Case report

Varicella vasculopathy as a cause for stroke in a patient with diabetes – an uncommon cause for a common disorder

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Background

Varicella zoster is a humanotropic alpha herpes virus that causes two distinct diseases. The primary infection results in varicella (chickenpox). Then, the virus lies latent in the ganglionic neurons, becoming reactivated to cause herpes zoster when the host ages or becomes immunosuppressed.

It is estimated to cause neurologic complications in 1-3 per 10,000 cases[1]. Vascular disease following varicella infection encompasses a wide spectrum of presentations and arterial territory involvement – ranging from transient ischaemic attacks, acute strokes, aneurysms, subarachnoid and intracerebral haemorrhage, arterial ectasia and dissection, cerebral venous sinus thrombosis, spinal cord infarction, cranial neuropathy and peripheral arterial disease. A temporal arteritis mimicking giant cell arteritis has also been reported.

These can occur following either form of the infection, in both immune-competent and immune-compromised individuals. Though the exact incidence is unknown, several studies have indicated that there is an increased risk of stroke after varicella zoster[2].

Herein we report a female with stroke secondary to varicella vasculitis involving large intracranial vessels followed by a brief review of the literature.

Case report

A 67-year-old recently diagnosed diabetic woman presented seven weeks after acute onset painless left sided vision loss following herpes zoster of the left V2, T2, and T3 dermatomes a week prior. The left optic disc was pale, suggesting a late presentation of ischaemic optic neuropathy. She complained of memory impairment as well and was disoriented to time, but not to place or person. We also noted that she had a right sided hemiparesis with an MRC (Medical Research Council) scale of four with an extensor plantar on the right side though she did not specifically complain of weakness. The rest of her physical examination was normal.

Her inflammatory markers were normal, as were her full blood count, renal and liver functions. A left sided sub-acute haemorrhagic parieto-occipital infarct was seen on MR scan of the brain (Figure 1), with magnetic resonance angiography (MRA) showing absence of flow in the left internal carotid artery (ICA). The cerebrospinal fluid was haemorrhagic and showed high titres of anti varicella zoster IgG of 559.43 U/mL. Vasculitic screen including antinuclear antibodies, anti-neutrophil cytoplasmic antibodies and perinuclear neutrophil antibodies were negative. MR scan of the brain with black blood protocol failed to show vasculitic (intimal) changes which could be due to the late presentation.

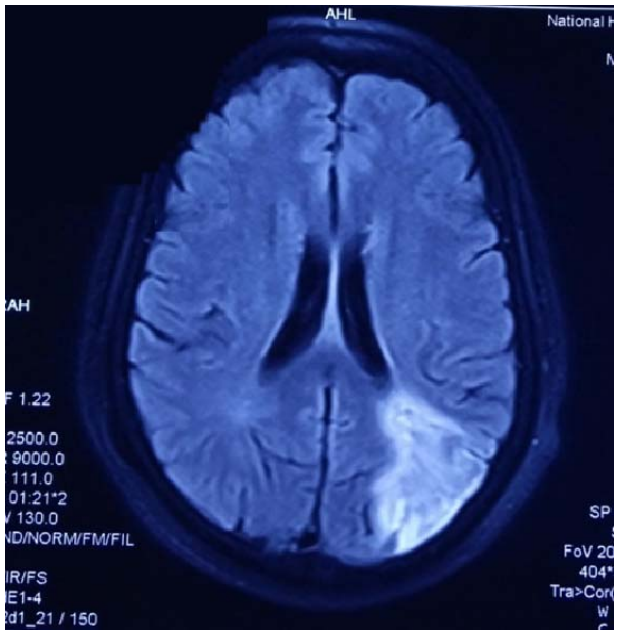

Figure 1. Subacute haemorrhagic left sided parieto-occipital infarct.

