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Letter to the Editor: New Observation

Cerebellar Vascular Malformation of Unknown Aetiology with Recent COVID-19 Infection

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The form of intracranial vascular malformation lies in its pathogenesis.[1] For example, a brain arteriovenous malformation (AVM) most frequently initiates as a venous derangement, either congenital or thrombotic, which creates an obstacle to flow, resulting in higher pressures that force upstream veins to retain their embryonic arterialised morphology.[1] These arterialised veins lead to chronic venous hypertension, causing decreased tissue perfusion and activation of angiogenic transcription factors, which promote the formation of disorganised, pathological flow bypasses – the AVM nidus.[2] Similarly, dural arteriovenous fistulas (AVFs) arise from obstructed dural venous sinus flow forcing meningeal arteries to develop fistulous connections with the dural sinus or cortical veins as the path of least resistance.[3] We present a highly unusual case of arteriovenous shunting of indeterminate vascular aetiology.

A man in his 70s with a medical history significant for hypothyroidism, hypertension and a recent severe COVID-19 infection presented to an outside hospital emergency department after experiencing two recent falls attributed to an imbalance with no head strike and 36 hours of headaches, nausea, vomiting and further imbalance.

Non-contrast head CT showed an acute right cerebellar intraparenchymal haemorrhage. The patient was started on corticosteroids, and after a series of stable CT scans and examinations, he was discharged home. Weeks later, after weaning off the steroids, his symptoms returned, and he re-presented. MRI noted an acute on chronic 1.5 cm right cerebellar haemorrhage. Magnetic resonance venography (MRV) showed no major occlusion. He was referred to our institution, where an MRI with gadolinium showed leptomeningeal enhancement and scattered vasogenic oedema with intralesional diffusion restriction. Differential diagnoses at the time included leptomeningeal carcinomatosis, vascular malformation and meningoencephalitis. Neurologic examination identified left arm and leg ataxia and dysmetria, with gait disturbance.

Assessment for infectious processes was negative. Full body CT found no malignancy. Vasculitis workup yielded only a non-specific ANA 1:80, likely due to underlying thyroid disease, but negative Sjogren's and antiphospholipid antibodies.

CT angiography and digital subtraction angiography (DSA) showed diffuse right transverse and sigmoid sinus hypoplasia relative to the left. DSA was notable for enlarged right anterior inferior cerebellar artery (AICA) and left posterior inferior cerebellar artery (PICA) feeders into what appeared to be a diffuse right cerebellar AVM or AVF with early venous drainage through the right lateral inferior cerebellar vein and otherwise sparse venous outflow. A 4.2 mm peri-nidal aneurysm arising from the distal left PICA feeding contralaterally into the vascular lesion was identified, along with two remote right AICA aneurysms measuring 2.4 and 1.5 mm, respectively.

The patient consented to surgical resection. This was performed via a modified right far lateral and telovelar approach for clip ligation of the PICA and AICA aneurysms. The haemorrhagic cavity was evacuated, and feeding arteries along the pial surface were followed to identify and dissect what appeared to be a diffuse AVM. The veins throughout the right cerebellar hemisphere appeared severely dilated. Post-operative DSA showed interval resolution of the early draining veins with no arteriovenous shunting. The patient has recovered well post-operatively after a few weeks of physical rehabilitation.

Histologic sections of the lesion were stained with haematoxylin and eosin (H&E), elastic Verhoeff-Van Gieson stain, Masson trichrome and Congo red, along with immunohistochemistry for smooth muscle actin, CD34 and Abeta40. A thorough pathological examination by vascular neuropathology expert Dr Harry Vinters found no definite pathological features of AVMs (abnormal arteries with duplicated elastic lumina) or cavernomas (aggregates of hyalinised vascular channels). Fragments of the cerebellar cortex contained markedly hyalinised leptomeningeal and parenchymal vessels with pronounced intimal thickening and myxoid degeneration and apparent thrombosis without evidence of recanalisation (Figure 1). Some vessels showed fibrinoid necrosis of their

