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Case report

CADASIL in a patient with bilateral internal carotid artery agenesis

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ABSTRACT

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a well-recognised cause of stroke in the young. Bilateral internal carotid artery (ICA) agenesis is a rare congenital malformation, with few previous reported cases in the literature. CADASIL is not reported to be associated with ICA agenesis. We report the case of a 41 year old man who presented with recurrent orthostatic symptoms associated with increasingly frequent falls. Initial investigation with CT angiography revealed absent bilateral ICAs with an ectatic vertebrobasilar arterial tree supplying the intracranial circulation. Skull base CT revealed simultaneous absence of ICAs and bilateral carotid canals, confirming agenesis of bilateral ICAs. MRI of the brain revealed extensive areas of confluent high T2 signal intensity in the subcortical and periventricular zones of both hemispheres. The patient subsequently developed episodic and progressive headache, dysarthria, ataxia, cognitive impairment and personality changes. Radiological progression of cerebral subcortical and periventricular abnormalities was demonstrated with established lacunar infarcts and generalised atrophic changes. Genetic testing confirmed the diagnosis of CADASIL with the presence of a heterozygous c.994C > T (p.Arg332Cys) mutation in exon 6 of the NOTCH 3 gene. We report the first case of coexistent bilateral ICA agenesis and CADASIL. This case highlights the need to consider CADASIL in patients with cerebral subcortical and periventricular imaging abnormalities, even with coexistent large vessel pathology.

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1. Case

A 41 year old adopted man initially presented to another institution with recurrent, transient orthostatic dizziness, limb weakness and collapse. Background medical history was significant for hypertension managed with irbesartan and metoprolol, hypercholesterolaemia, tobacco use, hypothyroidism on thyroxine replacement, and urethral strictures of unknown cause requiring intermittent catheterisation.

Initial investigation with CT angiography of the brain revealed absent bilateral internal carotid arteries (ICAs), with an ectatic vertebrobasilar arterial tree supplying the anterior and posterior intracranial circulation. Skull base CT demonstrated variant anatomy of the foramina at the skull base, with no normal common carotid canal identified bilaterally, consistent with agenesis of bilateral ICAs (Fig. 1). MRI of the brain (not shown) showed extensive areas of confluent high T2 signal intensity in the subcortical and periventricular zones of both hemispheres in keeping with infarction, extending in the typical distribution and location for the watershed between anterior and middle cerebral arteries,

and to a lesser extent between the middle and posterior cerebral artery. In addition there were lacunar infarcts in the basal ganglia on both sides, left greater than right. Diamox SPECT scan of the brain demonstrated preserved baseline perfusion, with some hypoperfusion in the left temporal lobe in response to Diamox. There were no marked changes in the anterior circulation territory. Transoesophageal echocardiogram and 24-hour holter monitor were normal. He was commenced on aspirin and rosuvastatin, and metoprolol was ceased on the assumption that his symptoms were a result of hypoperfusion secondary to internal carotid artery agenesis.

Over the following 10 years the patient had recurrent presentations with episodic headache, dysarthria, ataxia, worsening cognitive function and personality changes. He was also noted to have disinhibited behaviour and persecutory delusions, leading to numerous interactions with law enforcement. As he relocated to our catchment area, his care was transferred to our institution, prompting re-evaluation of the diagnosis. Examination demonstrated a mildly spastic gait, bilateral lower limb spasticity and positive palmo-mental reflex. The Montreal Cognitive assessment score was 16/30. Serial MRI brain studies demonstrated radiological progression of cerebral subcortical and periventricular abnormalities with both acute diffusion restricting and established

