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CASE REPORTS

CACNA1A channelopathy with reversible cerebral ischaemia and vasospasm

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Abstract

The autosomal dominant *CACNA1A* gene encompasses episodic neurological disorders likely related to calcium-channelopathy. We report on an 8-year-old boy with a pathogenic heterozygous *CACNA1A* mutation (c.4067C>T) who developed seizures, encephalopathy, and left hemiplegia. Brain magnetic resonance imaging showed restricted diffusion in the right parieto-temporo-occipital lobes with concomitant narrowing of the proximal segments of the right middle cerebral artery. Flow velocities were elevated on transcranial doppler evaluation, confirming vasospasm as a mechanism for the stroke-like episode. Treatment with the calcium channel blocker verapamil resulted in normalisation of TCD flow velocities as well as ischaemic changes on brain magnetic resonance imaging. Our patient is the youngest reported paediatric patient to benefit from the utilisation of serial TCD studies in the detection and management of cerebral vasospasm within the reported *CACNA1A* population.

Keywords: CACNA1A, paediatric stroke/stroke-like episodes, transcranial doppler

INTRODUCTION

The established paediatric manifestations of *CACNA1A* variants include mild-to-severe developmental delay as well as developmental and epileptic encephalopathy. The expanding phenotype of *CACNA1A* encompasses episodic neurological disorders resulting from the calcium-channelopathy caused by malfunctioning proteins in the α1A pore-forming subunit of the neuronal calcium channel P/Q. Cerebral vascular smooth muscle vasospasm has been implicated in patients with *CACNA1A* variants presenting with hemiplegia and hemiconvulsions, suggesting a role for transcranial doppler in confirming the presence of vasospasm, as well as the administration of calcium channel blockers in the management of patients with acute symptoms.

CASE REPORT

An 8-year-old boy of Malay ethnicity with a known *de novo* pathogenic heterozygous *CACNA1A* c.4067C>T (p.Thr1356Ile) variant and confirmed severe learning disability (motor and language function at 4-6 months' and 3 months' developmental age respectively). He presented to a district hospital with recurrent focal motor seizures, encephalopathy, and left hemiplegia during Influenza A infection. Prior to this event, he had experienced 2 episodes of febrile seizures at 2 years, 6 months and at 3 years. He had no seizures subsequently and was not on treatment with any antiseizure medication. He had no previous episodes of hemiparesis and there was no family history of migraine. Blood investigations were unremarkable with total white cell count 6.7 x 10^9/L and C-reactive protein 1.7 mg/L. Cerebrospinal fluid examination was

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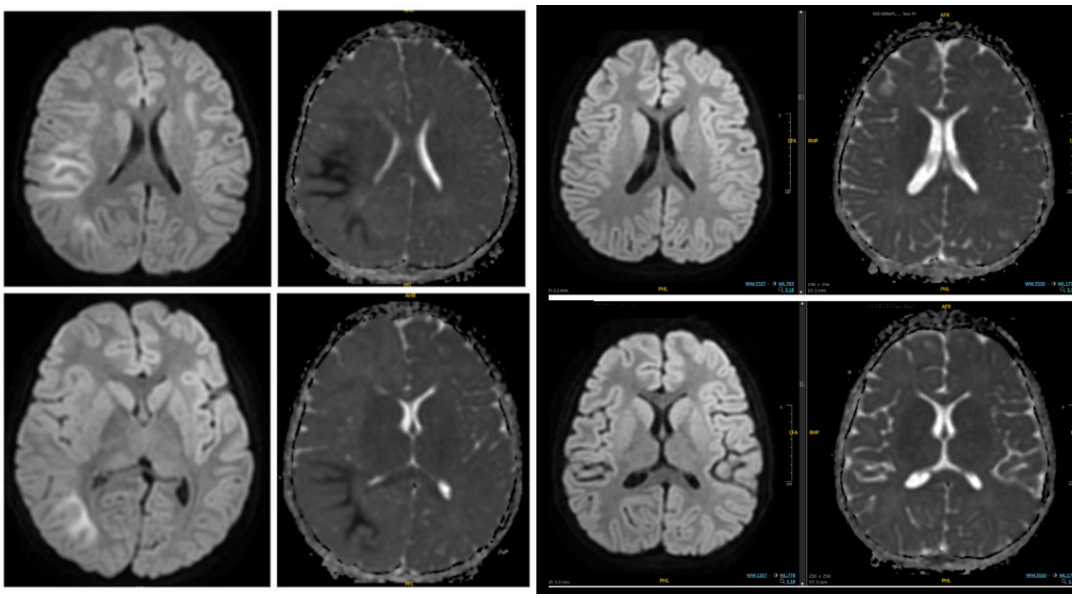