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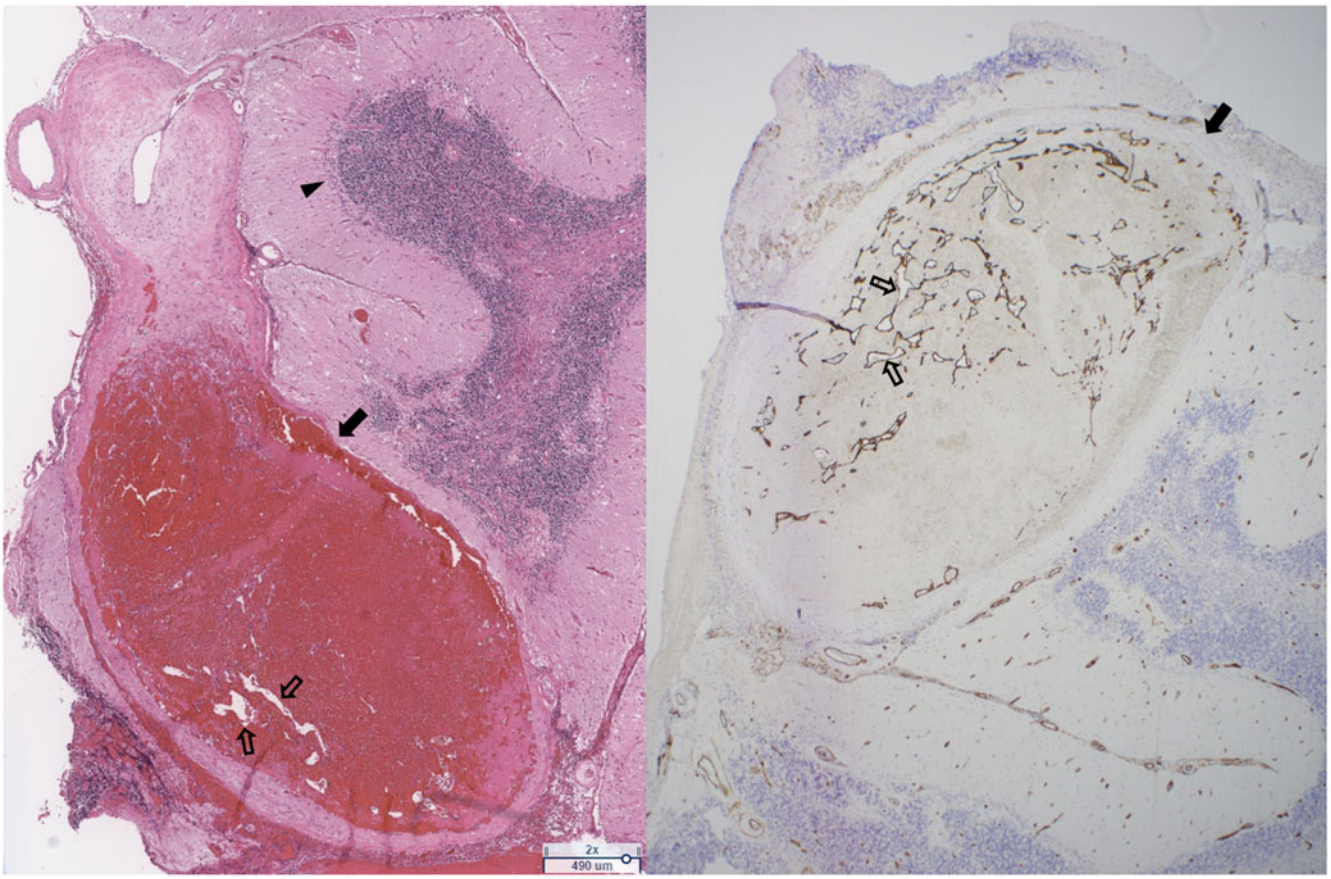

Figure 1. Haematoxylin and eosin (HE) stain (left) and CD34 immunostained section (right) showing thickened abnormal vessels, most consistent with venous pathology with irregular calibre, marked intimal thickening, focal thrombosis (solid arrow) and recanalisation (empty arrows). There are multifocal microinfarcts with loss of Purkinje cells and Bergmann gliosis (arrowhead on HE stain) in the adjacent cerebellar cortex.

