Case report

Utilisation of advanced MRI techniques to understand neurovascular complications of PHACE syndrome: a case of arterial stenosis and dissection

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SUMMARY
PHACE syndrome is a rare disorder with posterior fossa brain malformations, segmental infantile haemangiomas, arterial anomalies, cardiac defects and eye anomalies. Cerebral and cervical arterial abnormalities occur commonly in these patients, predisposing subjects with PHACE syndrome to neurovascular complications including migraine-like headaches, moyamoya vasculopathy, arterial dissection and arterial ischaemia stroke. We leveraged institutional MRI protocols developed for adult neurovascular disease to better elucidate the pathogenesis of the arterial alternations observed in PHACE. Using high-resolution vessel wall and 4D flow MRI, we demonstrated enhancement, focal dissection and altered blood flow in a 7-year-old girl with PHACE syndrome. This is the first-time vessel wall imaging has been used to detail the known arterial changes in PHACE, and these findings may indicate that progressive vascular narrowing and vessel wall changes/inflammation are a factor in chronic headaches and other arterial complications seen in subjects with PHACE syndrome.

BACKGROUND
PHACE syndrome is an acronym to describe a rare neurovascular disorder with posterior fossa brain malformations, segmental infantile haemangiomas, arterial anomalies, cardiac defects and eye anomalies.1 Cerebral and cervical arterial abnormalities are the most common non-cutaneous anomaly in PHACE syndrome occurring in over 85% of patients, including vessel narrowing, dysgenesis, anomalous course and/or origin, and non-visualisation.2 These neurovascular anomalies predispose infants and children to highly morbid complications including headaches,3 moyamoya vasculopathy (MMV),4 arterial dissection,5,6 transient ischaemic attacks (TIAs) and arterial ischaemia stroke.7 While there is anecdotal evidence that progressive vascular narrowing and vessel wall abnormalities may be a factor in these neurovascular complications, no study or case report to date has characterised the vessel wall in PHACE syndrome, specifically not a case of PHACE syndrome with documented, progressive vascular stenosis. In addition, there is no evidence in the literature for vascular inflammation playing a potential role in the progressive arterial abnormalities that can occur in these subjects. We present a case of PHACE syndrome in a child with chronic migraine-like headaches and known progressive vascular narrowing using both high-resolution vessel wall and 4D flow MRI.

CASE PRESENTATION
The patient is a 7-year-old girl with previously diagnosed PHACE syndrome presenting for both clinical evaluation and surveillance imaging. She originally presented at birth with a sternal cleft and an infantile haemangioma on the left aspect of the upper and lower lips as well as involving the adjacent oral mucosa. The patient has had surgical resection of residual fibrofatty tissue on the lower lip and pulsed dye laser therapy to the lips, cheek and nose. A screening echocardiogram documented mild aortic arch hypoplasia without blood flow limitation. Prior cervical and intracranial vascular imaging has demonstrated left internal carotid artery (ICA) narrowing involving the distal aspect of the left cervical ICA extending into the carotid canal. Collateral blood supply to the left anterior circulation is supplied by a prominent left posterior communicating artery (PCOM).

The patient was interviewed with her mother, both reporting she has three to four migraine-like headaches per week which are often occupied by nausea and blurry vision. These headaches limit her activities during their occurrence with an average of 1–2 missed school days per week. Given her pre-existing vascular disease, no vasoactive medications have been initiated, and the family usually treats the headaches with rest, hydration and over-the-counter pain medications. No prescription medications have been used.

INVESTIGATIONS
MRI with angiography (MRA) was performed in December 2019 with inclusion of 4D flow MRI and high-resolution vessel wall imaging. 4D flow MRI is a technique which encodes the velocity field in the image phase, providing both volumetric angiography and quantitative assessment of blood flow velocities throughout the cardiac cycle.8 While scan times for 4D flow MRI have been prohibitive in the past, recent advances in accelerated imaging have made these techniques available for comprehensive neurovascular haemodynamic assessment. Studies have demonstrated the capability to derive advanced haemodynamic parameters from the velocity field captured using 4D flow, including measures of wall...
Findings that shed new light on the possible pathogenesis of a disease or an adverse effect

shear stress, pulse wave velocity (PWV), pressure gradients and vessel tracking. On structural imaging, fullness and heterogeneous signal was present involving the left aspect of the upper and lower lips, consistent with the reported, treated haemangioma at this location. The brain parenchyma was normal with normal appearance of the posterior fossa.

On 3D time-of-flight and post-contrast time-resolved imaging of contrast kinetics MRA, there was redemonstration of luminal narrowing of the left distal cervical ICA extending into the carotid canal (figure 1). At the site of greatest narrowing, the ICA measures 1.5 mm in diameter, representing approximately 60% stenosis, mildly progressed compared with the most recent prior in April 2015 at which time the stenosis was approximately 50%. There is reconstitution of left ICA calibre in the petrous segment with additional collateral filling of the anterior circulation via a prominent left PCOMM artery. Otherwise, there is notable diffuse dolichoectasia of the intracranial vasculature without additional focal cerebral or intracranial arterial or venous abnormalities.

On post-contrast, high-resolution vessel wall imaging (figure 1), there is wall thickening of the left distal cervical ICA segment in the areas of luminal narrowing with associated vessel wall enhancement. Intracranially, there is a focal, linear filling defect in the left petrous ICA, concerning for a small, focal dissection with mild focal stenosis (figure 2). No other areas of vessel wall abnormality are present without any additional vessel wall thickening or enhancement.

