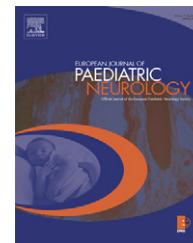




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Original article

Siblings with infantile cerebral stroke and delayed multivessel involvement—A new hereditary vasculopathy?

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ABSTRACT

We describe an unusual vasculopathy in two sisters of non-consanguineous parents.

The first child developed an acute hemiparesis and focal seizures at the age of 6 months during a febrile illness. Magnetic resonance imaging (MRI) of the brain showed bilateral cortical–subcortical infarction not confined to a vascular territory. Subsequently, the child had a persistent stable neurological deficit. Her younger sister had a similar encephalitis-like episode at the age of 4 months, with left-sided cortical–subcortical ischaemic lesions. Two months later she had left-sided focal seizures. MRI showed a right-sided cortical enhancement, magnetic resonance angiography (MRA) was normal. The neurological deficit was stable and she was seizure free. These episodes were initially interpreted as metabolic strokes, but work-up was normal and mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) was excluded. In their teens both sisters were diagnosed with pulmonary and systemic hypertension and, due to the arterial hypertension, myocardial hypertrophy. Renal artery stenosis, pathological pulmonary arteries, and stenosis and rarefaction of coronary arteries were found; the aorta and retinal vessels were normal. Repeat cranial MRI and MRA showed multiple collaterals, while the carotid and basilar arteries were extremely narrowed (moyamoya appearance).

We suggest the diagnosis is a hereditary systemic vasculopathy of unknown origin.

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1. Introduction

Multisystemic vascular diseases in children are rare and may be under-recognised. We report on two sisters with a very unusual presentation and course of a cerebral and systemic vasculopathy with encephalitis-like symptoms

in infancy that were initially interpreted as metabolic strokes. Many years after the neurological insult they developed symptoms of systemic vascular involvement with pulmonary and renovascular hypertension that led to further investigations and the diagnosis of systemic vasculopathy.

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We discuss the patients' history and imaging findings and review the literature.

2. Patients

The patients described are two sisters of non-consanguineous healthy Swiss parents, without healthy siblings. Family history was unremarkable for neurological diseases. The first child presented at the age of 6 months with a high temperature and 2 days later developed epileptic seizures, impaired consciousness and right-sided hemiparesis. Magnetic resonance imaging (MRI) revealed bilateral, predominantly right-sided, cortical occipito-parietal and fronto-opercular swelling due to a subacute lesion (Fig. 1a and b). On the presumption of viral encephalitis, she was treated with acyclovir. Examination of cerebrospinal fluid (CSF) was normal; herpes simplex virus could not be detected (PCR negative) and no other viral or bacterial agent was detected in blood, urine or CSF. During follow up, she developed a spastic right-sided hemiparesis, motor coordination deficits on the left side, orofacial dyspraxia, central visual and cognitive impairment. Her neurologic deficits were stable thereafter. During the acute illness she had focal seizures, but was seizure free on phenobarbital for 2 years and later without medication, except for one febrile seizure at the age of three.

Two years later, her younger sister developed a very similar episode with fever, seizures, alteration of consciousness and hemiplegia on the right side at the age of 4 months. Cerebral MRI showed extensive predominately left-sided cortical-subcortical temporo-parietal-occipital lesions within the arterial supply of the middle and posterior artery (Fig. 2a and b). Two months later, MRI was repeated because of left-sided seizures and revealed a new ischaemic lesion on the right side. Magnetic resonance angiography (MRA) (performed in 1993) was unremarkable for major vessel disease or vasculitis and no collaterals were identified (Fig. 2c). Like her sister, her neurological deficits were stable with right-sided hemiparesis, coordination problems, cognitive impairment and orofacial dyspraxia. Hereditary disease with metabolic stroke was considered but lactate was normal and mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) mutations were excluded. At the time of the acute phase, no viral antigen could be detected in nasopharyngeal secretions, faeces or CSF. Antibodies against HSV, EBV, VZV and CMV were negative. Lactate was normal in blood and CSF. Organic acids and amino acids in urine were normal. Autoantibodies against myeloperoxidase, proteinase 3 (PR3) and antineutrophil cytoplasmic autoantibodies were negative. C-reactive protein (CRP) and sedimentation rate were normal. Toxicological screening was negative and there were no indications for intoxication from the history. Arterial embolic stroke was not considered because of the distribution of the cerebral lesions and there is no documentation of a cardiac echocardiogram to exclude cardiac emboli.

