Varicella zoster vasculopathy associated with deep intracerebral haemorrhage

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Statements and Declarations

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Dear Sir or Madam,

Varicella zoster virus (VZV) related vasculopathy is a rare cause of ischaemic stroke, most often characterised by ophthalmic shingles infection followed by contralateral hemiparesis in association with single or multifocal, deep, borderzone or juxtacortical cerebral ischaemia. Cases can be associated with primary varicella zoster infection, almost always in children, or more commonly with reactivation of latent virus, termed herpes zoster infection. CT and MR angiography is abnormal in 74% of cases, typically with mixed large and small vessel stenoses with post-stenotic dilatation [1]. A case series reported evidence of de-novo intrathecal anti-VZV IgG synthesis in the cerebrospinal fluid (CSF) in 93% of 30 cases [2]. Another larger case series, involving 62 patients, reported anti-VZV IgG detection in 95% of cases, without explicitly reporting raised serum/CSF IgG index [1].

The association of VZV with deep intracerebral haemorrhage (ICH) is much less well established; we are aware of only four previous reports, none of which comprehensively described the cerebrovascular imaging and CSF immunological findings [3-6]. Here we describe a case of deep ICH shortly after developing ophthalmic shingles infection, with a complete set of investigations.

A 46-year-old right-handed woman presented with sudden onset right hemiparesis and sensory disturbance affecting the face, arm and leg, with slurred speech. This was on a background of a two-week history left sided facial rash, and she had been diagnosed with herpes zoster ophthalmicus (HZO) with corneal involvement by the ophthalmology department. This was being treated with oral and topical acyclovir at the time of presentation. Apart from a history of mild well-controlled asthma she had no significant past medical history. She took inhaled steroids and no other long term medications. She had a history of childhood chickenpox but no previous episodes of shingles.

On clinical examination she was alert and oriented, but slightly agitated. Presenting blood pressure was 123/91 and all other vitals were within normal limits. She had a vesicular herpetic rash affecting the ophthalmic division of the left trigeminal nerve (figure 1, D). She had mild dysarthria, dense upper motor neurone pattern right facial weakness and dense flaccid right hemiparesis, with a National Institute for Health Stroke Scale (NIHSS) of 11.

Complete blood count showed a mild lymphopaenia of 0.84×10^9/L. There was a very mild liver transaminitis (ALT = 40 IU/L), but otherwise renal, bone and liver biochemistry were

normal. Autoantibody testing showed a weakly positive antinuclear antibody (ANA) at 1:80 dilution. Extractible nuclear antibodies (ENA) and anti-nuclear cytoplasmic antibody (ANCA) were negative. Thrombophilia screen was negative.

Computerised tomography (CT) of the brain showed a 5 mL acute intraparenchymal haematoma centred on the posterior limb of the left internal capsule. There was no evidence of leukoaraiosis. CT and magnetic resonance (MR) angiography were normal with no sign of arterio-venous malformation (AVM), aneurysm or cerebral vasculitis (figure 1, B). She had an MRI brain scan which showed no evidence of cerebral small vessel disease as a possible cause of the ICH (figure 1, A). After discussion in the neuro-vascular multidisciplinary meeting she went on to have intra-arterial digital subtraction angiography (DSA) of the cerebral vessels as a more sensitive test for vasculitis. This was also normal (figure 1, C).

Since she had a typical presentation for VZV related vasculopathy she went on to have a lumbar puncture which a very mild mononuclear pleocytosis but otherwise normal constituents (white cell count 7 / μL, protein 0.44 g/L, glucose 3.57 mmol/L) and was negative for VZV DNA. Apart from the mildly raised WCC count, there was no other evidence of inflammation in the CSF: the serum/CSF albumin and total IgG indices were normal. There were no oligoclonal bands. This sample was not sent for VZV IgG detection. An infectious diseases opinion was sought and a repeat lumbar puncture was recommended, since the time interval between onset of the rash and the first CSF sample was less than one month. This time VZV IgG was detected, but serum/CSF IgG index was normal.

