Angiogenesis in Steno-Occlusive Vasculopathies as a Common Pathway for Intracranial Haemorrhage

A Report of Six Cases

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Summary

Vasculopathies, including vasculitis of the central nervous system, can lead to stenosed, cicatrized vessels and the development of arterio-arteriolar collateral vessels.

Bleeding due to these vascular changes, although rare, does occur. We describe six patients (all female, age range, 21-52 years; mean age, 42 years) with steno-occlusive lesions of intracranial vessels who presented with an acute intracranial haemorrhage.

All had arterial steno-occlusive changes in conjunction with extensive leptomenigeal and arterio-arteriolar collaterals. Within the collaterals, focal dilatations could be identified, which were in close spatial relationship with the intracranial haemorrhage.

Cause of bleeding was depicted on CT angiography in four out of six patients. One patient presented in childhood with acute stroke, one patient was diagnosed with Buerger's disease and one with sickle cell disease; the other three patients had no relevant history and the exact cause remained unclear.

Outcome was favourable in all patients. Despite focal vascular weaknesses, no recurrent haemorrhage was seen during follow-up, supporting, at least in this small patient group, a conservative wait-and-see policy.

Introduction

Vasculopathies, including vasculitis, of the central nervous system (CNS) can present with a wide variety of clinical signs and symptoms, however a typical pattern has not been described. Several causes have been described, and the different aetiologies have been re-arranged into a new classification system in which primary (PACNS) and secondary causes of angiitis of the CNS have been categorized¹⁻⁴. A haemorrhagic presentation is quite infrequent and when present is mostly related to the so-called reversible cerebral vasoconstriction syndrome (RCVS)^{5,6} recently identified as a distinct entity, separate from PACNS⁷. Other vasculopathies such as moyamoya disease can also present with subarachnoid or intracranial haemorrhage, although much less frequently^{8,9}.

The importance of identifying the exact cause of an intracranial (subarachnoid) haemorrhage, other than an aneurysm, lies in the fact that patients with structural vascular abnormalities can have a far more complicated clinical course than patients with a perimesencephalic haemorrhage¹⁰. Digital subtraction angiography (DSA) has the ability to depict these other rare causes¹¹.

We describe a series of six patients with a variety of vascular changes in relation to vascu-

lopathies, who presented with an intracranial haemorrhage. This clinical report describes the CT angiographic and DSA findings and discusses the different patterns of arterio-arteriolar collateral system development.

Case Series

Six patients (all female; age range, 21–52 years mean age, 42.3 years) presented with the combination of intracranial haemorrhage and steno-occlusive vascular changes with collateral formation. These patients were extracted from our prospective neurovascular database registry in the period January 2007 until December 2012.

All cases were re-assessed, for (1) clinical presentation, (2) bleeding pattern on CT scan and (3) angiographic findings. Clinical outcome was assessed according to the modified Rankin Scale at three months. As this was a strict retrospective analysis, according to our institutional review board protocol, no informed consent was necessary.

Demographic data, clinical presentation, and relevant history of the six patients are reported in Table 1. Examples of five patients with more extensive clinical data are given in the figure legends for patients 1–5.

In one patient, old ischaemic changes were present in the frontal opercular and insular regions. She was known to have mild aphasia

and spastic paresis since childhood. None of the patients were on any kind of medication. Table 2 shows the details of the haemorrhage pattern and location on CT scan. CT angiography was performed in all patients, and a focal contrast accumulation could be demonstrated as the cause of bleeding in four patients presenting with parenchymal and ventricular bleeding. These contrast accumulations were in close relation to the small arterio-arteriolar collateral vessels, which were more clearly depicted on DSA than on CT angiography. The one patient who presented with a pure subarachnoid haemorrhage showed normal CT angiographic findings, DSA however, revealed vessel narrowing in conjunction with small arterial collateral vessels.

Angiographic findings in all six patients (Table 2) showed multiple vessel segment involvement; from the proximal intracranial internal carotid to the distal pericallosal and M4 segment branches. In two patients, focal stenoses were ‘bypassed’ by small arterio-arteriolar collaterals that were localized at the proximal (M2–M3) segments of the middle cerebral artery (MCA) and the pericallosal artery. These collaterals were the source of an insular subarachnoid haemorrhage in one and a focal callosal haemorrhage in the other. In the other four patients, leptomeningeal, transmedullary and choroidal collateral vessels were present causing parenchymal and ventricular haemorrhage.

Table 1 Demographics and clinical presentation of six female patients with steno-occlusive lesions of intracranial vessels who presented with an acute haemorrhage.

