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Cerebral amyloid angiopathy-related hemorrhages

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Abstract Cerebral amyloid angiopathy (CAA) is defined by the accumulation of amyloid in the walls of small- and medium-sized cerebral arteries. One of the most recognized complications of CAA is spontaneous, often recurrent, intracerebral hemorrhage, usually involving the cortex and/or subcortical white matter ("lobar hemorrhage"). Several useful animal and in vitro models as well as specific neuroimaging techniques have been recently developed, which are expected to provide detailed insight into the pathogenesis of CAA and contribute to the development of targeted antiamyloid therapies.

Keywords Cerebral amyloid angiopathy · Intracerebral hemorrhage · Stroke

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Amyloid is an in vivo deposited material, which can be distinguished from nonamyloid deposits by circumscript physical characteristics: β-pleated sheet configuration, apple green birefringence under polarized light after Congo red staining, fibrillary structure, and high insolubility [1]. There are about 30 proteins or their proteolytic products that can accumulate as amyloid in humans, and many different disease processes that can lead to amyloid formation. Amyloidosis is part of the expanding group of "disorders of protein folding" in which normal proteins improperly folded accumulate intra- and extracellularly in the form of aggregates and/or amyloid fibrils. Because of the specific tissue affinity of amyloid deposition, which leads to accumulation in specific organs or at specific sites, only a minority of human amyloid proteins are implicated in diseases of the central nervous system (Table 1). The reasons for tissue selectivity are not known and may reflect exacerbated local synthesis, protein–protein interactions with specific tissue factors, resistance to enzymatic degradation, differential blood-brain barrier permeability, disregulated brain clearance mechanisms, or a combination of these factors.

The term cerebral amyloid angiopathy (CAA) is used to describe the pathological process during which an amyloid protein progressively deposits solely or predominantly in cerebral blood vessels, with a preference for small vessels (leptomeningeal and cortical arteries, arterioles, capillaries, and rarely veins), and with subsequent degenerative vascular changes. Depending on the severity of CAA, amyloid depositions have been shown primarily in the abluminal portion of the tunica media, often surrounding smooth muscle cells (SMCs), and in the adventitia. With increasing severity, amyloid infiltrates all layers of the vessel wall, which shows loss of SMCs. Finally, the vascular architecture is severely disrupted and ''double barreling,'' microaneurysm formation, fibrinoid necrosis,

Table 1 Amyloid peptides causing CAA in humans

Amyloid peptide	Precursor protein	Chromosome	Disease	Mutation	AA substitution		Hemorrhagic stroke
Aβ	APP		Sporadic CAA				+
			CAA related to sporadic AD				-
		21	CAA related to familial AD			Associated to PS-1 and PS-2 mutations	-
		21	CAA in Down syndrome				-
		21	HCHWA-Dutch type	G to C (693)	Glu22Gln	Described in two large families from the Netherlands Age at onset: 50 yrs	+
						Lobar hemorrhages, focal neurological deficits, dementia, and leukoencephalopathy	
			HCHWA-Italian type	G to A (693)	Glu22Lys	Described in 3 Italian families Age at onset: 50 yrs Lobar hemorrhages and dementia	+
			HCHWA-Flemish type	C to G (692)	Ala21Gly	Described in a Dutch family (discovered in Belgium, therefore called "Flemish") and a British family	+
						Age at onset: 45 yrs Progressive AD-like dementia, in some patients associated with a lobar hemorrhage	
			HCHWA-Iowa type	G to A (694)	Asp23Asn	Described in an Iowa family and a Spanish family Age at onset: 50–66 yrs	+
						Memory impairment, expressive language dysfunction, personality changes, myoclonic jerks, short-stepped gait, no clinically manifest ICH (family from Iowa) Lobar hemorrhages (family from Spain)	
			HCHWA-Piedmont type	G to C (705)	Leu34Val	Described in one family from the Piedmont region of Italy Age at onset: 50–70 yrs	+
						Recurrent lobar hemorrhages, cognitive decline	
			HCHWA-Arctic type	A to G (693)	Glu22Gly	Described in one family from northern Sweden	-
						Age at onset: about 60 yrs	
						Progressive cognitive decline (no strokes)	

Cont table →

Cont. Table 1

Amyloid peptide	Precursor protein	Chromosome	Disease	Mutation	AA substitution		Hemorrhagic stroke
ACys	Cystatin C	20	HCHWA-Icelandic type	A to T (68)	Leu68Gln	Described in 9 sub-families in Iceland (one sporadic case in the US); systemic amyloidosis Age at onset: 20–30 yrs Recurrent lobar hemorrhages	+
ATTR	Transthyretin	18	Meningovascular		Multiple mutations	Polyneuropathy is the main clinical symptom; in a small number of patients ataxia, spasticity and dementia; systemic amyloidosis	In some families
AGel	Gelsolin	9	FAF	G to A (654)	Asp187Asn	Progressive corneal lattice dystrophy, cranial and peripheral neuropathy, cutaneous amyloidosis; systemic amyloidosis	-
PrPS[c]	Prion protein	20	GSS (Y145Stop)	T to G (145)	Y145STOP	Described in one family Progressive cognitive decline	-
ABri	ABri precursor protein	13	FBD	T to A (266)	Stop to Arg	Described in 4 families Age at onset: 45–50 yrs Progressive dementia, cerebellar ataxia, spastic tetraparesis	-
ADan	ADan precursor protein	13	FDD	10-nucleotide duplication insertion after codon 265	Described in 1 dementia (previously known as "heredopatia ophtalmo-oto-encephalica")	- family from Denmark Age at onset: 30 yrs Cataracts, deafness, progressive ataxia,	

