

A Case of Isolated Central Nervous System Vasculitis

Vasculitides are a diverse group of disorders which can prove difficult to diagnose and treat. We report a case of a young woman who was found out to have an isolated angiitis of central nervous system that involved inflammation of blood vessels in an unusual distribution.

Case report

A 24-year-old woman was admitted following an unwitnessed collapse at home, whilst sitting at her computer. There were no warning signs and she was well earlier that day. She had a past history of syncope and mild depression but no history of drug abuse. A maternal grandmother had a myocardial infarction at a young age.

She was pyrexial on admission (38.5°C), this subsequently settled. On neurological examination she was drowsy and confused, but no focal neurological signs were found. In the first 48 hours post admission, her Glasgow Coma Scale (GCS) fluctuated between 11 and 15 and she developed bilateral internuclear ophthalmoplegia, loss of up gaze, a mild left hemiparesis, dysarthria and left sided ataxia.

Her routine investigations including C-reactive protein and erythrocyte sedimentation rate were all normal. She was empirically commenced on a combination of broad spectrum antibiotics (cefotaxime, metronidazole and meropenem) and also aciclovir.

A computed tomography (CT) head scan showed multiple infarcts in the left cerebellum, right thalamus and left temporal lobe.

Magnetic resonance imaging (MRI - Figure 1a and b) confirmed multiple infarcts predominantly in the posterior circulation but also in the anterior circulation bilaterally. These infarcts included the left superior cerebellar artery territory, right thalamus, four small areas in the right side of the pons, right frontal lobe and left temporal lobe. Magnetic resonance angiography (MRA - Figure 2a) revealed irregular narrowing of the basilar artery with two discrete areas of narrowing and post stenotic dilatation. Both posterior cerebral arteries and posterior communicating arteries also showed irregularities. There were no abnormalities seen in the internal carotid, middle cerebral or anterior cerebral arteries on either side.

The findings on MRA in the posterior circulation raised the possibility of vasculitis although an embolic process was also considered. She was commenced on oral aspirin and intravenous methylprednisolone fol-

lowed by oral prednisolone.

The following investigations were found to be within the normal range: B12, folate, thyroid function, autoimmune profile, ANCA, anti double stranded DNA, antiphospholipid screen, coagulation and thrombophilia screen, LDH, multiple blood cultures, serum virology, retroviral tests, Lyme and syphilis serology, white cell enzymes and genetic testing for MELAS (Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes). Trans-thoracic and trans-oesophageal echocardiography, carotid and vertebral ultrasounds were normal and excluded the possibility of embolisation. A CT aortogram showed a normal aortic arch and the vertebrals, internal carotids, anterior and middle cerebral arteries were also normal. The basilar artery was beaded and the posterior cerebral vessels appeared small. Cerebrospinal fluid (CSF) showed a mildly raised protein of 0.61g/l (normal ≤ 0.5) with unmatched positive CSF oligoclonal bands and a normal cell count.

Repeat MRA (Figure 2b) a month after presentation showed progression of the vascular disease. There was an increase in the length of stenotic segment of basilar artery with almost complete obliteration of the left posterior cerebral artery. The right posterior cerebral artery also appeared narrowed and beaded proximally. One of the insular branches of the right middle cerebral artery appeared narrowed.

The clinical picture pointed towards an isolated CNS vasculitis, both large and medium sized blood vessels were involved, predominantly in the posterior circulation. Therapeutic anticoagulation with warfarin was commenced.

Formal angiography (Figure 3) showed stenosis in the basilar artery and skip-like lesions, particularly in the left posterior cerebral artery that had been seen on MRA.

Clinically, she started making a good recovery within a few days of commencing steroids. Azathioprine was added later as a steroid sparing agent for maintenance. Two months after her initial presentation she was left with a degree of disinhibition, mild left sided weakness and diplopia. She improved further with a month of intensive neuro-rehabilitation. At the time of discharge her power returned to normal but she had some residual cognitive difficulty, especially impaired organisational skills and personality change with a mild degree of diplopia.