At the age of ten, the elder sister started to be dyspnoeic during exercise and had several syncopes while running. Cardiological work-up showed severe pulmonary arterial as well as systemic arterial hypertension (maximal 150/100 mmHg) with myocardial hypertrophy. The younger sister

was asymptomatic but also had an elevated blood pressure (maximal 180/100 mmHg). Further investigations in both sisters revealed pulmonary arterial hypertension (PAH) (severe PAH in the elder, mild PAH in the younger sister) with rarefaction of peripheral pulmonary vessels (Figs. 1c and 2d). The pattern of vascular changes with rarefaction and stenosis was not compatible with idiopathic PAH. Both had left-sided renal artery stenosis in addition (Figs. 1d and 2e). Coronary arteries were abnormal in both; the younger sister had a very thin left coronary artery and the older a proximal stenosis that was not considered suitable for dilatation or stenting (Figs. 1e and 2f).

Repeat cerebral MRI and MRA at the age of 13 and 15 years, respectively, revealed chronic cortical ischaemic lesions as seen previously and, in contrast to the first imaging, an extensive moyamoya pattern with occlusion of terminal carotid arteries, very small basal cranial vessels without flow, and a network of collateral arteries (Figs. 1f and 2g). Retinal vessels and the aorta were normal.

Vessel involvement is summarised in Table 1.

At re-evaluation, no dysmorphic features suggesting an underlying disorder such as PHACE syndrome, angioliomatosis, or cutaneous signs of Fabry's disease or Neurofibromatosis type 1 were detected. Karyotype analysis was normal. Inflammatory markers including CRP, sedimentation rate, antinuclear antibodies (ANA), antinuclear DNA, complement factors C3, C4, CH 100 and AP 50 suggestive of vasculitis were normal. Both sisters were always in good general health, and there was no indication of an immune deficiency.

The PAH was treated with the endothelin receptor antagonist bosentan in the elder sister, renal artery stenosis by dilatation in both, and the older sister needed an endovascular stent implantation. Blood pressure was still elevated in the younger sister and she remained on antihypertensive treatment after dilatation (betablocking agent and Ca channel blocker). The older sister developed cardiac failure with severely impaired left ventricular function despite successful dilatation and stenting of the renal artery. She died suddenly at the age of 15 while attending school; an autopsy was denied.

3. Discussion

We describe a hereditary vasculopathy with symptomatic onset in infancy with extensive cerebral infarctions with normal MRA at the time of insult and the development of symptomatic systemic vascular involvement of pulmonary, coronary and renal vessels many years later. The onset of symptoms and the course and pattern of vascular involvement differ from the known vasculopathies discussed below.

Moyamoya disease (spontaneous occlusion of the circle of Willis) is characterised by bilateral stenosis of the terminal portions of the carotid arteries and an abnormal collateral network at the base of the brain, with the angiographic appearance of a puff of smoke. The typical symptomatology in children is stroke, transient ischaemic attacks (TIA) or seizures. The typical angiographic pattern is detectable at the time of first symptoms. Familial cases are described and so far, five gene loci have been found through linkage analysis.^{1,2,3} There are disorders that lead to a moyamoya syndrome

