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Main features of hereditary cerebral amyloid angiopathies: A systematic review

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ABSTRACT

The term Cerebral Amyloid Angiopathy (CAA) refers to a group of neurovascular disorders characterized by amyloid deposition within the walls of leptomeningeal and cortical blood vessels of the brain, with specific predilection for arterioles, and (less often) capillaries and veins. Most CAA cases in the general population are sporadic in nature, and represent primarily an age-related condition affecting individuals in the fifth decade of life and beyond. Sporadic CAA is caused by deposition of amyloid-β (Aβ), originating from proteolytic cleavage of the Amyloid Precursor Protein (APP), within the walls of cerebral small caliber vessels. However, hereditary forms of CAA have also been described, generally presenting as rare familial disorder with monogenic (predominantly autosomal dominant) inheritance patterns. Hereditary CAA forms tend to affect younger individuals, and their course and clinical progression is more severe. Studies to date primarily focused on the vascular manifestations of sporadic and hereditary CAA, chiefly symptomatic lobar Intracerebral Hemorrhage (ICH). However, in the past decade sporadic CAA has also been consistently linked to progressive neurocognitive, neurobehavioral, and neuropsychiatric symptoms. This systematic review focuses on the genetics, pathogenesis, neuroimaging, neuropathology, and clinical manifestations of hereditary CAA with specific emphasis on previously overlooked cognitive, behavioral, and psychiatric symptoms.

Introduction

Cerebral Amyloid Angiopathy (CAA) is a group of genetically and biologically diverse degenerative disorders affecting the vasculature of the Central Nervous System (CNS). Although differing considerably in terms of clinical manifestations and findings on neuroimaging, all forms of CAA share characteristic findings on pathological examination. The diagnostic hallmark of CAA on histopathological samples are amyloid deposits within in the walls of small to medium-sized CNS blood vessels (mostly arterial), and less consistently within parenchymal and leptomeningeal capillaries [1–5]

The vast majority of CAA cases are sporadic in nature, with no discernible inheritance pattern identified from examination of pedigrees for affected individuals [2,6] Recent advances in genomic technology allowed investigators to identify a substantial genetic contribution to sporadic CAA. The genetic architecture of sporadic CAA was determined to be polygenic in nature, consistent with the combined effect of hundreds to thousands of low potency variants [5,7] However, a minority of CAA cases are rare familial forms with a monogenic (usually autosomal dominant) inheritance pattern [5,7,8] These monogenic familial forms of CAA are sometimes referred to as hereditary (in contrast to sporadic CAA), and tend to affect younger patients and generally lead to more severe clinical manifestations.

Although more than 25 human proteins were shown to form amyloid deposits in vivo, only 7 have been implicated in CNS disorders [2] Most hereditary forms of CAA are caused by mutation affecting the ß-amyloid peptide (Aβ-CAA), although non-Aβ forms of CAA have been reported (Table 1). This review will present the main features of established forms of hereditary (i.e. familial monogenic) CAA, with specific and novel emphasis on neurocognitive, neurobehavioral, and neuropsychiatric manifestations.

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Materials and methods

In order to obtain an initial list of manuscripts of interest we queried PubMed, Embase, Ovid, Medline, and Google Scholar (query completed on December 10th, 2021). Pre-defined search terms included: CAA, Cerebral Amyloid Angiopathy, Familial CAA, Monogenic CAA, Hereditary CAA, Hereditary Congophilic Amyloid Angiopathy, Hereditary Amyloidosis, and Hereditary Hemorrhagic Stroke. All possible combinations of these search terms were entered as separate queries, and results then combined to arrive at a combined list of relevant publications.

Table 1
Sporadic and Hereditary Cerebral Amyloid Angiopathies.

