinical and radiographic picture observed in these patients, and the responses to immunosuppressive treatment has suggested that the inflammation is playing a direct role.

In isolated case-reports CAA has been described with a reversible leukoencephalopathy, sometimes associated with documented vessel inflammation, and other times with hypertension though these are not frequent presentations [51,52].

3.5. Hereditary forms of CAA

Hereditary forms of CAA are rare and account for a minority of the CAA cases. [2] Most of these forms of CAA are associated with amyloid precursor protein mutations while they also occur with mutations of cystatin C, presenilin, prion protein, transthyretin, gelsolin and in other amyloidoses [30,31,53–80]. There is some recognized phenotypic variability where the clinical characteristics within the hereditary group include a broader spectrum of presentations than within sporadic disease, usually with a younger age of onset (Table 1). Clinical signs in the hereditary forms can include spastic paraparesis, extrapyramidal signs, progressive ataxia or ocular disturbances, features that have not been part of the spectrum of sporadic cases [66–75].

These already characterized families (Table 1) demonstrate the pleomorphism of CAA clinical presentations and the need for further characterization of sporadic CAA to elaborate whether these are systematic differences between the hereditary and sporadic forms.

3.6. Aging and CAA

CAA is a frequent finding in autopsy series of individuals without dementia (3–50%), particularly over the age of 65. It is not clear if in this context CAA is part of the normal aging process [3,7,18] or whether individuals were completely asymptomatic as these relationships are most often addressed retrospectively. The majority of these individuals have mild or moderate CAA, with symptoms and signs that may be very subtle or remain unnoticed by clinicians [2,3].

4. Conclusion

CAA describes pathological changes that occur in cerebral blood vessels, both leptomeningeal and cortical resulting from the deposition of amyloid proteins. The spectrum of clinical manifestations of CAA is evolving with recognition of hemorrhagic complications that range from subtle siderosis to large lobar hemorrhages. CAA has important relationships with cerebral white matter disease, subarachnoid hemorrhage and intraparenchymal lesions. Vascular function may be impeded in a variety of ways in CAA which allows for a broad clinical spectrum to be appreciated. In rare instances it may act as a trigger to a more aggressive dementia and inflammatory vasculopathy. Intracerebral hemorrhage in a cortical–subcortical location remains the most reliable method for diagnosing CAA during life aided through the use of gradient echo MRI.

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