



Cerebral Corticoarterial Malformations

A Case Series of Unilateral Polymicrogyria and Ipsilateral Arterial Dysplasia

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Introduction

Development of the cerebral cortex and its vasculature occurs as a coordinated, codependent process, tightly controlled by robust genetic algorithms [1, 2]. Advances in medical imaging are providing phenotypic examples where aberrancy in the development of one of these systems directly affects the other, producing focal corticovascular malformations [3–5]. The development of the cerebral cortex invokes a progressive increase in cortical blood flow during the second half of gestation and into the early days following birth [6–8]. This provides an especially vulnerable period to in utero hypoxic insults that can affect both the cerebral cortex and its adaptive remodeling vascular supply.

Malformations of cortical development (MCDs) occur in a spectrum of morphologic abnormalities, with polymicrogyria being the most common form. Radiologically, it

has been defined as cortex demonstrating (i) an irregular surface, (ii) thickening/over-folding, and (iii) stippling or irregularity along the grey-white matter junction [9]. Bilateral perisylvian and diffuse generalized patterns of polymicrogyria comprises 80% of cases. Interestingly, vascular malformations or disruptive lesions have a propensity to colocalize with unilateral, focal forms of MCD [4, 10, 11]. This article presents three such cases that demonstrate arterial dysplasia of the anterior cerebral circulation on neuroimaging with ipsilateral perisylvian polymicrogyria, a unique form of corticoarterial malformation. Case clinical presentations and imaging findings are discussed followed by consideration of their potential interdependency.

Case Reports

Case 1

A 22-year-old right-handed woman with epilepsy since the age of 12 years presented with increasing seizure frequency over the previous year. Her most recent seizures were nocturnal and focal dyscognitive with secondary generalization. Physical examination was unremarkable with the exception of a subtle left pronator drift. Seizure control used a combination of carbamazepine and clobazam, with irregular compliance. Magnetic resonance imaging (MRI) demonstrated an abnormally high density of vessels within the right Sylvian fissure overlying a focal region of polymicrogyria (Fig. 1). Further characterization with a computed tomography (CT) angiogram confirmed increased vascularity adjacent to the cortex and increased tortuosity of the distal right middle cerebral artery (MCA) branches. Suspicion for associated arteriovenous shunting prompted a time-resolved MR angiogram to be performed that did not reveal a shunting lesion.

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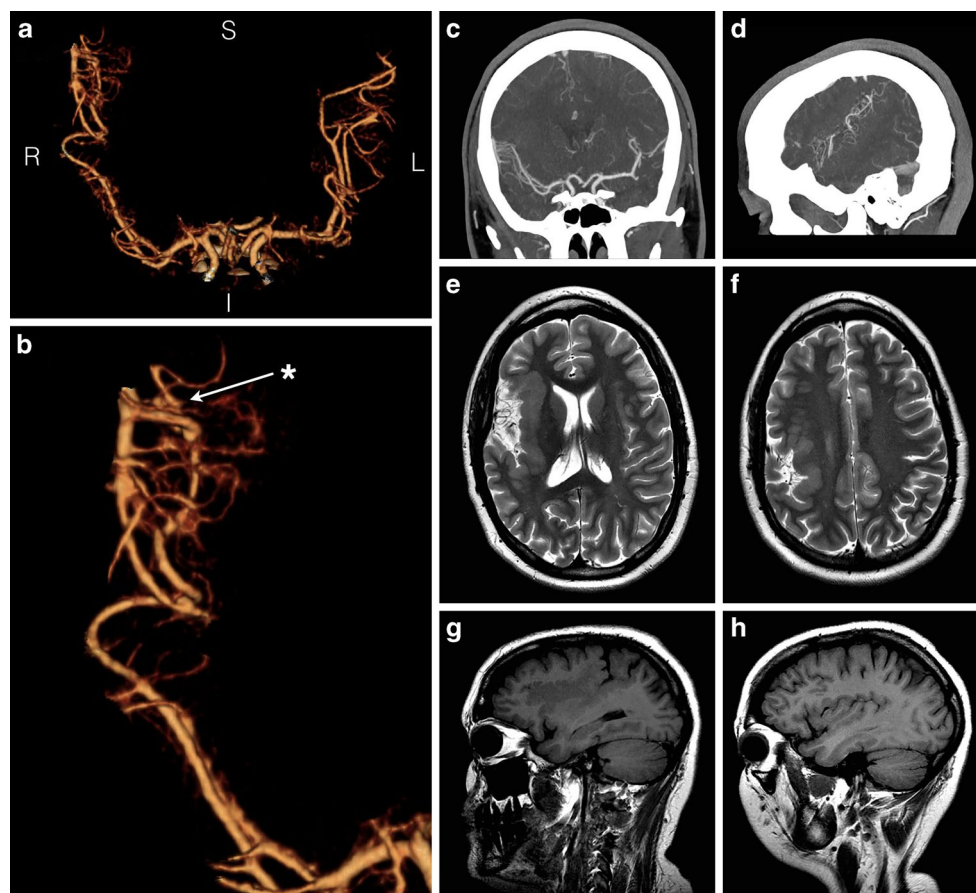
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Fig. 1 Right MCA pure arterial malformation with ipsilateral perisylvian polymicrogyria in a 22-year-old woman with epilepsy. **a** Anteroposterior projection of a 3D reconstruction of the malformation using CT angiography. Note the abnormal dilatation and branching of the distal right MCA vessels. **b** Zoomed in 3D rendering of the right MCA pure arterial malformation, highlighting a focal region of aneurysmal clustering of the distal vessel (*asterisk*). **c** Sample coronal and **d** sagittal MIP reformats from the same CT angiogram demonstrate increased vascularity along the right Sylvian fissure. **e, f** T2-weighted axial images demonstrated this increased vascularity as flow voids in the right Sylvian fissure with abnormally thickened subjacent cortex. **g** T1-weighted sagittal images demonstrate the abnormal cortical thickening, aberrant sulcation, and stippling at the grey-white matter junction along the right Sylvian fissure compared to (**h**) the left



