[*Original article*: 2 tables; 2 figures]

Diagnosis of vertebral artery dissection in childhood posterior circulation arterial ischaemic stroke

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ABBREVIATIONS

AIS   Arterial ischaemic stroke

CASCADE   Childhood Arterial Ischaemic Stroke Standardized Classification and Diagnostic

Evaluation

CTA   Computed tomographic angiography

MRA   Magnetic resonance angiography

PCAIS   Posterior circulation arterial ischaemic stroke

VAD   Vertebral artery dissection

[Abstract]

AIM Review a series of children with posterior circulation arterial ischaemic stroke (PCAIS) to identify diagnostic modality and associations in cases of vertebral artery dissection (VAD).

METHOD Retrospective analysis of 30 cases of childhood PCAIS identified from two tertiary centres over 11 years. Clinical and demographic details were recorded. Brain and cerebrovascular imaging were reviewed. Aetiology was classified using the Childhood Arterial Ischaemic Stroke Standardized Classification and Diagnostic Evaluation criteria. Outcome was evaluated using standardized paediatric stroke outcome scores. Logistic regression was used to explore variables associated with diagnosis.

RESULTS Twenty-three patients were male (77%). VAD was the most commonly identified aetiology, in 15 cases (50%). Aetiology was undetermined in 12 (40%), probable cardioembolism in two, and reversible cerebral vasoconstriction syndrome in one. In those with VAD, diagnosis was made on initial magnetic resonance angiography (MRA) in six (40%). Further cases of VAD were diagnosed with catheter angiography ($n=6$), computed tomographic angiography ($n=1$), or follow-up MRA ($n=2$). Presence of multiple infarcts was associated with a diagnosis of VAD.

INTERPRETATION Endoluminal cerebrovascular imaging increases the rate of diagnosis of VAD in childhood PCAIS and should especially be considered if there are multiple infarcts.

What this paper adds

- Multiple infarcts are associated with a diagnosis of VAD in childhood PCAIS.

- Endoluminal imaging and follow-up MRI improve the diagnostic yield.

[Main text]

Childhood arterial ischaemic stroke (AIS) involves the posterior circulation territory in a third of cases, with distinctive demographic features and risk factors.[1] It is recognized that many cases are secondary to vertebral artery dissection (VAD), usually extracranial. Currently this diagnosis significantly alters management as clinical guidelines recommend anticoagulation—as opposed to antiplatelet therapy for other arteriopathies. Magnetic resonance angiography (MRA) is recommended as the modality of choice for characterizing the cerebrovascular

circulation in childhood AIS.[2,3] With increasing awareness of the importance of cervical arteriopathies in childhood AIS, it is advocated that MRA includes the cerebral circulation from the aortic arch to the circle of Willis.[2] The role of endoluminal cerebrovascular imaging techniques (catheter angiography and computed tomographic angiography [CTA]) in the investigation of childhood AIS remains unclear. This is especially pertinent in cases of posterior circulation AIS (PCAIS), where MRA is known to have limitations in both sensitivity and specificity.[4,5] Here we review cases of PCAIS with the aim of describing imaging modality, and clinical and imaging features associated with VAD.

METHOD

This was a retrospective analysis of a series of sequential children (aged >28d) with PCAIS identified from stroke clinics at Great Ormond Street Hospital NHS Foundation Trust, London, UK, and Addenbrooke's Hospital, Cambridge, UK, between 2003 and 2013. Neonates, children with co-existing anterior circulation AIS, and children without cervical vascular imaging were excluded. Both institutions confirmed that formal ethical review was not required to review this retrospective material.

All patients had been investigated for AIS risk factors and managed according to UK national paediatric stroke guidelines.[2] Radiological evaluation included time-of-flight MRA of the cervical and intracranial circulations and cross-sectional fat-saturated T1-weighted imaging through the neck, as well as standard brain magnetic resonance imaging (MRI) in both centres. More detailed investigations, such as catheter angiography or CTA, were undertaken at the discretion of the treating clinician, as were any follow-up investigations or imaging. Clinical and demographic data were recorded from case notes. Specific risk factors and additional investigations recorded (based on review of those identified in previous studies of PCAIS) were preceding trauma, pre-existing migraine, hypertension, cardiac defects (results of

echocardiography), results of upper cervical spine radiographs, prothrombotic states, iron deficiency anaemia, recent *varicella* infection, hyperhomocysteinemia, mitochondrial disease, and results of biochemical screening for Fabry disease.