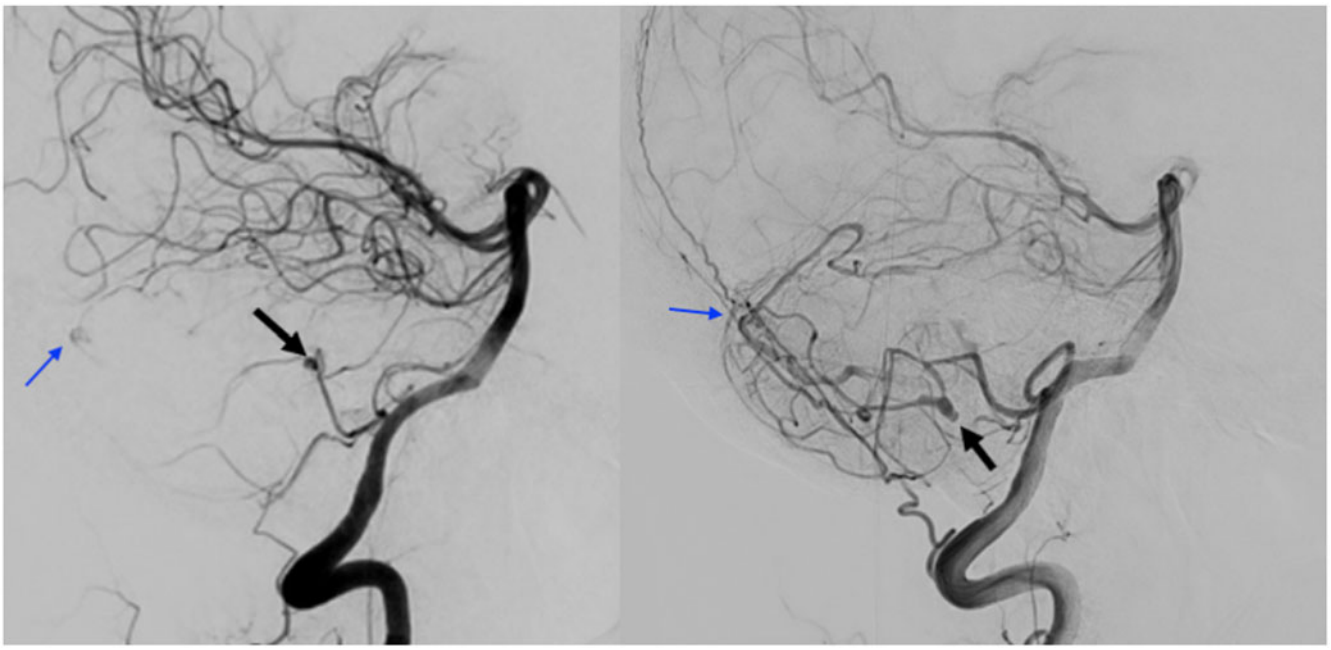

Figure 2A. Pre-operative cerebral angiogram of the right vertebral artery (left) and left vertebral artery (right) runs, demonstrating the peri-nidal feeding artery aneurysms (black arrows) of the distal right anterior inferior cerebellar artery (right) and left posterior inferior cerebellar artery (left) and the left cerebellar early venous arteriovenous fistula (blue arrows).

