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Short clinical case

Spontaneous appearance of de novo intracranial arteriovenous malformation in hepatic cirrhosis

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ABSTRACT

Background. – Intracranial arteriovenous malformations (AVMs) are rare lesions that can be congenital or acquired in early childhood, with fatal outcome in approximately 30% of cases. De novo formation during adulthood without established predisposing vascular pathology or previous brain insult is even less frequent.
Case Description. – We present a case of de novo brain AVM in an alcoholic Child-B cirrhosis setting. Thirty previously reported cases presented de novo AVM in patients of all ages that had another previous brain pathology or insult, such as AVM resection. Seventeen of those cases occurred in adult patients, with only 2 showing no significant predisposing factor. The present pathophysiological review covers and completes Mullan's hemodynamic "two-hit" model, associating probable thrombotic predisposition to AVM with brain insult triggering a later stage based on angiogenic stimuli.
Conclusions. – This case report and literature review renews previously discussed hemodynamic theories and contributes to a fuller understanding of the pathogenesis and progression of AVM. We postulate a causal link between hepatopathy and de novo AVM, which should be strengthened and interpreted based on recent genetic data and future prospective studies.

1. Introduction

Intracranial arteriovenous malformation (AVM) is rare (incidence, 0.02-0.05%) [1–3] and presents an annual hemorrhage rate of 2-4% [1–3] with fatal outcome in approximately 30% of cases [3]. This risk of bleeding depends on factors such as size, vessel morphology, intranidal aneurysm, etc. [1,2,4].

The currently known pathophysiological concept describes AVM as either congenital or acquired in early childhood, developing gradually with time. Nevertheless, the fundamentals of AVM biology is still the subject of discussion and investigation [3].

De novo formation during adulthood is rare but reported in several predisposing contexts and concomitant pathologies: radiotherapy, ischemia, moya-moya disease, venous sinus thrombosis, stem cell implantation, telangiectasia, traumatic brain injury, inflammatory/demyelinating conditions, sickle cell disease, seizure or resection of another similar lesion [3,5]. Only two cases have been described in adults where AVM developed without such vascular insults to the brain tissue[5].

We report here the case of de novo intracranial AVM in adulthood in a patient suffering from severe liver cirrhosis and with exclusion criteria for liver transplant, focusing the discussion on the possible angiogenesis and pathophysiologic mechanisms connecting the two diseases.

Abbreviations: AVF, Arteriovenous Fistula; AVM, Arteriovenous Malformation; Child, Child-Pugh Classification Scale (severity of liver cirrhosis); CT, Computed Tomography; CVM, Cerebral Venous Malformation; DSA, Digital Subtraction Angiography; DVA, Developmental Venous Anomaly; HHT, Hereditary Hemorrhagic Telangiectasia; HPS, Hepato-Pulmonary Syndrome; IL-6, Interleukin-6; MMP-3 and MMP-9, Matrix Metalloproteinases 3 and 9; MRI, Magnetic Resonance Imaging; PAVF, Pulmonary Arteriovenous Fistula; NO, Nitric Oxide; TGF, Transforming Growth Factor; TNF- α, Tumor necrosis factor- α; VEG, Vascular Endothelial Growth Factor.

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2. Case report

A 57-year-old female patient presented at the emergency department complaining of acute gait imbalance and left hemiparesis together with new dysarthria. The patient was known for chronic alcoholism with subsequent Child-B cirrhosis, complicated by hepato-pulmonary syndrome (HPS) and portal hypertension with gastropathy. A right-sided pre-central developmental venous anomaly (DVA without cavernoma) had also been incidentally diagnosed 2 years following head-trauma secondary to acute alcohol poisoning (Fig. 1). At this point, despite T1-weighted gadolinium-enhanced 1 mm MRI, no nidus, arterial feeder or edema was identified.

Neurological examination confirmed a left-sided proportional hemiparesis with a pyramidal syndrome and slowed speech.