All imaging was reviewed by a neuroradiologist (DS) unaware of the clinical details. The arterial territory of the infarct(s) was categorized into proximal, middle, and distal segments of the posterior circulation (summarized in Fig. S1, online supporting information).[6] Aetiology was categorized using the Childhood Arterial Ischaemic Stroke Standardized Classification and Diagnostic Evaluation (CASCADE) criteria.[7] Arterial dissection was only diagnosed if one of three patterns stipulated in CASCADE were seen (Table SI, online supporting information). Aetiology was categorized as undetermined when arterial abnormalities were observed but not categorizable within CASCADE, or if the arterial imaging was normal and no other aetiology was identified. Where available, follow-up imaging was reviewed for the presence of new infarcts and the progression of arterial abnormalities.

Clinical outcome was evaluated retrospectively based on case notes at the most recent follow-up appointment. The Pediatric Stroke Outcome Measure evaluates impairment in five domains (sensorimotor [left and right], language [production and comprehension], and cognition/behaviour), each scoring from zero (no deficit) to two (severe deficit). The total score equates to the outcome; anything more than a mild deficit in one sphere equates to a poor outcome.[8,9] Bulder et al.[10] coupled the modified Rankin score with the type of school attended to reflect outcome after childhood AIS, with a modified Rankin score of two or less and attending a mainstream school representing good outcome, and a modified Rankin score of three or more, or attending a special school because of learning difficulties, representing poor outcome.

A univariable logistic regression model was used to explore whether age, prior trauma, time to MRA, multiple infarcts at presentation, or recurrence (clinical or radiological) were

associated with a diagnosis of VAD. Risk factors were entered into univariable regression analyses with VAD versus not-VAD as the outcome category .

RESULTS

Thirty children with PCAIS were identified, of whom 23 were males (77%). Median age at diagnosis was 7 years (range 10mo–14y 10mo) and median duration of follow-up was 16 months (range 6wk–96mo). Four children had pre-existing neurodevelopmental impairments (developmental delay, learning difficulties, and autism).

Clinical and radiological characteristics are summarized in Table I. Focal symptoms or signs were reported in 25 children at presentation, commonly hemiparesis ($n=20$), and ataxia ($n=8$). Diffuse symptoms occurred in 21 children at presentation, commonly headache ($n=14$), vomiting ($n=11$), and reduced conscious level ($n=7$).

All children had been investigated with at least one brain MRI scan, and angiography extending from the aortic arch to circle of Willis (MRA, catheter angiography, or CTA). In two cases, extracranial vascular imaging was only performed at follow-up. Fourteen children had catheter cerebral angiography and six had CTA as part of the initial evaluation. Twenty-four had later follow-up MRA.

Segmental infarct topography is summarized in Figure S1 (online supporting information). Topographical infarct distribution was not associated with diagnosis (single territory vs more than one territory, Fisher's exact test, $p=0.26$). Nineteen children had multiple infarcts at presentation. A diagnosis of VAD according to CASCADE criteria was made in 15 cases (50%). Of these, seven met pattern 4a (1), two pattern 4a (2) and six pattern 4a (3) in terms of criteria described in Table SI. Other diagnoses were reversible cerebral vasoconstriction syndrome ($n=1$ and probable cardioembolism ($n=2$).