Amyloid peptide	Precursor protein	Chrom	Disease	Notes	Hemorrhagicstroke	Cognitive Decline	Behavioral / Psychiatric Symptoms
Aβ	APP	–	Sporadic CAA		+	+	+
Aβ	APP	–	CAA related to sporadic AD	No increase in lobar ICH risk	–	+	+
Aβ	APP	21	CAA related to familial AD	Associated to Presenilin-1 and Presenilin-2 mutations	–	+	+
Aβ	APP	21	CAA in Down syndrome	Lobar ICH is rarely observed	–	+	+
Aβ	APP	21	Hereditary Cerebral Hemorrhage with Amyloidosis: Dutch type	Age at onset: 50 years Lobar ICH, focal neurological deficits, dementia, and leukoencephalopathy	+	+	–
Aβ	APP	21	Hereditary Cerebral Hemorrhage with Amyloidosis: Italian type	Age at onset: 50 years Lobar ICH and dementia	+	+	–
Aβ	APP	21	Hereditary Cerebral Hemorrhage with Amyloidosis: Flemish type	Age at onset: 45 years Progressive AD-like dementia. Some patients present with lobar ICH	+/-	+	–
Aβ	APP	21	Hereditary Cerebral Hemorrhage with Amyloidosis: Iowa type	Age at onset: 50 - 66 years Memory impairment, expressive language dysfunction, personality changes, myoclonic jerks, short-stepped gait.	+/-	+	+
Aβ	APP	21	Hereditary Cerebral Hemorrhage with Amyloidosis: Piedmont type	Age at onset: 50 - 70 years Recurrent lobar ICH, cognitive decline	+	+	–
Aβ	APP	21	Hereditary Cerebral Hemorrhage with Amyloidosis: Arctic type	Age at onset: ~ 60 years Progressive cognitive decline, personality changes, paranoia, and hallucinations. No reports of lobar ICH.	–	+	+
ACys	Cystatin C	20	Hereditary Cerebral Hemorrhage with Amyloidosis: Icelandic type	Systemic amyloidosis Age at onset: 20 - 30 yrs Recurrent lobar ICH	+	–	–
ATTR	Transthyretin	18	Meningovascular amyloidosis	Systemic amyloidosis Polyneuropathy as main clinical symptom Rarer findings: ataxia, spasticity and dementia	in some families (rare)	+/-	–
AGel	Gelsolin	9	Familial Amyloidosis – Finnish Type	Systemic amyloidosis Progressive corneal lattice dystrophy, cranial and peripheral neuropathy, cutaneous amyloidosis	–	–	–
PrPSc	Prion Protein	20	Gerstmann-Sträussler-Scheinker syndrome	Progressive cognitive decline	–	+	+
ABri	ABri precursor protein	13	Familial British Dementia	Age at onset: 45 - 50 years Progressive dementia, cerebellar ataxia, spastic tetra paresis	–	+	–
ADan	ADan precursor protein	13	Familial Danish Dementia	Age at onset: 30 years Cataracts, deafness, progressive ataxia, dementia Previously known as "heredopatia ophtalmo-oto-encephalica"	–	+	–

Abbreviations: AD = Alzheimer's Disease, CAA = Cerebral Amyloid Angiopathy, Chrom = Chromosome, ICH = Intracerebral Hemorrhage, US = United States of America.

We identified additional studies via manual review of references for identified publications. .We then subsequently eliminated via manual review publications failing to meet all these criteria: 1) published after 1990; 2) full text available in English; 3) presenting novel data (duplicate publications, opinion and viewpoints, meta-analysis and reviews excluded); 4) presented clinical, neuroimaging, genetic or pathological data from human participants and/or specimens.

Aβ-related forms of hereditary (familial monogenic) CAA

The vast majority of hereditary CAA forms are caused by abnormal formation and deposition of vascular amyloid deposits comprised of Aβ protein [5,8] These familial CAA forms are caused by point mutation in the APP gene (Fig. 1), and generally are inherited in an autosomal dominant pattern. Although multiple clinical (earlier age at onset, more severe course) and neuropathological (severe CAA on tissue examination) features are shared across individuals carrying different APP mutations, in other respects each form differs in terms of symptoms at presentation and during disease progression.

Dutch mutation

From an historical perspective the Dutch form of familial CAA, also known as Hereditary Cerebral Hemorrhage with Amyloidosis Dutch (HCHWA-Dutch) type was the first to be identified and characterized. To this day, it remains by far the best described and investigated form of hereditary CAA. HCHWA-Dutch type is a rare autosomal dominant disorder caused by a mutation at codon 693 of the APP gene (E693Q), resulting in the substitution of a glutamine for a glutamic acid at position 22 of the Aβ sequence [9,10] The original report identified affected individuals among two large Dutch families originating from Katwijk, a coastal village in the Netherlands. Although a common founder is hypothesized to be responsible for all identified cases in these kindreds, his/her identity could not be determined leveraging genealogical records tracing back the early 17th century. To date investigators have analyzed clinical, neuroimaging and histopathological data for over 200 patients (either alive or deceased), with another 400 individuals being at 50% risk for inheriting the disease. Almost all affected patients presented with recurrent, clinically symptomatic intracerebral hemorrhages and infarcts, usually between the age of 45 and 55 years old and often leading to early death [11,12] In some affected individuals stroke onset was preceded by recurrent non-specific or migraine-like headaches, with or without transient focal neurological deficits. Cognitive decline is a frequent observation among HCHWA-Dutch type patients age 40 and above, and appears to be primarily attributable to CAA and independent of plaque and neurofibrillary tangles pathology. No specific behavioral and neuropsychiatric disturbances have been reported to date among affected individuals. Pathological examination of affected individuals was notable for extensive vascular Aβ deposition leptomeningeal, cerebral cortical and cerebellar cortical in arterioles and arteries. Although different types of diffuse amyloid parenchymal deposits were present in the brain of older participants, neuritic plaques or neurofibrillary tangles were rarely observed [8]

