A rare cause of monogenic cerebral small vessel disease and stroke: Cathepsin A-related arteriopathy with strokes and leukoencephalopathy (CARASAL)

Letter to the editor

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Abstract

Background

Cathepsin-A related arteriopathy with strokes and leukoencephalopathy (CARASAL) is a rare monogenic cause of cerebral small vessel disease. To date, fewer than 15 patients with CARASAL have been described, all of common European ancestry.

Methods

Clinical and imaging phenotypes of two patients are presented. Genetic variants were identified using targeted Sanger and focused exome sequencing respectively.

Results

Both patients carried the same pathogenic p.Arg325Cys mutation in *CTSA.* One patient of Chinese ethnicity presented with migraine, tinnitus and slowly progressive cognitive impairment with significant cerebral small vessel disease in the absence of typical cardiovascular risk factors. She later suffered an ischaemic stroke. A second patient from Brazil, of Italian ethnicity developed progressive dysphagia and dysarthria in his 50s, he later developed hearing loss and chronic disequilibrium. Magnetic resonance imaging in both cases demonstrated extensive signal change in the deep cerebral white matter, anterior temporal lobes, thalami, internal and external capsules and brainstem.

Conclusions

CARASAL should be considered in patients with early onset or severe cerebral small vessel disease, particularly where there are prominent symptoms or signs related to brainstem involvement, such as hearing dysfunction, tinnitus or dysphagia or where there is significant thalamic and brainstem involvement on imaging.

Keywords: Stroke, Genetics, Small Vessel Disease, CARASAL, Leukoencephalopathy

Monogenic forms of cerebral small vessel disease are a rare but important cause of stroke and cognitive impairment. The most common disorder is cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) caused by mutations in *NOTCH3*[1]. A less common autosomal recessive disorder with clinical and imaging similarities to CADASIL is CARASIL (cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy), which is caused by mutations in *HTRA1*[1].

In 2016, Bugiani *et al* described two families affected by an autosomal dominant form of cerebral small vessel disease and stroke caused by a mutation in *CTSA*, which encodes the carboxypeptidase enzyme Cathepsin-A. They reported 13 patients with symptom onset between the third and fifth decade, with migraine and gait disturbances, transient ischaemic attacks and both ischaemic and haemorrhagic stroke. They named this disorder Cathepsin-A related arteriopathy with strokes and leukoencephalopathy (CARASAL)[2].

We later described an additional patient with CARASAL with prominent brainstem symptoms and signs, in particular hearing abnormalities, tinnitus and vertigo[3]. Haplotype analysis of that British patient demonstrated a common ancestor with the Dutch families described by Bugiani *et al*. However, since then, no further patients with CARASAL have been reported.

Here we describe an additional two patients with CARASAL, in whom hearing abnormalities and tinnitus were also prominent features, in addition to cognitive impairment, ischaemic stroke and extensive small vessel disease. These patients were of Chinese and Italian ethnic origin, respectively, confirming the importance of considering this diagnosis in diverse populations.

Patient 1

A 64-year-old woman of Chinese ethnicity developed migraine headaches aged 42 years. The headaches were unilateral and occurred 4-5 days per week. In subsequent years, she developed progressive hearing loss, affecting the left more than right side, followed by left sided tinnitus. At age 46 years, mild cognitive difficulties emerged, including impaired registration of new information, difficulty remembering names and understanding the meaning of some words. This slowly progressed; by age 50 years she also had difficulty with spelling, losing items, and navigation.

She was a non-smoker, did not drink alcohol, and did not have hypertension, hypercholesterolaemia or cardiac disease. Birth and early life were unremarkable. Her father died at the age of 63 years from stroke, but her maternal family history was unknown.

At age 49 years, MRI of the head demonstrated extensive signal change within the dorsal pons, superior cerebellar peduncles and predominantly deep cerebral white matter including the temporal lobes, without volume loss (Figure 1 A, B). A vasculitis and thrombophilia screen including anticardiolipin antibodies was negative. White cell enzyme levels were in the normal range. Skin biopsy demonstrated mild solar elastosis and mild perivascular chronic inflammation, but no granular osmiophilic material. A lumbar puncture was performed; the cerebrospinal fluid white cell count was less than 1.

At age 61 years, performance IQ was measured at 89 with weaknesses in executive function and memory. Naming, visual perceptual and processing speed were normal.

At age 64 years, she was admitted with wake-up right sided hemisensory symptoms in the face, arm and leg. On examination she had a mild right facial droop, and a mild pronator drift on the right. Power was MRC Grade 5/5 throughout. Reflexes were present throughout without spread, and plantar responses were flexor bilaterally. The patient was able to detect temperature differences on the right but found this more challenging than on the left. Pinprick sensation was equal bilaterally. MRI head demonstrated acute infarcts in the left pulvinar and left parietal cortex, as well as white matter hyperintensities in the internal and external capsules, brainstem and thalami, without cerebral microbleeds (Figure 1 – D-G). She was treated with a 300mg loading dose of aspirin and subsequently aspirin 75mg once daily. Two days after this event, she developed new sudden onset right sided hemisensory loss and weakness. Repeat MRI head demonstrated a new focus of restricted diffusion in the left lateral thalamus. Clopidogrel 75mg daily was then added in addition to aspirin. No significant steno-occlusive disease was found on CT Angiogram of neck and intracranial vessels.

A next generation sequencing panel targeting the following genes revealed no potentially pathogenic variants: *NOTCH3, HTRA1, APP, CSF1R, ITM2B, MAPT, FUS, VCP, PRNP, PSEN1, PSEN2, TREM2, TARDBP, DNMT1, GRN, CMHMP2B*

Targeted sanger sequencing of *CTSA* revealed the c.973C>T p.(Arg325Cys) heterozygous variant associated with CARASAL.