We treated her with a prolonged course of oral acyclovir and high doses of steroids following a presumptive diagnosis of varicella vasculopathy. However, though her clinical condition remained stable, her vision did not improve. A carotid doppler done two months later showed complete resolution of the thrombus with normal intima.

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Discussion

VZV (Varicella zoster virus) is thought to enter through the axons following either primary infection or reactivation to involve the cerebral arteries, which then undergo vascular remodeling resulting in thrombosis, dissections or aneurysms.

The presence of a multi-dermatomal rash suggestive of zoster within weeks of onset of the neurological symptoms, CSF pleocytosis and the presence of intrathecal production of varicella IgG in the CSF coupled with the presence of large artery involvement on imaging lends support to the diagnosis of varicella vasculitis in the above patient.

The infarct seen in our patient may represent an external (cortical) border zone or watershed infarct between the middle cerebral and posterior cerebral territory. Border zone infarction may be explained by invoking a combination of two often interrelated processes: hypoperfusion and embolization. Hypoperfusion, or decreased blood flow, is likely to impede the clearance (washout) of emboli in this case originating from the left internal carotid artery. This type of infarct occurs in 12.7% of all cerebral infarcts and may occur in situations involving severe systemic hypotension, such as when a person rises from the supine position, excess exercise, Valsalva's maneuvers, administration of antihypertensive drugs, bleeding, and anemia[3].

VZV causing strokes in adults has generally been described as a contralateral hemiplegia occurring weeks to months following herpes zoster of the ophthalmic division[4]. However, any arterial territory can be involved, and the manifestations can range from confusion and headache to hemi-sensory loss. A waxing and waning pattern is often recognised.

In a Taiwanese study, the risk of stroke increased by 30% within the following year in adults with zoster[2]. When zoster involved the ophthalmic distribution of the trigeminal nerve, the stroke risk increased 4.5 fold[2]. However it is important to note that in a study by Nagel et al.[5] one-third of patients with virologically verified VZV vasculopathy had no preceding rash.

Upon analysis of previously published reports of varicella vasculopathy causing ischaemic strokes in adults specifically (Table 1), at least half of those noted have been in immune-competent patients. A CSF pleocytosis can be an important pointer towards diagnosis especially in the absence of a rash, though this has been notably absent in cases six and seven, perhaps due to their immuno-compromised states.

A study of 30 subjects by Nagel et al. with virologically confirmed VZV vasculopathy[5] revealed a CSF pleocytosis in 67%. Haemorrhagic CSF can also be seen[6]. In nearly a third of the subjects in the above study, CSF contained VZV DNA. However anti-VZV IgG antibody was found in the CSF of 93% with reduced serum: CSF ratio of anti-VZV IgG confirming intrathecal antibody synthesis. Therefore detection of anti-VZV IgG antibody is considered a more sensitive diagnostic test compared to VZV DNA, since viral DNA is detected by polymerase chain reaction (PCR) in early disease and disappears late in the disease. VZV vasculopathy is often chronic and protracted and can occur on average four months after the rash which would make testing for anti VZV IgG more prudent. The longest period noted in the cases we have analyzed was six months. Intrathecal anti VZV IgG was detected in high titres in our patient which confirmed the diagnosis.

Brain imaging is abnormal in upto 97% cases of varicella vasculopathy[5]. MR scan of the brain may reveal superficial or deep, grey or white matter lesions – however lesions at the grey-white matter junction is considered more suggestive[7]. The lesions can also be haemorrhagic as seen in our patient. Angiographic abnormalities such as stenosis and occlusion were seen in upto 70%, with large and small arteries involved in 50%, small arteries only in 37% and large arteries only in 13%[4]. Any arterial territory can be involved. Multifocal involvement is also seen. The absence of angiographic abnormalities does not preclude the diagnosis, however normal brain imaging strongly argues against the diagnosis. Black blood MRI is a newer modality[8] that has been deemed useful though we did not demonstrate intimal changes in our patient.

