A curious case of small vessel vascular dementia

Whitney CT Ip, YF Shea *, HF Tong, CY Law, CW Lam, Patrick KC Chiu

Hong Kong Med J 2023;29:174.e1-3
https://doi.org/10.12809/hkmj2210093

A 63-year-old man was referred to the memory clinic of Queen Mary Hospital in December 2021 for early-onset dementia. He had stepwise deterioration in cognitive function over the previous 6 months, especially in short-term memory, poor judgement, and spatial and temporal disorientation. His home environment was poor with rotten food. Physical examination revealed symmetrical parkinsonism. Montreal Cognitive Assessment Hong Kong version score was 10/30 (<2nd percentile). Vitamin B_{12}, folate and thyroid function tests were normal. A review of his medical history revealed three episodes of stroke since the age of 50 years. These episodes presented as left lower limb monoplegia, left-sided hemiplegia and slurring of speech 12 years, 8 years, and 1 year ago, respectively. Extensive workup including 24-hour Holter monitoring and transthoracic echocardiogram was unremarkable. He had hypertension and hyperlipidaemia and was prescribed amlodipine 5 mg and rosuvastatin 20 mg daily. His blood pressure was under control and the latest low-density lipoprotein was 1.7 mmol/L. A review of his computed tomography of the brain over the last 11 years showed a progressive increase in periventricular hypodensities (Fig 1). Brain magnetic resonance imaging (1 year previously) showed extensive periventricular hyperintensities and an old ischaemic insult over bilateral external capsules (Fig 2). Family history was notable for multiple first-degree relatives with young-onset stroke in their fifties and a suspected autosomal dominant inheritance pattern (Fig 3). Genetic testing of the neurogenic locus notch homolog protein 3 (NOTCH3) gene revealed a heterozygous mutation with a pathogenic variant (c.1630C>T, p.Arg544Cys), confirming the diagnosis of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). The family was referred for genetic counselling.

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy is caused by cysteine-altering pathogenic variants in the NOTCH3 gene, with consequent vasculopathic changes, predominantly involving small penetrating arteries, arterioles, and brain capillaries.[1,2] The mutation leads to an odd number of cysteine

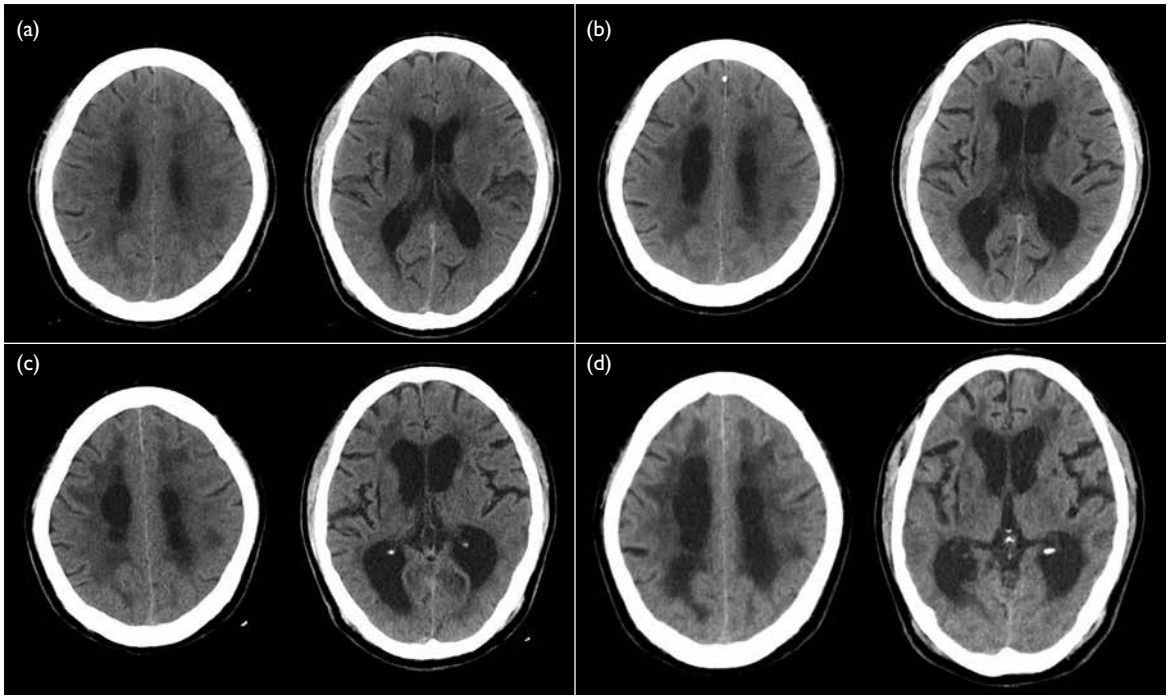

FIG 1. Plain computed tomography of the brain showing the progressive increase in bilateral periventricular hypodensities and external capsule infarctions through (a) 2009, (b) 2014, (c) 2017, and (d) 2021