Figure 1. DWI/ADC images on day 8 of illness (left) and day 66 post-treatment (right) showing cytotoxic oedema in the right parieto-temporo-occipital region and subsequent resolution.

normal. Non-contrasted computed tomography imaging on day 2 of illness was normal. The patient was transferred to a university hospital on day 8 of illness. Neurological examination showed profound encephalopathy with Glasgow Coma Scale score of 8 (E3 V1 M4). He had axial hypotonia and absence of movement in the left upper limb and left lower limb. His brainstem functions were preserved.

Electroencephalogram showed diffuse and continuous delta slowing over the right hemisphere. Brain magnetic resonance imaging with cerebral angiography on day 8 of illness showed subcortical restricted diffusion on diffusion weighted imaging in the right temporo-parieto-occipital region, with cerebral angiography showing concomitant narrowing of the M1 and proximal M2 segments of the right middle cerebral artery (MCA).

Transcranial Doppler ultrasound on day 9 of illness detected focal stenosis with vasospasm of the right MCA and the right anterior cerebral artery (ACA). Sampled at a depth of 54 mm, the right MCA showed a mean flow velocity 139 cms^{-1}

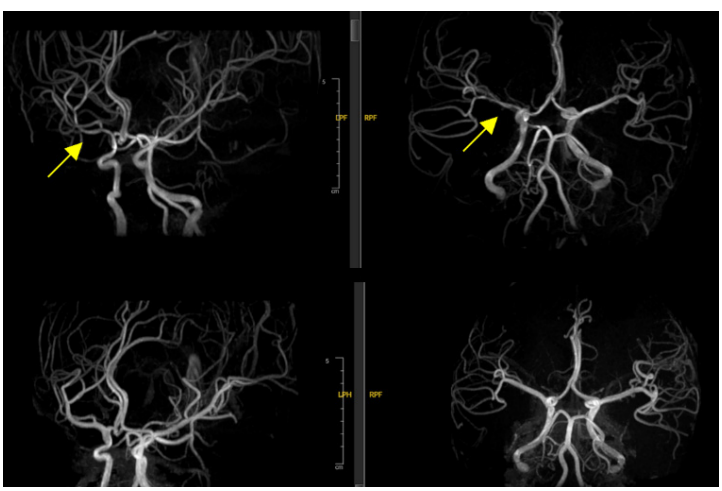

Figure 2. MRA brain on day 8 (top) showing narrowing of the right M1 and proximal M2 segments, and MRA reevaluation on day 66 post-treatment (bottom) showing normal patency of the affected arteries.

