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De Novo Arteriovenous Malformation in a 4 Year-Old Boy with Headache, with No Previous Cerebrovascular Disease

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Abstract

Intracerebral arteriovenous malformations (AVM) have traditionally been considered congenital lesions. This model of pathogenesis has recently been challenged following a small number of reports describing de novo presentation of AVM in patients with pre-existing cerebrovascular disease.

However, we present the case of a 4 year-old boy presenting with headache, with no history of cerebrovascular disease, whose imaging demonstrated a Spetzler-Martin grade 3 AVM in the left superior temporal gyrus. The patient was previously investigated for seizures as a neonate and at this time magnetic resonance imaging identified no underlying abnormality.

We present a case of de novo AVM in a child without pre-existing cerebrovascular disease, adding to a limited number of pre-existing reports and discuss it in context of recent advances in the understanding of AVM pathogenesis.

Keywords: Cerebral arteriovenous; Malformation

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The Case

A 4 year-old boy presented to clinic with a 6-month history of headache. The headaches were severe and localised over the right temporal cranium. The headaches would last 10-15 minutes and triggered crying, causing the boy to lie down until his symptoms resolved. At onset, the headaches were limited to two episodes daily, however their frequency and duration have increased; 3 months prior to his first meeting with the neurosurgical service, headache frequency had increased to 5 times per day before becoming constant in nature. Importantly, the headaches were not associated with photophobia, nausea or vomiting nor had his parents noticed any specific triggers. His mother had treated his symptoms with daily ibuprofen.

The 4 year old was born via normal vaginal delivery after an uncomplicated pregnancy, however during the neonatal period he was reported to have suffered seizures. Head magnetic resonance imaging (MRI) performed at the time revealed no underlying abnormality (**Figure 1**). The patient was commenced on phenobarbital, which was discontinued at 2 years following complete seizure cessation and he continues to be seizure-free. The boy's medical and family history were otherwise insignificant, particularly regarding migraines, and there were no developmental concerns.

On examination, the patient was neurologically intact with a height, weight and head circumference within the normal range for his age. The patient underwent further head imaging to identify the origin of his new onset headaches. MRI demonstrated a diffuse arteriovenous malformation (AVM) in the posterior portion of the left superior temporal gyrus (**Figure 2**), which was confirmed by angiography (**Figure 3**). On later questioning, there was no family history of AVM and after comparison with the MRI performed during infancy, it was confirmed that this patient had acquired an AVM de novo. The patient now awaits surgical management and his care is overseen by neurology services for the management of his headaches.

Discussion

In 1928, Walter Dandy suggested AVMs were derived from enduring embryonic arteriovenous connections that failed to regress after foetal development [1]. Since then, there has been a prevailing view in neurosurgical texts describing AVM formation

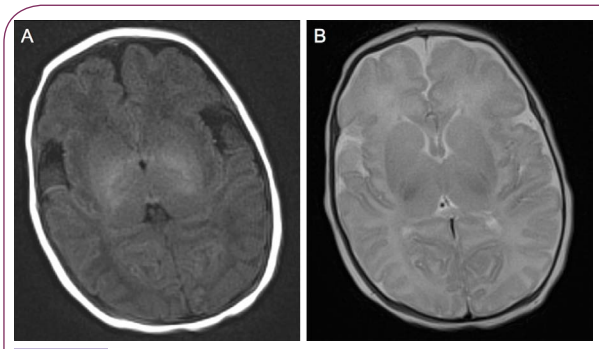

Figure 1 Normal magnetic resonance imaging (MRI) after investigation for seizures. (A) T1 and (B) T2 weighted MRI was performed on xx day old for investigation of seizures, which demonstrated no underlying structural abnormality.