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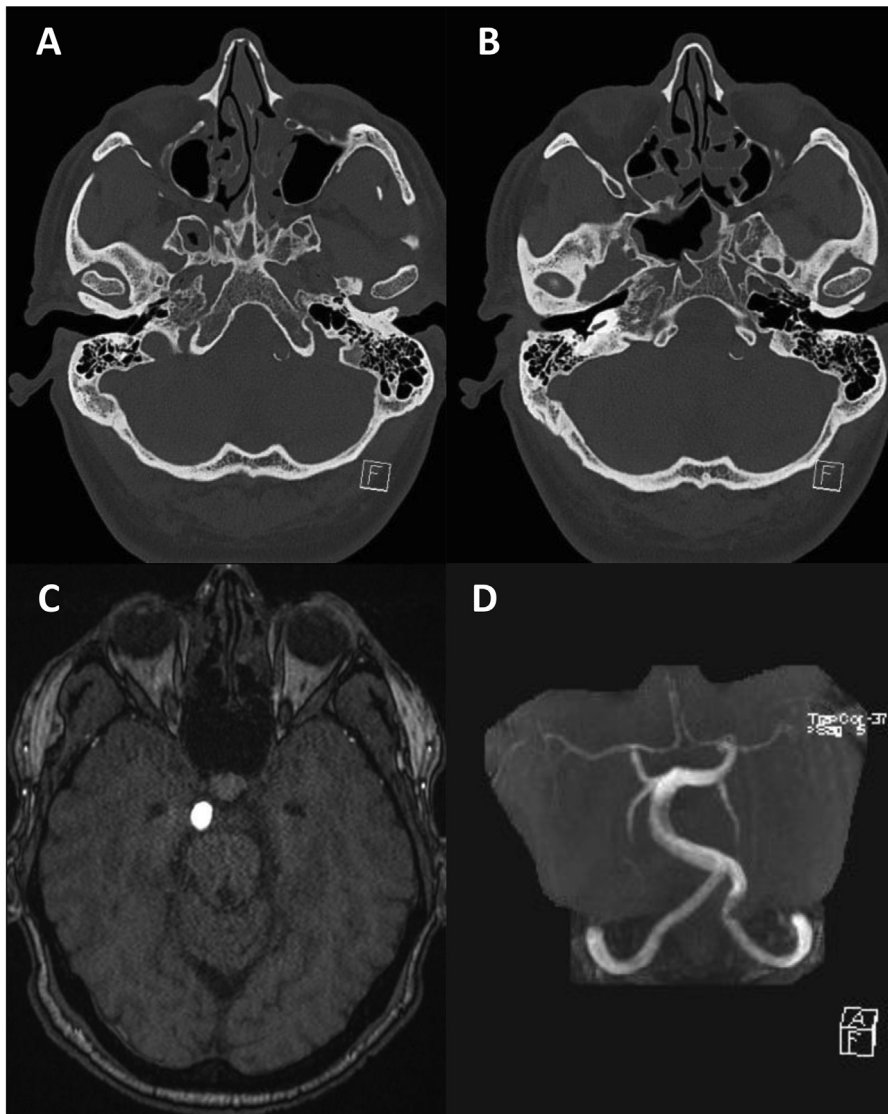


Fig. 1. A,B - CT bony windows through skull base demonstrate absence of carotid canal in petrous temporal bones bilaterally. C - Axial time of flight MRA demonstrating grossly enlarged basilar artery anterior to the pons and absent MRA opacification of the intracranial carotid arteries adjacent to the sella. D- Time of flight MRA MIP (Waters projection) showing the posterior circulation through enlarged posterior communicating arteries reconstitute the anterior circulation via the Circle of Willis.

lacunar infarcts, and generalised atrophic changes (Fig. 2). Genetic testing confirmed the diagnosis of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) with the presence of a heterozygous c.994C > T (p. Arg332Cys) mutation in exon 6 of the *NOTCH3* gene.

