CASE REPORT

Recurrent non-aneurysmal subarachnoid haemorrhage in Takayasu arteritis: is the cause immunological or mechanical?

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SUMMARY

Aneurysmal subarachnoid haemorrhage (SAH) is rarely associated with Takayasu's arteritis (TA). The present report describes a 21-year-old woman with recurrent SAH and TA. In addition, she also had recurrent spells of postural weakness in the bilateral lower limb occurring at the same time. Sequential CT of the head and MRI showed bilateral cortical SAH. Vascular imaging with MR angiogram and CT angiogram showed bilateral subclavian arteries and left common carotid artery occlusion with multiple hypertrophied collateral vessels in the neck. There was no evidence of aneurysms in the intracranial vasculature in the conventional angiogram. The CT angiogram of the aorta showed severe stenosis of the abdominal aorta above the renal arteries. The patient was treated with immunomodulatory therapy and had a favourable outcome without further recurrence at end of 1 year of follow-up. A review of the literature showed 21 cases with aneurysmal SAH and three cases non-aneurysmal SAH in patients with TA have been reported. Various factors are responsible for the reorganisation of the intracranial of the arteries in patients with chronic vasculitis in the presence of extracranial stenosis and occlusion, which could possibly explain the SAH in absence of aneurysm in patients with TA.

BACKGROUND

Takayasu arteritis (TA) is a monophasic or multiphasic female predominant systemic illness with chronic large vessel vasculitis having a wide spectrum of presentation and a variable prognosis. The most common neurological symptom is headache occurring in up to 40–60% of patients¹; other manifestations include seizures, transient ischaemic attack and ischaemic stroke occurring as a result of hypoperfusion or artery-to-artery emboli from the stenotic or occluded extracranial arteries present variably in up to 10–20% of patients.² Aneurysm formation has been reported in all the involved vessels in TA and rupture of the aneurysm can be catastrophic. Rarely, subarachnoid haemorrhage (SAH) occurs in patients with TA who develop aneurysmal rupture in intracranial vessels.³ We report a case of a young woman with TA presenting with recurrent non-aneurysmal SAH. We provide a detailed review of the literature of patients presenting with SAH in TA and discuss potential mechanisms involved.

CASE PRESENTATION

A 21-year-old Caucasian woman presented to the emergency department with recurrent neurological deficits. Two weeks prior to her index admission, she developed a sudden onset of right-sided weakness, numbness, aphasia and confusion, lasting for 4 h. As her deficits subsided, she developed diffuse, dull aching and moderate-to-severe intensity headache, which lasted for 2 weeks. In the subsequent period, she developed two events of transient ascending marching right-sided numbness lasting for few seconds for which she was started on tegretol 600 mg/day. Over the 2 weeks prior to her admission, she described three spells of sudden onset bilateral leg weakness with fall upon rising from sitting to standing without presyncopal symptoms. There was neither sensory disturbance nor back pain, and the weakness in legs resolved in less than a minute. A day prior to her admission, she developed a sudden onset of paresthesias and mild clumsiness of her left arm and leg, which lasted for 2 h, also associated with headache. On examination in the emergency department, she was afebrile and her blood pressure was 140/88 and 110/60 mm Hg in the left and right arm in the supine position, respectively. An asymptomatic drop 20 mm Hg systolic in blood pressure was noted on standing in the right arm. Her neurological examination was unremarkable except for mild clumsiness and a pronator drift in her left hand.

INVESTIGATIONS

Two years ago, she developed multiple episodes of transient visual blurring and headache; on examination absent pulse was noted in the left arm. She was investigated with a CT of the brain (figure 1A) and neck vessel Doppler. The Doppler revealed an occlusion of the bilateral subclavian arteries and left common carotid artery at the origin. The inflammatory markers revealed elevated C reactive protein (CRP) and erythrocyte sedimentation rate (ESR). She was diagnosed to have TA. She also underwent positron emission tomography (PET) imaging of the large vessels prior to start of the immunosuppression. PET imaging did not reveal any increased enhancement of the large vessels. Brain MRI with fluid-attenuated inversion recovery (FLAIR) sequence images early into illness showed hyperintensities in subarachnoid spaces, suggestive of sluggish flow in the leptomeningeal arteries and no parenchymal lesions (figure 1A). Catheter angiogram showed an occlusion of the bilateral

