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Stroke in childhood neurofibromatosis type 2

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This commentary is on the case series by Lascelles et al. To view this paper visit https://doi.org/10.1111/dmcn.

The paper by Lascelles et al.[1] adds three cases of stroke in children with neurofibromatosis type 2 (NF2) to three previously reported. Ischaemic stroke is part of the Wishart NF2 phenotype presenting in childhood with multiple intracranial and spinal tumours, as well as rapid loss of hearing and cranial nerve palsies related to schwannomas of cranial nerves III to VIII. Interestingly, hemiplegia was reported in nearly 25% of patients presenting aged less than 20 years in the Japanese NF-2 registry.[2] One of the cases from the literature reported by Lascelles et al.[1] underscores the difficulty in distinguishing focal ischaemia from tumour. In addition, stroke may present before the characteristic vestibular schwannomas can be diagnosed clinically or radiologically. The association between cerebral

infarction and NF2 has probably been missed previously; ocular and skin signs of NF2[2] should be looked for in posterior fossa stroke.

These cases further our understanding of stroke pathophysiology in those with NF2 gene variants or deletions leading to reduced production of Merlin, a tumour suppression protein. The involvement of the Ras signalling pathway (important in in NF1 and Noonan syndrome) is not currently clear for NF2. When vascular imaging includes the neck vessels, children with NF1 may have carotid and vertebrobasilar disease as well as moyamoya.[3] Two of the children reported by Lascelles et al. have left-sided internal carotid disease, but so far moyamoya has not been reported in NF2. Focal cerebral blood flow (CBF) abnormalities occur in NF1, particularly in the posterior circulation.[4] But any relationship with arteriopathy is not clear and in NF-2 the focus has been CBF imaging in the tumours. It is possible that focal hypoxia-ischemia or modifying genes (such as *RNF213*) play a role in whether compensating vascular changes (including moyamoya collaterals) develop in a wide variety of conditions predisposing to steno-occlusive arteriopathy, including NF2. This would be easier to study in NF1, which is ten times more common.

All the infarcts reported[1] were in the posterior circulation, but the available arterial imaging of the vertebrobasilar system was normal. As only one case had conventional angiography soon after the acute stroke, it is possible that dissection or small vessel pathology small vessels was missed. Alternatively, the infarcts could be venous, generally considered rare in the posterior fossa because of the collateralization, although there

are few data available in cases of NF2. There is no evidence of venous sinus thrombosis (VST) or haemorrhage,[1] but this pathology may also reverse quickly. Fever, anaemia, and dehydration[1] are triggers for VST, which has been reported after surgery for vestibular schwannoma in adults.[5] Rapid progression of hearing loss, as well as cerebellar and brain stem infarction, could be secondary to lateral sinus and/or internal jugular vein thrombosis. Even in the absence of VST in a young brain in which the cerebrovascular system is also developing, the growth of schwanommas in a small posterior fossa might lead to compression or stretching of the basilar, internal jugular, and superior petrosal or small perforating veins, eventually compromising the circulation. Interestingly, tortuosity of the ocular veins has been documented in NF1.

Now that these cases have been reported, it is clinically important that the vascular pathology is understood, particularly as surgical or medical treatment may increase stroke risk. As part of magnetic resonance imaging surveillance of children with NF2 and studies in acute stroke (as well as population-based studies), it is worth including venography, susceptibility weighted imaging of venular density, CBF, and angiography of the neck and aorta as well as the circle of Willis. Dehydration and iron deficiency anaemia should be avoided. This will improve outcomes for individuals as well as furthering our understanding.

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