Italian mutation

The Hereditary Cerebral Hemorrhage with Amyloidosis Italian (HCHWA-Italian) type is caused by an APP mutation at codon 693 (E693K), resulting in substitution of a glutamic acid for a lysine at residue 22 of Aβ. It was identified in several members of three unrelated kindreds from Italy, who presented in the sixth and seventh decade of life with progressive, predominantly amnestic, cognitive impairment

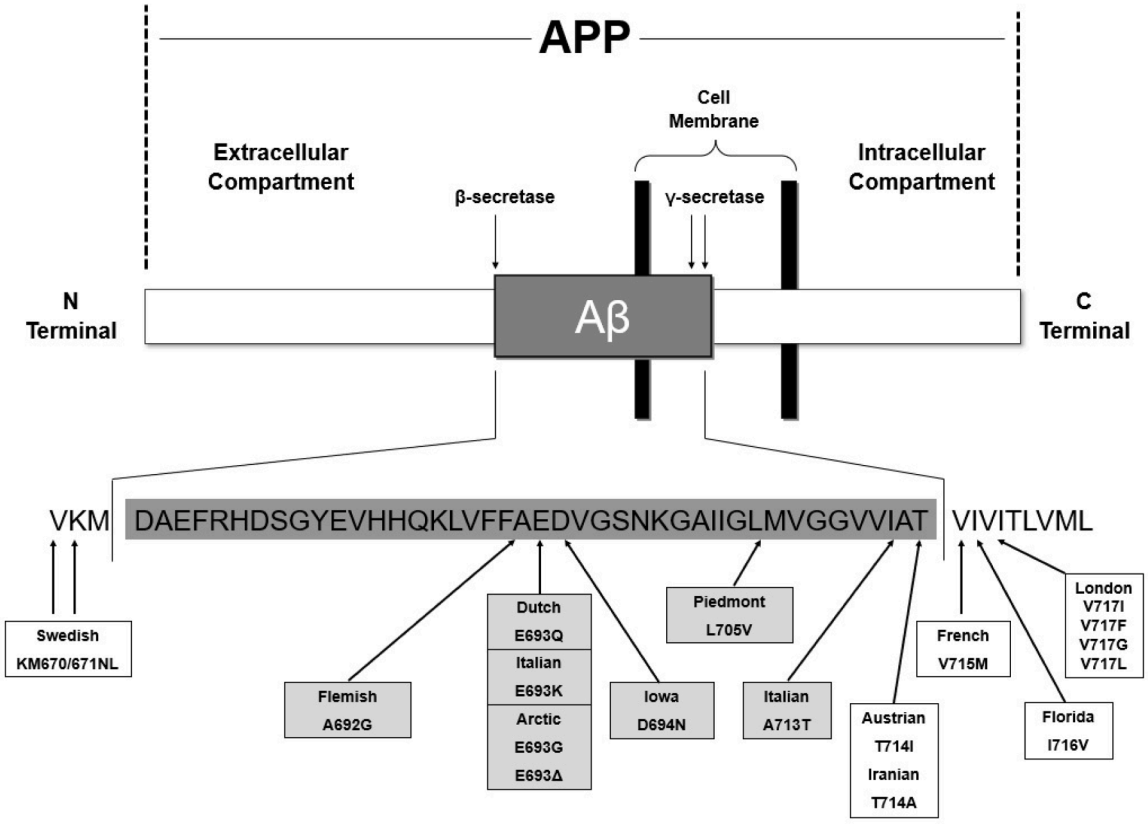

Fig. 1. APP Gene Mutations Resulting in Hereditary CAA. Mutations with a gray background were determined to predominantly manifest as severe CAA in tissue samples from affected individuals, out of proportion for concomitant parenchymal amyloid beta deposition.
Abbreviations: APP = Amyloid Precursor Protein.