She was continued on immunosuppressive therapy and anticoagulation. Her steroids were tapered down very

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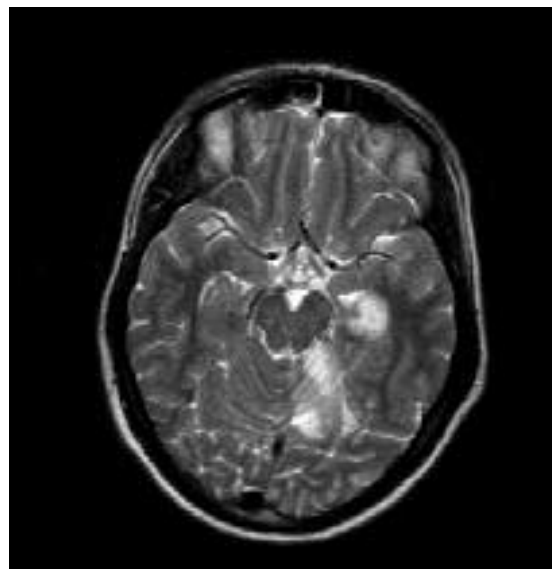


Figure 1a and 1b: MRI T2 axial views at the time of presentation, showing multiple infarcts - left superior cerebellar artery territory, right thalamus, four small areas in the right side of the pons, right frontal lobe and left temporal lobe.



Figure 2a (top): MRA coronal views of posterior vasculature showing discrete areas of narrowing of the basilar artery with post stenotic dilatation, there were also changes in the posterior cerebral and posterior communicating arteries.

Figure 2b: MRA a month after presentation showed progression of the vascular disease, with an increase in the length of the stenotic segment of basilar artery, there was also almost complete obliteration of the left posterior cerebral artery.



Figure 3: Conventional angiography showing presence of stenotic lesions in basilar artery and skip-like lesions in the left posterior cerebral artery.

slowly and stopped seven months after initial presentation. She continued warfarin for six months and then converted back to aspirin 75mg daily. She was last seen 36 months after the initial presentation. Her upward gaze is still restricted and she continues to use prisms. She remains on azathioprine 50 mg daily.

Discussion

Vasculitides are a heterogeneous group of disorders with histopathological inflammation in the blood vessels as the core feature. These are classified on the basis of type of inflammatory infiltrate, the size of the blood vessel involved, which body system is involved and the clinical presentation. Various antibody and cell mediated mechanisms have been described to explain vasculitides.¹

Vasculitis involving the nervous system can be primary i.e. restricted to the nervous system only or secondary involving the nervous system as a part of a systemic process. The nervous system involvement can be central or peripheral.

Central Nervous System (CNS) vasculitis can cause ischaemia and / or infarction in any part of the brain at a micro- or macroscopic level depending on the size of the blood vessel involved. This can occur in an acute, sub-acute or chronic manner. The presentation can be in the form of diffuse neurological features such as headaches and encephalopathy, or as focal or multifocal neurological involvement e.g. stroke, seizures, cognitive impairment, movement disorders and cranial neuropathies.² Three broad categories of clinical presentation have been described: an acute or sub-acute encephalopathy; an 'atypical multiple sclerosis'; and mimicking an intracranial mass lesion. There are few reported cases of hypersomnia described secondary to isolated CNS angiitis.³ Our patient presented with a clinical picture of a combination of acute encephalopathy initially and multiple strokes.

Primary (isolated) angiitis of the CNS, as in the present case, is a disorder of neurological dysfunction with changes on cerebral angiography or biopsy in the absence of systemic involvement and with normal systemic laboratory investigations.⁴ There is remarkably little literature available on this subject. Lie (1992)⁵ reported that it can affect people at any age but with a mean age of 45. Arteries such as the carotids, vertebrals and other major cerebral blood vessels can be involved but isolated angiitis characteristically involves small leptomeningeal blood vessels. In our case large, medium sized and small leptomeningeal blood vessels were affected.

The aetiology is unclear. Lie (1996)⁶ suggested that primary angiitis is a non-specific reaction to a number of ill-defined insults. Several infections have been associated with it, for example herpes zoster, herpes simplex, HIV, HTLV-III, hepatitis C, cytomegalovirus, mycoplasma and bartonella. Other associations include various lymphomas and immunological conditions such as Sjogren's syndrome.⁷

The diagnosis of an isolated CNS vasculitis can be challenging and relies on a high index of suspicion, as the clinical presentation is usually diverse, and there are number of causes and mimickers.⁸ Blood tests are generally normal. Occasional abnormalities such as anaemia, leucocytosis, eosinophilia, raised ESR and CRP or positive autoimmune screen might point towards a systemic vasculitis. CSF analysis may be completely normal but a lymphocytosis may be found with a raised protein in 50-80% of cases with cerebral vasculitis.⁹ Oligoclonal bands are positive in 40-50% of the patients with cerebral vasculitis from a small series.¹⁰ An EEG might be helpful in confirming the presence of encephalopathy.

