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Case report

Immunologic factors may play a role in herpes simplex virus 1 reactivation in the brain and retina after influenza vaccination

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ABSTRACT

Herpes simplex virus 1 (HSV-1) is a nearly ubiquitous human pathogen, remaining dormant in its human host the majority of the time. The interaction between HSV-1 and the immune system represents a complicated balance of power that allows the virus to persist in the host for a lifetime. However, disruptions in the immune system can activate the virus with the potential to cause devastating infections in the central nervous system (CNS). We present a patient who suffered three consecutive yearly HSV-1 CNS episodes (encephalitis, seizure, and retinitis), each within days of his influenza vaccination. We highlight subtle immunologic defects in this patient that may have allowed unchecked viral replication and resultant disease manifestations, as well as the potential role of influenza vaccine in tipping this balance in favor of HSV-1.

Introduction

Between 52% and 84% of the human adult population is latently infected by HSV-1 [1]. The large double stranded DNA virus maintains lifelong infection by establishing a predominantly latent infection within the trigeminal ganglia that is punctuated by recurrent episodes of productive replication, or reactivation, that results in clinical disease and dissemination of virus either within the host or to new hosts. Rare manifestations of HSV-1 reactivation include Herpesvirus encephalitis (HSE) and acute retinal necrosis (ARN).

We present a case of HSV-1 HSE followed by post-HSE encephalitis or seizure and HSV-1 ARN in which HSV infection or reactivation was temporally associated with administration of influenza vaccination in three consecutive years.

Case presentation

A 47-year-old male with insulin-dependent diabetes mellitus, hypertension and dyslipidemia presented to an outside hospital in November of 2012 with acute fever, aphasia and dysnomia as well as a several day history of weakness, malaise and hiccups. He was tachycardic and laboratory evaluation revealed a leukocytosis (12,400/mm^3) without bandemia as well as hyponatremia (129 meq/L), hypochloremia (93 meq/L) and hyperglycemia (270 mg/dL). He was admitted to the ICU for sepsis and dehydration. His lumbar puncture revealed clear fluid with elevated WBC (7), RBC (271) and glucose (188), normal protein and no organisms.

An MRI of his brain revealed edema of the left temporal lobe and pre-insular cortices without enhancement. His EEG demonstrated bilateral temporal lobe slowing without epileptiform changes, prompting treatment with intravenous acyclovir for presumed HSV encephalitis. His CSF PCR was positive for HSV-1 DNA at 100 copies/ml and negative for HSV-2.

An MRI, repeated two weeks later, showed enhancement of the left temporal lobe and bilateral insular cortices (Fig. 1 top left and top right). His anti-herpetic therapy was transitioned to foscarnet 6 g IV BID and his condition improved. He was discharged to a rehabilitation facility after one month and experienced a good recovery.

His medical history was notable for cold sores as a child as well as an influenza vaccination ten days prior to this presentation (Fluvarix, 2012–2013 formula, GlaxoSmithKline, London, England). He tested negative for influenza A or B. His absolute lymphocyte counts were consistently low throughout his hospitalization, between 400 and 800/mm^3 (normal range 1300–3600/mm^3).

The patient presented eleven months later with aphasia and dysnomia three days after receiving an influenza vaccination (Agriflu, 2013–2014 formula, Novartis, Basel, Switzerland). He was