associated with recurrent lobar hemorrhages. No specific behavioral or neuropsychiatric disturbances were reported. In some individuals (three based on direct confirmation) seizure disorder was also part of the clinical presentation. Pathological examination was notable for extensive Aβvascular deposits in the leptomeningeal and cortical small blood vessels, which appeared amorphous rather than fibrillar in morphology. Aβ deposition was also present, albeit to a lesser extent, in the cerebral parenchyma with plaque morphology in the absence of neurofibrillary changes and neuritic plaques [13,14]. A separate mutation (A713T) also occasionally referred to as "Italian" was separately described in two Italian families with members affected by autosomal dominant AD and with evidence of multiple infarcts on pathology [15,16] Substantial heterogeneity among affected individuals was reported in terms of neuropathological findings, ranging from minimal CAA with prominent parenchymal amyloid and tau accumulation to severe widespread CAA associated with micro-hemorrhages and infarcts.

Iowa mutation

The Iowa mutation at codon 694 within the Aβ region of APP results in substitution of an asparagine for aspartic acid (D694N) at Aβ position 23 [17] It was originally described in an Iowa family of Saxon German descent spanning three generations, and including 12 symptomatic individuals [18] A second family from Spain carrying the identical mutation was also described, and included four affected members [19] More recently seven individuals affected by early-onset ICH over three generations in a Polish family were identified as carrying the Iowa mutation [20] In all these families the initial presentation usually consisted of progressive cognitive decline, initially amnestic and later prominently involving aspects of language process and naming. No specific mention was made of prominent behavioral or neuropsychiatric symptoms in either family. Although microhemorrhages could be identified on MRI and postmortem examination in the Iowa pedigree, there were no reported episodes of clinically manifest ICH. In contrast, three of four symptomatic members of the Spanish family and four of seven symptomatic members of the Polish family did experience ICH. Taken together, these findings suggest considerably heterogeneity in the clinical presentation for the same APP point mutation. Neuropathologically all these patients are characterized by severe CAA with numerous small cortical hemorrhages and both cortical and subcortical infarcts. Aβ plaques, while present, were relatively sparse and generally of diffuse morphology. Abundant neurofibrillary tangles and dystrophic neurites were also identified. a notable contrast to carriers of the Dutch mutation.

Flemish mutation

The Flemish APP mutation (A692G) is located at codon 692 of the APP protein, and results in substitution of an alanine by a glycine at residue 21 of the Aβ sequence. This mutation was first reported in a four-generation large Dutch family with 17 affected members, which were retrospectively identified from family informants or medical records [21] An additional report identified a British family including 5 affected members over three generations, also identified via a combination of family informants and medical records [22] Symptomatic individuals presented with progressive cognitive impairment between the ages of 39 and 54, with neuropsychological testing consistent with predominantly amnestic cognitive impairment. In two cases behavioral symptoms (irritability and resistance to care) were noted later in disease course, though reportedly were mild in severity. Most individuals also manifested clinical and radiographic evidence of lobar hemorrhages (usually later in disease course), which were more common in the Dutch than British family. In both families neuropathology was consistent with severe CAA (including in most cases cerebral micro- or macro-hemorrhage) superimposed with AD with large core plaques, enclosing parenchymal vessel or associated with vascular walls.

Piedmont mutation

This APP mutation has been more recently identified in association with CAA and lobar hemorrhages. The identified mutation (L705V) lies within the Aβ region of APP, but it is located further away from the previously identified cluster of mutations in the 21 to 23 positions. This G to C transversion in APP codon 705 leads to a valine for leucine substitution at Aβ residue 34. In the original report four members of a family from the Piedmont subalpine region of Italy spanning three separate generations presented with multiple lobar hemorrhages at ages ranging from 50 to 72 [23] Brain pathological data was available via autopsy for a single individual, and notable for widespread severe vascular Aβ deposition, most pronounced in leptomeningeal vessels and to a lesser degree in cortical vessels and capillaries. No evidence of Aβ and tau parenchymal deposition or hypertensive arteriopathy were identified. An additional report identified a single case from the United States of America (Boston, Massachusetts) with similar clinical presentation and autopsy findings [24] Only one of the individuals described in the literature displayed evidence of cognitive impairment, and only after having suffered at least four separate lobar hemorrhagic strokes (implying accumulation of acute, hematoma-related injuries as most likely mechanism). No pre-hemorrhage cognitive complaints or symptoms were identified among otherwise symptomatic individuals. No specific behavioral symptoms were mentioned in either published report, either pre-dating or after hemorrhagic stroke.