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Figure 1 Sequential brain imaging demonstrating alternating subarachnoid haemorrhage and resolution. (A–D) Axial non-contrast CT scan performed 3 years prior with no haemorrhage, axial fluid-attenuated inversion recovery (FLAIR) MRI scan performed 2 years prior which shows vascular hyperintensities in the bilateral hemisphere; (B) axial non-contrast CT scan and FLAIR MRI performed on the day of onset of headache shows sulcal subarachnoid haemorrhage (SAH) in the left cerebral hemisphere; (C) axial non-contrast CT scan and FLAIR MRI performed after occurrence of new symptoms shows residual sulcal SAH in the left cerebral hemisphere and new sulcal SAH in the right hemisphere; (D) CT and MRI of the brain, FLAIR and susceptibility weighted imaging (SWI) sequence performed after 1 year of the SAH shows resolution of the SAH in FLAIR sequence but persistence in the SWI sequence.

subclavian arteries and left common carotid artery (CCA) (figure 2D) and stenosis of the right CCA and bilateral vertebral arteries (VA). The right internal carotid artery (ICA) injection showed normal right middle cerebral artery (MCA) and anterior cerebral artery filling (figure 2A). The left CCA injection shows minimal filling of the left ICA and left MCA (figure 2B). The right VA injection shows normal filling of basilar artery and filling of the bilateral MCA through the posterior communicating arteries (figure 2C). The CT angiogram of the aorta and heart showed severe stenosis of the postrenal artery abdominal aorta (figure 2E). MR perfusion-weighted study showed

hypoperfusion and a delayed flow in the left cerebral hemisphere (see online supplementary figure S3). She was asymptomatic and regularly monitored with serological markers and imaging, CRP and ESR that were moderately elevated. MRA arch of aorta performed 1 year into illness showed increased uptake in the late postcontrast source images suggestive of active inflammation. The whole body PET-CT scan of the great vessels did not show any abnormal uptake. She was tried on prednisone, methotrexate, azathioprine and cyclophosphamide with variable success and was on mycophenolate mofetil 1 gm twice daily during the present events.

Figure 2 Angiogram showing stenosis and occlusion of the vessels: (A) Right internal carotid injection showing normal right middle cerebral artery (MCA) and anterior cerebral artery flow; (B and F) Left common carotid artery (CCA) injection shows minimal flow in the CCA, internal carotid artery and MCA. The left CCA is reconstituting with help of the collateral arteries in the neck; (C) right vertebral artery injection shows normal flow in the basilar artery and filling of the bilateral MCA via posterior communicating artery; (D) injection of the thoracic aorta is showing significant stenosis of the right subclavian artery and the right CCA at the origin also there is occlusion of the left subclavian artery and left CCA which formed distally with multiple collaterals; (E) CT angiogram of the abdominal aorta shows critical stenosis below the level of the renal arteries.

A CT of the brain performed at the time of her headache, right hemiparesis and aphasia 2 weeks prior to her index admission showed left hemispheric sulcal SAH (figure 1D). CT angiogram of the brain did not show any abnormal vasculature or aneurysm. Brain MRI with FLAIR imaging showed subarachnoid sulcal hyperintensity which was also suggestive of subarachnoid bleed (figure 1B). At this time, the CRP was 8 and the ESR was 11 mm/h. Two days later, she underwent conventional angiogram with right carotid injection which showed significantly delayed flow from arteries to veins. There were no aneurysms noted in the proximal arteries or distal arterioles. A repeat CT of the brain performed for the new symptoms a day prior to her index admission (figure 1C) showed new subarachnoid hyperdensity in the right frontal sulcus suggestive of fresh SAH. The previous SAH over the left hemisphere had resolved.