2. Discussion

Agenesis of the internal carotid arteries is a rare developmental abnormality, with fewer than 200 reported cases in the literature. Patients are usually asymptomatic due to well-developed collaterals [1–3]. The majority of cases are unilateral [2]. When bilateral ICAs are absent, the anterior and middle cerebral arteries are usually supplied by the vertebrobasilar system via the posterior communicating arteries [2], as for our patient. Congenital agenesis of the ICAs is associated with a high incidence (25–43%) of intracranial aneurysm, much higher than that found in the general population (2–4%). [4] Other reported associations include cerebral hemiatrophy, epilepsy, facial haemangiomas, cerebral cortical dysplasia, psychomotor developmental delay, congenital Horner syndrome, neurofibromatosis, meningocele, coarctation of the aorta,

and cardiac anomalies [1–4]. When ICA agenesis is unilateral, associated maldevelopments typically occur on the ipsilateral side [4]. To date there are no confirmed genetic causes, though individual cases associated with a *FOXI3* deletion and *OTX2* mutation have been reported [5,6]. Typically no surgical or interventional management is required for ICA agenesis, though evaluation to exclude the presence of associated significant intracranial aneurysms is recommended [1,3,4].

CADASIL typically manifests with a combination of migraine, cognitive deficits, psychiatric disturbance, and cerebral ischaemic episodes [7]. In contrast to the large artery pathology involved in ICA agenesis, it is a small-artery disease of the brain, with pathological changes also found in the skin and kidneys [7,8]. It is an autosomal dominant disease resulting from various mutations in the *NOTCH3* gene, which is predominantly expressed in vascular smooth muscle cells [7]. To date, more than 200 different mutations have been reported [7,9]. MRI changes typically precede symptom onset by 10–15 years. [8] CADASIL is not known to be associated with ICA agenesis or other large vessel abnormalities [9].

We present the first reported case of coexistent bilateral internal carotid artery agenesis and CADASIL. ICA agenesis was likely an