Arctic mutation

The "Arctic" APP mutation (E693G) at codon 693 of APP/residue 22 of Aβ consists of an A to G transition resulting in substitution of glycine for glutamine [25] It was first identified in an extended family from a small village in northern Sweden including 11 affected individuals spanning four generations [26] And additional six individuals with the Arctic mutation and presenting with early-onset dementia over four generations were identified in the United States of American in a family of Swedish descent, and thus likely to be related to the Swedish family with the same mutation [27] Symptomatic individuals presented between the age of 54 and 72 years with progressive, predominantly amnestic cognitive decline. Most individuals also displayed spatial and temporal disorientation, dysphasia, and dyspraxia relatively early in the course of the disease. Psychiatric and behavioral symptoms affected more than half of participants and usually followed onset of cognitive impairment, and included primarily anxiety, paranoid ideation and hallucinations [27] Although clinical history was notable for no report of ischemic or hemorrhagic strokes, in the two autopsy cases of Arctic mutations carriers were notable for severe vascular amyloid deposition in leptomeningeal and cortical vessels, as well as numerous micro-infarcts. Interestingly, no neuroimaging or pathological evidence of amyloid-related hemorrhagic lesions were identified.

Other hereditary Aβ-CAAs

Several other mutations within the APP gene have been reported in the literature (see Fig. 1). From a neuropathological and clinical standpoint, affected individuals presented with early-onset AD characterized by accelerated parenchymal amyloid deposition but are generally not associated with disproportionate CAA severity due to vascular Aβ deposits. These mutations involve substitutions of residues flanking the Aβ region of APP, with their proposed mechanism of action primarily revolving around altered APP processing and consequent abnormal Aβ production [28]

Non-Aβ forms of hereditary (familial monogenic) CAA

Non-Aβ amyloidosis without prominent angiopathy

A number of non- Aβ forms of CAA have been identified and described in previous reports, and are attributable to formation of vascular amyloid deposits of the following proteins (see Table 1): 1) amyloid-British protein (ABri), responsible for familial British dementia (FBD); 2) amyloid-Danish protein (ADan), responsible for familial Danish dementia (FDD); 3) gelsolin, responsible for familial amyloidosis Finnish type (FAF); 4) prion protein (PrP), responsible for Gerstmann-Sträussler-Scheinker (GSS) syndrome; 5) TTR, responsible for meningovascular amyloidosis; and 6) cystatin C, responsible for the Hereditary Cerebral Hemorrhage with Amyloidosis Icelandic (HCHWA-Icelandic) type of CAA. Vascular amyloid involvement of leptomeningeal or cerebral vessels has been described in essentially all of these syndromes, which also generally display evidence of progressive cognitive decline among relatively young individuals - with or without focal neurological deficits. However, clinically manifest hemorrhagic or ischemic strokes are relatively rare among affected individuals, with the exception of HCHWA-Icelandic type.

Icelandic mutation

HCHWA-Icelandic type (also referred to as Hereditary Cystatin C amyloid angiopathy, or HCCAA) was first identified in the Breidafjordur Bay region of Iceland, with over 200 individuals affected within 9 sub-families across six generations, as determined via postmortem diagnosis, patient medical records, and death certificates, or by tracing obligatory gene carriers through the families. Although a common founder has not been identified to date, all sub-families share the same mutation at codon 68 of Cystatin C gene at chromosome 20 resulting in a glutamine for a leucine in the cystatin C gene (l68Q) [29,30] Transmission has been determined to be autosomal dominant. HCCAA usually presents with acute hemorrhagic in an otherwise previously healthy young adult, usually without precipitating events. Most patients survive the first hemorrhagic strokes, only to develop recurrent ones. Those surviving two or more events eventually develop progressive cognitive decline, though to result from cumulative CNS damage from repeated acute injuries. A very small percentage of individuals present without acute hemorrhagic stroke, but rather with progressive cognitive decline (multi-domain, with predominant involvement of memory and executive functions) or with neuropsychiatric symptoms (refractory depression with or without paranoid ideation and hallucinations). Non-stroke initial presentations are more common among patients developing symptoms in the fifth decade or later, which are a small minority of all affected individuals. Affected individuals were usually in the third decade of life at time of death, although the youngest patient died at age 15 and the oldest lived past age 50. From a pathophysiological standpoint, mutated Cystatin C has been shown to form amyloid deposits. These are primarily involving cerebral arteries and arterioles, though tissues outside the CNS (such as skin, lymph nodes, testis, spleen, submandibular salivary glands, and adrenal cortex) are affected to a substantially lower degree. Vascular amyloid deposition within vessel walls is thought to result in thickening, leading to occlusion and rupture - ultimately resulting in acute brain hemorrhagic events. Although mutated Cystatin C amyloid deposits can be identified outside the CNS, clinical manifestation are almost exclusively restricted to the brain [29] Histopathological findings include widespread vessel wall Cystatin C staining and hyalinization throughout the brain (including the optic nerve) and spinal cord, resulting in concentrically narrowing vessels ultimately resulting in occlusion. in some cases to the point of complete occlusion. Affected vessels frequently display media damage and microaneurysm formation, as well as increased volume of surrounding perivascular spaces, sometimes containing hemosiderin loaded macrophages.

