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Letter to the Editor: New Observation

Herpes Simplex 2 Encephalitis and Acute Retinal Necrosis

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This case illustrates the importance of establishing a correct diagnosis of optic neuritis (ON) and timely consideration of alternative etiologies in patients who lack typical imaging findings.

A 27-year-old Caucasian, healthy and immunocompetent female presented to the local hospital emergency department with 1-day history of left eye pain and vision loss, after seeing her optometrist who described unspecified "inflammation of the optic nerve." Initial examination identified decreased visual acuity to finger counting, red color desaturation, with full visual fields, and no observed anterior segment abnormalities in the left eye; right eye examination was within normal limits. She had no fever, headache, nausea, nuchal rigidity, or focal neurological signs. Following phone consultations with neurology and ophthalmology, she was started on prednisone 1250 mg oral daily for 3 days for presumed ON.

Two days later, magnetic resonance imaging (MRI) (Figure 1A) showed bilateral T2 signal abnormalities in both anterior temporal lobes, sparing optic nerves.

She returned to medical attention on day 9, with precipitous worsening of left eye visual acuity, severe ocular pain, fever, headache, frequent vomiting, and neck stiffness. She also noticed reappearance of a vesicular rash on her left buttock. She was transferred to our tertiary care center. On admission, her examination showed unilateral ocular findings, with left eye visual acuity of 20/800, left relative afferent pupillary defect (RAPD) of the left eye, and left chemosis. There was a mild degree of nuchal rigidity; Kernig and Brudzinski signs were negative. No other focal neurological deficits were noted; Montreal cognitive assessment (MoCA) score was 23/30. Prednisone was stopped, and she was started on IV acyclovir 10 mg/kg q8h for 21 days for presumed viral encephalitis. She received two doses of acyclovir before lumbar puncture cerebrospinal fluid (CSF) was sent for human herpesviruses.

Urgent ophthalmological assessment revealed unaided visual acuity of 20/20 in the right eye and hand motions in the left eye, which did not improve with pinhole. The intraocular pressure was 8 mmHg in the left eye and 13 mmHg in the right. Anterior segment examination of the left eye showed signs of inflammation, including conjunctival injection, corneal edema, posterior synechiae, anterior chamber cells (grade 1+), and flare (grade 1+). Dilated fundus exam was limited by vitreous haze (grade 3+) and poor dilation, but patches of hypopigmented retina consistent with occlusive vasculitis were noted in the superonasal and inferotemporal retina. Examination of the right eye was within normal limits. Given the evidence of anterior segment inflammation, vitritis, and retinitis, a diagnosis of acute retinal necrosis (ARN) secondary to herpes simplex virus (HSV)-2 was given, and an anterior chamber paracentesis for polymerase chain reaction (PCR) was performed along with an intravitreal injection of 400 mcg of ganciclovir.

Repeat MRI on day 10 post-symptom onset showed abnormal subcortical white matter signal in the temporal lobes (Figure 1B). CSF revealed one nucleated cell and eight red blood cells. Protein was 166 mg/L, negative for bacterial and fungal cultures. CSF tested negative/normal for cryptococcus, enterovirus, acid-fast bacilli, angiotensin-converting enzyme, cytology. Despite aqueous humor PCR revealing presence of HSV-2 infection, CSF PCR results were negative. A skin swab of the vesicular lesion also confirmed the presence of HSV-2 via PCR. Serum was negative/normal for human immunodeficiency virus (HIV), syphilis, West Nile virus, flavivirus, lyme, HSV, VZV, toxoplasmosis, cat-scratch fever, hepatitis B, aquaporin-4, myelin oligodendrocyte glycoprotein, dsDNA, ANA, ACE; vitamin B12 levels were 368 pmol/L.

Given her bilateral anterior temporal lobe enhancement and cognitive impairment, she was treated as presumed HSV-2 encephalitis. Negative CSF was attributed to the antiviral regimen having been started before lumbar puncture.

Ultimately, she developed a macula-on retinal detachment (RD) in the left eye 5 days after the first intraocular ganciclovir injection. She underwent a successful pars plana vitrectomy for RD repair with silicone. On discharge, vitritis had resolved and the eye remained quiet with no inflammation and no indication of active ARN. Her right eye remained healthy and despite the delays in initiating treatment never developed evidence of inflammation or infection. MoCA improved to 27/30. At 1-month post-op, left eye vision was at counting fingers, retina flat under oil with inactive retinitis. Silicone was removed after 8 months; post-op she