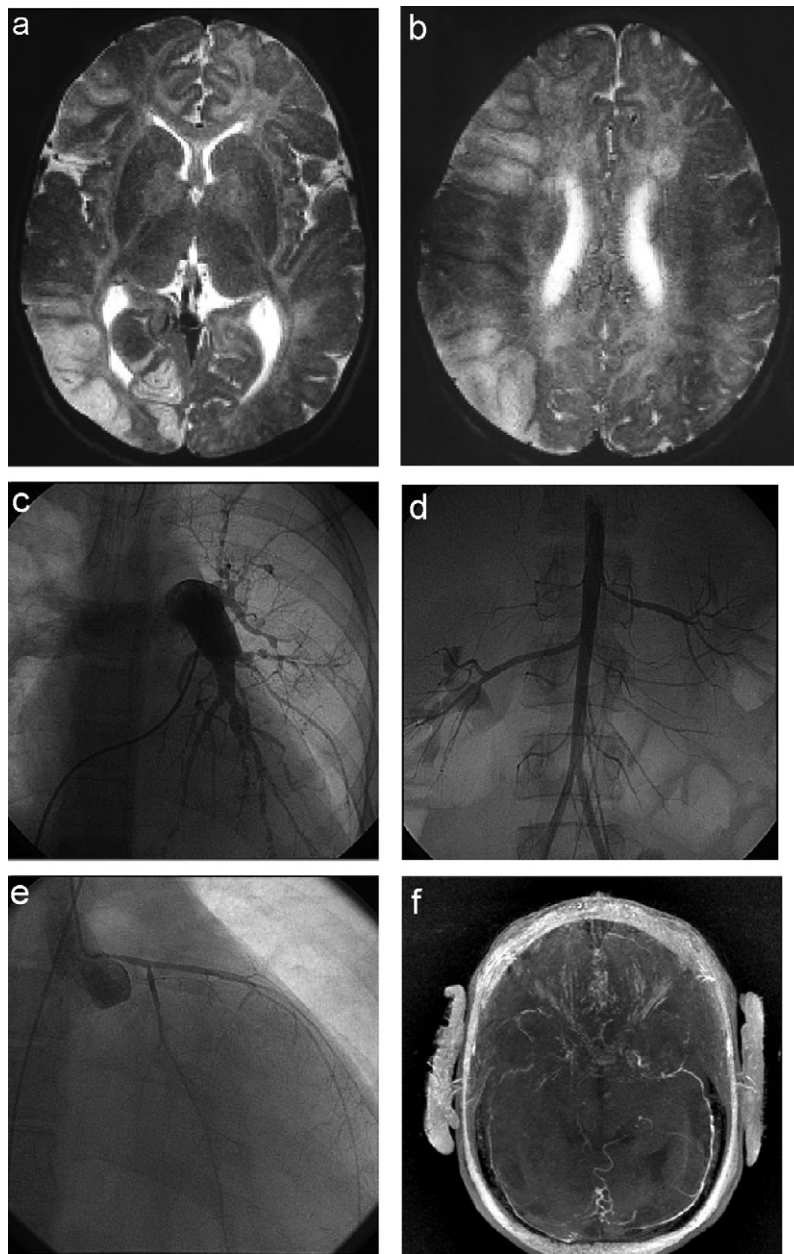


Fig. 1 – (a, b) Axial T2-weighted spin-echo MR images of patient 1 at the age of 6 months. Bilateral, predominantly right-sided T2-hyperintense signal of the fronto-opercular and parieto-occipital and occipital cortex. This hyperintense cortical swelling results from subacute ischaemia in the watershed zones between the anterior and middle cerebral artery as well as middle and posterior cerebral artery. The central grey and white matter appear spared. (c) Left pulmonary artery angiogram showing slightly enlarged central pulmonary arteries, multiple peripheral pulmonary artery stenosis and a marked rarefaction of the pulmonary artery tree. (d) Abdominal aortic angiogram showing a small abdominal aorta and thin iliac arteries. The left renal artery presents itself with an elongated proximal stenosis. (e) Left coronary artery angiogram showing a severe proximal left coronary artery stenosis and a very thin left anterior descending and circumflex artery with rarefaction of the coronary branches. (f) Follow-up axial non-enhanced time-of-flight MR angiogram (maximum intensity projection) at the age of 15 years. The circle of Willis is significantly rarefied. The distal internal carotid artery, basilar artery as well as the anterior, middle and posterior cerebral arteries are bilaterally occluded. Distal branches of the middle cerebral arteries are supplied by collaterals of the external carotid arteries. Multiple small collaterals are seen within the basal cisterns mimicking a “moyamoya” appearance.

such as neurofibromatosis type 1, Down syndrome and sickle cell anaemia. The definitive cause and pathogenesis of moyamoya disease is still unknown. Inflammatory, autoimmune and thrombotic mechanisms have been discussed.⁴ On

histological examination, involved vessels show fibrous, or sometimes nodular, thickening of the intima and minimal lipid deposition.⁴ The first incidence peak is in early childhood with the typical symptomatology of TIA, stroke or

seizure. The youngest child described in literature was 7 months old.⁵ Extracranial involvement in moyamoya disease is rare, renal artery stenosis being the most frequent.⁶ Choi et al.⁵ found renal artery stenosis in 7% of 72 paediatric moyamoya patients, but coronary,⁷ pulmonary,⁴ and mesenteric⁵ artery involvement has also been described. Renal artery stenosis in the context of extracranial involvement of moyamoya disease is typically proximal in contrast to the more distal involvement in the most frequent form of fibromuscular disease with the appearance of a string of beads.⁶ In cases of moyamoya with involvement of extracranial vessels, intimal fibroplasia has been suggested as the underlying aetiology and has been found in some cases on histological examination of involved renal arteries.⁵

Our patients did not show any signs for moyamoya syndrome, moyamoya disease is possible but some features such as

time and symptomatology of presentation, as well as the extent of extracranial vessel involvement would be very unusual.