Aetiology could not be ascertained in 12 cases. Of these, only three had endoluminal cervical vessel imaging (catheter angiography or CTA) acutely. Two did not have cervical vascular imaging acutely. Vascular imaging showed non-diagnostic abnormalities in three of these cases: in two of these the first cervical vessel imaging was delayed (more than 2mo); in one the abnormality was present in the acute phase and remained stable on follow-up MRA, but no endoluminal cervical vessel imaging was done. The undetermined group were all investigated with transthoracic echocardiogram, and for the presence of prothrombotic tendencies, according to UK guidelines.[2]

The modality and timing of VAD diagnosis is illustrated in Figure 1. Most cases had intracranial and cervical vascular imaging performed within 1 week of the initial MRI ($n=25$); however, in three cases it was between 8 and 28 days, and in two cases cervical vascular imaging was only performed at follow-up. In the group with VAD ($n=15$), diagnosis was made on the initial MRA in six children, on catheter angiography in six (Fig. 2), and on CTA in one. In two cases VAD was only diagnosed on follow-up MRA—both meeting category 4a (3) CASCADE criteria: one had non-diagnostic vertebral artery irregularity on acute MRA with no additional acute imaging, and one had a normal acute MRA and a non-diagnostic vertebral artery irregularity on acute catheter angiography; both showed unilateral vertebral artery occlusion at follow-up.

Seven children had initially abnormal but non-diagnostic acute MRA. VAD was eventually diagnosed in five of these after further or follow-up imaging. Another specific diagnosis was made in one (reversible cerebral vasoconstriction syndrome). One had a non-diagnostic calibre change in one vertebral artery, which was stable on follow-up MRA. In total, nine of the fourteen catheter angiographies performed were diagnostic (one for reversible cerebral vasoconstriction, eight for VAD [see Fig. 2]); thus we estimated that every 3.5 catheter angiography yielded a positive diagnosis.

Fifteen children were evaluated for cervical spine abnormalities, 11 from the VAD group. Only one abnormality was found: hereditary exostosis in a child with VAD, thought to have been aetiologically relevant. Surgical options for secondary prevention were explored but not pursued as the vessels had occluded at the site adjacent to the exostoses.

All patients were managed according to UK paediatric AIS guidelines (Table I).[2] Only one child received neither aspirin nor anticoagulation—seen 2 years after acute presentation and the parents declined treatment. Outcome was scored at the time of the most recent follow-up, at a median interval of 16 months; data were available for 29 out of 30 children. Although the four children with pre-existing neurodevelopmental difficulties were rated as having poor outcome on both scales, most of the impairments were pre-existing, with little additional functional impairment caused by AIS. In the children without pre-existing impairment (n=25), two had a poor outcome using modified Rankin score/school (8%), compared with 10 using the Pediatric Stroke Outcome Measure (40%). In the eight cases where the outcome measures were discordant, children had moderate deficits on neurological examination (poor outcome on Pediatric Stroke Outcome Measure) but only minor functional impairment (good outcome using modified Rankin score/school).

Six children had new infarcts on follow-up. Only one of these was symptomatic—a female with VAD who had a new stroke 6 weeks after initial presentation, despite treatment with warfarin and a therapeutic international normalized ratio (2–3). She had a good outcome and no further infarcts at 8 month follow-up. Three children with VAD, one with probable cardioemolism and one with reversible cerebral vasoconstriction, had asymptomatic new infarcts, seen on first follow-up imaging available, between 2 and 28 months later. Two of these VAD cases were on treatment with both warfarin and aspirin, the third VAD case and the other cases were on aspirin alone. Three children (all with VAD) had transient ischaemic attacks without new infarcts, at 3, 3, and 19 months after initial presentation. Recurrences were

managed by adding aspirin to anticoagulation, increasing the duration of aspirin or anticoagulation therapy, or closure of patent foramen ovale. Seven of these nine had a good outcome (on both measures) despite the recurrence or new infarct.

Univariable logistic regression age, antecedent trauma, time to MRA, and recurrence were not significantly associated with VAD diagnosis (Table II). However, the presence of multiple infarcts at presentation was associated with VAD (OR 9.75, p=0.014, Table II). The number of events (15 out of 30, 50%) would allow a multivariable predictive model that included only 1.5 variables,[11] hence we did not perform multivariable analysis.

