LETTER TO THE EDITOR

To The Editor

Chronic Atrial Intestinal Dysrhythmia Syndrome Is Associated with Cerebral Small Vessel Disease and Predominantly Cerebellar Microbleeds

Keywords: Stroke, Stroke in young adults, Stroke genetics, Small vessel disease, Microbleeds, CAID syndrome

Chronic atrial intestinal dysrhythmia (CAID) syndrome is an autosomal recessive cohesinopathy in which *SGOL1* K23E mutation leads to disruption of cardiac and intestinal pacemaker cells, leading to sick sinus syndrome (SSS) and chronic intestinal pseudo-occlusion (CIPO).[1] Neurologic manifestations of CAID syndrome have not been described. This case series reports two patients with cerebral small vessel disease (CSVD) associated with CAID syndrome.

A 46-year-old woman presented with a bilateral acute pontine hemorrhage. Her past medical history was positive for genetically confirmed CAID syndrome with CIPO and SSS since adolescence. She was anticoagulated with warfarin on account of multiple thromboses of her total parenteral nutrition (TPN) jugular catheter. Other comorbidities included hypertension, glucose intolerance, and left-sided hearing loss attributed to a labyrinthitis. She did not smoke nor consume alcohol and illicit drugs. Her family history was unremarkable.

Initial laboratory findings revealed an international normalized ratio of 2.9 (normal 0.8–1.15) and platelet count of 208×10^9/L (normal 145–470×10^9/L). Following initial imaging, she received prothrombin complex concentrate. CT angiography was normal. Brain MRI revealed periventricular white matter T2/FLAIR hyperintensities greater than expected for her age, sparing the anterior temporal lobes, as well as multiple (> 50) cerebral microbleeds on susceptibility weighted imaging (SWI), predominantly (>40) within the cerebellum (Figure 1). In hindsight, cerebellar microbleeds were present on imaging performed for hearing loss 8 years earlier.

Additional workup including CSF analysis was negative for an infectious or inflammatory vasculitis (negative ANA, ENA, ANCA, antiphospholipid antibodies, syphilis, and normal CRP). Neuro-ophthalmological examination and fluorescein angiography were normal. A genetic microangiopathy panel (*NOTCH3, HTRA1, COL4A1, COL4A2, FOXC1, GLA,* and *TREX1*) was negative.

A 42-year-old man presented for sudden-onset clumsiness of the left hand. His past medical history was positive for a presumptive diagnosis of Crohn's disease, treated with azathioprine, and atrial fibrillation diagnosed at the age of 23. He was not under antithrombotic therapy. He reported regular tobacco and cannabis consumption. His brother was known for CIPO and died at the age of 20 following an idiopathic non-aneurysmal subarachnoid hemorrhage, according to his autopsy report.

Cerebral CT scan revealed embolic appearing chronic infarcts in the left cerebellum and right frontal lobe. CT angiography detected a 2.5 mm partially thrombosed aneurysm on the right anterior cerebral artery. Brain MRI confirmed acute ischemic lesions in the right frontal lobe and left cerebellum and revealed the presence of periventricular and central pontine T2/FLAIR hyperintensities, greater than expected for age and sparing the anterior temporal lobes, as well as multiple (> 50) cerebral microbleeds, predominantly (> 40) within the cerebellum (Figure 2).

Transesophageal echocardiogram was normal. Inflammatory, hypercoagulable, and infectious workups including lumbar puncture were unremarkable (CSF: negative varicella zoster virus PCR; serum: negative ANA, ENA, ANCA, antiphospholipid antibodies, syphilis, HIV, and normal CRP). Neuro-ophthalmological evaluation and hereditary microangiopathy panel (*NOTCH3, HTRA1, COL4A1, COL4A2, FOXC1, GLA,* and *TREX1*) were normal. He was normotensive during his hospital stay.

Previous CT enterography and intestinal biopsies were reviewed and were inconclusive for Crohn's disease. Due to the common phenotype with patient 1 (documented bradycardia compatible with SSS, gastrointestinal disease, and cerebral microbleeds with a predominantly cerebellar pattern), genetic testing was ordered and revealed a homozygous K23E mutation in *SGOL1*, confirming CAID syndrome.

He was empirically referred for left auricular appendage closure for secondary stroke prevention, as the risk of intracranial hemorrhage was considered too high to maintain long-term anticoagulation. Azathioprine was discontinued. While impossible to confirm, it was deduced that CAID syndrome was likely in his deceased brother due to the presence of CIPO.

We report two cases that expand the spectrum of CAID syndrome to involve neurological manifestations, namely CSVD, with a unique pattern of predominantly cerebellar microbleed development. This finding may be of importance for patients with confirmed CAID syndrome, regarding risk stratification for management of atrial arrhythmias, present in 35% of cases.[1] Although rates of CAID-associated intracranial hemorrhage are unknown, these patients may be at an increased risk. CAID syndrome has been mostly described in French–Canadian patients with SSS and CIPO requiring TPN. Mutations in *SGOL1* have also been detected in European populations.[1] Brain MRI could help identify patients with a potentially milder cardiac and gastrointestinal phenotype, such as patient 2.