Patient number	Age (yrs)	Ethnicity	Presenting symptoms	History	Outcome (at 6 months)
1	47	Caucasian	Progressive speech disorder	Spastic paresis since infancy	mRS 2
2	45	Caucasian	Temporary unconsciousness Memory disturbances	None relevant	mRS 1
3	52	Asian	Severe headache, nausea, unconsciousness	None relevant	mRS 1
4	48	Caucasian	Unconsciousness Left-sided central facial nerve paresis and hemiparesis with unconsciousness	Buerger's disease	mRS 1
5	21	Creole	Unconsciousness	Sickle cell disease	mRS 2
6	41	Asian	Acute headache, slowly progressive loss of consciousness (E1M4V1)	None relevant	mRS 2

mRS: modified Rankin Scale score.

Table 2 Details of haemorrhage pattern and location on CT scan in relation to angioarchitecture on DSA in seven patients with steno-occlusive lesions of intracranial vessels who presented with an acute haemorrhage.

Patient	Haemorrhage	Location Hx	DSA findings	Diagnosis
1 (figure 1)	– Subarachnoid	– Left frontal insular (convexity)	– Bilateral occlusion frontal opercular M2-M3 branches MCA (left>right) – Arterio-arterial anastomoses left angular and temporo-occipital MCA branches	Progressive arteriopathy/ childhood PACNS
2 (figure 2)	– Ventricular	– Quadri-ventricular	– Supraclinoid occlusion right ICA – Collateral circulation through PCA towards MCA territory – Ophthalmic artery dural supply to right frontal lobe – Left ICA – MCA lenticulostriate collaterals to right ACA	Unclear
3 (figure 3)	– Subarachnoid – Parenchymal – Ventricular	– Parafalcine SAH – Corpus callosum – Lateral and 4th ventricles	– Multifocal stenoses: bilateral PCA, left MCA, right ACA – Dural supply from the middle meningeal artery – Arterio-arterial anastomoses: left MCA M3 segment and left pericallosal artery	Unclear
4 (figure 4)	– Parenchymal – Ventricular	– Right thalamic – Quadri-ventricular	– Occlusion right ICA – Interhemispheric collaterals left to right ACA – Leptomeningeal and choroidal PCA/MCA and MCA / ACA anastomosis (aneurysm at choroidal anastomosis)	Buerger's Disease
5 (figure 5)	– Intraparenchymal – Ventricular	– Right frontal lobe	– Transmedullary lenticulostriate – choroidal anastomosis	Sickle cell disease
6	– Ventricular	– Quadri-ventricular	– Supraclinoid narrowing distal left ICA – Multiple left MCA branch occlusions with proximal lenticulostriate to M2 and M3/ M4 leptomeningeal collaterals – Transmedullary MCA-ventricular – ACA collaterals (with aneurysm) – left ACA A1-A2 segment occlusion – Reconstitution of left ACA through PCA-(splenial pericallosal) anastomoses	Unclear

Hx: haemorrhage, SAH: subarachnoid haemorrhage, PCA: posterior cerebral artery, ACA: anterior cerebral artery, ICA: internal carotid artery, MCA: middle cerebral artery, PCOM: posterior communicating artery, PACNS: Primary angiitis of central nervous system.

Discussion

This clinical report describes patients with long-lasting steno-occlusive vasculopathies in whom extensive arterio-arteriolar collateral pat-

terns developed, either in the more proximal M1, A1, or P1 segments or in more distally located leptomeningeal and transmedullary-choroidal collaterals. Focal weaknesses in these collaterals were responsible for the haemorrhages.

Figure 1 A 47-year-old woman presenting with a sudden progressive speech disorder. A right-sided hemiparesis had been present since childhood during which she also had transient speech problems. A) Plain CT scan shows a SAH (arrows) with a frontal distribution with additional old ischaemic changes in the left basal ganglia. B) T2-weighted MRI image shows cortical left-sided insular oedema (arrows). C) Diffusion restriction is apparent on the ADC map (arrowheads). D) DSA of left-sided internal carotid artery (ICA) in lateral view shows occlusion of distal (M3) insular MCA branches (arrowheads) and extensive arterio-arteriolar anastomoses (arrows). E) DSA of left-sided ICA in AP view. In addition to the insular anastomoses (arrows), leptomeningeal collaterals from the anterior circulation have opened (arrowheads) filling the MCA territory. Additional laboratory tests showed a slightly increased CRP, signs of systemic infection but no signs of systemic vasculitis. At follow-up, her speech disorder slowly improved. At 24 months' follow-up, she had not encountered a repeat haemorrhage.