DISCUSSION

VAD was a common cause of childhood PCAIS in our series, as seen previously. The key new, and clinically important, messages from this analysis were that diagnostic yield was improved by endoluminal vascular imaging (mostly catheter angiography in this series), and that the presence of multiple infarcts at presentation is associated with a diagnosis of VAD. This may be due to the embolic nature of VAD-related stroke. We accept that the non-VAD group we have described were often not comprehensively investigated and thus it is possible that some of those cases were misclassified. Although Mackay et al. observed a high rate of arteriopathy in their series of 27 children with PCAIS, only three had a diagnosis of VAD.[12] Of note, it was not their routine practice to perform cervical vascular imaging, and only 15 children had this (catheter angiography or MRA)—thus, our data suggest that the rate of VAD diagnosis might have been increased both by targeting the cervical circulation as well as by using endoluminal techniques.

We recognize the difficulties of making a firm diagnosis of VAD on radiological grounds; to ensure transparency of our data, diagnosis of VAD required the diagnostic criteria set out in CASCADE to be fulfilled. In our patients, initial MRA misclassified 54% of the eventually

diagnosed VAD cases—similar to the experience of Rollins et al.[13] The most sensitive imaging modality has not been established in children with PCAIS or suspected VAD, although this question has been investigated in adults. MRI with MRA has been shown in a systematic review to be less sensitive for VAD diagnosis than the endoluminal techniques of catheter angiography and CTA.[13] Both catheter angiography and CTA visualize dissection flaps and calibre change but have the disadvantage of not visualizing the vessel wall. CTA has been shown to be highly sensitive for the diagnosis of VAD in a few adults;[14,15] however, CTA has been found to be falsely negative in trauma cases where the vertebral artery may be obscured at the skull base, and catheter angiography is still considered the criterion standard for the diagnosis of VAD. We found that catheter angiography and CTA were useful in children who did not fulfil the CASCADE criteria for dissection on MRA, with only calibre change or irregularity, and resulted in a definitive diagnosis being made in all cases. It is also important to point out that one patient, with initial non-diagnostic catheter angiography, had the diagnosis of VAD made on follow-up MRA. Mackay et al. also reported some cases, with a recurrent course, where VAD was only diagnosed on delayed catheter angiography.[12] Thus a high index of clinical suspicion remains paramount both to targeting acute imaging appropriately and to revisiting the question of diagnosis after an interval. Given the high rate of subclinical recurrence in patients with VAD, we feel a case can be made for early (3mo) re-evaluation with MRI and MRA; where recurrence is not controlled by medical therapy, there may be a role of endovascular intervention.[16]

Cardioembolism accounted for a few cases, although this is a frequent diagnosis in other series, and is likely to have treatment implications if present. As with anterior circulation AIS, anaemia was common, and is correctable. Investigation for specific risk factors for PCAIS, such as cervical spine abnormality, was unrewarding in this cohort, although even a low prevalence would have important clinical implications.

Many of the children had abnormalities of the vertebrobasilar circulation that could not be further delineated. Catheter angiography may have increased both the diagnostic rate for VAD and enabled better characterization of the other abnormalities. The risk factors of those children with indeterminate diagnosis suggest possible diagnoses of focal cerebral arteriopathy of childhood (as observed in many of the patients of Mackay et al.[12]), a more generalized arteriopathy, or an embolic aetiology. CASCADE categories 4a (2) and 4a (3) are less robust than category 4a (1) and it is possible that some category 4a (3) cases were misclassified cases of cardioembolic AIS.

We acknowledge that the optimal management of VAD is not established; the randomized CADISS study could not demonstrate superiority comparing antiplatelet and anticoagulant therapy, and concluded that a sufficiently powered randomized controlled trial was not feasible[17]. However, anticoagulation is currently recommended for extracranial VAD in children in both the Royal College of Physicians and American Heart Association paediatric stroke guidelines.[2,3] In addition, accurate characterization of cerebrovascular abnormality may enable more specific prediction of recurrence risk as arterial morphology and course are the most consistent determinants of recurrence risk.[2] Given the safety of catheter angiography in experienced hands,[18] and the importance of making a diagnosis in terms of prognosis and treatment, we feel there is a strong case for catheter angiography in PCAIS unless a definite diagnosis can be made with non-invasive imaging, especially in children with multiple infarcts at presentation. The relative merits of CTA versus catheter angiography in this context have not been established, but it is relevant to consider that both entail exposure to irradiation and catheter angiography is the criterion standard. In the future, the detection of vessel wall thrombus (bright crescent sign on T1-weighted imaging) may be improved by implementation of new magnetic resonance techniques such as high-field, high-resolution magnetic resonance

and high-resolution fast spin-echo black-blood techniques that have been used in some adult centres and which may reduce the need for invasive imaging.[19,20]