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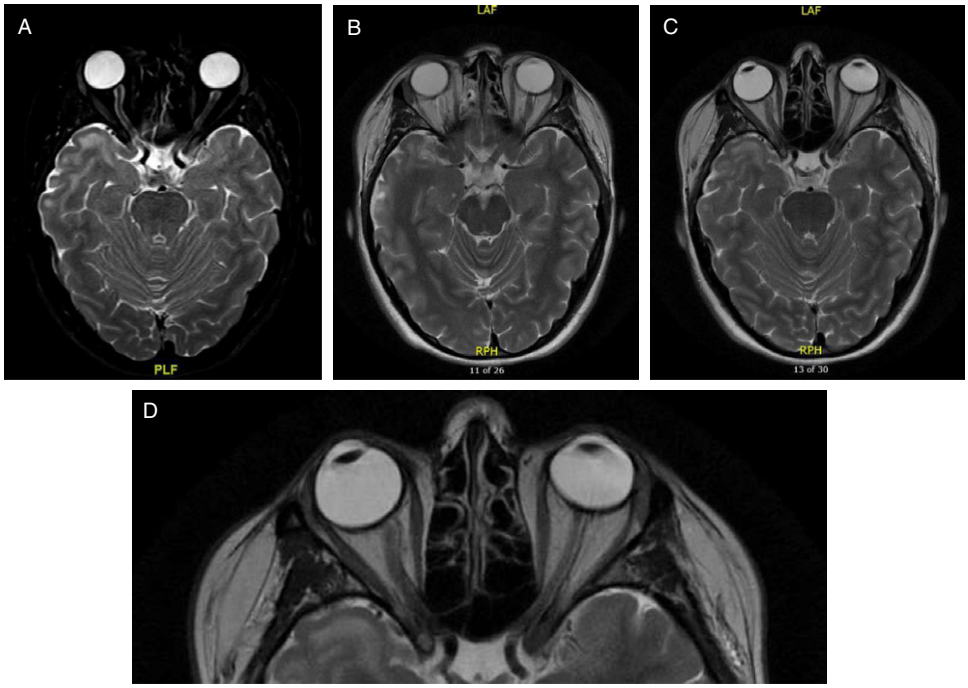

Figure 1: (A) Day 4, axial T2 MRI: No significant abnormality noted within the orbits, but extensive bilateral abnormal T2 hyperintensity in the white matter of the anterior temporal poles. No abnormal contrast enhancement is identified (not shown). (B) Day 16, axial T2 MRI: Abnormal subcortical white matter signal in the temporal poles, right more than left with mild fullness, with subtle focal enhancement on the right (not shown). Mild thickening and increased T2 signal in the left ON in the orbit. Somewhat oblique cut of the slice explains why the right ON appears obscured. (C and D) Eight-month follow-up, axial T2 MRI: Stable to minimally decreased extent of signal abnormality in the subcortical white matter of the anterior temporal lobes, more so on the right. Atrophic left ON with subtle associated signal abnormality. Abbreviations: MRI – magnetic resonance imaging, ON – optic nerve.

developed significant cataract, vision at hand motions, and low intraocular pressure (2 mmHg). At a 2-year follow-up, she had a shallow RD. Due to persistent hypotony (3 mmHg) and significant associated risks, repeat surgical intervention was not warranted.

MRI showed interval development of left optic nerve atrophy (Figure 1D) and minimally decreased T2 signal abnormality in the white matter in the anterior temporal lobes, more so on the right (Figure 1C).

This case highlights the need for a proper fundoscopic examination prior to initiating corticosteroids. In addition, we present two relatively rare complications of HSV-2 infection co-occurring in a single patient: HSV-associated encephalitis and ARN. The most common cause of infectious encephalitis is HSV.[1] HSV encephalitis is a known risk factor for ARN and current literature endorses a brain-to-eye transmission of HSV.[2] However, the vast majority of ARN cases occur in isolation, without any other CNS complications, and few reports describe ARN with encephalitis.[3–5] ARN is characterized by acute panuveitis and occlusive vasculitis picture, which may progress to diffuse necrotizing retinitis and RD.[6] Symptoms of ARN may mimic ON; however, ARN and ON may be easily differentiated with fundoscopic examination. Fundoscopic features of ON include swelling of the optic disk (papillitis), or involvement of the optic nerve sheath (perineuritis) or optic disk edema (neuroretinitis), none of which occur in patients with ARN; in cases of retrobulbar neuritis, optic disk may have a normal appearance.[7] In addition, ON does not have an association with vitreous cells and inflammation. ARN carries a high risk of RD and subsequently, poor visual prognosis, especially when diagnosis is delayed, due to rapid disease progression and in some instances bilateral involvement over time.[6] The development of any ocular symptoms in the setting of non-ocular manifestations of HSV or VZV should therefore be immediately referred for urgent ophthalmology assessment due to the risk of ARN.

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Son, Maksim	Department of Clinical Neurological Sciences, Western University, London, ON, Canada	Gathered data, wrote and reviewed the manuscript
Bessemer, Robin	Department of Clinical Neurological Sciences, Western University, London, ON, Canada	Gathered data, co-wrote the manuscript
Vinokurtseva, Anastasiya	Schulich School of Medicine, Western University, London, ON, Canada	Gathered data, co-wrote the manuscript
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Morrow, Sarah	Department of Clinical Neurological Sciences, Western University, London, ON, Canada	Conceived the study, reviewed the imaging and manuscript.

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