Fibromuscular dysplasia (FMD) is a systemic vascular disease affecting small- to medium-sized vessels. Renal artery involvement is most common, followed by cervico-cranial and cerebral arteries. Involvement of mesenteric, coronary and iliac arteries has been described. Familial cases are known. Pathological classification differentiates medial fibroplasia, the most frequent form (75–80%) with the typical string of beads appearance on angiography, from intimal fibroplasia that occurs in less than 10% and that appears as concentric stenosis with a histological characteristic eccentric deposition of collagen in the intima.^{8,9} An association of FMD with hypertrophic cardiomyopathy has been described.¹⁰ Peak incidence is early adulthood. Cerebral artery involvement in FMD occurs usually in women in early adulthood and consists of concentric stenosis of the distal carotid artery. There is only one case report of an infant with congenital FMD with renovascular hypertension from birth and moyamoya disease.¹¹

Grange syndrome (OMIM 602531)¹² is probably an autosomal recessive syndrome with systemic as well as cranial vessel involvement, combined with brachysyndactyly and bone fragility. In our cases, there were no dysmorphic traits or history of fractures.

There are other hereditary vasculopathies affecting predominantly small cranial vessels like cerebral autosomal dominant arteriopathy with stroke and ischaemic leukoencephalopathy (CADASIL) (OMIM 125310), and hereditary endotheliopathy, retinopathy nephropathy and stroke (HERNS) (OMIM 192315). However, they are not reported as presenting in infancy and do not lead to systemic vascular involvement of medium-sized arteries. The retinal vessels in our patients were normal.