Similar findings were noted in the brain MRI FLAIR sequence images with resolving left and new right frontal sulcal subarachnoid hyperintensities (figure 1C). She underwent a non-traumatic lumbar puncture which was haemorrhagic suggestive of SAH. Late contrast-enhanced MR angiogram of the aortic arch showed an increased uptake in the distal abdominal aorta and the aortic arch suggesting continued inflammation. Whole body PET-CT scan of the great vessels did not show any abnormal uptake.

TREATMENT

During the hospital course of 11 days, she did not have any further recurrence of focal symptoms. She underwent transcranial Doppler which showed low-resistance flow with low-pulsatility index in all the proximal and distal intracranial arteries suggesting a non-pulsatile perfusion pattern to her brain (see online supplementary figure S4). It was decided to further optimise her immunosuppression and she received two doses of rituximab 1 month postdischarge with azathioprine as maintenance therapy.

OUTCOME AND FOLLOW-UP

At her 1-year follow-up visit, she was asymptomatic without any focal symptom or recurrence of headache.

DISCUSSION

SAH is a rare complication of TA with a total of 24 cases published in the world literature to date since its first description in 1972. The most common cause of SAH is the rupture of cerebral aneurysm (21 cases),³ but as in our case and three others reported that no aneurysm was detected.^{4 5} We reviewed the literature in regard to patients with TA having cerebral aneurysm without SAH, cerebral aneurysm with SAH and SAH without cerebral aneurysms (table 1). We found differences in TA patients presenting SAH with and without cerebral aneurysms (table 2). Patients presenting as SAH with cerebral aneurysms were older, more commonly had aneurysms in the posterior intracranial circulation, had aneurysms present in extracerebral locations and commonly had hypertension. Furthermore, SAH with cerebral aneurysm had an overall poor prognosis and high mortality. On the other hand, SAH without aneurysm had a relatively good prognosis although the case volume is too low for definitive conclusions.

TA is a panarteritis with predominantly a stenotic and occlusive pathology. The mechanism for aneurysm formation is unclear. Mechanical factors such as hypertension and turbulence in the intracranial arteries may cause haemodynamic stress thus increasing the propensity of aneurysm formation. The immune destruction of the vessel wall makes the arterial wall vulnerable to aneurysm formation.³ These mechanisms are inadequate to explain SAH in the absence of aneurysm.^{4 5} TA is primarily a large vessel vasculitis affecting aorta and its proximal branches, but there is evidence that it affects small vessels as well in the form of cutaneous manifestations like erythema nodosum, necrotising vasculitis occurring in up to 12% of patients. These manifestations improve and disappear with disease remission.⁶ None of the patients with SAH without aneurysm had brain biopsy, but an analogy can be drawn between SAH cases and the cutaneous manifestations suggesting the possibility that small vessel vasculitis can occur elsewhere in TA. Small vessel vasculitis by itself can present with SAH without aneurysm. We found no evidence to confirm any vasculitic abnormalities of vessels inside the skull so that the above discussion is speculative.

Table 1 Patients with subarachnoid haemorrhage and/or intracranial aneurysm Takayasu's arteritis