Case 2

A 48-year-old left-handed woman with epilepsy since the age of 3 years presented for evaluation of potential surgery in the setting of increasing seizure frequency. Her seizures were complex partial in nature, and she was experiencing dyscognitive episodes lasting about 30 s, sometimes accompanied by arm shaking. Physical examination demonstrated 3/5 power to the right hand, 4/5 power to the right arm, and 4/5 power to right dorsiflexion, but 5/5 power to the remainder of the right leg. Mild decreased sensation of the right hand to light touch was noted, with complete astereognosis and agraphesthesia. The MRI examination revealed extensive left-sided perisylvian polymicrogyria (Fig. 2). A follow-up time-of-flight MR angiogram demonstrated smooth narrowing along the entire course of the upstream M1 segment of the left MCA. Distal to a left MCA trifurcation, vessel calibers were identical relative to contralateral branches, and no abnormal parenchymal vessels or venous drainage was detected.

Case 3

A 30-year-old, right-handed man presented with a history of medically refractory epilepsy since the age of 8 years. Seizure frequency increased at age 27 years when his wife noticed nocturnal episodes: two types of complex partial seizures were described that were focal dyscognitive, with occasional secondary generalization. Physical examination was unremarkable. Examination of the T2-weighted imaging flow voids on MRI revealed subtle, smooth reduction in caliber of the right M1 segment relative to the contralateral side, upstream of extensive polymicrogyria of the right frontal, parietal, and temporal lobes (Fig. 3a, b). Like case 2, no definite abnormal parenchymal vessels or venous drainage was identified; however, dedicated vascular imaging was not performed. Subsequent brain Fluorodeoxyglucose (FDG)-positron emission tomography (PET) showed reduced radiotracer activity along the right superior temporal lobe, correlating with right MCA vascular territory distal to the M1 segmental stenosis (Fig. 3c).

