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Case report

Ocular histopathology in Eastern equine encephalitis: A case report

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ABSTRACT

Purpose: To describe the ophthalmic symptoms and histopathological findings in a human case of Eastern equine encephalitis (EEE).
Observations: The patient was a septuagenarian male whose presentation and clinical course were thought to be most consistent with viral meningoencephalitis. ELISA suggested recent infection with EEE virus. Microscopic analysis of the brain demonstrated perivascular lymphohistiocytic cuffing which was consistent with viral type encephalitis. Similarly, both eyes manifested a lymphohistiocytic infiltrate in the retina and optic nerve and a reduced number of ganglion cells.
Conclusions and importance: To our knowledge, this is the first report of ophthalmological and ocular pathology observations in an EEE patient. Interestingly, the inflammatory findings in the retina are reminiscent of the central nervous system effects of EEE virus. These findings are relevant given the recent epidemic of microcephaly and ophthalmic complications secondary to another arboviral virus, the Zika virus.

1. Introduction

Eastern equine encephalitis (EEE) is an arboviral infection transmitted by mosquitos that is rarely symptomatic in humans, unless there is central nervous system involvement progressing to coma and death.[1,2] The life cycle of EEE virus in North America involves enzootic transmission among songbirds and mosquitos,[2] followed by transmission to horses and man (dead-end hosts).[2] The incubation period in humans typically ranges from 4 to 10 days.[3] The virus multiplies in the blood,[4] then it passes to the nasal mucosa and to the brain.[4,5]

Most patients have abrupt onset of high fever, chills, nausea, myalgias, and intense headache with neck stiffness.[3,6] Encephalitis ensues in 1–2 days, results in altered mental status and possibly impaired vision,[7] and progresses to coma and/or death.[6] Feemster and Haymaker (1958) included impaired vision as a possible sequel to eastern equine encephalitis.[7] In another form of arboviral infection that may result in encephalitis, Rift Valley fever, ocular manifestations are well-described.[8] The Zika virus has been recently shown to cause pathological changes in the retina and the optic nerve in the majority of affected infants.[9,10] However, no published ophthalmological observations in patients with EEE have been documented. We describe the first report of ophthalmic histopathological findings in a human case of EEE, which parallel the changes in the brain.

2. Case report

A septuagenarian man developed malaise, gait unsteadiness, left arm weakness, fever, vomiting, and headache. The patient was in good health prior to admission with the exception of medication-controlled hypertension. No prior ophthalmic records were available. On admission, the patient was lethargic but opening eyes to voice. His pupils were reactive, extraocular movements were full, and the corneal reflexes were intact. Computed tomography of the brain and blood cultures were unremarkable. Within 24 hours of admission, he no longer had oculocephalic movements but had a few cranial nerve functions that remained intact including small pupils and intact corneal reflexes. An ophthalmology consult was not performed due to his rapid deterioration. Within two days, he developed severe lethargy, left hemiplegia, a right gaze preference and a poor gag reflex. He was intubated for airway protection and admitted to the Intensive Care Unit. Computed tomography of the brain was again performed and demonstrated a linear band of low attenuation within the right external capsule, thought to represent infarction in the lenticulostriate distribution. Analysis of cerebrospinal fluid (CSF) revealed a moderate neutrophilic pleocytosis (73%

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neutrophils, 17% lymphocytes, 9% monocytes, glucose = 91, and protein = 96), but cultures of CSF and blood failed to identify any causative agent. The patient was treated empirically with ceftriaxone, ampicillin, doxycycline, and acyclovir for presumed meningoencephalitis. Electroencephalography revealed periodic lateralized epileptiform discharges within the right frontotemporal region, and the patient was empirically loaded with Dilantin, given the possibility of ongoing seizure activity.

The patient's hospital course was marked by a progressive decline in his level of consciousness and progressive neurologic impairment, with eventual loss of all brainstem reflexes. His course was also complicated by a left-sided pneumothorax, gastrointestinal hemorrhage, bilateral pulmonary edema, recurrent fevers, and septic shock. Consultants from the Division of Infectious Disease thought the patient's presentation and clinical course were most consistent with viral meningoencephalitis, and their differential diagnosis included West Nile virus, EEE, Western EE, St. Louis encephalitis, Cache Valley fever, LaCrosse virus infection, and rabies.

Magnetic resonance imaging (MRI) of the brain two days after admission to DUMC demonstrated diffuse signal enhancement within the leptomeninges, brainstem, basal ganglia, and medial portions of the temporal lobes, consistent with meningoencephalitis. CSF obtained on the same day as the MRI had a negative India ink examination and fungal culture was negative.