Ref year	Author	Age (years)	Sex	SAH	Aneurysm	Treatment	Prognosis
2011	Present case	20	F	Yes	No	None	Good
2011	Hyun <i>et al</i>	44	F	Yes	No	Steroid	Good
2002	Kim <i>et al</i>	44	F	Yes	No	Steroid	Not known
2002	Kim <i>et al</i>	31	F	Yes	No	Steroid	Not good
2008	Takayama <i>et al</i>	70	F	No	Yes	Coil embolisation	Good
1998	Asaoka <i>et al</i>	54	F	No	Yes	Clipping	Good
1981	Arita <i>et al</i>	48	F	No	Yes	Clipping	Good
2010	Maramottam <i>et al</i>	29	M	Yes	Yes	Coil embolisation	Not known
2008	Weiss <i>et al</i>	1.6	F	Yes	Yes	Clipping	Death
2008	Magge <i>et al</i>	1.6	F	Yes	Yes	Clipping	Death
2004	Sonwalkar <i>et al</i>	50	F	Yes	Yes	Clipping	Death
2004	Kanda <i>et al</i>	48	F	Yes	Yes	Clipping	Not known
1994	Nishimura <i>et al</i>	48	F	Yes	Yes	Clipping	Good
1989	Dimitrijevic <i>et al</i>	53	F	Yes	Yes	Not known	Not known
1987	Sunami <i>et al</i>	55	F	Yes	Yes	None	Good
1987	Kurimoto <i>et al</i>	48	F	Yes	Yes	Clipping	Good
1986	Masuzawa <i>et al</i>	64	F	Yes	Yes	Clipping	Good
1985	Mizuno <i>et al</i>	55	F	Yes	Yes	None	Good
1985	Wakabayashi <i>et al</i>	56	F	Yes	Yes	None	Death
1984	Masuzawa <i>et al</i>	55	M	Yes	Yes	Clipping	Good
1983	Satoh <i>et al</i>	38	F	Yes	Yes	Clipping	Good
1982	Imaizumi <i>et al</i>	48	F	Yes	Yes	Clipping	Good
1982	Masuzawa <i>et al</i>	54	F	Yes	Yes	None	Death
1982	Masuzawa <i>et al</i>	26	F	Yes	Yes	None	Death
1981	Kumagai <i>et al</i>	41	F	Yes	Yes	Clipping	Death
1981	Kumagai <i>et al</i>	55	F	Yes	Yes	Clipping	Good
1980	Izawa <i>et al</i>	55	F	Yes	Yes	None	Good
1972	Niitsu <i>et al</i>	26	F	Yes	Yes	None	Death

The second mechanism to be considered for non-aneurysmal SAH is chronic hypoperfusion and hypoxia leading to arteriogenesis and angiogenesis with formation of abnormal collateral vessels prone to rupture. Hypoperfusion leads to the opening of leptomeningeal collateral channels which we could see as FLAIR vascular hyperintensities (figure 1A,D). The transcranial Doppler finding of low-resistance flow with reduced pulsatility index (see online supplementary figure) in all the intracranial vessels as in our patient and others reported in the literature⁷ suggest significant haemodynamic compromise and possibly some degree of mild tissue hypoxia. This borderline situation in

our patient was suggested by her three episodes of bilateral leg weakness upon postural change. We presume that this represents postural hypoperfusion to the medial frontal cortex bilaterally as there was no evidence of compromised blood flow to the spinal cord. The spells did not recur after attention to hydration and slow postural change. The situation may be analogous to Moya-Moya syndrome where low perfusion invites the formation of abnormal collateral vessels. The brain in this circumstance is entirely dependent on collateral vessels that, we propose, are stretched to their limits and occasionally prone to rupture.

Table 2 Difference between aneurysmal SAH and non-aneurysmal SAH in Takayasu's Arteritis

	Aneurysmal SAH	Non-aneurysmal SAH	Aneurysm without SAH
Number of patients	21	4	3
Females	19	4	3
Age range (years)	1 1/2–64	20–44	48–70
Age mean (years)	43.1+17	34.8+10	57.3+9.3
Non-intracranial aneurysm	Common	Uncommon	Common
Posterior circulation aneurysm	Common	None	Uncommon
Recurrent SAH	Common	Uncommon	Not seen
Hypertension	Common	Uncommon	Common
Treatment used	Clipping and coiling	Steroids and immunotherapy	Clipping and coiling
Prognosis	Poor	Good	Good
Mortality	Common (8/21)	None	None

SAH, subarachnoid haemorrhage.

Non-aneurysmal recurrent SAH in patients with TA is rare. The pathology is unknown, but may represent small vessel involvement from vasculitis or rupture of weak collateral vessels. Whether subarachnoid haemorrhage alone warrants an increase in anti-immune therapy is unknown.

Learning points

- ▶ Takayasu's arteritis (TA) with subarachnoid haemorrhage (SAH) is a unique presentation.
- ▶ SAH in TA can be with or without aneurysms.
- ▶ The mechanism of SAH in TA without aneurysms can be mechanical or immunological.
- ▶ Small vessel involvement in TA may play role in SAH.
- ▶ Persistent hypoxia and aberrant collaterals can be cause of SAH.

Competing interests None.

Patient consent Obtained.

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