Although no new shingles lesions were appearing at this stage, the infectious diseases advice was to give 10 days of intravenous acyclovir to treat potential ongoing inflammation of the cerebral vessel walls caused by viral replication. She completed this treatment and made a reasonable functional recovery from her stroke, allowing her to walk without assistance, but her upper limb remained weak.

We are aware of four cases of intracerebral haemorrhage in adults, possibly caused by VZV, which were diagnosed at autopsy [7-10]. The first case from 1944 had herpes zoster of the left side of the chest, and 23 days later had a headache rapidly followed by coma and death. He was found to have a “massive” haemorrhage in the right basal ganglia. They did not look for evidence of VZV or angiitis in the cerebral vasculature. The second case comes from an ophthalmological case series running from 1975 to 1980. Out of 86 patients with HZO, two of the patients had contralateral hemiplegia. One of these died and post-mortem examination

revealed cerebral haemorrhage with evidence of “granulomatous angiitis of the cerebral vessels”. No further details were given. The third case from 1982 reported a 69-year-old man with a rapidly ascending paraplegia associated with a herpetic rash on the left thigh. 27 days after admission he developed left sided weakness shortly followed by stupor. Autopsy revealed a massive right frontal cortical haematoma. Vasculitis of the leptomeningeal vessels was found, including a necrotic vessel with aneurysmal dilatation found inside the haematoma. They did not find clear microscopic evidence of viral particles in the vessels. The fourth case involved a 62-year-old woman with right-sided HZO, who had a hospital admission for disorientation and hallucinations. She later developed left hemiparesis with multiple right hemisphere infarcts and evidence of angiitis of the right internal carotid and middle cerebral arteries on cerebral angiography. 60 days after her first symptoms she died and a large haemorrhage at the caudate was found, with no evidence of active angiitis at that time. Haemorrhagic transformation of an infarct could have been the cause.

A case series published in 2014 describes 62 cases of confirmed or suspected VZV vasculopathy [1]. Brain imaging was abnormal in 84.4% of cases. The vast majority showed ischaemic lesions. Just one of their cases reported an isolated ICH, with a further new case of multifocal ischaemic and haemorrhagic lesions. 74.4% of those that underwent angiographic studies showed evidence of angiitis. 74.5% of 59 cases where lumbar puncture was performed had a leukocytosis in the CSF. 42 cases were tested for VZV IgG in the CSF, and 95.2% of these were positive. The authors did not state whether there was evidence of intrathecal VZV IgG synthesis in each of these cases, but they did recommend that a reduced serum/CSF ratio should be detected to demonstrate intrathecal synthesis in their discussion. In this case series VZV DNA detection was much less sensitive. DNA PCR was only positive in 46.1% of those tested.

Outside of this case series, we are aware of seven recent case reports of ICH in adults related to possible or likely VZV vasculopathy. Three of these were multifocal haemorrhages, one in an immunosuppressed patient [11], another in an immunocompetent patient [12] and a third in a patient with cerebral amyloid angiopathy with a high cerebral microbleed burden [13]. All three had either VZV DNA PCR or IgG detected in the CSF. Two out of three had clinical as well as laboratory evidence of encephalitis. Two out of three had evidence of vasculitis on MR angiography.

As mentioned in the introduction, there are just four reports of patients surviving an acute stroke and a single deep ICH likely caused by VZV vasculopathy (table 1). Three of these cases had a haematoma ipsilateral to HZO infection. The first, reported in 1987, declined to undergo cerebral angiography and the CSF analysis was not tested for VZV [3]. The second, from a dermatological journal in 2009 [4], had a CT angiogram but the authors did not comment on any evidence of vasculitis, simply stating that there was no aneurysm. This patient also did not undergo lumbar puncture. The third case from 2013 had normal intra-arterial digital subtraction angiography [5], much like our current case. However, this patient also did not undergo CSF examination, and he was significantly older at 66. The report does not state whether there was any leukoaraiosis as a possible alternative explanation for the ICH. In 2018 a 30-year-old man presented with headache and left sided weakness and was found to have a deep right basal ganglia ICH [6]. MR angiogram did not show any evidence of vasculitis. Unlike our present case this ICH was associated with primary chickenpox infection and the patient did not undergo DSA or CSF analysis.

