[1 case series; 1 table; 1 figure]

Cerebral vasculopathy in childhood neurofibromatosis type 2 (NF2) –cause for concern?

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ABBREVIATIONS

MRI Magnetic resonance imaging

MRA Magnetic resonance angiography

NF2 Neurofibromatosis type 2

[abstract]

Unlike adult neurofibromatosis type 2 (NF2), which presents with symptoms related to bilateral vestibular schwannomas, affected children most frequently present with ocular, dermatological, and neurological symptoms. Arteriopathy, a well-established feature in neurofibromatosis type 1, is not a widely recognised feature of NF2. Here we report three children with NF2 with cerebral arteriopathy and/or arterial ischaemic stroke. Bevacizumab, a vascular endothethial growth factor inhibitor, is an established treatment for rapidly growing vestibular schwannomas, however carries a risk of both ischaemic and haemorrhagic stroke. Thus the role of screening and risk to benefit ratio of bevacizumab in NF2 merit further consideration.

What this paper adds

- Children with neurofibromatosis type 2 (NF2) may be at increased risk of cerebral vasculopathy and arterial ischaemic stroke.
- Targeted magnetic resonance angiography should be performed in children with NF2 who are being considered for Bevacizumab therapy.

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[main text]

Neurofibromatosis type 2 (NF2) and neurofibromatosis type 1 are distinct autosomal dominant tumour predisposition syndromes. The *NF2* gene is located on chromosome 22q12 and encodes the protein merlin. In contrast to neurofibromatosis type 1, NF2 is rare, with an incidence of 1 in 25 000 to 33 000[1] in the UK, and approximately 85 affected children are followed-up in four nationally commissioned NF2 centres (Cambridge, London, Manchester, and Oxford).

The hallmark of NF2 is bilateral vestibular schwannomas but patients also develop schwannomas of other cranial, spinal, and peripheral nerves, meningiomas, and spinal ependymomas. Unlike adults, who present with symptoms related to vestibular schwannomas, children present with ocular, dermatological, or focal neurological deficits secondary to tumour formation, and there are often delays in diagnosis. The natural history of NF2 is for growth of vestibular schwannomas over time, for which intervention is limited and associated with significant morbidity. Recently bevacizumab, a vascular endothethial growth factor inhibitor, has been shown to reduce vestibular schwannomas growth and to preserve hearing and quality of life.[2,3] However bevacizumab, when used in treatment of cancer, has been shown to significantly increase the risk of both ischaemic and haemorrhagic stroke.[4]

Here we describe three cases of ischaemic stroke in children with NF2, and summarize features of previously reported cases (Table I).

CASE REPORTS

Case 1

A 13-year-old female presented with headache, slurring of speech and left arm, leg, and facial weakness 1 week after an episode of menorrhagia leading to symptomatic anaemia with a haemoglobin of 74 grams per litre, for which she received a blood transfusion and tranexamic acid. She was mildly anaemic with a haemoglobin of 108 grams per litre but had normal ferritin and platelets. Magnetic resonance imaging (MRI) of the brain revealed an acute right pontine infarct and additionally an old ‘silent’ left pontine infarct (Fig. 1, top row). Magnetic resonance angiography (MRA) of intracranial and neck vessels was normal. Cardiac echocardiogram and extensive thrombophilia screen were normal. Further review of

her MRI led to the suspicion of a diagnosis of NF2. NF2 mutation testing identified a frame shift mutation in exon 12. She went on to make a full neurological recovery and was discharged on aspirin and the progesterone only contraceptive pill. Recently she presented with rapidly progressive bilateral vestibular schwannomas and under UK national NF2 guidelines is eligible for bevacizumab therapy as a means of preserving hearing and slowing growth of her tumours; however there are significant reservations in instituting therapy in view of her stroke history.

Case 2

A 12-year-old male presented with pupillary asymmetry and was found to have a partial left third nerve palsy as well as partial left twelfth nerve palsy. MRI of the brain was diagnostic of NF2. The left internal carotid artery was noted to be small and a vasculopathy was suspected without evidence of infarction. Intracranial MRA (Fig. 1, middle row) showed a small and tortuous left internal carotid and left posterior cerebral arteries with prominent posterior circulation collaterals, but without significant occlusive disease and he has therefore has not been started on aspirin.

