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Varicella zoster virus reactivation antedating ipsilateral brainstem stroke

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Abstract

Varicella zoster virus (VZV) infection and reactivation are associated with a number of neurologic conditions. Unifocal large vessel infarcts may follow zoster in the trigeminal or cervical distribution as a result of transaxonal transport of virus from trigeminal or cervical afferent fibers that innervate vessels. Ophthalmic zoster (HZO) might cause ophthalmoplegic syndromes, with secondary optic neuritis. Mechanisms include local orbital muscle inflammation and, viral spread from the ophthalmic branch of the fifth nerve with associated vasculopathy. A 72-year-old man developed a vesicular rash in the territory of C5-T5-6. Within four weeks, the patient developed headache, dysphagia, left facial and extremity ataxic weakness. Magnetic resonance imaging (MRI) revealed a right pontine infarction. A 66-year-old woman presented with right-sided painful HZO. One week later she developed complete external ophthalmoplegia and blurred vision. MRI showed ill-defined signal alteration in the retrobulbar tissue. Three weeks later, the patient was admitted because of dysarthria, deviated tongue, left-sided limb weakness, and tactile hypoesthesia. Spinal fluid contained 23 lymphocytes/mm³ and increased protein. The serum contained antibodies to VZV IgG and IgM in both cases. The patients received intravenously acyclovir with improvement. This report confirms unusual occurrence of ipsilateral brainstem stroke after VZV reactivation in immunocompetent subjects.

Keywords: varicella zoster reactivation, viral spread; pontine stroke, cervical rash, ophthalmic zoster, vertebrobasilar circulation

Introduction

Varicella zoster virus (VZV) is an exclusively human neurotropic alpha-herpesvirus. Primary VZV infection causes varicella (chickenpox). Thereafter, the virus becomes latent in ganglionic neurons along the entire neuraxis [1-10]. Decades later, when VZV specific cell-mediated immunity declines with age, the virus may reactivate, usually leading to zoster with dermatomal distribution, pain, and rash. VZV infection and reactivation can be complicated by serious neurological diseases, such as delayed vasculopathy [1-10]. The incidence and severity of VZV is best viewed as relating to a continuum ranging from a natural decline in VZV-specific immunity with advancing age to more serious host immune deficits, as encountered in organ transplant recipients and patients with cancer [1-7]. Grose [11] suggested heightened risk for ischemic stroke following recent HZO.

Having experienced two cases of VZV with an associated ischemic lesion in the posterior circulation, we offer some comments on the pathogenesis of VZV-related vascular events. Maurya et al. [1] recently described three patients; two had stroke within a span of 4 to 6 weeks of herpes zoster ophthalmicus (HZO), whereas the third patient had the rash in a cervical dermatome.

Case Synopsis

Case 1

A 72-year-old normotensive man developed a typical vesicular rash in the right C5-6 to T5-6 dermatomes. Despite treatment with acyclovir (800mg, 3 times daily for two weeks), zoster spread to C3-4. Within 4 weeks, the patient was admitted to the hospital because of temporal headache and waddling gait. Neurological examination showed a flattened left nasolabial fold, halting speech, dysphagia, tongue weakness, left-sided ataxic hemiparesis, and ipsilateral loss of touch in the face and upper arm. Laboratory tests ruled out a variety of infections, including cytomegalovirus (CMV), hepatitis C, *Mycoplasma pneumoniae*, and Lyme disease. Negative or normal tests included erythrocyte sedimentation rate, C reactive protein, and antinuclear antibodies. IgM and IgG antibodies to VZV were evaluated in serum and CSF by commercial the enzyme-linked immunoabsorbent assay (ELISA, Heath care Diagnostic Products GmbH, Marburg, Germany and Enzygnost). By day 20 after the onset of neurological signs and symptoms, the serum antibodies to VZV were 1.50 IgG and 0.17 IgM. Antibody values were expressed as absorbance value; cut off for positive results, both for IgG and IgM was 0.20 and borderline value was 0.11-0.20. Spinal fluid (CSF) was acellular which showed increased protein (48 mg/dl, normal < 40). Brain MRI revealed a T2 hyperintense lesion in the right pons, compatible with ischemic stroke. Our patient received intravenous acyclovir (15mg per kg, 3 times daily for 7 days). His neurological deficits improved within 4 weeks.

Case 2

A 66-year-old woman developed painful HZO over the first division of the right trigeminal nerve for which she received acyclovir 800mg, 4 times daily for 10 days. Within a week, she developed ipsilateral complete external ophthalmoplegia, ptosis, and diplopia in either direction, followed by blurred vision in the same eye. Sensory examination revealed hyperesthesia over the right ophthalmic division of the 5th nerve. Visual-evoked responses showed prolonged P100 latency in the right side (130msec, normal <110) suggestive of a retrobulbar optic

neuritis. MRI revealed a right proptosis with ill-defined infiltration of retrobulbar soft tissues, surrounding the optic sheath; the optic nerve was mildly swollen. Three weeks later, the patient was newly admitted for evaluation of mild dysarthria, left facial droop sparing forehead, loss of taste, tongue deviation towards left, weakness in the left upper limb, diminished tactile sensibility in the arm, and extensor plantar responses. Deep reflexes were brisk on both sides. Her hemogram, blood sugars, renal function tests, lipid profile, and liver function tests were normal; the echocardiography and doppler for carotids were normal. **On ELISA, the serum antibodies to VZV IgG was 2.59 and IgM was 0.24 (absorbance, positive results >0.20).** Spinal tap yielded a colorless fluid that contained 23 lymphocytes/mm³, increased protein (60 mg/dl), normal glucose, and a few oligoclonal bands. CSF proved negative for HSV1, HSV2, and VZV DNA, whereas CSF VZV IgG was 0.51 Abs. This finding in the CSF was considered a further indicator of a VZV related disorder. Repeated MRI revealed a right pontine stroke. Our patient received intravenous dexamethasone for 5 days and acyclovir (15mg per kg, 3 times daily for 10 days). Her neurological deficit improved.