Patient 2

This Brazilian man developed slowly progressive dysphagia and dysarthria aged 55 years. At the age of 67 years, he had severe dysphagia, and experienced several episodes of syncope; on one occasion he fell while holding hot water and sustained burns to the chest and neck. After this he required a tracheostomy and gastrostomy for feeding. Cardiac and autonomic testing revealed only mild orthostatic hypotension on the tilt table. Progressive hearing loss also developed at age 67 years, worse on the left side, and associated with progressive visual impairment. He developed depression as well as mild cognitive impairment but remained independent in daily life.

Medical history included prostatic hyperplasia treated by transurethral resection of the prostate aged 69 years. He was an ex-smoker and had a history of mild hypertension. There were no other relatives affected and there was no known consanguinity. He was born in Brazil, to a family with ethnic origin in Italy.

On physical examination, he was alert, oriented, and mildly inattentive with a depressed affect. He scored 26/30 in mini-mental state examination (losing 3 points for memory and 1 point for copying pentagons). Clock drawing was normal. He had a broad based, ataxic gait, with mild bilateral dysmetria and dysdiadochokinesis. There were hypometric saccades and the oculocephalic reflex was absent bilaterally. There was bilateral sensorineural hearing loss. The gag reflex was absent on the left side. The ankle jerks were absent, and there was reduced vibration sensation in the feet. Power, tone, and the remainder of the sensory examination were normal.

MRI at age 72 years (Figure 1 H-L) demonstrated extensive, symmetric and confluent T2W/FLAIR high signal in the supratentorial white matter, internal and external capsules, thalami and pons, with scattered deep cerebral microbleeds.

Auditory evoked potentials were prolonged bilaterally. Nerve conduction studies and EMG were normal.

He was examined again at age 75 years, by which point he had developed a pervasive sense of disequilibrium and sialorrhoea in addition to his previous symptoms. Physical examination was unchanged. He died from a community-acquired pneumonia later that year.

Focused exome sequencing revealed the *CTSA* c.973C>T p.(Arg325Cys) heterozygous variant associated with CARASAL. No other potentially pathogenic variants were detected (specifically there were no variants in other small vessel disease genes such as *NOTCH3, HTRA1, COL4A1/2*).

Discussion

We report two patients with cerebral small vessel disease and ischaemic stroke associated with the recurrent c.973C>T variant in *CTSA.* Since the original description of CARASAL in 2016, describing 13 patients from two families[2], only one further case has been published, a British patient published by our group in 2017[3]. Our description of two additional cases provides further evidence supporting disease causation, but also suggests that although rare, this disorder is likely not being detected in large cohorts of patients with ischaemic stoke or cerebral small vessel disease, potentially due to lack of testing. It is likely that the family described by Hervé et al in 2012 were affected by CARASAL, given the overlapping clinical, imaging and pathological features, and the genetic linkage to the 20q13 chromosomal region encompassing *CTSA*, although this has not been confirmed[4].

This report provides further evidence that brainstem symptoms such as vertigo, tinnitus, sensorineural hearing loss or dysphagia may be prominent symptoms of CARASAL, consistent with our previous report;[3] these symptoms may be related to the extensive brainstem involvement on MRI. Imaging of both cases reported here demonstrated symmetric, confluent signal change affecting most of the supratentorial white matter, with progressive involvement of the external and internal capsules, anterior temporal lobes, deep grey nuclei and brainstem. When compared to CADASIL, CARASAL patients show more signal change in brainstem structures and the thalamus, although these findings are not unique[5, 6]. Significant brainstem involvement is seen in pontine autosomal dominant microangiopathy and leukoencephalopathy (PADMAL), although thalamic involvement is not typical[7]. Fabry disease can cause widespread white matter lesions and microbleeds, but the classical pulvinar sign is hyperintense on T1W imaging, rather than T2W/FLAIR imaging[8].

Previous reports of CARASAL have been in Western European patients from the Netherlands, the UK, and possibly France. This report expands the ethnic background of CARASAL to include China and Italy and reinforces the need to screen for *CTSA* mutations in patients presenting with a possible

monogenic cause of cerebral small vessel disease or stroke, regardless of their geographical location or ethnic origin.

Declarations

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Ethical standards:

This study was performed in line with the principles of the Declaration of Helsinki and received ethical approved by the NHS National Research Ethics Service.

Consent to participate and publish:

Both patients gave their informed consent prior to genetic testing and gave their consent for publication of their anonymised clinical data.

Conflict of interest statement:

The authors have no relevant financial or non-financial interests to disclose.

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Figure legend

Panels A-G show MRI findings in Patient 1: (A) Axial T2W image (age 49) showing confluent white matter hyperintensity of the subcortical white matter; (B-D) T2W imaging showing progressive signal change to the internal and external capsules and thalami (aged 49y, 59y, and 63y in B,C, and D, respectively); (E) diffusion-weighted imaging demonstrating an acute infarct in left posterior thalamus; (F) corresponding apparent diffusion coefficient map; (G) Axial FLAIR image demonstrating anterior temporal lobe and pontine high signal.

Panels H-L show MRI findings in Patient 2: (H) Axial FLAIR image Patient 2 showing similar anterior temporal lobe involvement and pontine involvement; (I) Axial FLAIR demonstrating extensive confluent signal change in the supratentorial white matter, internal and external capsules and thalami; (J) Axial FLAIR showing extensive confluent signal change in the supratentorial white matter; (K, L) Axial mIP susceptibility-weighted images demonstrating scattered deep microbleeds.