Conclusion

Upon review of currently available evidence in regard to hereditary forms of CAAs, several consistent trends emerge. The monogenic familial forms of CAA are generally far more severe than sporadic forms of CAA, owing in large part to the usually highly penetrant autosomal dominant mutations. In most cases familial CAA presents with earlier age at onset, whether in the form of acute stroke or progressive cognitive decline. It is, however, worth noting that substantial variations in age at onset exist both across different mutations and within affected kindreds, ranging from the second to sixth decade of life. Affected patients are also younger at time of death or severe neurological compromise, once again with substantial differences across different mutations and individuals.

Existing evidence points to similarities in clinical manifestations between sporadic and hereditary CAA, with lobar hemorrhages (in the form of ICH or microbleeds) and progressive cognitive decline that is often found to be independent of concomitant AD pathology [31,32] In recent years multiple investigative groups provided evidence of specific patterns in cognitive impairment emerging on neuropsychological testing of individuals diagnosed with both sporadic and hereditary CAA [3,4,6,33] Specifically, deficits in perceptual speed and (less prominently) perceptual memory have been consistently associated with CAA, independently of concomitant AD pathology. These findings reinforce the hypothesis that CAA, in its sporadic and familial forms alike, represents an independent contributor to cognitive decline. Mirroring previous observations in sporadic CAA, individuals diagnosed with hereditary CAA appear to develop progressive cognitive decline owing in large part to two (often coexisting) mechanism: 1) step-wise accumulation of CNS injury due to repeated symptomatic hemorrhagic and/or ischemic strokes; and 2) chronically progressive and diffuse CNS injury due to accumulation of microvascular ischemic and hemorrhagic lesions [34,35] Future studies of CAA-related neurocognitive symptoms will therefore continue to benefit from addressing this mechanistic heterogeneity, which is likely to result in different therapeutic approaches in clinical practice, i.e. acute interventions to limit ICH-related injury vs. long-term treatments to delay or arrest progression of diffuse vasculopathy related to amyloidosis.

Recent evidence has also linked CAA to neurobehavioral and neuropsychiatric symptoms as well, chiefly depression and apathy [36–39] However, systematic exploration of these manifestations in hereditary CAA has been limited to date [5] Some forms of familial CAA (those with the Iowa and Arctic mutations in particular) appear to be more consistently associated with neurobehavioral and neuropsychiatric symptoms, usually in the form of personality changes, paranoia, and hallucinations. Minor neuropsychiatric symptoms are occasionally diagnosed among individuals affected by other forms of hereditary CAA, usually in the form of anxiety or depression. It remains unclear from review of currently available evidence whether these findings reflect either: 1) lower rates of behavioral and psychiatric symptoms, compared to acute stroke and cognitive decline, among patients with familial CAA; or 2) limited ability to capture and characterize these symptoms due to most studies focusing on progressive neurological manifestations. The aforementioned findings linking sporadic CAA with multiple behavioral and psychiatric symptoms imply that future dedicated studies may be needed to fully characterize these same clinical manifestations in familial CAA. Furthermore, our insight into the biological mechanisms responsible for neurobehavioral and neuropsychiatry symptoms in sporadic and hereditary CNS amyloid angiopathies is currently limited. Better characterization of fundamental process linking CAA to non-stroke clinical manifestations would directly inform patient care, as well as potentially identify novel treatment targets for these conditions in patients affected by both sporadic and familial forms.

Declaration of Competing Interest

No conflicts of interest to disclose

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