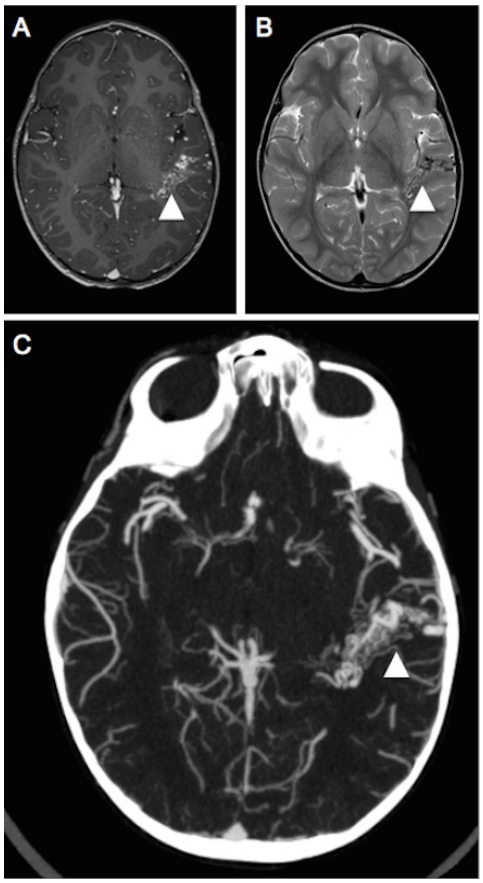

Figure 2 Magnetic resonance imaging (MRI) of a 4 year-old boy with headache. (A) T1 weighted MRI with gadolinium demonstrates a diffuse tangle of tiny vessels in the left superior temporal gurus extending into the gyrus of Heschl and into the posterior striatum (B) T2 weighted MRI demonstrates flow voids and peri-nidal hyperintensity within the deep component of the nidus, however no hemosiderin ring is present. (C) MR angiography demonstrates the arteriovenous malformation with superficial venous drainage.

as a congenital phenomenon [2]. AVMs are thought to originate when the embryo is between 40 and 80 mm in length, during which time processes such as vasculogenesis, angiogenesis, vascular remodelling and differentiation take place [3,4]. It has therefore been widely accepted that cerebral AVMs are present

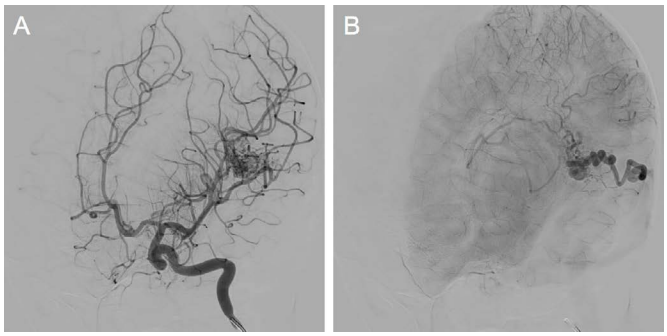

Figure 3 Left internal carotid artery (LICA) digital subtraction angiography (DSA) of a 4 year-old boy presenting with headache. LICA DSA demonstrates an arteriovenous malformation within the left superior temporal gyrus with (A) feeder arteries from the anterior choroidal arteries, posterior and temporal and Sylvian branches of the middle cerebral arteries and (B) superficial drainage via the vein of Labbé.

at birth and follow a silent course before becoming clinically evident [5,6].

The case presented herein adds to only 15 reported cases of de novo AVM [7-21] that challenge the concept of congenital aetiology. Furthermore, this case is only the eighth case described in a child without underlying cerebrovascular disease such as moya-moya disease, or a history of previous vascular malformation (**Table 1**). It has been argued that the appearance of de novo AVM is due to limitations in imaging sensitivity; thrombosis, haemorrhage and oedema can obscure arteriovenous flow visualised by angiography [22]. However, this case and the majority of the previous reported cases demonstrate de novo AVM using sensitive high-resolution cross-sectional imaging such as MRI (**Table 1**). Importantly, with the increasing availability of MRI, it is likely that we will recognise more cases of de novo AVM in the future.

In addition to the reports of de novo AVM development, the exceedingly rare diagnosis of cerebral AVMs in utero further questions the assumption that AVMs originate during embryonic development [23-25]. The current standard of prenatal imaging techniques is such that abnormalities such as vein of Galen aneurysmal malformations are frequently detected in utero or in the early post-natal period [26]. This indicates the lack of peri-natal cerebral AVM diagnosis should not be blamed on technological inadequacy, but instead point towards the need for a new understanding of cerebral AVM pathogenesis.

The exact mechanism of cerebral AVM formation remains unclear, though is thought to involve a combination of genetic and environmental factors. The most common genetic abnormality appears to derive from mutations in the gene coding for activin-like kinase 1 (Alk1) [26]. Several studies have found loss-of-function mutations in Alk1 in hereditary haemorrhagic telangiectasia (HHT) type 2 [27]. HHT is an autosomal dominant condition that can present with cerebral AVMs [26]. Mutations in Alk1 affect transforming growth factor-β (TGF-β), which is

Table 1 Summary of documented cases of de novo arteriovenous malformation (AVM) in patients with and without pre-existing cerebrovascular disease.