The extensive formation of collaterals has been acknowledged in patients with moyamoya disease. Besides an ischaemic presentation, a bleeding rate of up to 40% has been described in moyamoya disease^{12,13}. The arterial collateral vessels are more fragile because of a fragmented elastic lamina, thinned media, and the presence of microaneurysms. Bleeding usually occurs in the fourth decade of life. The moyamoya collateral pattern has also been described in a more focal pattern in relation to MCA stenosis in two reports^{14,15}. Rupture of dilated collateral arteries was believed to be the cause of haemorrhage in these circumstances. In 'case 1' the subarachnoid haemorrhage was in the area of M2-M3 collateral vessels, whereas in 'case 3', the haemorrhage in the corpus callosum was in clear spatial relationship to the small pericallosal arterio-arterial collateral vessels. Additional small collateral networks were present at the MCA. These collateral changes might have developed secondary to earlier, uneventful, occlusive changes. A recent report showed development of fragile collaterals and aneurysmal dilatations in other than moyamoya collateral arterial networks¹⁶. In another recent report, ruptured peripheral aneurysms in a collateral pathway were associated with stenosis of a major cerebral artery. These authors conclude that even if aneurysms are located in the distal

Figure 2 A 46-year-old woman presenting with sudden loss of consciousness (E3M5V3). Her history was unremarkable. She smoked 10 cigarettes a day. A) CT scan reveals a mostly right-sided intraventricular haemorrhage and hydrocephalus. B) Sagittal MPR of the CT angiography shows a focal contrast opacification (arrow) within the right-sided choroid plexus as the probable cause of bleeding. C) DSA, lateral view with injection of the right ICA shows occlusion of the supraclinoid ICA, MCA and ACA. Extensive leptomeningeal collaterals are seen from the PCA to the MCA territory. Two focal aneurysmal dilatations (arrows) are now depicted. The ophthalmic artery gives rise to an enlarged artery of the falx cerebri, supplying the frontal lobe (arrowheads). D) DSA, AP view with left-sided injection shows normal patency of the ICA and MCA. The left ACA (A1 segment) is hypoplastic, the left ACA territory is filled through leptomeningeal collaterals (arrowheads). The right-sided ACA territory is reconstituted through an extensive network of lenticulostriate arteries from the hypoplastic A1-segment (white arrows). Three weeks after the haemorrhage she was transferred to a rehabilitation centre because of severe cognitive and memory disturbances; otherwise she made a good clinical and neurological recovery. The six months' angiographic follow-up showed complete resolution of the aneurysm.

cerebral territories, these can be true aneurysms, the exception being patients with underlying vascular anomalies such as moyamoya disease or AVM¹⁷.

An important finding in this series of six patients was that an underlying vascular lesion could already be acknowledged on CT angiography in four patients. These four patients all presented with a parenchymal or ventricular haemorrhage, and a focal contrast accumulation within an area of abnormal vessels could be seen in close relationship to the haemorrhage. The focal contrast accumulation should not be confused with the focal spot sign¹⁸, which can be seen in patients with hypertensive bleeding. Foci of contrast enhancement within a haematoma can be present without direct connection to a vessel, and this should be distinguished from contrast accumulations resulting from focal vessel weaknesses such as aneurysm, pseudoaneurysms, intranidal aneurysm in AVM, and venous pouches. Vascular ectasias were present within the network of arterio-

teriolar collaterals, suggesting that these focal contrast accumulations were an aneurysm or pseudoaneurysm and potentially the source of haemorrhage. No delayed CT angiography was performed in any of our patients. All aneurysmal dilatation could be confirmed with angiography. No treatment was performed in these patients and at least in these cases, it appeared to be a 'self-limiting disease'.

In three of the presented patients, the cause of the vessel changes was unclear. An earlier PACNS was suspected based on imaging findings but in the absence of earlier clinical symptoms and positive laboratory findings, the diagnosis is difficult to make. No brain biopsy was performed in any of our cases. Pathological examination in PACNS will show affected small-sized and medium-sized arteries with segmental, mostly lymphocytic, inflammation. Half of the patients will show evidence of multinucleate giant cells and 25% can show necrosis of the media and internal elastic lamina. Findings at DSA can be unremarkable, especially when

only small vessels are affected¹⁹. Inflammatory changes in PACNS are less likely to improve, including failure of medium-sized vessels to return to normal, when no immunosuppressive treatment is started. Alhalabi et al. demonstrated progression of angiographic changes prior to therapy and improvement or stabilization in patients with a clinical response to therapy²⁰. However, in this report, some vessels show persistent narrowing over time despite treatment. According to Alhalabi et al., during six to nine months' follow-up, these irreversible stenotic cicatrized changes can cause ischaemia-initiated revascularization, either as enlargement of existing leptomeningeal collateral vessels (non-sprouting angiogenesis) or as neovascularisation (sprouting angiogenesis) and this might be the only hint to support the development of long-term vascular changes.