On 4D flow MRI acquired using the previously described accelerated 3D radial technique, velocity images (figure 3) displayed reduced velocities in the left cervical ICA compared with right cervical ICA and basilar artery. Further, higher velocities were observed in the prominent left PCOMM artery. Blood flow rates quantified from velocity data were: 1.31±0.64 mL/s in the left cervical ICA, 4.26±1.76 mL/s in the right cervical ICA, 4.44±1.58 mL/s in the basilar artery and 2.16±0.62 mL/s in the left PCOMM artery. From the cardiac-resolved flow waveforms, pulsatility indices (PIs) were estimated (PI=(Qmax−Qmean)/Qmean, Q=flow). PI was largest in the left cervical ICA (PI=1.48±0.16), followed by right cervical ICA (PI=1.38±0.05). The PI in the basilar artery was 1.03±0.09 and 1.02±0.05 in the left PCOMM artery. By estimating the temporal shift of the cardiac waveform along the arteries, PWV was quantified as previously described using the relationship $PWV = \Delta x/\Delta t$, where $\Delta x$ is the distance travelled by the pulse wave and $\Delta t$ is the time of traversal. The PWV in the left cervical ICA was 2.9 m/s and 7.3 m/s in the right cervical ICA.

TREATMENT

Consensus guidelines for the prevention of neurovascular complications were published in 2016. Daily aspirin was
recommended for patients at high risk for acute ischaemic stroke. High risk was defined as: (1) significant narrowing (>25%) or occlusion of principal cerebral vessels within or above the Circle of Willis that results in an ‘isolated’ circulation, (2) tandem or multiple arterial stenoses associated with complex blood flow that may potentially result in diminished cerebral perfusion, (3) imaging findings in the brain parenchyma suggestive of chronic or silent ischaemia, or progressive steno-occlusive disease. Imaging findings from conventional MRI/MRA imaging performed on our patient did not meet criteria for aspirin therapy; however, after identification of the vessel wall enhancement and dissection she was started on 81 mg of aspirin each day.

OUTCOME AND FOLLOW-UP
Within 4 weeks of starting aspirin, the patient’s headaches improved. She experienced a decrease in both frequency and severity of her headaches. The improved headache symptoms have persisted through to the most recent 3-month follow-up. No complications including TIA or stroke have resulted from the left ICA stenosis or focal dissection to date.

DISCUSSION
With the utilisation of advanced high-resolution vessel wall imaging and 4D flow MRA, we are able to detect vessel wall enhancement and altered blood flow in an arterial segment with known progressive luminal narrowing as well as detect a focal dissection not visible on more conventional vascular imaging sequences. This is the first time these advanced imaging techniques have been used in a patient with PHACE syndrome and progressive arteriopathy. These imaging findings directly led to the addition of aspirin therapy despite not meeting the criteria for aspirin per the consensus guidelines for the prevention of neurovascular complications with notable improvement in the subject’s headaches after beginning treatment.

PHACE is an acronym coined by Frieden et al for posterior fossa, haemangiomas, arterial, cardiovascular, eye anomalies and ventral developmental defects. Though the acronym PHACE is also used sometimes due to the presence of sternal abnormalities, such as sternal cleft present in this case. While the underlying aetiology of PHACE syndrome remains unknown, many believe that the clinical manifestations of the syndrome are downstream events that originate from developmental defects of small-sized and medium-sized arteries of the head and neck. Given the ipsilateral and segmental nature of the clinical features, post-zygotic somatic mutation(s) have been proposed; however, extensive genomic investigation has not yet identified pathogenic mutations shared by patients.

Although the most apparent and often presenting feature of PHACE is infantile haemangioma, the long-term morbidity is the result of the arterial and aortic arch abnormalities observed in this syndrome. Arterial anomalies are extraordinarily common in PHACE and approach or exceed the incidences observed in well-known connective tissue disorders such as Marfan’s syndrome. Over 85% of patients with PHACE are born with abnormalities of cervical and cerebral arteries, and progressive changes may lead to devastating neurovascular complications. As existing PHACE cohorts reach adolescence and adulthood, these complications of PHACE are increasingly being recognised and include migraine-like headaches, TIAs, AIS, MMV and rarely arterial dissection. Although we know patients are at increased risk of these emerging neurovascular-related morbidities, very little is known about the nature of the arteriopathy (ie, no good imaging and no pathology).

Despite this being the first reported case of vessel wall enhancement in PHACE syndrome, other similar arterial pathologies have documented vessel wall enhancement, supporting our findings. For example, enhancement has been seen in cases of other causes of secondary MMV, idiopathic moyamoya disease, both paediatric and adult AIS, and multiple types of vasculitides. Specifically, in the paediatric population, the Vascular Effects of Infection in Pediatric Stroke Study was the largest study evaluating stroke in the paediatric population, prospectively enrolling 355 children with arterial ischaemic stroke (2010–2014). This study not only documented vessel wall enhancement...
Funding in the public, commercial or not-for-profit sectors.

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Acknowledgements

The project described was supported by the National Institute of Neurological Disorders and Stroke (NINDS), grant U10NS098253, and the National Institute of Child Health and Human Development (NICHD), grant R21HD088609. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. None declared.

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