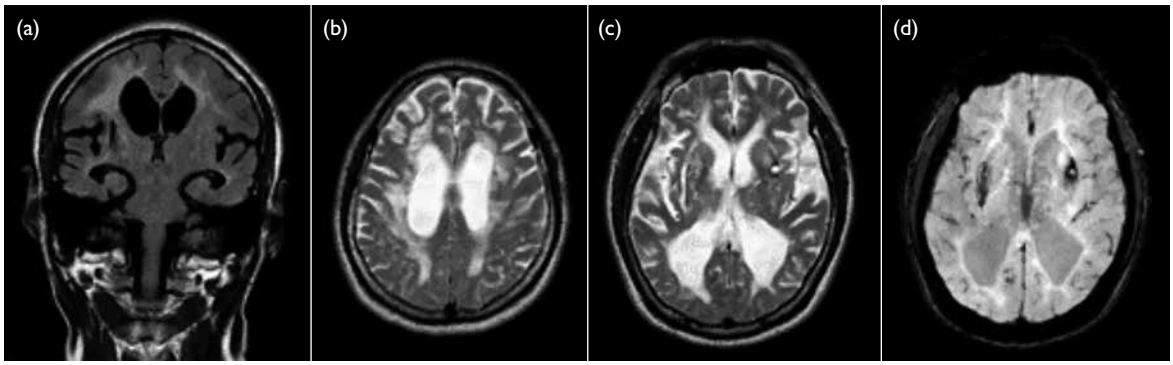

FIG 2. Brain magnetic resonance imaging (MRI) revealed extensive white matter abnormalities compatible with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). (a) Coronal fluid-attenuated inversion recovery sequence MRI showing periventricular hyperintensities. Temporal lobes had focal subcortical white matter hyperintensities, which are common findings in CADASIL. (b) Axial T2- weighted MRI showing extensive white matter hyperintensities. (c) Axial T2-weighted MRI showing the infarcts located at bilateral basal ganglia and external capsules. (d) T2 gradient echo sequence showed hemosiderin deposition over the bilateral external capsules suggestive of previous haemorrhage over the infarcted areas