MRI scans in isolated angiitis can show infarcts, ischemia, inflammatory enhancement or mass lesions. The MRI appearances may be normal even in the presence of vasculitis on catheter angiography¹¹ and on histopathology.¹² On conventional angiography smooth narrowings of affected vessels in multiple vascular distributions are the most frequent abnormality. Other features include segmental arterial dilatations, vascular occlusions, collateral formation and prolonged circulation time. Single stenotic areas in multiple vessels are more frequent than multiple stenotic areas along single vessel segments.¹¹ Segmental narrowings initially result from reversible inflammation with vasospasm and later on are secondary to irreversible scarring.¹¹ Angiographic changes can be used for diagnostic assessment in medium and large vessel involvement but cannot be reliably used in follow-up. There is a 10% risk of transient and a 1% risk of permanent neurological deficit with catheter angiographic studies.¹³ Conventional catheter angiography is considered the 'gold standard'

radiologically although MRA can provide useful information without additional risk.

The diagnosis of small vessel angiitis is difficult to make on angiographic assessment alone and may require biopsy. Biopsy helps distinguish between primary and secondary CNS inflammation and also from non-inflammatory vascular disease. It provides sensitivity in up to 70% of the cases¹⁴ but there is a significant amount of morbidity (0.5-2%) associated with this procedure. There are also practical difficulties in obtaining biopsies. Lie (1997)¹⁵ states up to 75% of cases are diagnosed without biopsy. Alrawi et al. (1999)¹⁶ suggested that brain biopsy should be the primary diagnostic tool in the setting suspicious of primary angiitis of CNS. False negative biopsy results can occur due to a large extent by incorrect sampling. Moore (1989)¹⁷ suggested taking a 1cm wedge of affected cortex in the non-dominant hemisphere including leptomeninges and a cortical blood vessel or a non-dominant temporal tip in cases of 'blind biopsy'. Histopathology may show granulomatous, necrotising, lymphocytic or a mixed inflammatory response.¹⁵ Rare cases of isolated eosinophilic CNS vasculitis have also been reported.¹⁸ There is no consensus on the 'gold

standard' investigation and conventional angiography is considered comparable to histopathology in the diagnosis of cerebral vasculitis.²

In our case the diagnosis relied on angiographic studies and progression of the disease process was also established by comparative imaging.

Indium-labelled white-cell scans in systemic vasculitis and fluorescein angiography of the anterior chamber of the eye have also been shown to be helpful to some extent in systemic, cerebral and localised ocular vasculitis.¹⁰

CNS angiitis usually requires an aggressive treatment approach. Different regimens and immunosuppressive agents have been used. It has been suggested that initial treatment with high dose intravenous methylprednisolone (1g daily) and oral cyclophosphamide (2.5mg/kg body weight daily) is followed by oral prednisolone (60mg daily) over 9-12 weeks along with maintenance phase treatment with azathioprine (2mg/kg body weight daily) and oral prednisolone (20-30mg daily) for a further 10 months.² Treatment is best tailored on an individual basis. Alternative treatment options include methotrexate, intravenous immunoglobulin and plasmapheresis. For systemic vasculitis other treatment options are Campath-1

especially for Bechet's disease¹⁸ and PEGylated interferon α -2b for hepatitis C associated vasculitis.²⁰ There is no reliable indicator for monitoring the disease process.

Little is known about the course of the isolated CNS angiitis because of its rarity. Benign angiopathy of the CNS has been described as a monophasic illness with mild abnormalities on CSF analysis and angiographic evidence of vasculitis, as suspected in the present case, but on longer follow-up a proportion of these appeared to behave aggressively requiring intense immunosuppression.⁴ MacLaren et al (2005)²¹ suggested that small vessel CNS angiitis was responsive to immunosuppressive treatment but relapsed during prolonged periods in all patients on maintenance, or after the withdrawal of the treatment, causing recurrent severe and irreversible CNS injury whereas middle sized CNS angiitis had isolated episodes at presentation, with a paucity of recurrence during prolonged follow-up.

The present case was unusual as there was an odd distribution of lesions and it involved blood vessels of variable size, mainly in the posterior circulation. Improvement occurred with a relatively benign therapeutic regimen.

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