New CT-angiography followed by MRI showed the previously diagnosed DVA, larger and completely changed, with an arteriovenous shunt and subsequent venous insufficiency and congestion resulting in surrounding vasogenic pre-central parenchymal edema. Cerebral digital subtraction angiography (DSA) confirmed this newly formed arteriovenous shunt between the DVA (draining in the superior sagittal sinus via the Trolard vein) and a peripheral cortical branch of the right anterior cerebral artery and also a distal branch of the external carotid artery (intra-osseous shunt), the whole meeting the diagnostic criteria of Spetzler-Martin grade 2 AVM [6] (Figs. 2 and 3).

Taking into account the poor general condition of the patient, the eloquent AVM location and the overall prognosis, radiotherapy was discussed. Unfortunately the patient died 2 weeks later due to severe decompensated hepato-renal and hepato-pulmonary syndromes and rapidly progressive encephalopathy.

3. Discussion

This is a rare case of de novo AVM in an adult aged over 35 years without history of hereditary hemorrhagic telangiectasia (HHT), moya-moya disease, intracranial aneurysm, arteriovenous fistula or venous sinus thrombosis, stem cell implantation, brain tumor resection and radiation, ischemic or hemorrhagic stroke, severe brain trauma, inflammatory state or any other hereditary or acquired brain condition. Although there are an increasing number of case reports of de novo AVM, only 6 [5,7–10] of the 36 reported cases [5,7–31] occurred in adult patients without confirmed predisposing or concomitant pathology or brain insult. Four of these 6 cases occurred in a setting of chronic seizures [7–10], 1 after a transient ischemic attack [5] and 1 in a context of hepatopathy similar to the present case [5].

In 21 cases [2,12,14–17,19,20,22–24,28–31], reported de novo AVM was reported in patients that had another vascular pathology, such as prior resection of an AVM in a different brain location during childhood, previous hemorrhagic stroke or intracranial aneurysm. The majority of the cases (n = 19) were pediatric

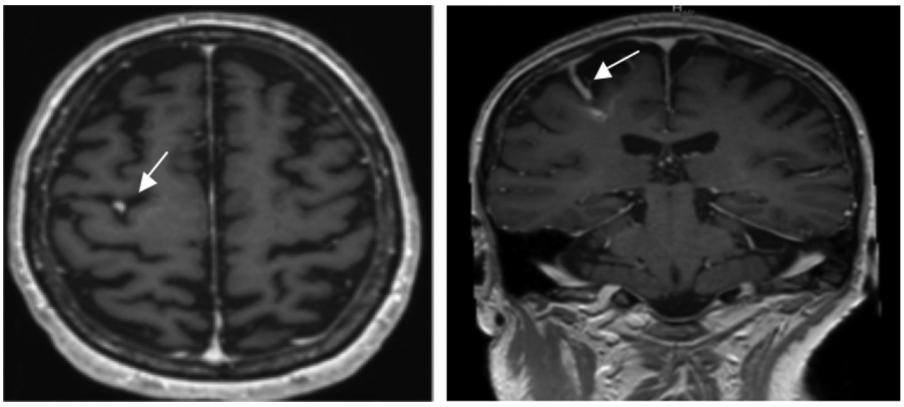

Fig. 1. T1-weighted MRI after gadolinium injection showing the presence of a developmental venous anomaly two years earlier without arteriovenous malformation (white arrows).