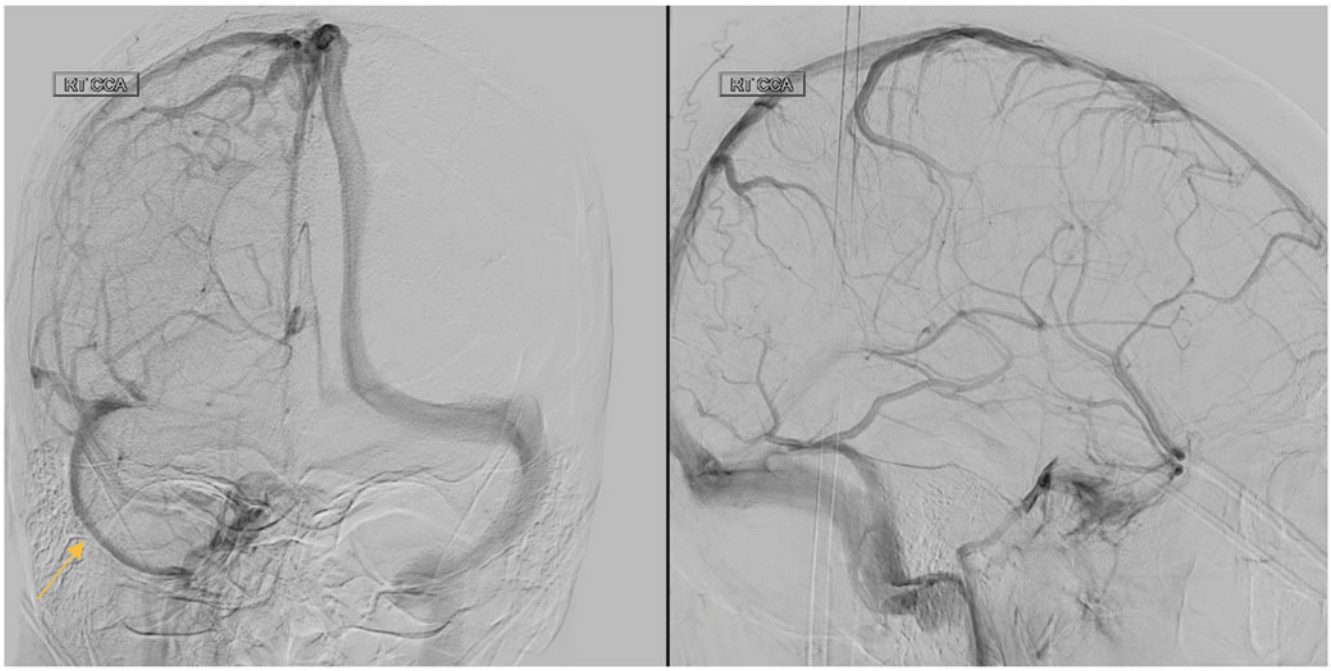

Figure 2B. Pre-operative angiogram demonstrating a delay in right venous outflow compared to the left and right cerebellar drainage through an abnormal emissary vein draining into the right jugular bulb (yellow arrow) and the absence of normal petrosal vein or sinus drainage on anteroposterior (left) and lateral (right) projections of a right common carotid artery injection.