Case 3

A male aged 4 years 6 months presented with an acute relapsing remitting left ophthalmoplegia at 10 months of age. On further assessment, he was noted to have two cutaneous schwannomas and a right twelfth nerve palsy. Ophthalmology assessment revealed retinal hamartoma on the right eye combined with bilateral epiretinal membranes, a classical feature on NF2 and a left third and partial sixth nerve palsy. Acute MRI showed a lesion in the right middle cerebellar peduncle with diffusion restriction which on subsequent imaging showed shrinkage and gliosis, suggesting an infarct (Fig. 1, bottom row). In addition, there were radiological features of NF2. A diagnosis of NF2 was suspected and he was found to have a heterozygous deletion in exon 10 of the *NF2* gene. On review of his brain imaging, which included MRA of neck and intracranial vessels, he was found to have narrowing of the left internal carotid artery, which appeared to have progressed over time (Fig. 1, bottom row). There was no posterior circulation abnormality to account for the right sided lesion. He has been started on aspirin.

REVIEW OF LITERATURE

On review of the literature, we found three case reports of posterior circulation stroke in children aged 2, 6, and 15 years with NF2 and in one patient this was the presenting feature that led to the diagnosis of NF2. The first case[5] is of a 2-year-old female who presented with acute ataxia and was noted to have café au lait patches. MRI showed a left pontine infarct and MRA was normal. MRI of the spine showed a cervical cord ependymoma and lumbar root schwannomas and a diagnosis of NF2 was suspected. *NF2* gene testing revealed a truncating mutation in the *NF2* gene (c.169 C>T).

The second case[6] report describes a 6-year-old female with an acute right hemiplegia who, on ophthalmological examination, was noted to have combined pigment epithelial and retinal hamartoma. Computed tomography scan of the brain showed an acute left brain stem infarct and conventional angiography did not reveal any abnormality of the posterior circulation. At 26 years of age she presented with bilateral hearing loss and MRI of the brain and spine was diagnostic of NF2. Genetic studies revealed a frameshift mutation in exon 8 of the *NF2* gene.

The third case[7] is of a male aged 15 years with an inherited 448-1G>A point mutation in the *NF2* gene who presented with acute right hemiplegia after gastroenteritis. MRI showed a left pontine infarct with normal MRA.

DISCUSSION

Arteriopathy is not a widely recognized complication of NF2; however, NF2 is associated with hypertension in adults[8] and there are isolated case reports of renal artery stenosis in children with NF2.[9] The current UK cohort of approximately 85 children under 16 years of age includes a child with renal artery stenosis and one with hypertension. None of the remaining 83 children have had strokes or known cerebral arteriopathy; however, targeted cerebrovascular imaging is not currently performed in patients with NF2. Three of the reported cases, as well as one of ours, had posterior circulation infarcts with normal neck and intracranial MRA and no cardiac source of embolism. Only one of the reported cases had conventional angiography.[6] Given that it is well recognized that vertebrobasilar abnormalities can be missed on MRA in the context of posterior circulation stroke,[10] it

seems reasonable to include these cases in discussion of arteriopathy and NF2. It is hard to explain the preponderance of posterior circulation lesions, which contrast with the distribution of childhood arterial ischaemic stroke due to other causes. Factors associated with posterior circulation stroke are vertebral dissection or cardiac embolism, and it is difficult to understand why patients with NF2 should be especially prone to these. It is also noteworthy that in several cases the ischaemic lesions were relatively occult. The first of our cases emphasizes the importance of identifying and treating any additional precipitating factors, such as anaemia in this case.

We identified a prevalence of cerebral aneurysms in 4.4 per cent of our adult NF2 cohort, which is higher than would be expected in the background population.[11] We have seen one young adult patient who subsequently had an ischaemic stroke associated with left middle cerebral artery vasculopathy.[12]

The tumour suppressor protein, merlin, may play a role in vascular endothelial development and has been found in the endothelial lining of blood vessels in mice harbouring the *NF2* gene.[13] In animal studies, merlin has been shown to maintain physiological angiogenesis of the nervous system by regulating antiangiogenic factors such as semaphorin 3F.[14] The variable morphology of arteriopathy reported (occlusive disease, dysplasia, and aneurysm) support the hypothesis that these are due to variable disruption of the vascular homeostatic mechanisms described above.