Case Discussion

Clinical, neuroradiological, and serological features in our patients suggested a VZV-related vasculopathy after viral reactivation. The diagnosis was easy to establish on account of the typical recent vesicular eruption. Both cases were promptly diagnosed and treated until complete resolution of the neurologic deficits. In the first patient, VZV infection developed in a cervical distribution, followed possibly by a vasculopathy in an ipsilateral pontine branch of the basilar artery, which could be secondary to viral spread via cervico-vascular connections. In our second patient, the HZO was followed by a sudden loss of vision in the right eye, suggesting an ischemic optic neuropathy. Furthermore, her stroke was unequivocally and temporally associated with HZO, suggesting that the cranial artery vasculopathy could arise from direct spread of the VZV infection via afferent branches of

the ophthalmic branch of the trigeminal nerve and hematogenous dissemination [5, 8-10].

VZV is the only human virus that has been proven to replicate in cerebral arteries [1-7, 9]. Concerning pathogenesis, several authors suggested a direct infection of cerebral arteries and, venous sinuses via transaxonal spread from neural ganglia of cranial and peripheral nerves, leading to inflammatory and noninflammatory changes including thrombosis, vessel wall necrosis, dissection, and aneurysm [1, 5]. The notion that virus spreads transaxonally after reactivation from trigeminal and other cranial nerve ganglia is supported by the demonstration that afferent fibers from trigeminal ganglia reach intracranial blood vessels, venous sinuses, and dural structures [1-4, 6]. This mechanism could also explain the pathogenesis of stroke after HZ located outside the head and neck, particularly in the presence of other proinflammatory or immunosuppressive conditions, which might increase together with the lifetime risk of vascular events [1]. The discovery in recent years that VZV DNA can be detected in saliva and blood in subjects whose rash is outside the head and neck and are even asymptomatic may provide an explanation for asymptomatic reactivation of VZV from latency, even in absence of cutaneous rash [1]. Most unifocal infarcts associated with VZV infection

occur in the distribution of the carotid, anterior, or middle cerebral arteries; this was demonstrated by the report of Maurya et al. [1]. Bourdette et al. [8] reported a series of cases with acute cerebral infarction owing to arteritis affecting the anterior circulation ipsilateral to an outbreak of HZO. The involvement of the posterior circulation as in our two patients is very uncommon. A 3-year-old child with history of medulloblastoma resection developed a posterior pontine stroke one year after thoracic herpes zoster [7]; Filloux et al. [4] in a case of cerebellar infarction suggested a role of trigeminal vascular projections from the ophthalmic division to the superior cerebellar arteries. Furthermore, Snow et al. [2] proposed a direct viral invasion causing focal vasculitis and subsequent brainstem infarction. Patrick et al. [6] described a pontine infarction related to viral migration from C2 dorsal root ganglia with related angiitis and thrombosis in the vertebrasilar circulation. This view was supported by other authors [6], who showed that bilateral removal of feline C1-3 dorsal root ganglia decreased the concentration of substance P in cerebellar, basilar, and vertebral arteries. In patients who underwent pathological examination, a granulomatous angiitis of the basilar artery was demonstrated [5]. Table 1 summarizes the clinical features of patients with VZV

Table 1. Recent cases of delayed stroke in the vertebrasilar circulation after VZV infection/reactivation.

Reference	Age/Sex	Location of zoster rash	Site of stroke	Delay before stroke onset	
Linnemann et al. [9]	20/M	R. HZO with dissemination	Pons, medulla oblongata, cervical cord	3 weeks	
Filloux et al. [4]	79/M	L. HZO	L. cerebellum, L. brainstem	2 weeks	
Ojeda et al. [5]	71/M	R. cervical C 2	R. pons, middle cerebellar pedicle	1 month	
Snow et al. [2] ²	61/F	R. cervical C2	Pons paramedian	5 weeks	
Ross et al. [3]	49/F	L. cervical C2	Bilateral pons	1 month	
Patrick et al. [6]	56/M	L. cervical C2	Bilateral pons, R. tegmentum	5 weeks	
Fukutake et al. [10]	32/M	L. HZO	L. pons, midbrain	8 weeks	
Chiang et al. [7]	3/M	L. trunk	Posterior pons	1 year	
Present study	case 1	72/M	R. cervical C5 to Th5-6	R. pons	1 months
	case 2	66/F	R. HZO	R. pons and chronic basal ganglia lacunae	5 weeks

R: right; L: left; VZV: varicella zoster virus; HZO: herpes zoster ophthalmicus

associated vasculopathy and strokes in the vertebrobasilar circulation.

Conclusion

VZV vasculopathy is an important cause of stroke; neurologists and dermatologists should be aware of such conditions, which needs to be readily identified

for proper treatment. With regard to anti-viral treatment, Grose [11] suggested that since stroke occurs more commonly after HZO, there may be value in a clinical trial to test whether a longer treatment than a one-week regimen with valacyclovir will reduce the likelihood of subsequent stroke. This notion might be especially useful for dermatologists who see the patients initially.

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