Our study has several limitations. Investigation was not uniform across cases, either in terms of timing or tests used; if all children had undergone catheter angiography, we would have obtained a more accurate comparison of MRA and catheter angiography, and perhaps a more complete spectrum of final diagnoses. We may not have identified all cases that presented because of the retrospective nature of case ascertainment. A larger, more consistently investigated cohort may have allowed the identification of additional predictors of diagnosis. The potential for missed cases of VAD in the undetermined group may be a confounding factor in the univariate analysis. A larger sample would be required for the construction of a predictive multivariable model. Our results suggest potential indicators of VAD. Outcome measures were based on a retrospective note review, and at a median follow-up of 16 months; longitudinal prospective follow-up would be preferable. Finally the accuracy of CASCADE categorization is open to debate as the criteria have not been validated against a criterion standard; however, this is the most current and widely used paediatric AIS classification.

CONCLUSION

VAD is a common cause of PCAIS in childhood, and is an important diagnosis to make as it changes management and counselling for recurrence risk. We have shown that the diagnostic yield is improved with endoluminal imaging techniques. Multiple infarcts were associated with a diagnosis of VAD; exploring this further in the context of a prospective study may be illuminating. These data suggest that there is a good case for undertaking endoluminal cerebrovascular imaging, with catheter angiography or CTA, in cases of childhood PCAIS where a diagnosis has not already been made, especially if there are multiple infarcts.

SUPPORTING INFORMATION

The following additional information may be found online:

Table SI: Childhood Arterial Ischaemic Stroke Standardized Classification and Diagnostic Evaluation (CASCADE) criteria for classification of dissection[7]

Figure S1: Segmental infarct topography

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Table I: Summary of clinical and radiological features of patients with vertebral artery dissection (VAD) and non-VAD diagnosis (undetermined and other) (*n*=30)

	VAD (*n*=15)	Non-VAD (*n*=15)	
		Undetermined (*n*=12)	Other (*n*=3)
Median age (y)	6.5	7.6	13.8
Male gender (%)	13 (87%)	8 (67%)	2 (67%)
Risk factors			
Head/neck trauma	6	3	0
Microcytic anaemia	4	2	0
Cardiovascular abnormality			
Patent foramen ovale	2 (no shunt)	4 (no shunt)	1 (right–left shunt)
ASD	0	0	1 (right–left shunt)
Other	0	1 (midaortic syndrome and renovascular hypertension)	
Cervical spine abnormality	Hereditary exostoses, 1	0	0
Migraine	1	2	1
Infection	0	*Varicella zoster*, 1 Gastroenteritis, 2	0
Treatment			
Anticoagulation	12	1	0
Aspirin	14	11	3
Anticoagulation and aspirin	6	0	0
Other	0	Posterior fossa decompression, 1 Renal angioplasty, 1	ASD/patent foramen ovale closure 2, clot retrieval 1
Imaging and recurrence			
Median interval between presentation and angiography including neck (d)	2	0	0
Clinical recurrence	Stroke, 1 TIA, 3 (single events)	0	0
Final MRI: new infarcts	4 (3 asymptomatic)	0	2 (both asymptomatic)
Any recurrence (clinical or radiological)	7	0	2
Multiple infarct at presentation	13	4	2
Median interval to final imaging	29mo	25mo	27mo
CASCADE classification, chronic	Progressive 2 Stable 11 Reversible 2	N/A 12	Reversible 1 N/A 2

ASD, atrial septal defect; CASCADE, Childhood Arterial Ischaemic Stroke Standardized Classification and Diagnostic Evaluation; N/A, not applicable; MRI, magnetic resonance imaging.