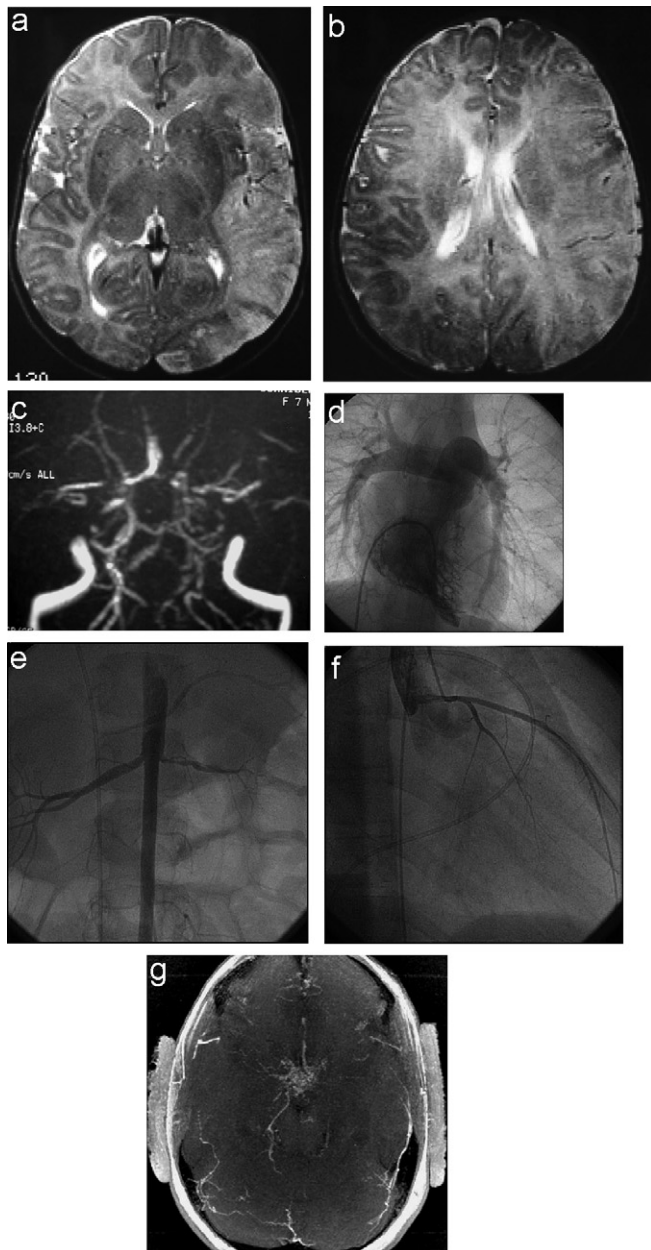


Fig. 2 – (a, b) Axial T2-weighted spin-echo MR images of Patient 2 at the age of 4 months. An extensive cortical-subcortical hyperintense swelling within the vascular territory of the left middle and posterior cerebral artery is seen without signs of haemorrhage. The adjacent subarachnoid spaces are compressed due to the cortical swelling. (c) Axial phase contrast MR angiogram (maximum intensity projection) of patient 2 at the age of 6 months: The complete circle of Willis is displayed, the source images excluded significant stenosis of the major intracranial vessels. There was no “moyamoya” appearance. (d) Right heart angiogram showing a normal-sized right ventricle, slightly enlarged central pulmonary arteries, peripheral pulmonary artery stenosis and rarefaction of the peripheral pulmonary arteries. (e) abdominal aortic angiogram showing a small abdominal aorta. The left renal artery shows a severe elongated stenosis with a string of beads appearance. (f) Left coronary artery angiogram showing a thin left anterior descending and circumflex artery with rarefaction of the further coronary artery branches. (g) Follow-up axial non-enhanced time-of-flight MR angiogram (maximum intensity projection) at the age of 13 years. The circle of Willis is almost completely rarified, the major vessels cannot be identified. Multiple small collaterals are seen within the basal cisterns mimicking a “moyamoya” appearance. A short segment of the right posterior cerebral artery is preserved.

Table 1 – Vessel involvement in two sisters with a hereditary vasculopathy

Vessels	Patient 1	Patient 2
Cerebral		
At insult	Not examined	Small basal vessels, no collaterals
On follow-up	Extremely narrowed basal vessels, without flow. Extensive collaterals	Extremely narrowed basal vessels, without flow. Extensive collaterals
Renal	Left-sided long proximal stenosis	Left-sided long proximal stenosis, string of beads appearance
Coronary	Rarefied capillary bed, proximal left main coronary artery stenosis (75% of lumen)	Rarefied capillary bed of the left coronary artery
Pulmonary	Rarefied peripheral vessels Severe pulmonary hypertension	Rarefied peripheral vessels Mild pulmonary hypertension
Aorta	Normal	Normal
Retinal	Normal	Normal

Infantile arterial calcification leads to calcification of large- and medium-sized arteries and arterial hypertension in infancy. We did not find any signs of calcification and the aorta was normal in our patients. In PHACE syndrome (OMIM 606519), intracranial arterial anomalies have been described, but our patients lack the ocular, cerebral and cutaneous signs of this syndrome. Autoimmune or chronic viral vasculitis is unlikely with lack of inflammatory markers, negative autoimmune antibodies, repetitive negative viral cultures and the general clinical course.

In our opinion, the sisters have a hereditary systemic vasculopathy, starting in carotid or small intracranial vessels and already symptomatic in the first year of life with cerebral ischaemic lesions. The distal part of the carotid artery was not depicted in the first MRA, therefore relevant stenosis there cannot be ruled out as the cause of the ischaemic lesions during an infection. Another possibility would be a rarefaction of small peripheral cerebral vessels, comparable to the findings in the pulmonary vessels, leading to ischaemia during an infection with fever and seizures. For the diagnosis of moyamoya disease the very early and monophasic course of neurological insult with an initially normal MRA without collaterals would be unusual, as well as the extensive extracranial involvement. A conventional arteriography was not performed; this would be superior to the MRA to pick up vascular pathologies. Nevertheless, the pattern of cranial vascular involvement in our patients on follow up is compatible with moyamoya disease.

Imaging identifies the pattern of involvement and the complications of the underlying vascular disease; however, it is unable to provide a specific diagnosis. Histological examination of involved vessels may contribute to the diagnosis but it was not possible to perform this in our cases.

We suggest a new hereditary systemic vasculopathy. The pattern of vascular involvement and the clinical course over time do not fit into the previously described vasculopathies of childhood.

In stable neurological diseases of unclear origin, vascular pathology should be considered even if previous MRA is

reported as normal. Signs of other organ involvement must be looked for. In moyamoya disease or other cerebral vasculopathies, extracranial involvement can be extensive and should be sought because of possible treatment options.

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