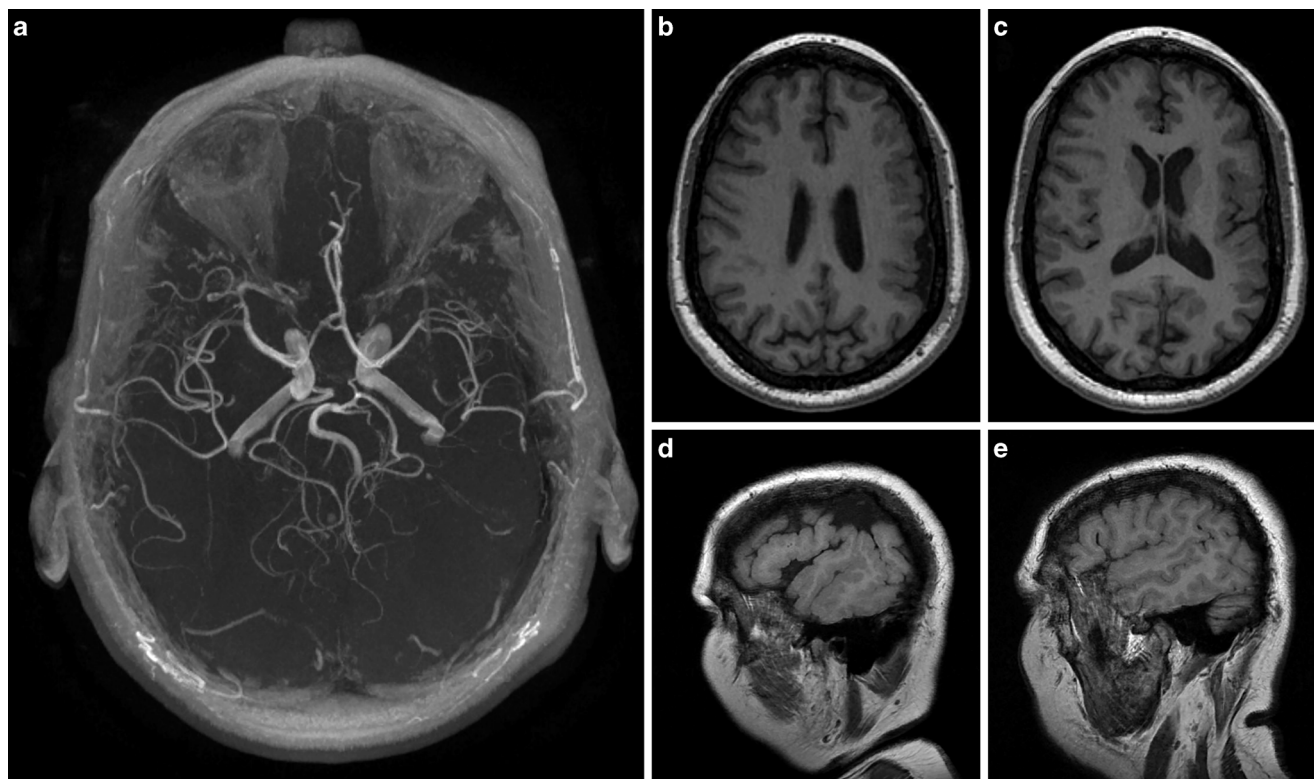


Fig. 2 Proximal left MCA narrowing with ipsilateral perisylvian polymicrogyria. **a** Axial MIP of a 3T time-of-flight MR angiogram that demonstrates narrowing of the left M1 segment relative to the contralateral side. Note how the distal MCA branches are normal in caliber and no significant collateral vessels are present. **b, c** T1-weighted axial and **d** sagittal images demonstrate the abnormally thickened cortex with aberrant sulcation along the left perisylvian region compared to **e** the contralateral side

Fig. 3 Proximal right MCA narrowing with right perisylvian polymicrogyria. **a** Careful attention to the flow voids on a coronal T2-weighted image with fat suppression demonstrates a subtle narrowing of the right M1 branch relative to the contralateral side. **b** T1-weighted sagittal images demonstrate abnormal cortex along the right perisylvian fissure that also extends to involve parts of the right frontal and parietal lobes. **c** Fluorodeoxyglucose(FDG)-positron emission tomography (PET) axial image demonstrates decreased radiotracer activity, reflective of cerebral blood flow and/or hypometabolism, along the region of abnormal cortex within the right middle cerebral artery territory that correspond to the malformed cortex