Table II: Vertebral artery dissection (VAD) diagnosis—associations

	VAD (*n*=15)	Non-VAD (*n*=15) (undetermined, *n*=12, other, *n*=3)	Univariable analysis, OR (95% CI)
Median age (y)	6.5	12.7	0.9 (0.76–1.07) *p*=0.22
Head/neck trauma (yes vs no)	6 (40%)	3 (20%)	2.7 (0.52– 13.66) *p*=0.24
Median interval between presentation and angiography including neck (d)	2	0	0.99 (0.94–1.04) *p*=0.65
Any recurrence (clinical or radiological; yes vs no)	7 (47%)	2 (13%)	5.7 (0.94–34.46) *p*=0.06
Multiple infarct at presentation (yes vs no)	13 (87%)	6 (40%)	9.75 (1.6–59.7) *p*=0.014

OR, odds ratio; CI, confidence interval.

Figure 1: Modality and timing of vertebral artery dissection (VAD) diagnosis. MRA, magnetic resonance angiography; CA, catheter angiography; CTA, computed tomographic angiography. *Twenty-two performed within 7 days, three between 8 and 28 days. †Three also had acute catheter angiography after diagnostic MRA.
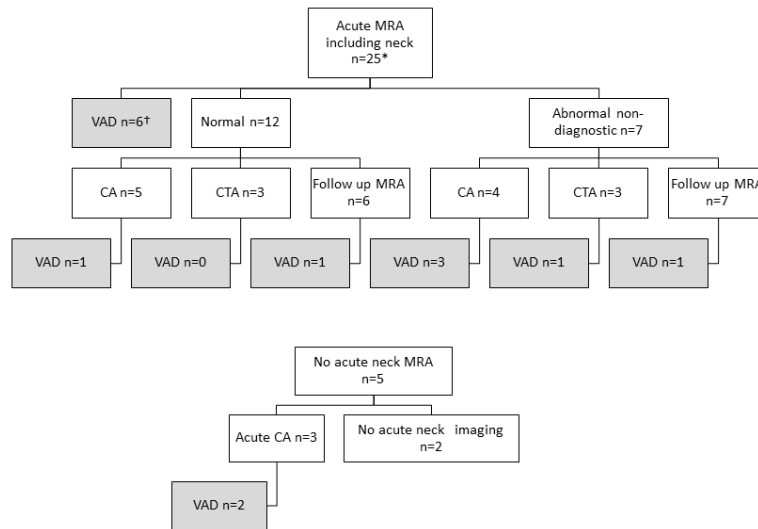
Acute MRA including neck n=25*

VAD n=6† | Normal n=12 | Abnormal non-diagnostic n=7

CA n=5 | CTA n=3 | Follow up MRA n=6 | CA n=4 | CTA n=3 | Follow up MRA n=7

VAD n=1 | VAD n=0 | VAD n=1 | VAD n=3 | VAD n=1 | VAD n=1

No acute neck MRA n=5

Acute CA n=3 | No acute neck imaging n=2

VAD n=2

Figure 2: Imaging. (a) Non-diagnostic abnormality of vertebral artery on magnetic resonance angiography (MRA). A 6-year-old male presented with a hemiparesis, headache, and ataxia, with no risk factors other than an insignificant patent foramen ovale. Imaging revealed a pontine infarct. Rotated two-dimensional time-of-flight MRA images with irregularities of the V3 loop suggestive of a dissection but not fulfilling the requirements for a diagnosis of vertebral artery dissection (VAD). No further imaging to confirm a diagnosis and the child was categorized as undetermined. The patient was treated with aspirin for 2 years with no recurrence. (b) Image from 10-year-old male with multiple posterior territory infarcts. The extracranial time-of-flight MRA demonstrated irregularities of the V2–V4 segments of right vertebral artery (between short arrows) but with no definite diagnostic features of VAD. (c) Image from 10-year-old male with multiple posterior territory infarcts. Conventional cerebral

angiography revealed a focal abnormality of the right vertebral artery (arrowhead) at V3 and mural thrombus within a dural tear/flap of the proximal intradural component (long arrow) as well as irregularities of the basilar artery. Appearances fulfilled Childhood Arterial Ischaemic Stroke Standardized Classification and Diagnostic Evaluation (CASCADE) category 4a (1) for a diagnosis of right VAD.