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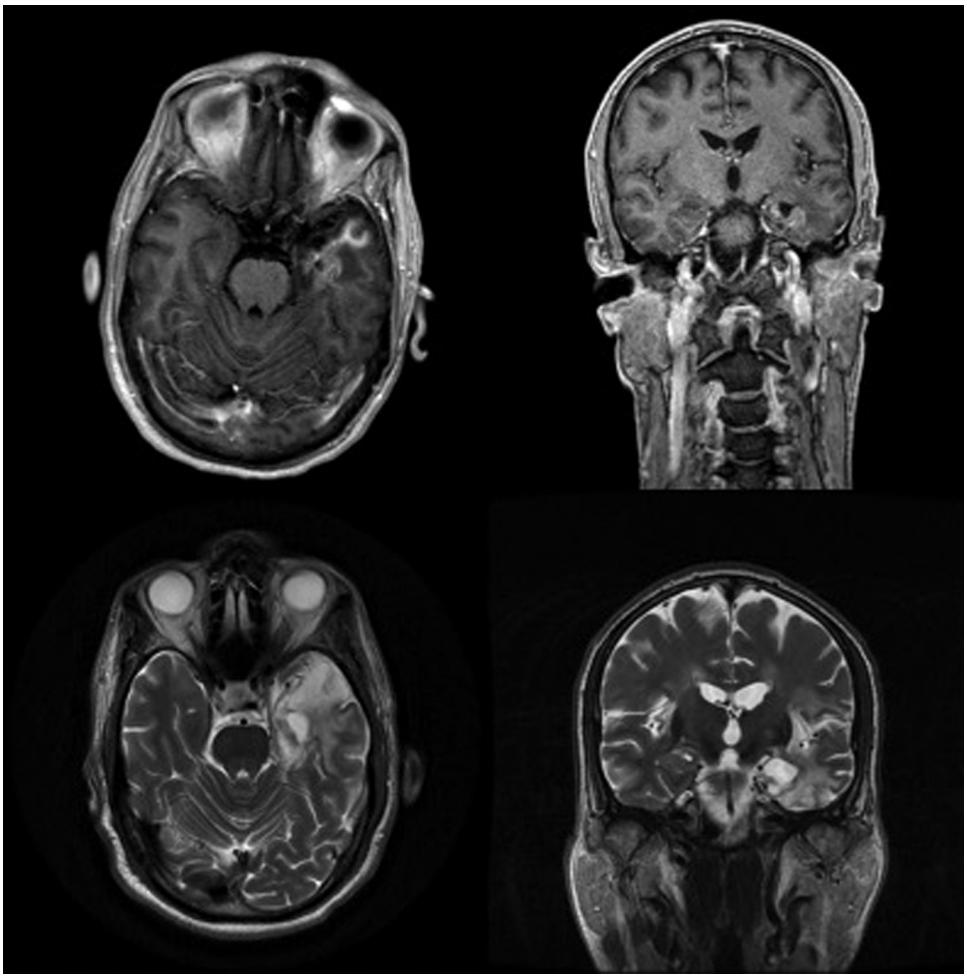

Fig. 1. Herpes simplex encephalitis. MRI brain at one month (top left, top right) and one year (bottom left, bottom right) following the initial presentation. T1 with contrast axial (top left) and coronal (top right) images taken one month after the initial presentation showing enhancement in the left temporal lobe and subinsular cortex as well as signal abnormality in the right and left insular cortices. T2 without contrast axial (bottom left) and coronal (bottom right) images taken at one year when the patient presented with transient recrudescence of his symptoms.

afebrile with a normal total leukocyte count, however his lymphocyte count was again low at 1100/mm^3. His symptoms resolved within hours without anti-viral treatment and a non-contrast MRI demonstrated only left temporal lobe encephalomalacia (Fig. 1 bottom left and bottom right), which was felt to be sequelae of his prior HSE. EEG demonstrated bilateral temporal slowing without epileptiform discharges. This episode was diagnosed as a temporal lobe seizure related to structural compromise and he was started on prophylactic levetiracetam (Keppra; LEV) at 500 mg BID.

One year later, he developed eye pain, tearing and loss of vision in the left eye one day after receiving influenza vaccination (Fluzone, 2014–2015 formula, Sanofi Pasteur, Paris, France). On presentation two days later, his vision was limited to hand motion and he had a left afferent pupillary defect, conjunctival hyperemia, optic nerve and retinal edema and scattered retinal hemorrhages. He was referred to our retina service the following day, at which time his vision had deteriorated to light perception only. His fundus exam revealed mild vitritis, retinal whitening, vascular sheathing and peripheral choroidal effusions (Fig. 2 left). Fluorescein angiography demonstrated occlusive vasculitis (Fig. 2 right).

An aqueous fluid sample was sent for PCR and the patient was empirically treated for viral retinitis (acute retinal necrosis) with intravitreal foscarnet (2.4 mg/0.1 ml), subtenon's triamcinolone (40 mg) and oral valacyclovir (1000 mg BID). The aqueous fluid PCR was positive for HSV-1 (150,000 copies/mL) and negative for HSV-2, VZV and CMV. Four days later, his visual acuity was still light perception although improvement was noted in his retinitis and vitritis. He was additionally treated with a 5-day course of oral prednisone at 60 mg daily.

Over the ensuing weeks severe retinal atrophy progressed with the development of several atrophic holes and the retina became totally detached. The patient underwent a pars plana vitrectomy, air-fluid exchange, endolaser and silicone oil fill. His vision improved to hand motion in the temporal field at one year, however his retina remains ischemic with a chronic inferotemporal detachment still under silicone oil tamponade. His exam also shows pallor of the optic nerve and severe vascular attenuation. He is being maintained on valacyclovir (500 mg daily) for life and has been advised to avoid future influenza vaccination.

Laboratory studies at this time again revealed decreased total lymphocytes 1200/mm^3 as well as CD4T cells at 461/mm^3 (normal 496–2186/mm^3), despite overall normal total leukocyte counts. His immunglobulin subset levels were normal and demonstrated good reactivity to influenza, tetanus and Varicella zoster.