In one of our patients (case 1), a clinical ischaemic episode in childhood was confirmed on CT and MR imaging because of old ischaemic changes with parenchymal loss. Vessel occlusion and extensive collateral vessels were now visible in the ipsilateral hemispheric territory. The exact cause of the ischaemia remains unknown, but because of the sustained vascular changes it should be labelled as progressive arteriopathy instead of the more common transient cerebral arteriopathy (TCA)²¹. The bilateral distribution of abnormalities is atypical, but Benseler et al. described a bilateral distribution pattern in children with progressive and non-progressive childhood PACNS, the latter stated to be similar to TCA²². In the report by Braun et al.²¹, patients with cerebral arteriopathy rarely developed collateral vessels (5%) in case of transient arteriopathy, but much more frequently (80%) in progressive arteriopathy. Jones et al. found that at 18-months follow-up, only a quarter of the patients with evidence of intracranial stenosis in relation to transient cerebral arteriopathy showed a resolution of abnormalities²³.

Thromboangiitis obliterans, also known as Buerger's disease (case 4), is not included within the group of PACNS. It is a chronic inflammatory disease, involving medium-sized arteries and veins throughout the body, resulting in distal ischaemia in the extremities, ischaemic ulcers, and frank gangrene of toes and fingers. Preservation of the internal elastic lamina distinguishes it from true necrotizing forms of arteritis²⁴. Very few cases have shown evidence of cerebral involvement, the reported incidence varying between 0.5-18%^{25,26}. In our case exam-

ple, extensive collateralization from the left to the right A2 segment of the anterior cerebral artery (ACA) and additional collateralization from the posterior cerebral artery (PCA) to MCA and ACA territory was seen in the presence of complete internal carotid artery occlusion. The vulnerable collaterals resulted in a ventricular haemorrhage, the whole pattern showing great similarity to what can be seen in moyamoya disease.

Patients with sickle cell disease (case 5) can also develop occlusive vasculopathies. Adherence of sickle cells can cause damage to the endothelium resulting in a pro-inflammatory state with leucocyte and platelet aggregation, promoting increased vasomotor tone and a proliferation of small muscle cells causing progressive luminal narrowing²³. Some vessels show total occlusion due to exuberant intimal hyperplasia and organizing thrombi. Patients with sickle cell disease can also develop an extensive collateral network, similar to moyamoya vessel changes²⁷. An increased bleeding rate has also been described²⁸, but most bleedings are caused by rupture of small intracranial aneurysms²⁹.

The cerebral vasculature compensates for vessel occlusions and stenoses in several ways, depending on the localization of the vascular lesion. As most PACNS-related vascular changes are beyond the circle of Willis, collateral pathways will develop accordingly. The development of leptomeningeal pathways depends on physiological factors such as autoregulatory-induced vessel dilatation (non-sprouting angiogenesis) and can occur at different levels. First, a leptomeningeal anastomosis may open in the watershed areas between the major territories. Second, more proximal cortical branches can anastomose, by dilatation of the small, interconnected arterioles and capillaries. Third, hypertrophy of the lenticulostriate artery system can 'bypass' an occluded artery, inducing the so-called 'puff of smoke' as is the typical imaging finding in moyamoya disease. Finally, a collateral circulation may develop through the vasa vasorum. Although not frequently seen in the intracranial arteries, and even less often in the MCA, the tunica media has been shown to contain these small vessels^{30,31}. An increased presence of the vasa vasorum in the elderly has been described but is extremely rare and its development is limited to restricted pathological conditions, such as severe atherosclerosis and other cerebrovascular diseases³⁰. Reconstitution has been described more frequently in the

Figure 5 A 21-year-old woman presented with progressive headaches and subsequent loss of consciousness and was transferred to the ICU with an E1M4Vt. She was known to have a homozygous form of sickle cell disease. Neurological examinations prior to this event were normal despite deep white matter ischaemia in the watershed areas. A) CT at time of presentation shows a small parenchymal haemorrhage at the level of the anterior horn of the right ventricle with ventricular extension. B,C) CT angiography shows hypertrophy of the lenticulostriate vessels (B: white arrowheads) at the right-sided proximal MCA (M1) segment. Slightly more posterior, a focal contrast accumulation (C: white arrow) is visible at the ventricular lining. D) DSA confirms the presence of extensive lenticulostriate collateral vessels (white arrow), with distal transmedullary anastomosis. In concordance with the CT angiographic findings, fusiform vascular dilatation (black arrow) is present at the level of the ventricular lining. Extensive MCA arterial collateral formation is seen at the M2 and M3 insular vessel segments (arrowheads). E) In retrospect on the 2007 MR angiography at the anterior horn of the ventricle, collateral vessels are already visible (white arrow). Although she made a good neurological recovery with complete independence, the patient still suffers from persistent cognitive disturbances.

rhage later in life, comparable to what can be seen in moyamoya disease. Despite the focal weakness, no re-haemorrhage occurred during

follow-up in our patient group, supporting, at least in this small patient group, a conservative wait-and-see policy.

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