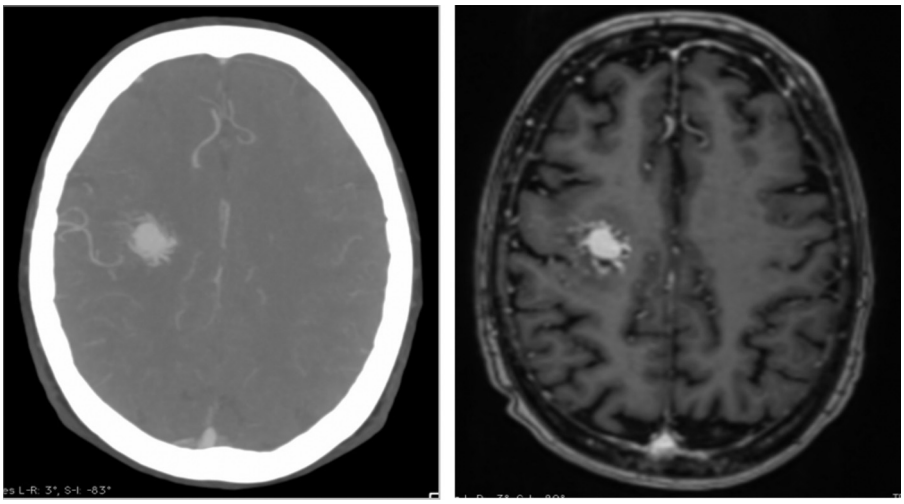

Fig. 2. CT-angiography and T1-weighted MRI with contrast showing the presence of a pre-central arteriovenous malformation with an arteriovenous shunt and subsequent venous insufficiency and congestion resulting in peripheral vasogenic pre-central parenchymal edema.

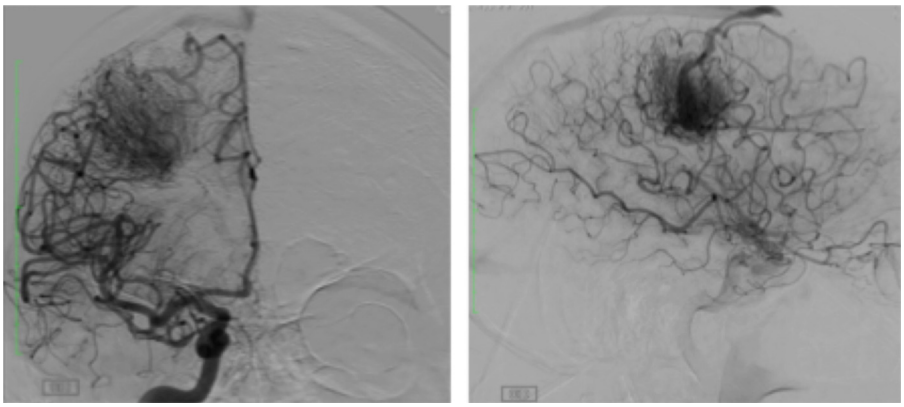

Fig. 3. Cerebral digital subtraction angiography (DSA) confirmed this newly formed arteriovenous shunt between the developmental venous anomaly (draining in the superior sagittal sinus via a cortical vein) and a peripheral cortical branch of the right anterior cerebral artery and also a distal branch of the external carotid artery (intra-osseous shunt), the whole meeting the diagnostic criteria of Spetzler-Martin grade 2 arteriovenous malformation.

[11,15–26,31] and only 9 involved young adult patients (< 35 years old) [2,5,7,9,10,13,14,27,29].

In vitro experimentation to evaluate AVM pathogenesis is limited in humans for clear ethical reasons. This gave rise to several theories based on scattered data from different fields, such as molecular biology and genetics, radiology, clinical reports and basic science [1,3,5]. Converging evidence suggests that AVM develops during the first trimester as, after this time, the adult forms of arterial and venous anatomy are complete and the number of pial-dural connections decreases. According to Mullan et al., after this initial shunt phase in the first trimester, the process of enlargement (to a point where the AVM becomes radiologically and/or clinically manifest) continues later in in-utero development or even after birth. It is followed by thrombosis within or loss of the developing cortical venous drainage in a particular location of the brain, diverting venous blood into deeper veins merging into a "venous star" within the developing white matter. This venous star drains into a neighboring venous channel that may have superficial or deep venous drainage. Later on, this venous cluster fistulates and thus the region recruits arterial feeders. This theory was illustrated by 4 cases of mixed cerebral venous malformation (CVM) with AVM characteristics, described as 'transition lesions' demonstrating the progression from one to the other and suggesting that AVM is a fistulized CVM and that both relate to a failure in the development of the cortical venous mantle [32]. This process was theoretically claimed to be the main mechanism accounting for the association between DVA and cavernoma. In the present case, it can also be postulated that some preexisting form of small cavernoma or AVM unseen on imaging may have led to an early shunt-phenomenon with disruption of the normal endothelial spaces.