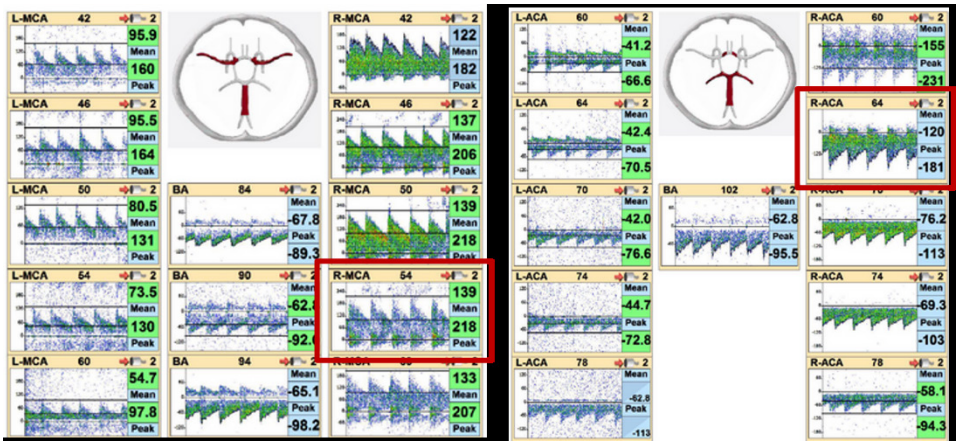

Figure 3. TCD at diagnosis showing elevated MFV and PSV in the right MCA (at depths of 42-60 mm, corresponding to M1). The highest velocities were detected at 54 mm.

and peak systolic velocity 219 cms^{-1}. The right ACA, sampled at 64 mm depth, showed mean flow velocity 120 cm^{s-1} and peak systolic velocity 181 cms^{-1}. These parameters were 73% and 238% higher than the corresponding contralateral arterial segments. The known association of calcium-channelopathy in pathogenic *CACNA1A* mutations prompted treatment with intravenous verapamil 0.1 mg/kg/dose on day 9, followed by maintenance oral therapy 2.7 mg/kg/day for 3 months. Oral acetazolamide was instituted for 2 weeks. Oral topiramate was titrated to a dose of 5.3 mg/kg/day, on which he remains. Serial transcranial doppler showed dramatic improvement in motor function at 48 hours of verapamil therapy with normalisation of serial MFV in the implicated cerebral vessels at 1 week, 2 weeks, and 2 months post-event. Baseline motor function was achieved by day 16 of illness. Repeat brain MRI/MRA at 2 months showed complete resolution of the subcortical restricted diffusion and normal patency of the MCA.

DISCUSSION

To the best of our knowledge as shown in Table 1 there have been 10 patients (age range 2-16 years, M:F 2:3) published with *CACNA1A* mutations have been reported to have experienced recurrent stroke-like episodes. The variant c.4046G>A was most frequently observed to be associated with the phenomenon (n=4).[1-4] Stroke-like episodes in patients with *CACNA1A* variants result in ischaemic lesions which do

Figure 4. (left) and 5 (right). TCD 48 hours (Fig. 4) and 14 days (Fig. 5) post-therapy showing gradual normalisation of MFV and PSV in the affected arteries.

Table 1: Summary of patients with CACNA1A mutations and stroke-like episodes

Authors	Country	Year	Age	Sex	Ethnicity	CACNA1A mutation	Development	Clinical presentation	Recurrence	MRI restricted diffusion	MRA	TCD	Treatment of stroke-like episode
Bozkaya-Yilmaz et al[1]	Turkey	2025	2	F	Not disclosed	c.4046G>A	Abnormal	Hemiplegia (SLE), epilepsy	Not reported	Cerebellar atrophy	Normal	No	Acetazolamide, verapamil
Bolte et al[9]	USA	2022	13	F	Not disclosed	c.2137G>A	Abnormal	SLE, neonatal-onset refractory epilepsy	Yes	Left temporal, parietal, frontal, and lateral occipital lobes	Not disclosed	No	Verapamil
			10	F	Not disclosed	c.4015T>C	Abnormal	SLE (at 17mo), refractory epilepsy	Yes	Parietal lobe	Normal	No	Verapamil
Le Roux et al[2]	France	2021	6	M	Not disclosed	c.5083G>C	Abnormal	SLE, dystonia	Not reported	Lenticulostriatum, occipital	Not disclosed	No	-
			3	F	Not disclosed	c.2815_2816del	Abnormal	SLE, epilepsy	Not reported	Bilateral stroke sequels	Not disclosed	No	-
			8	M	Not disclosed	c.4046G>A	Abnormal	SLE, dystonia	Not reported	Lenticulocaudal, occipital	Not disclosed	No	-
Ho et al[3]	USA	2021	7	M	Not disclosed	c.4046G>A	Abnormal	SLE, epilepsy	Yes	Right cortical and left hippocampus	Reduced blood flow to the right basal ganglia	No	Verapamil
Choudhari et al[6]	USA	2021	16	M	Black American	c.5141T>C	Abnormal	SLE	Yes	Left parieto-occipital	Diffuse narrowing of the left MCA	Elevated flow velocities in the right MCA and right ACA	Verapamil
Gudenkauf et al[10]	USA	2020	4	F	Hispanic	c.5075T>A	Abnormal	SLE, epilepsy	Yes	Multifocal	Normal	No	-
Knierim et al[4]	Germany	2011	6	F	Not disclosed	c.4046G>A	Abnormal	SLE, epilepsy	Yes	Left frontal and parietal lobe	Normal	No	Verapamil