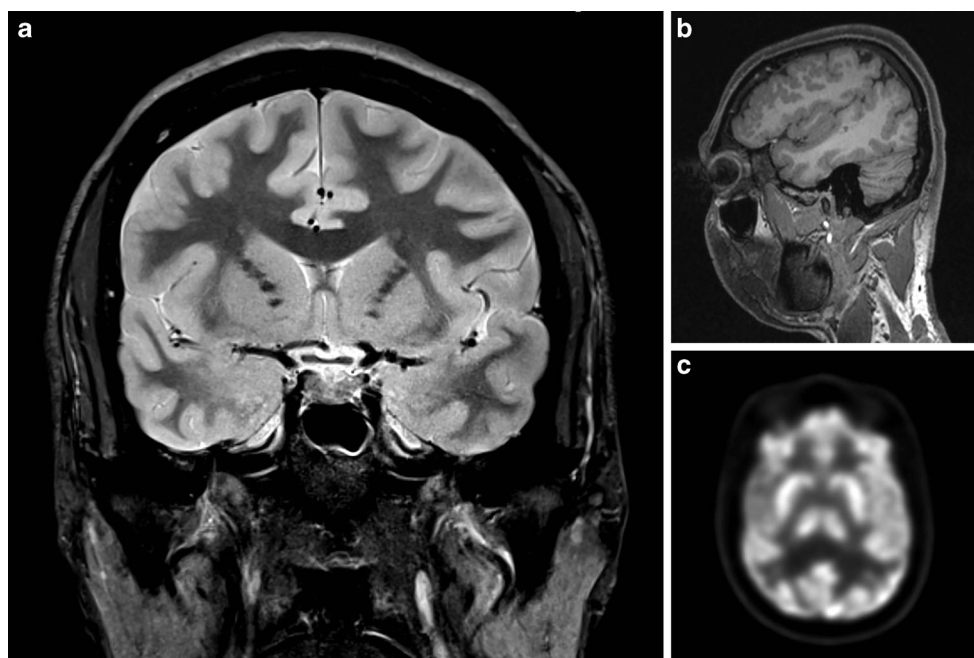


Table 1 Case information for presented corticoarterial malformations

Patient	Age at Presentation (years)	Gender	Age at first seizure (years)	Seizure character	Polymicrogyria	Arterial dysplasia
1	20	F	12	Nocturnal; complex partial with secondary generalization	Right perisylvian	MCA pure arterial malformation
2	48	F	3	Complex partial with secondary generalization	Left perisylvian	Left M1 segmental narrowing
3	30	M	8	Complex partial with occasional secondary generalization	Right perisylvian	Right M1 segmental narrowing

F female, M male

Discussion

While the incidence of polymicrogyria is so low that proper epidemiologic data are lacking, the form of the malformation presented here (unilateral perisylvian) is even uncommon amongst cases of this condition. The presented cases demonstrated ipsilateral arterial dysplasia, producing a corticoarterial malformation pattern that, to our knowledge, has not been reported in the literature (Table 1).

Venous drainage abnormalities are associated with some forms of polymicrogyria, suspected to result from impaired coalescence of the embryonic dural plexus tributaries to form proper cortical veins [12]. Some authors have proposed this may result in impaired venous drainage and focally reduce in utero cerebral perfusion. This mechanism has been used to explain why there is occasional presence of polymicrogyria subjacent to the pial angiomas in Sturge-Weber syndrome [12, 13]; however, it is unclear whether this leptomeningeal pathology is responsible for the genesis or caused by the MCD. Conversely, few examples associating arterial abnormalities with MCDs exist in the literature to date. Aeby et al. presented two cases of young female epilepsy patients with facial hemangiomas and arterial dysplasia in close proximity to supratentorial polymicrogyria [14]. These cases, however, also demonstrated other significant cerebral malformations in keeping with a syndromic etiology. Shankar et al. presented a case where periventricular nodular grey matter heterotopia was associated with an adjacent arterial dysplasia arising from a distal branch of the right posterior cerebral artery in the absence of any venous anomaly [5]. Similarly, an abnormal arterial network in the left Sylvian fissure was demonstrated by Abe et al. adjacent to abnormally thickened insular and temporal cortex [3].

To consider development of these corticoarterial malformations, review of in utero temporal and spatial patterning may be helpful. For polymicrogyria, the timing of an insult is between 16–24 weeks gestation, being an abnormality of late neuronal migration and/or early cortical organization. Although equivocal work-ups for polymicrogyria are common, the two most frequently proven causes are hy-

poxia and infections [9, 15]. Seeing as the cortical pattern presented in these cases is focal and unilateral with ipsilateral arterial abnormalities, confined hypoxia seems a more likely cause than congenital viral infections, such as cytomegalovirus (CMV), which would be expected to result in a generalized, bilateral pattern.