VZV CSF DNA is positive in 30% of intracranial vasculopathy, therefore a negative result in our case was expected [2]. The gold standard test for confirmation of VZV intracranial vasculopathy uses indirect methods to demonstrate VZV-specific antibody response in the CSF by determining the viral antibody index, a modification of Reiber antibody index [14]. The reason for this is that specific IgG levels can be raised in the CSF when the blood-brain-barrier is impaired, as is the case with ICH. Therefore, their presence does not definitively indicate an infective process. Although we were able to show anti-VZV IgG antibody in the CSF we did not show a monoclonal intrathecal response to the virus. This could have been owing to the timing of the sampling. Increased IgG response can take 4-12 weeks to be detected, and our interval lumbar puncture was at 6 weeks. The timing of VZV reactivation and subsequent ICH occurring at a peak risk interval, as well as the lack of any alternative explanation for ICH after detailed investigation, points to a probable causal association between VZV and ICH. We found a mild mononuclear pleocytosis, providing some evidence of inflammation in the CSF. However, a mute CSF response in a definitive herpesvirus reactivation-associated stroke has been described before and does not deter from a potential link [15].

In summary, to the best of our knowledge this is the first report to describe likely VZV small vessel vasculopathy associated with isolated deep ICH, with detailed negative cerebral vessel imaging and presence of VZV IgG in the CSF. Since confirmed VZV vasculopathy does

not always cause a rash, future work should identify whether CSF analysis for VZV antibodies and IgG index is useful in the investigation of unexplained ("cryptogenic") ICH. We also suggest that further longitudinal studies should be carried out to determine the efficacy of VZV vaccination in preventing the neurological sequelae of infection with this virus.

Fig. 1 ***A*** T2-weighted fluid attenuated inversion recovery (FLAIR) MRI of the brain; ***B*** time-of-flight MR angiography of cerebral vessels; ***C*** intra-arterial digital subtraction angiography; ***D*** vesicular rash affecting ophthalmic branch of the left trigeminal nerve