A histopathological study of varicella vasculopathy suggested the presence of VZV antigen in the arterial adventitia in early VZV vasculopathy and in the media and intima of protracted cases of VZV vasculopathy. This supports the notion of virus persistence in the artery and spread from the "outside-in"[9]. The authors also demonstrated a thickened arterial intima composed of myofibroblasts and cells most likely of medial smooth muscle origin; a disrupted internal elastic lamina and a disrupted medial layer with a significant loss of normal smooth muscle cells. These changes help to explain why there is arterial occlusion and loss of vascular contractility, contributing to stroke.

Treatment of strokes due to varicella includes intravenous acyclovir for 14 days and oral prednisolone at 1mg/kg daily in immunocompetent patients, while those who are immunocompromised may need a longer course of antivirals[10]. Though our patient received oral acyclovir and steroids there was no clinical improvement. The treatment may have stabilized the course of her illness however.

Table 1.

Case	Age (Y)	Sex	Relevant underlying disorders	Rash	Rash to neurologic symptoms and signs	Neurologic symptoms and signs to virologic analysis	CSF pleocy-tosis	RBC in CSF	MRI/ CT focal lesions	Focal vascular abnor-malities	Artery involve-ment	CSF	VZV	Reduced serum/ CSF ratio of VZV IgG	Refer-ence
												DNA	IgG		
1	73	M	None	-	NA	4W	+	+	+	+	Large	NA	+	NA	(1)
2	54	M	AIDS	-	NA	3d	+	+	+	ND	Small	+	+	+	(2)
3	34	M	AIDS	+	6m	3w	+	+	+	ND	Small	-	+	+	(2)
4	42	M	None	-	NA	10-14d	+	-	+	+	Mixed	-	+	+	(3)
5	28	M	HIV, Hep C	-	NA	3 m	+	-	+	-	Mixed	+	+	+	(4)
6	71	M	Leukemia	+	1 m	6 m	-	+	+	+	Large	-	+	+	(5)
7	51	F	CREST syndrome	-	NA	2 m	-	+	+	+	Mixed	-	+	+	(6)
8	36	M	HIV	+	7 d	14 d	+	NA	+	+	Mixed	+	+	+	(7)
9	39	M	-	+	1 w	NA	+	NA	+	+	Large	-	-	ND	(8)
10	51	M	Glomerulo nephritis ǂ	+	2w	NA	+	NA	+	ND	NA	-	+	ND	(9)
11	61	M	-	+	4 w	NA	ND	NA	+	+	Small	ND	ND	ND	(10)
12	48	M	-	+	6 w	NA	ND	NA	+	+	Large	ND	ND	ND	(10)
13	55	F	-	+	6 w	NA	ND	NA	+	-	Small	ND	ND	ND	(10)
14	62	M	-	+	2 d	NA	ND	NA	+	+	Large	ND	ND	ND	(11)
15	67	F	DM	+	1w	8W	+	+	+	-	Mixed	ND	+	ND	Present case

Table redrawn from Nagel et al, with emphasis on cases that included ischaemic stroke as a presentation. Cases 1-10,15 are virologically proven definite cases of varicella vasculopathy. Cases 11-14 are of possible varicella vasculopathy.

Abbreviations: Y = Years, AIDS = Acquired Immunodeficiency syndrome, Hep C = Hepatitis C, CREST = Calcinosis, Raynaud's phenomenon, oesophageal dysmotility, sclerodactyly, and telangiectasia, DM = Diabetes Mellitus, ND = Not done, NA = Not available, ǂ = Antineutrophilic cytoplasmic antibodies - associated pauciimmune glomerulonephritis.

In our patient, the stroke could have been attributed to her already existing vascular risk factor. However, the sequence of events in her clinical course led to the diagnosis of varicella vasculopathy as the eventual cause for stroke. This enabled us to extend her treatment options.