The first case demonstrates a pure arterial malformation of the right MCA (Fig. 1). The pattern described for pure arterial malformations is partially demonstrated here, with regions of coiled vessels and a few superimposed aneurysm clusters along the right Sylvian fissure, but without significant calcifications [16]. The location of the abnormal vessels along the cortical surface as opposed to within the parenchyma leads to the suspicion that the lesion may have developed from focally aberrant vasculogenesis prior to corticogenesis. The formation of the primitive forebrain arteries requires coordinated interactions between neural crest and mesoderm-derived endothelial precursor cells [14, 17, 18]. A focal in utero insult may disrupt the normal formation of the primitive MCA, interrupting its coalescence from an initial plexiform morphology [19–21]. If the anomalous arterioarchitecture demonstrated in Fig. 1 results, it may be hemodynamically insufficient and give rise to distal focal polymicrogyria.

The second pattern of arterial dysplasia demonstrated in these cases is narrowing of the ipsilateral M1 segment upstream of perisylvian polymicrogyria without significant collaterals (Figs. 2 and 3). This imaging finding suggests that at the time of vessel maturation, a relative difference in blood flow to the MCA distributions existed, with reduced vessel caliber on the side of low flow in order to maintain a preset level of endothelial shear stress [20]. Such a blood flow difference seems to persist into adulthood in case 3, where FDG-PET shows reduced radiotracer activity within the right MCA vascular territory distal to the M1 segmental narrowing (Fig. 3c). Although commonly explained by interictal hypometabolism of epileptogenic substrates, in this case reduced perfusion secondary to arterioarchitecture may also contribute to the imaging finding [22]. With no other definite vascular abnormality present, the cause for decreased perfusion to this portion of the cerebrum may

be found at the parenchymal capillary bed level, which arises from secondary sprouting angiogenesis [23]. If a focal region of the cerebral cortex experiences aberrant angiogenesis from its onset, the timing of this hypoxic insult would correspond with the polymicrogyria temporal window. The underlying cause for this aberrancy has several potential candidates, including thrombosis, a focal infectious/inflammatory response, or a genetic predisposition that can be triggered under the right physiologic circumstances [17]. The authors have recently proposed such a mechanism for the latter to explain focal, ipsilateral polymicrogyria with coincident brain arteriovenous malformations seen in HHT patients [10].

As pointed out by Raybaud, asymmetric blood supply to the cerebral hemispheres during gestation is evident by the different compensatory variations that occur within the circle of Willis [18]; however, these cases of corticoarterial malformations suggest such variable perfusion conditions are less permissible distally during development. During early cortical organization blood flow is severalfold reduced from postnatal conditions while other protective measures, such as cerebral autoregulation and neurovascular coupling, have yet to mature [24, 25]. This puts the developing fetal brain in a vulnerable state where it is fully dependent on undisturbed distal arterial organization and maturation. Why the perisylvian region seems especially vulnerable is unclear; however, measurements of cerebral perfusion in children and adolescents have shown the parietal and temporal association region to be the last to mature, which corresponds to distal MCA territory [26].

From a clinical perspective, inclusion of dedicated vascular imaging in cases of MCDs that are focal and unilateral may be of importance. When surgical resection of dysplastic cortex is considered, the nature of overlying vessels (arterial versus venous) is important for preoperative planning. The first case demonstrates that assuming prominent vessels overlying focal polymicrogyria are venous can be incorrect. This information may also be of value when contemplating suitable trajectories for DBS electrode insertion in rare cases of inoperable, medically refractory epilepsy secondary to extensive polymicrogyria.

Study limitations include the small number of cases presented, which is difficult to avoid given the infrequency of both MCDs and arterial dysplasia. Also, at this institution like many others, dedicated vascular imaging is not performed as part of routine seizure imaging, making detection of related vascular abnormalities more difficult. Although interrogation of vessel flow voids on T2-weighted images is possible, proper angiographic imaging is necessary to accurately assess relevant angioarchitecture. Finally, histopathology of the regions of abnormal cortex may have provided additional information relevant to the underlying

mechanism for the dysplastic cortex; however, no specimens had been resected at the time of submission.

Conclusion

Fetal arterial insults have previously been suspected triggers for some cases of polymicrogyria, but no clear examples have been presented in the literature. This study presents three cases of arterial dysplasia with ipsilateral perisylvian polymicrogyria where imaging features could support such a pathomechanism. These unique forms of corticoarterial malformation endorse dedicated vascular imaging in cases of focal unilateral polymicrogyria to assess for related vascular anomalies.

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Conflict of interest J.M. Klostranec, W. Brinjikji, S. Mathur, E. Orru, D. M. Andrade and T. Krings report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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