Case	Details of initial presentation and imaging			Details of presentation with de novo AVM			
	Presentation	Imaging	Diagnosis	Presentation	Imaging	Diagnosis	Management
[7]	16 y female Right facial palsy	MRI	Bell's Palsy	30 y Chronic migraine	MRI	Left frontoparietal AVM	Unspecified
[8]	15 y male New onset seizures	MRI	None	24 y Seizure	MRI and DSA	Left parietal AVM	Operative resection
[9]	26 y female Multifocal neurological deficit	MRI	Unspecified midbrain hyperintensity	32 y Intracerebral haemorrhage	CT and MRI	Right temporal AVM	Operative resection
[10]	3 y female Trauma	MRI	Left frontal intracerebral haemorrhage	6 y Intractable epilepsy since trauma	MRI and DSA	Right temporal lobe AVM	Operative resection
[11]	6 y female Developmental delay and seizure	MRI	None	9 y Increased seizure frequency post-trauma	MRI and angiogram	Left temporal-occipital lobe AVM	Radiation therapy
[12]	25 y male Seizures	Angiogram	None	50 y Seizure and aura of vivid auditory hallucination	CT	Large left temporal lobe AVM	Conservative
[13]	4 y male Seizures	MRI	None	7 y Seizure	MRI and angiography	Right occipital lobe AVM	Operative resection
[14]	10 y female Transient ischaemic attack	MRI	Moya-moya disease	14 y Follow-up	MRI	Right occipital lobe AVM	Conservative
[15]	6 y male Seizures	MRI	Cavernous malformation, developmental venous anomaly	9 y Follow-up	MRI	Choroidal AVM	Unspecified
[16]	3 y male Left hemispheric infarct	CT and angiogram	Moya-moya disease	11 y Follow-up	MRI	Left posterior parietal AVM	Unspecified
[17]	9 y female Seizures	CT and MRI	Right parietal AVM treated with Gamma knife type B	11 y Follow-up	MRI and angiogram	Deeper, more medial right parietal AVM	Radiosurgery
[18]	10 y female Intraventricular haemorrhage	Angiogram	Splenium and left occipital lobe AVM managed by gross total resection	27 y Intracerebral haemorrhage	MRI	Midline cingulated gyrus, corpus callosum AVM	Operative resection
[19]	3 y female Left hemispheric stroke	MRI	Sickle cell disease and moya-moya disease	6 y Follow-up	MRI	Right Sylvian region AVM	Operative resection
[20]	3 y male Seizure	MRI and DSA	Right parietal AVM treated with embolisation with four coils and Onyx	7 y Seizure	MRI and angiogram	Left medial occipital AVM	Embolisation and Onyx
[21]	3 weeks female	MRI	Two enhancing extracranial masses	2.5 y Follow-up	MRI	Cerebellar AVM	Unspecified

*case with de novo AVM without pre-existing cerebrovascular disease
MRI: Magnetic Resonance Imaging
CT: Computer Tomography

critical for angiogenesis and inflammation. Alk1 deletion in mouse models is associated with cerebrovascular de novo AVM [28]. Importantly, these AVMs only occurred after stimulation with vascular endothelial growth factor (VEGF) [28]. Indeed, VEGF promotes vascular proliferation and is markedly increased in patients with cerebral AVM [29]. However, VEGF stimulation alone has never been shown to induce de novo AVM formation in animal models.

Similarly to the HHT studies, the genetic predisposition for AVM formation has been studied in familial clustering of sporadic cerebral AVMs. A recent systematic review included all studies reporting single-nucleotide polymorphisms (SNPs) associated with sporadic cerebral AVMs and describes a statistically significant association between an SNP in the ALK1 gene and a susceptibility to developing cerebral AVMs (OR 2.19, 95% CI 1.25-3.83) [26,30].

One proposed mechanism for AVM formation extrapolates the genetic predispositions demonstrated by animal models and illustrates an important potential interaction between primary genetic mutations and the cerebrovascular microenvironment in the formation of AVM. It is thought asymptomatic parenchymal venous thrombosis triggers local hypertension and ischaemia [26]. This in turn triggers uncontrolled vascular proliferation and ultimately arteriovenous shunt formation. The presence of the aforementioned genetic susceptibility, as well as abnormalities of the angiogenesis and inflammatory cascades prevents these processes from being self-limited [26]. Once the vascular lesion is subjected to high flow, endothelial shear stress contributes to a continued angiogenic stimulus and a hyperangiogenic environment. These phenomena can also explain the documented propensity of AVMs to increase and decrease in size spontaneously [31,32] and in some cases, dramatically recur years after AVM surgery, gamma knife and embolisation [33,34].

Conclusions

We describe a case of de novo AVM in a patient without previous cerebrovascular disease. The dynamic nature of cerebral AVM has been previously described, however, considering this further case of reported de novo AVM and recent animal models, we emphasize the need to re-examine the traditional ideas regarding AVM pathogenesis.

Conflict of Interest

The authors declare no conflict of interest

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