APP, amyloid precursor protein; *AD*, Alzheimer's Disease; *PS1*, Presenilin 1; *PS2*, Presenilin 2; *HCHWA*, hereditary cerebral hemorrhage with amyloidosis; *FAF*, familial amyloidosis, Finnish type; *GSS*, Gerstmann-Sträussler-Scheinker syndrome; *FBD*, familial British dementia; *FDD*, familial Danish dementia

and evidence of perivascular leakage may be seen. In most cases, the accumulated amyloid is composed of the amyloid-beta peptide (Aβ), the same found in the plaques of Alzheimer's disease (AD) patients.

The majority of CAA occurs as a *sporadic* disorder whose prevalence increases with ageing. In the rare *hereditary* forms, a precursor protein is abnormally metabolized by proteolytic pathways and accumulates as amyloid because of specific mutations in different genes inherited with an autosomal dominant pattern (Table 1).

Amyloid deposition in cerebral blood vessels can have several clinical consequences. First, it can remain asymptomatic, as suggested by the neuropathological observation that during "normal" ageing approximately 50% of individuals over 80 years of age have CAA. Second, it can weaken the vessel wall, causing rupture and intracerebral hemorrhage (ICH). Finally, it can obliterate the vessel lumen, leading to ischemia (cerebral infarction, "incomplete infarction," and leukoencephalopathy). Focal neurological deficits, disturbances of consciousness, step-wise dementia, and death can occur as a consequence of these vascular mechanisms. CAA-related hemorrhages (CAAH) account for 5%–20% of all spontaneous (non-traumatic) cerebral hemorrhages in elderly subjects, though ICH was found only in 5.4% of autopsy-confirmed CAA. The hallmark of CAAH and the basis for the clinical criteria set by the Boston group in the mid-1990s [2], is *lobar, cortical,* or *cortico-subcortical* cerebral hemorrhages, affecting normotensive individuals over age 55, frequently *multiple*, *recurrent*, which can extend from the cortex to the subarachnoid space or, less commonly, to the ventricles. The localization of CAAH follows the localization of CAA in the cerebral cortex and cortico-subcortical or lobar regions. Despite the high prevalence of CAA in the occipital cortex, CAAH has been shown to be more evenly distributed, with a slight predominance of occipital and frontal cortices. CAA and CAAH are typically absent in regions characteristic of hypertensive hemorrhages (deep brain regions, brainstem, and cerebellum). The diagnosis of CAA can only be made with certainty after histologic investigation of affected brain tissue, obtained at autopsy or brain-biopsy. In practice it is very often found unexpectedly at postmortem investigation. Noninvasive diagnostic criteria have been developed to reliably diagnose CAA during life [2]. This classification has been validated against pathological data. CAA is considered *"probable with supporting pathology"* when, in combination with appropriate clinical data, pathologic tissue from a biopsy performed at the time of hematoma evacuation reveals amyloid angiopathy. CAA is considered *"probable"* if there is an appropriate clinical history as well as imaging findings of *multiple* cortical-subcortical hematomas in a patient 55 years or older, with no other clinical or radiologic cause of hemorrhage. Finally, clinical data suggesting CAA and the imaging finding of a *single* cortical-subcortical hematoma in a patient older than 55 years, without other causes of hemorrhage, leads to a diagnosis of *"possible"* CAA. Hereditary CAA can be suspected based on the presence of a family history of cerebral hemorrhages and the young age of the patient.

As stated above, an important clue to diagnosis is the presence of multiple hemorrhages, most of which are petechial hemorrhages (*microhemorrhages*). CT and conventional or fast spin-echo T1- and T2*-weighted MR imaging sequences are relatively insensitive for such small microhemorrhages. Local magnetic field inhomogeneity related to the presence of hemosiderin in foci of microhemorrhages causes a marked loss of signal at T2*-weighted gradient echo (GRE) imaging, which is currently the most sensitive sequence for detection of the cortical-subcortical microhemorrhage associated with CAA. The presence of these cortical microhemorrhages lends specificity in patients presenting with acute ICH. More recently, positron emission tomographic imaging with the β-amyloid–binding compound Pittsburgh Compound B (PiB) has been reported as a reliable technique to detect cerebrovascular β-amyloid and a method for identifying the extent of CAA in living subjects [3].

In conclusion, CAAH is an important cause of morbidity and mortality in normotensive elderly patients. Early diagnosis of CAA, based on the recognition of clinical and imaging findings, may have practical implications in certain clinical situations, particularly when anticoagulation or thrombolysis are under consideration, and may allow the proper identification of those subjects who might benefit from future antiamyloid treatment strategies.

Conflict of Interest statement The Authors declare that they have no conflict of interest related to the publication of this manuscript

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