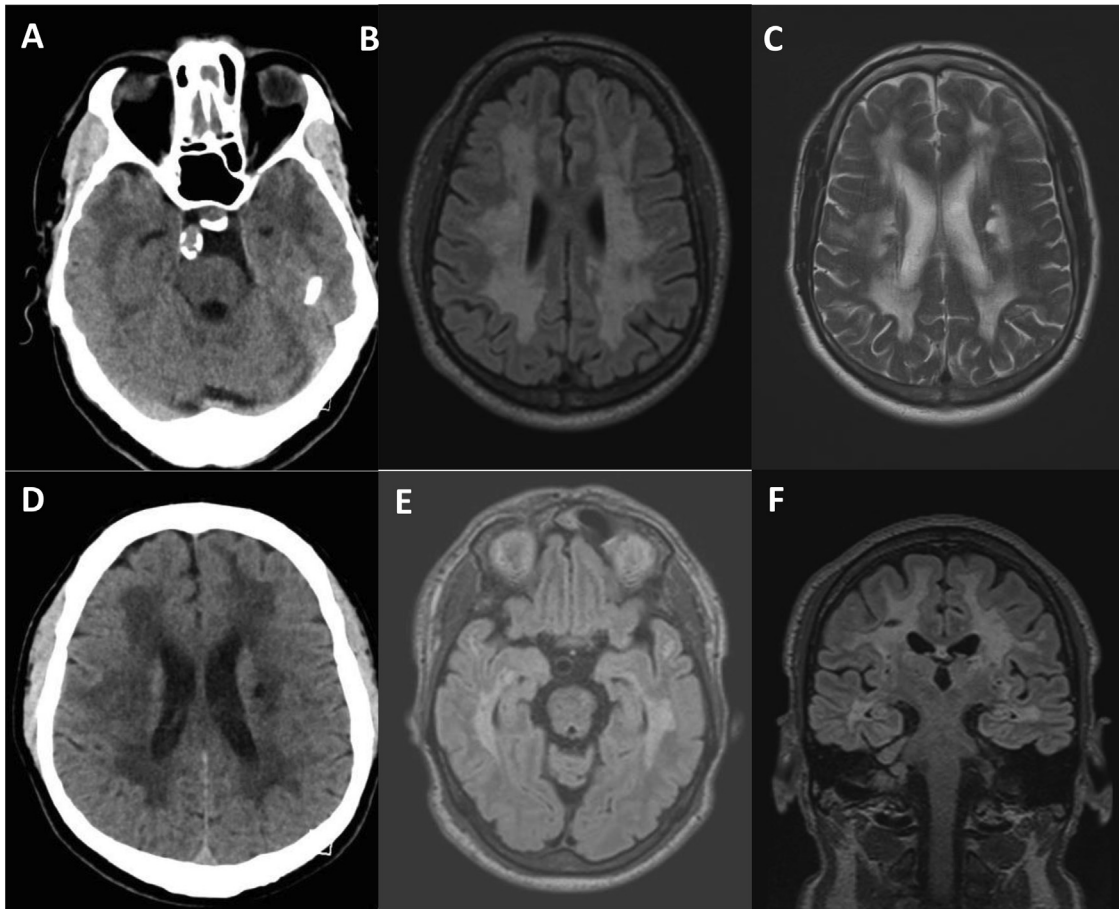


Fig. 2. CT brain (A,D), FLAIR (B, E, F), and T2 weighted (C) MRI brain images demonstrating extensive confluent subcortical and periventricular white matter T2 signal hyperintensity including the anterior temporal poles.

incidental finding in our patient, resulting in a delayed diagnosis of CADASIL. Care needs to be taken to consider cerebral small vessel disease pathologies, even with coexistent large vessel pathology.

3. Disclosures

Dr MacDonald and Dr Alvaro report no disclosures.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

- [1] Alexandre AM, Visconti E, Schiarelli C, Frassanito P, Pedicelli A. Bilateral Internal Carotid Artery Segmental Agenesis: Embryology, Common Collateral Pathways, Clinical Presentation, and Clinical Importance of a Rare Condition. *World*

- Neurosurgery* 2016;95:620.e9–620.e15. <https://doi.org/10.1016/j.wneu.2016.08.012>.
- [2] Nomura M, Tamase A, Mori K, Seki S, Iida Yu, Kawabata Y, Nakano T. Agenesis of the Left Internal Carotid Artery Associated with Dolichoectatic Intracranial Arteries. *J Stroke Cerebrovasc Dis* 2018;27(2):e24–6. <https://doi.org/10.1016/j.jstrokecerebrovasdis.2017.09.021>.
- [3] Li S, Hooda K, Gupta N, Kumar Y. Internal carotid artery agenesis: A case report and review of literature. *Neuroradiol J* 2017;30(2):186–91. <https://doi.org/10.1177/1971400917692162>.
- [4] Lee JH, Oh CW, Lee SH, Han DH, Steiger HJ, Goncalves Ferreira AJ. Aplasia of the internal carotid artery. *Acta Neurochir (Wien)*. 2003;145(2):117–25. <https://doi.org/10.1007/s00701-002-1046-y>.
- [5] Shimada A, Takagi M, Nagashima Y, Miyai K, Hasegawa Y. A Novel Mutation in OTX2 Causes Combined Pituitary Hormone Deficiency, Bilateral Microphthalmia, and Agenesis of the Left Internal Carotid Artery. *Horm Res Paediatr* 2016;86(1):62–9. <https://doi.org/10.1159/000446280>.
- [6] Tassano E, Jagannathan V, Drögemüller C, Leoni M, Hytönen MK, Severino M, Gimelli S, Cuoco C, Di Rocco M, Sanio K, Groves AK, Leeb T, Gimelli G. Congenital aural atresia associated with agenesis of internal carotid artery in a girl with a FOXI3 deletion. *Am J Med Genet* 2015;167(3):537–44. <https://doi.org/10.1002/ajmg.a.36895>.
- [7] Chabriat H, Joutel A, Dichgans M, Tournier-Lasserre E, Boussier M-G. CADASIL. *Lancet Neurol* 2009;8(7):643–53. [https://doi.org/10.1016/S1474-4422\(09\)70127-9](https://doi.org/10.1016/S1474-4422(09)70127-9).
- [8] Zhu S, Nahas SJ. CADASIL: Imaging Characteristics and Clinical Correlation. *Curr Pain Headache Rep* 2016;20(10). <https://doi.org/10.1007/s11916-016-0584-6>.
- [9] Kang HG, Kim JS. Intracranial arterial disease in CADASIL patients. *J Neurol Sci* 2015;359(1–2):347–50. <https://doi.org/10.1016/j.jns.2015.11.029>.