The *SGOL1* gene encodes for the shugoshin-like 1 protein and is implicated in the cohesin complex, holding together sister chromatids in the M phase of the cell cycle. It is thought that disruption in functions other than chromatic cohesion could lead to the clinical manifestations of cohesinopathies.[2] Chetaille et al. highlight upregulation of TGF-β signaling and fibrosis in intestinal biopsies of patients with the disease.[1] An association has been established between disturbed TGF-β signaling and multiple forms of CSVD (e.g., CADASIL).[3]

The pathophysiology of SSS and CIPO in CAID syndrome is not well understood. Normal function of the sinus node and intestinal Cajal cells at birth suggests an acquired component to the phenotype, possibly via premature senescence of specific cell subpopulations, as supported by accelerated cell turnover in fibroblast-based models.[1] Higher rates of valvular anomalies in CAID syndrome and its novel association with CSVD suggest that the disease does not uniquely affect pacemaker cells of the heart and gut.

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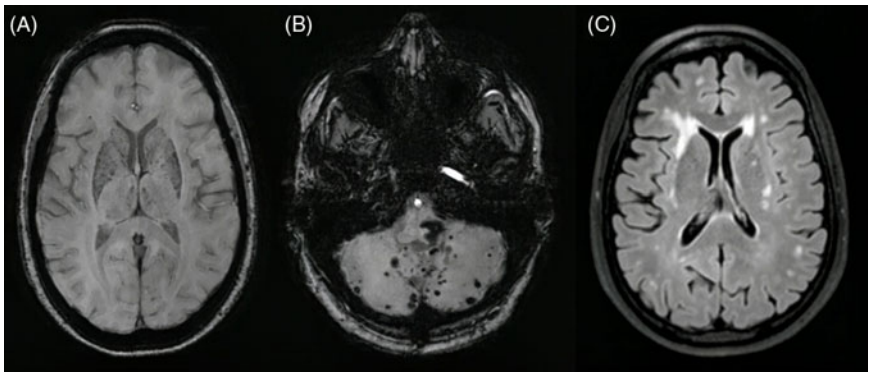

Figure 1: *Axial SWI images (A and B) reveal predominantly cerebellar microbleeds and left pontine hemorrhage in patient 1. Axial FLAIR (C) shows confluent white matter hyperintensities.*

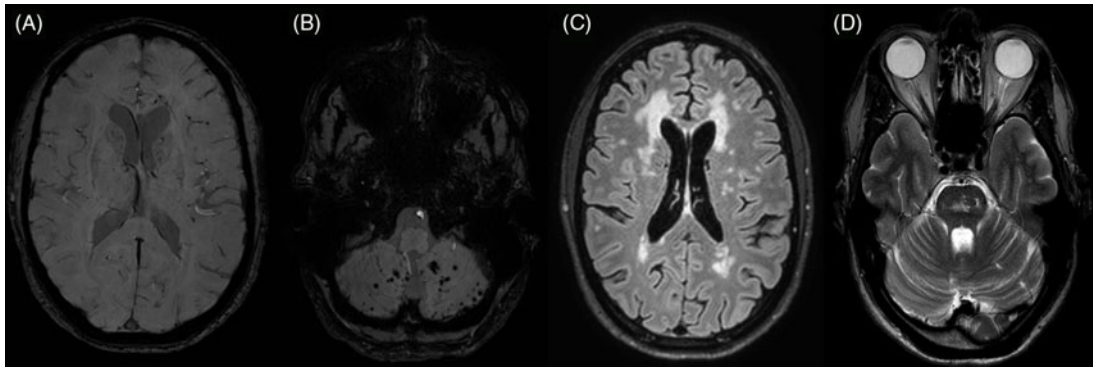

Figure 2: *Axial SWI images (A and B) demonstrate predominantly cerebellar microbleeds in patient 2. Axial T2/FLAIR shows confluent periventricular (C) and central pontine (D) white matter hyperintensities.*

Periventricular and central pontine white matter hyperintensities in our two patients are indistinguishable from imaging findings associated with hypertensive arteriolosclerosis. The presence of predominantly cerebellar microbleeds is however unique. Certain hereditary forms of CSVD show a predilection for specific brain regions, such as the anterior temporal lobe in CADASIL and the pons in pontine autosomal dominant microangiopathy and leukoencephalopathy.[4,5] With aging, posterior brain arteries have thinner walls and less elastin than their anterior counterparts.[6] We hypothesize that the posterior circulation might be more vulnerable to insults such as hypertension and aging and that *SGOL1* mutation might lead to primarily cerebellar microbleeds via premature senescence of cerebellar arterioles and TGF-β induced vessel wall fibrosis.

In conclusion, this case series reports a novel association between CAID syndrome and CSVD. The phenotype consists of periventricular/central pontine white matter T2/FLAIR hyperintensities and predominantly cerebellar microbleeds. Further research is needed to explain the mechanism behind *SGOL1* mutation and CSVD development.

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Disclosures

The authors declare no conflicts in relationship with the realization of this study.

Statement of authorship

AN designed the study, acquired data, and drafted the manuscript. LCG, GJ, AYP, LL, and CO acquired data and reviewed the manuscript.

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