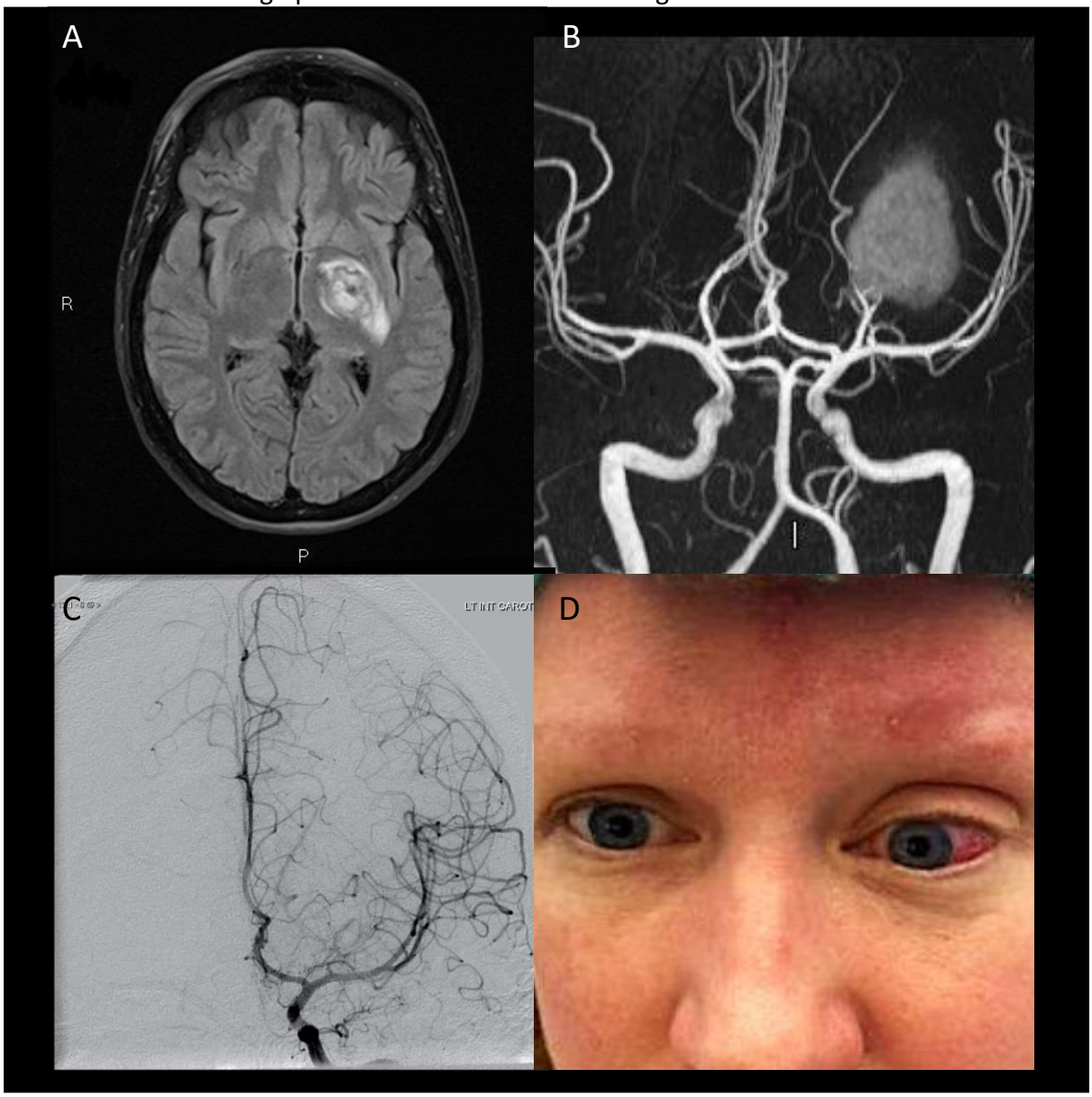

Table 1 Summary of cases most similar to our present case

Report	Clinical presentation	Imaging findings	CSF analysis
Mossuto-Agatiello *et al*, 1987 [3]	Left sided HZO with delayed right hemiparesis	Deep left basal ganglia ICH No dedicated vessel imaging	WCC 14, normal protein and glucose Varicella PCR or IgG not tested
Song *et al*, 2009 [4]	Right sided HZO, severe headache, vomiting and right facial pain	Deep right basal ganglia ICH CT angiogram negative for aneurysms, no comment on vasculitis	WCC 60, normal protein and glucose Varicella PCR or IgG not tested
Kim *et al*, 2013 [5]	Right sided HZO, with delayed left hemichorea	Deep right ICH affecting subthalamic nucleus DSA negative for aneurysms and angiitis	Not done
Harsha *et al*, 2018 [6]	Primary chickenpox infection with delayed headache and left sided weakness	Deep right basal ganglia ICH, acute caudate infarct MRI with contrast negative for angiitis	Not done
Present case	Left sided HZO with delayed right hemiparesis and hemisensory loss	Deep left basal ganglia ICH, centred on internal capsule MRI with contrast and DSA negative for angiitis	WCC 7, normal protein and glucose Varicella PCR negative Varicella IgG detected in CSF but serum / CSF Varicella IgG index negative

CSF cerebrospinal fluid, *HZO* herpes zoster ophthalmicus, *ICH* intracerebral haemorrhage, *WCC* white cell count, *PCR* polymerase chain reaction, *IgG* immunoglobulin G, *DSA* digital subtraction angiography, *MRI* magnetic resonance imaging

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