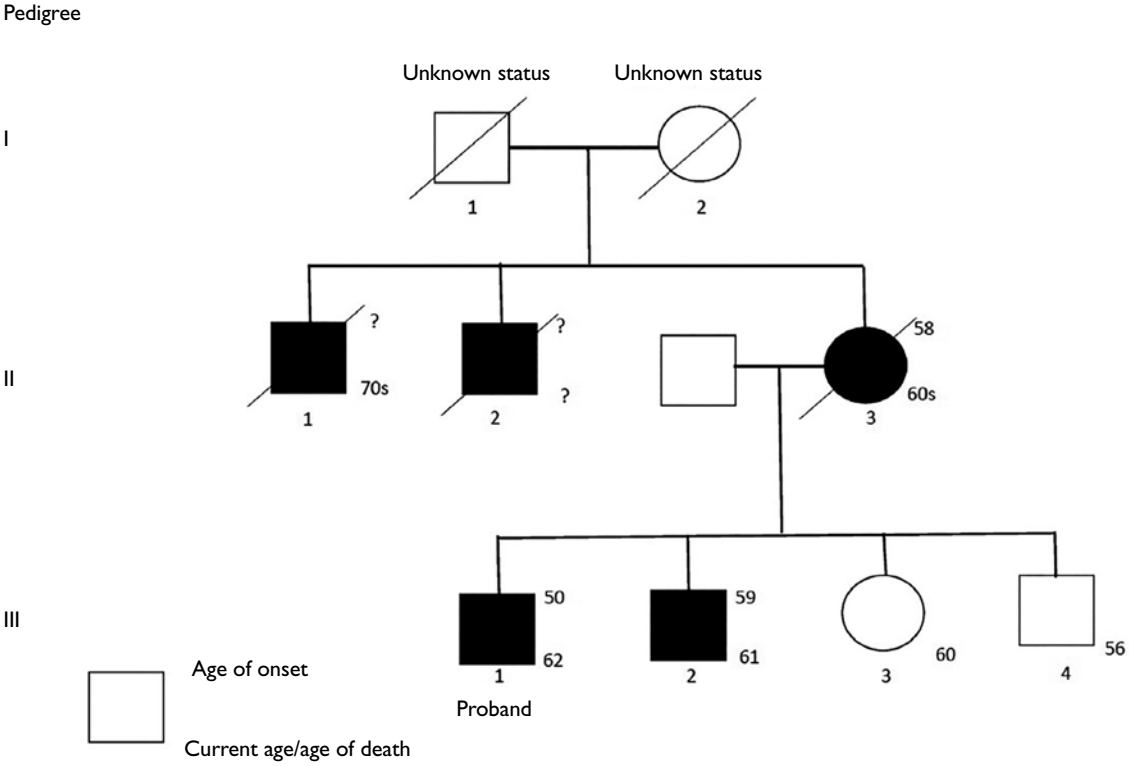

FIG 3. Pedigree of the patient's family showing the autosomal dominant inheritance pattern of disease transmission

residues with deposition of osmiophilic material and progressive degeneration of vascular smooth muscle cells.[1,2] The key to diagnosis includes a strong family history of young-onset stroke, an absence of strong vascular risk factors, and salient findings on brain magnetic resonance imaging, especially extensive white matter abnormalities and subcortical infarcts involving external capsules. Genetic testing for the NOTCH3 gene can be arranged after consultation with chemical pathologists in major

public hospitals.[3,4] The principle of management for symptomatic patients is similar to that of other patients with stroke, ie, antiplatelet therapy, lipid-lowering agents, and blood pressure control. There is no disease-modifying therapy currently available. Family members of affected individuals should be referred for genetic counselling with referral to tertiary centres for potential pre-implantation genetic testing to avoid transferring the mutation to offspring.[5] There have been four other reported families with CADASIL in Hong Kong with different mutations. The mean age of symptom onset for index patients of these families was 51 years.[3,4] The mutation in our patient has been commonly found in Fujian province and Taiwan, accounting for up to 14.5% to 70% of CADASIL cases.[1]

In summary, clinicians should obtain a detailed history and be alert to suspicious magnetic resonance imaging findings. Referral to chemical pathologists for genetic testing is key to the diagnosis of CADASIL.

Author contributions

All authors contributed to the concept or design of the study, acquisition of the data, analysis or interpretation of the data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

The authors have no conflicts of interest to disclose.

Funding/support

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Ethics approval

The patient was treated in accordance with the Declaration of Helsinki. Patient consent was obtained for all investigations.

[1] **WCT Ip,** MRCP (UK)
[1] **YF Shea *,** FHKAM (Medicine)
[2,3] **HF Tong,** FHKCPath
[2] **CY Law,** FHKAM (Pathology)
[2,4] **CW Lam,** FHKAM (Pathology)
[1] **PKC Chiu,** FHKAM (Medicine)

1 *Department of Medicine, Queen Mary Hospital, The University of Hong Kong, Hong Kong SAR, China*
2 *Division of Chemical Pathology, Department of Pathology, Queen Mary Hospital, Hong Kong SAR, China*
3 *Department of Pathology, Princess Margaret Hospital, Hong Kong SAR, China*
4 *Department of Pathology, The University of Hong Kong, Hong Kong SAR, China*

* Corresponding author: syf321@ha.org.hk

References

1. Chen S, Ni W, Yin XZ, et al. Clinical features and mutation spectrum in Chinese patients with CADASIL: a multicenter retrospective study. CNS Neurosci Ther 2017;23:707-16.
2. Hu Y, Sun Q, Zhou Y, et al. NOTCH3 variants and genotype-phenotype features in Chinese CADASIL patients. Front Genet 2021;12:705284.
3. Au KM, Li HL, Sheng B, et al. A novel mutation (C271F) in the Notch3 gene in a Chinese man with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. Clin Chim Acta 2007;376:229-32.
4. Hung LY, Ling TK, Lau NK, et al. Genetic diagnosis of CADASIL in three Hong Kong Chinese patients: a novel mutation within the intracellular domain of NOTCH3. J Clin Neurosci 2018;56:95-100.
5. Konialis C, Hagnefelt B, Kokkali G, Pantos C, Pangalos C. Pregnancy following pre-implantation genetic diagnosis of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). Prenat Diagn 2007;27:1079-83.