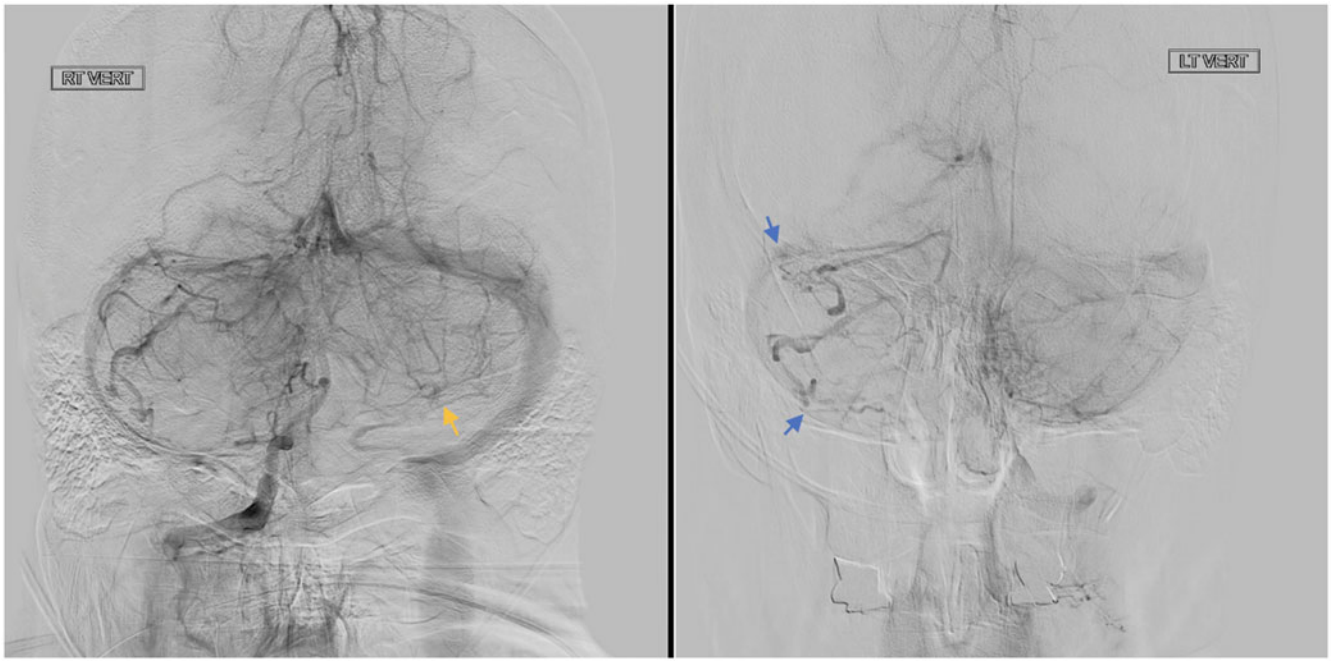

Figure 2C. Pre-operative angiogram demonstrating a relative absence of cerebellar veins in the right cerebellar hemisphere compared to the left (yellow arrow) and direct arterial feeders to the sinuses (blue arrows) on right vertebral artery injection (left) and left vertebral artery run (right).

walls, but none showed evidence of vasculitis or amyloid deposition. Extensive chronic microinfarcts (some haemorrhagic) were seen in the cerebellar granule cell layer with multifocal loss of Purkinje cells and Bergmann gliosis.

This vascular malformation defied classification by histopathology, MRI, DSA or intraoperative observation. However, baseline vascular anatomy may have been obscured by the haemorrhage.

Collectively, we speculate that the shunting in the vermis, fed by the large left PICA, was draining into the right cerebellar hemisphere veins, primarily through the emissary right petrosal vein into the right jugular bulb, a finding consistent with Cognard type 5 dural AVFs (Figures 2A, 2B and 2C).[4] Eventually, the right petrosal vein and sinus occluded due to high-flow venopathy or other vasculopathic factors such as COVID-19 infection. The occlusion of

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the right petrosal sinus then caused a haemorrhage and cerebellar oedema. The diffuse enhancement pattern visualised on MRI thus represented dilated venous collaterals rather than leptomeningeal enhancement. Features suggestive of of pial AVF leading to early venous drainage were also noted and could have developed due to an occluded or hypoplastic right transverse and sigmoid sinuses.

The presumed pathogenesis of the missing veins in this case parallels that seen in Sturge–Weber syndrome (SWS). The pathophysiology of SWS was first described as a paucity of functional superficial cortical bridging veins draining into the dural sinus system, leading to impeded venous flow and pooling and subsequent expansion of the leptomeninges.[5] This leads to the development of enlarged, dysplastic, tortuous, deep and superficial cerebellar veins. While SWS is a congenital disorder, this venous pathology is not exclusively congenital but may in fact be secondary to dural sinus hypoplasia or atresia.[6]

The timing of the COVID-19 infection and the onset of symptoms is particularly pertinent considering recent studies and unpublished experiences highlighting its thrombotic impact on immune dysregulation and macrophage activation.[7] In one case, a COVID-19-positive patient presented with a cerebellar infarct from an extensive vertebral artery occlusion. Pathological examination of the biopsied infarct found a thrombosed vein with a proliferative intima and focal intimal neutrophils, perhaps an earlier stage of the COVID-related pathophysiology described here.[8] Notably, in either case, there was no radiographical evidence of supratentorial abnormalities.

We describe the case of an elderly man with a recent severe COVID-19 infection presenting with a spontaneous cerebellar haemorrhage associated with an underlying arteriovenous shunting pathology and a highly unusual confluence of radiological and pathological findings. Histopathologic analysis demonstrated diffuse venous structures with significant intimal thickening, thrombosis and no focal recanalisation interspersed with chronically micro-infarcted gliotic cerebellar cortex – a combination of pathological findings not heretofore described in the literature. We postulate this was the result of an underlying pial AVF causing venous hypertension and high-flow stenosing venopathy, acutely exacerbated by COVID-19-associated hypercoagulability, leading to spontaneous cerebellar vein thrombosis.

Author contributions. DC – formal analysis, investigation, data curation, writing initial/final
NS – computation, investigation, data curation, writing critical review/revision
ST – writing critical review/revision
KH – data curation
HM – data curation
CB – data curation
GC – data curation, investigation
HV – study conception, methodology, formal analysis, writing review/revision
AW – supervision, data curation, writing review/revision

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