Management options for growing vestibular schwannomas include surgery (which carries significant morbidities including hearing loss and other neurological deficit) and stereotactic radiosurgery with attendant increased risk of malignancy. Bevacizumab has been shown to reduce vestibular schwannomas growth and improve hearing and quality of life. Since 2010, the UK nationally commissioned NF2 service has funded its use for rapidly growing vestibular schwannomas. The antiangiogenic effect of vascular endothethial growth factor seems most important in tumour inhibition; however, inhibition of vascular endothethial growth factor has multiple other effects, including on vascular endothelium, nitric oxide production, and promotion of proinflammatory cytokines.[15] Amongst our NF2 adult and paediatric cohort treated with bevacizumab there have been no reports of stroke or thrombotic events which may be because NF2 patients are generally healthier and younger than other cohorts, such as those with cancer.

Whilst we acknowledge that the association we report here remains relatively anecdotal, the clinical relevance, especially in relation to bevacizumab, means that this question merits further consideration. Pending a definitive study, we would recommend that children with NF2 who are undergoing brain imaging should have targeted imaging of the cerebral vasculature with MRA from the aortic arch to the circle of Willis, and that this should be mandatory in patients being considered for bevacizumab. Whilst we acknowledge that this could lead to identification of asymptomatic arteriopathies, such information could inform counselling of the risk to benefit ratio of bevacizumab in individuals, and the need for further surveillance.

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Table I: Combined cases of childhood NF2 cerebral vasculopathy

Age	Sex	NF2 clinical features	Stroke risk factors	NF2 intracranial/ spinal lesions	Stroke distribution	Vasculopathy	NF2 genetics
13y	F	None	Anaemia	Bilateral VS, third CN schwannoma	Bilateral pontine	None	Frameshift mutation exon 12
12y	M	Left third and twelfth CN schwannoma	None	Bilateral VS, third CN schwannoma meningioma, ependymoma	No ischaemia	Left ICA, PCA	Deletion exon 10
4y 6mo	M	Left third and right twelfth CN schwannoma, cutaneous schwannomas, CHRPE, Left brachial plexus neuropathy	None	Bilateral VS, meningioma	Right middle cerebellar peduncle	Left ICA	Deletion exon 2
2y[a]	F	Café au lait patches	Fever, cough	Ependymoma, left third schwannoma	Left pontine	None	Truncating mutation c.169 C>T
6y[a]	F	CHRPE	None	Bilateral VS, meningioma	Left brain stem	None	Frameshift mutation exon 8
15y[a]	M	None	Dehydration	Bilateral VS, Left third CN schwannoma	Left pontine infarct	None	Point mutation 448-1G>A

[a]Cases reported in the literature. NF2, neurofibromatosis type 2; VS, vestibular schwannomas; CN, cranial nerve; ICA, internal carotid artery; PCA, posterior communicating artery; CHRPE, combined hamartoma retina, retinal pigment epithelium.

Figure 1: Magnetic resonance images of cases 1, 2 and 3

Patient 1, top row: DWI, post contrast T1W coronal, and MRA sequences show an acute infarct in the right pons with subsequent maturation (arrow), bilateral vestibular schwannomas (middle image), and a normal MRA. Patient 2, middle row: post contrast axial T1W, T2W, and MRA images showing a small left ICA (dashed arrow) with collaterals around a small left PCA (solid long arrow). Patient 3, bottom row: acute DWI, follow-up axial T2W and MRA images show an acute infarct in the right middle cerebral peduncle with subsequent maturation and progressive narrowing of the left ICA (arrows). DWI, diffusion weighted imaging; T1W, T1 weighted imaging; MRA, magnetic resonance angiography; T2W, T2 weighted imaging; ICA, internal carotid artery; PCA, posterior communicating artery.