To complicate matters further, diabetes may be an independent risk factor for varicella vasculopathy even without a history of zoster infection in the past. In a study of cerebral arteries obtained from 4 subjects with diabetes and no history of zoster infection, transient ischemic attacks, stroke, or immunosuppression, less than 24 hours after they died, inflammation was found in the arterial adventitia in the temporal artery due to varicella with the presence of VZV DNA in one patient[11]. The authors concluded that it may be prudent to consider VZV vasculopathy as an additional cause of stroke in people with diabetes, particularly since it is treatable.

We believe a neurological event temporally related to a recent varicella zoster infection should alert the clinician to the possibility of varicella vasculopathy – especially in the absence of vascular risk factors and among immunocompromised individuals. Absence of the rash of zoster infection preceding the neurological

Box 1.

When to suspect varicella vasculopathy in a patient with stroke?

1. If a history of antecedent rash of varicella zoster is present in a patient presenting with stroke.
2. In the absence of a rash consider in an immuno-compromised state especially in the presence of diabetes.
3. If MR scan of brain demonstrates lesions in the grey-white matter junction or if lesions are haemorrhagic.
4. If an unusual sequence of neurological events occur with waxing and waning pattern.
5. CSF demonstrates pleocytosis or is haemorrhagic.

symptoms does not preclude a diagnosis of varicella vasculopathy. Diabetes may be an independent risk factor for varicella vasculopathy. In these cases, CSF pleocytosis and compatible brain imaging may be useful in making a definitive diagnosis (Box 1).

It is important to have a high index of suspicion and to be aware of important ancillary features in clinical presentation and brain imaging in varicella associated vasculopathy to aid in correct diagnosis.

References

1. Guess HA, Broughton DD, Melton LJ, et al. Population-based studies of varicella complications. *Pediatrics* 1986; **78**(4 Pt 2): 723-7.
2. Kang JH, Ho JD, Chen YH, et al. Increased risk of stroke after a herpes zoster attack: a population-based follow-up study. *Stroke* 2009; **40**(11): 3443-8.
3. Yong SW, Bang OY, Lee PH, et al. Internal and cortical border-zone infarction: clinical and diffusion-weighted imaging features. *Stroke* 2006; **37**: 841-6.
4. Reshef E, Greenberg SB, Jankovic J. Herpes zoster ophthalmicus followed by contralateral hemiparesis: report of two cases and review of literature. *J Neurol Neurosurg Psychiatry* 1985; **48**(2): 122-7.
5. Nagel MA, Cohrs RJ, Mahalingam R, et al. The varicella zoster virus vasculopathies: Clinical, CSF, imaging, and virologic features. *Neurology* 2008; **70**(11): 853-60.
6. Gilden D, Cohrs RJ, Mahalingam R, et al. Varicella zoster virus vasculopathies: diverse clinical manifestations, laboratory features, pathogenesis, and treatment. *The Lancet Neurology* 2009; **8**: 731-40.
7. Nagel MA, Mahalingam R, Cohrs RJ, et al. Virus vasculopathy and stroke: an under-recognized cause and treatment target. *Infect Disord Drug Targets* 2010; **10**(2): 105-11.
8. Tsivgoulis G, Lachanis S, Magoufis G, et al. High-Resolution Vessel Wall Magnetic Resonance Imaging in Varicella-Zoster Virus Vasculitis. *J Stroke Cerebrovasc Dis.* 2016; **25**(6): e74-6.
9. Nagel MA, Traktinskiy I, Azarkh Y, et al. Varicella zoster virus vasculopathy. *Neurology* 2011; **77**(4): 364 LP-370.
10. Nagel MA, Gilden D. Update on varicella zoster virus vasculopathy. *Curr Infect Dis Rep.* 2014; **16**(6): 1-8.
11. Nagel MA, Traktinskiy I, Choe A, et al. Varicella-zoster virus expression in the cerebral arteries of diabetic subjects. *Arch Neurol* 2012; **69**(1): 142-4.