not conform to vascular territories and often have normal magnetic resonance angiography studies, supporting vasospasm as a likely pathomechanism. Our patient is the first report of a stroke-like episode in a patient with a c.4067C>T variant.

Vasospasm of cerebral vascular smooth muscle had been postulated as a mechanism for cerebral ischaemia in a 5-year-old patient with a c.653C>T variant[5], in whom a flow void of the left proximal middle cerebral artery on magnetic resonance angiography showed complete resolution on brain angiography performed within 24 hours. However, anciliary testing with transcranial Doppler was not reported in this patient. The first reported utilisation of transcranial Doppler in the management of stroke-like episodes within the reported literature of *CACNA1A* patients was in a 16-year-old patient who had a c.5141T>C variant.[6] Elevated flow velocities were demonstrated on cerebral arteries which had appeared occluded on MR angiography. This guided the authors to initiate vasospasm treatment with the calcium channel blocker verapamil, which resulted in normalisation of transcranial Doppler flow velocities and significant clinical improvement.

The routine use of transcranial Doppler in paediatric stroke is currently limited to the surveillance for stroke risk in sickle cell disease. Transcranial doppler can be a valuable adjunct to brain neuroimaging, which does not of itself identify stroke mechanisms. Where there is clinical suspicion of a cerebral vasculopathy, such as in patients with calcium channelopathy due to *CACNA1A* mutations, transcranial doppler provides cerebrovascular flow measurements, assisting in stroke subtype diagnosis and appropriate treatment strategies. The use of serial transcranial doppler in our patient is only the second known instance in the published literature of paediatric *CACNA1A* patients presenting with a stroke-like episode. Our patient is also the youngest patient to have benefited from the use of transcranial doppler in his management of a stroke-like episode. The findings of markedly elevated mean flow velocities and peak systolic velocities in the cerebral arteries confirmed vasospasm as the stroke mechanism in our patient. Serial transcranial Doppler had previously been utilised to establish the presence of vasospasm and monitor treatment response in a 16-year-old male patient[6] with a *CACNA1A* mutation who experienced a stroke-like episode. These findings reason that in at least some patients with *CACNA1A* mutations, stroke-like episodes result from vasospasm, which respond well to treatment with verapamil.

The strengths of transcranial Doppler in the evaluation and management of paediatric stroke and stroke-like episodes lie in its accessibility, non-invasiveness and repeatability, allowing for dynamic studies of cerebral blood flow in real time. We have demonstrated its effective use in a patient with vasculopathy attributable to a calcium channelopathy. 49%[8] of paediatric acute ischaemic stroke are attributed to arteriopathies, the exact mechanism of which remains to be elucidated. Transcranial Doppler is not routinely utilised in the evaluation of such patients, for whom identification of vasospasm as a stroke mechanism in the context of an arteriopathy could prompt treatment strategies to include calcium channel blockers.

In summary, our report widens the reported clinical phenotype of patients with pathogenic *CACNA1A* mutation and highlight the usefulness of transcranial Doppler in the successful management of our patient. Its wider use in paediatric stroke and stroke-like episodes, particularly where cerebral vasculopathy and arteriopathy is suspected, should be explored in future research.in order to elucidate the underlying pathophysiology and improve therapeutic strategies.

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