The final step needed to complete this process is seen in brain AVM arising several years after an initial insult (thrombogenic, inflammatory, mechanical, ischemic/hypoxic or hormonal) in most patients. This suggests that these insults act as the "second-hit" to the existing acquired or genetic venous variant, [19,33] leading to the pro-angiogenic state necessary for the arterial phase of AVM formation. Applying these ideas to the present case, the trigger may have been the hepatopathy. As peripheral systemic AVMs constitute a feature of advanced chronic liver disease, intracranial AVMs may also share a common etiology and mechanisms. These may involve excessive synthesis of nitric oxide synthase, tumor necrosis factor-α (TNF- α), transforming growth factor (TGF) and vascular endothelial growth factor (VEGF), matrix metalloproteinases (MMP-3 and MMP-9), interleukin-6 (IL-6) or deficient estrogen hepatic metabolism, all of which are important in the inflammatory cascade and potent angiogenesis/fibrogenesis promotors, abundantly produced in AVM vessels, as revealed by immunohistochemistry [3]. A reported case of spontaneous resolution of AVM after liver transplantation favors this hypothesis [34]: after improvement of liver function resulting from the transplant, the AVM disappeared spontaneously together with the trigger factors. It should also be borne in mind that venous stenosis, occlusion, agenesis or thrombosis during embryologic development (as described by Mullan's hemodynamic theory) [32] or chronic venous hypertension (hepatopathy) during childhood and adulthood can result in tissue hypoxia and hence contribute to angiogenesis.

Lastly, our review showed that, 4 of the other 5 cases of de novo cerebral AVM without previous predisposing factors initially presented with seizures and 1 after TIA [5,7–10], both of which are known to cause hypoxic-ischemic brain damage. This may lead to abundant production of the above-mentioned potent angiogenic factors, such as VEGF and hypoxia-inducible growth factor 1 alpha (HIF-1α), in ischemic brain regions. Also significant overexpression of VEGF receptors and angioprotein receptors compared with controls was reported in patients with brain AVM [3].

Lasjaunias [35] questioned the congenital theory of brain AVM, suggesting that it forms postnatally during childhood while the vascular tree is undergoing remodeling in response to changing local metabolic demands. AVM thus results from an aberration in the cycle of proliferation and apoptosis during this process.

Looking at our case from a critical perspective, another interesting aspect was that prior DSA to formally rule out pre-existing AVM and better characterize the initial DVA would have been ideal. Several reports confirmed the sensitivity of MRI in detecting intracranial AVM [36]. Being non-invasive and affording enhanced sensitivity, MRI is now considered the screening tool of choice for AVM, whereas DSA remains the gold standard in the work-up. MRI demonstrated sensitivity in detecting unruptured AVMs comparable to that of as CTA (97% vs. 96%) [37].

Even so, the causal relationship discussed here has not yet been validated in vitro. With only a single case report it is not possible to conclude, or to recommend any change in follow-up protocol for this specific group of patients. Our understanding of the genetics, pathogenesis and progression of AVMs is in its infancy.

4. Conclusion

This was a rare case of spontaneous de novo brain AVM formation in an adult patient with liver cirrhosis. Together with previous reports and molecular and genetics studies, it highlights the need to explore new paradigms in brain AVM pathogenesis while renewing the hemodynamic theories already postulated in the past.

The pathophysiology of cerebral AVM remains incompletely elucidated, but the theory of systematically congenital formation being challenged as de novo AVMs are increasingly being reported.

We postulate a causal link between hepatopathy and de novo AVM, based firstly on venous hypertension/thrombosis-related changes plus a hepatic "second hit" that contributes to the pro-angiogenic state resulting in the final AVM. This two-hit model combines a probable genetic predisposition to AVM development to subsequent insult to the brain, causing ischemia, inflammation, vascular proliferation, abnormal shunting, higher flow, increased shear stress and continued angiogenic stimulation.

Disclosure of interest

The authors declare that they have no competing interest.

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