Serological studies of blood and cerebrospinal fluid were obtained again 5 days later and were sent to the Division of Vector-Borne Infectious Diseases, National Center for Infectious Diseases, and Centers for Disease Control, Fort Collins, CO. ELISA was positive for serum IgM antibodies to EEE virus and negative for serum IgG antibodies, results which were interpreted as consistent with recent infection with EEE virus. ELISA was not positive for IgM antibodies to EEE in the CSF. IgM and IgG antibodies against St. Louis encephalitis virus and LaCrosse virus were not detected in the serum. Despite aggressive measures, the patient's clinical condition continued to deteriorate rapidly, and the patient expired secondary to respiratory failure 7 days after admission to DUMC.

2.1. Central nervous system pathology findings

Pathologic examination of the brain revealed severe edema, with herniation of the cerebellar tonsils bilaterally and associated necrosis of the inferior temporal lobe. There were numerous petechial hemorrhages in the cortex, caudate nuclei, and pons, and large watershed infarcts in the right medial occipital lobe and left inferior cerebellum.

Microscopic analysis demonstrated perivascular lymphohistiocytic cuffing consistent with viral type encephalitis. Throughout several of the sections, scanty meningeal involvement was seen. Numerous scattered microglial nodules were seen beneath the pia in the cortical grey matter.

Several microscopic acute infarcts with surrounding parenchymal edema and hemorrhage were identified within both the basal ganglia and the pons. The hippocampus also demonstrated several areas of microscopic infarction with focal neuronal dropout. The cerebellum demonstrated multiple areas of myelin pallor and Purkinje cell dropout with Bergmann's type gliotic reaction, consistent with ischemic compromise. Within these areas of myelin pallor there were noted to be numerous punctate hemorrhages. No lesion of the spinal cord was identified. Viral inclusions were not identified within glial cells or neuronal cells.

2.2. Ophthalmic pathology findings

Both eyes were externally remarkable for a number of small retinal hemorrhages seen in the superior calotte, clustered around the equator in the right eye, and four small retinal hemorrhages in the posterior-inferior retina of the left eye varying in diameter from 0.1 to 0.3 mm. In addition, the retina had patchy areas that appeared cloudier than usual after formalin fixation.

H&E stained histological sections of both eyes disclosed a decreased number of ganglion cells and the presence of microcysts in the ganglion cell and nerve fiber layers, simulating a retinoschisis (Fig. 1A and B). Sections stained immunohistochemically for CD20 (B lymphocytes) and CD3 (T lymphocytes) revealed a few T lymphocytes within the retinal ganglion cell layer (Fig. 1C) and optic nerve (Fig. 1D). There were fewer lymphocytes within the posterior temporal retina than in the nasal retina, which correlated with a less degenerated appearance of the retina. Cells positive for CD68 (KP1 clone, a marker for macrophages, monocytes, and certain populations of microglia and myeloid cells) were present in areas of retina with ganglion cell loss (Fig. 1E) and the optic nerve (Fig. 1F). Many of the positively staining cells were small and morphologically appear to be neuroglia. Other CD68-positive cells were larger and were morphologically typical of macrophages; these were located mostly within the areas of the retina where the ganglion cell layer was degenerate. CD68-positive cells typical of macrophages were abundant in the ganglion cell layer and nerve fiber layer of the peripapillary retina and within the optic nerve head. Fewer macrophages were elsewhere in the optic nerve. No lymphocytes or macrophages were identified in the retinas or optic nerves of the eyes of two control patients (ages 34 and 76).

2.3. Systemic pathology findings

The major systemic pathology findings were coronary artery disease with focally moderate stenosis of the right and left main coronary arteries; acute bronchitis and bronchiolitis in both lungs; and fibrin microthrombi in the kidneys and left adrenal gland typical of terminal disseminated intravascular coagulation. No generalized lymphohistiocytosis was identified at autopsy, such as that described in association with EEE virus infection of an infant.[11]

3. Discussion

We are unaware of any published ophthalmological observations in EEE patients, although Feemster and Haymaker included impaired vision as a possible sequel to EEE.[7] One review stated that horses affected with EEE often have visual problems resulting in partial blindness.[6] In the guinea pig, the EEE virus was shown to produce an insignificant, non-specific reaction in the posterior chamber, with a few occasional leukocytes in the vitreous and retina, and rare necrotic ganglion cells. There was complete absence of overt necrosis or a focal reaction similar to that found in the brain.[12] By contrast, in Rift Valley fever, another form of arboviral infection that may result in encephalitis, ocular manifestations are well-described in patients including exudative lesions of the macula and paramacular region that are frequently associated with hemorrhage, edema, and less often with vasculitis, retinitis, and vascular occlusion.[8] A related arbovirus of recent importance, the Zika virus, has been associated with an epidemic of microcephaly in the western world. The ophthalmologic findings present in 85% of infants examined were focal pigmentary clumping, well circumscribed chorioretinal atrophy surrounded by hyperpigmentation, optic nerve hypoplasia and severe disc cupping, and possibly bilateral iris colobomas and lens subluxation.[9,10]

In this case of EEE, both eyes manifested a lymphohistiocytic infiltrate in the retina and optic nerve, sites which lack CD68-positive lymphocytes and macrophages in healthy eyes. The lymphohistiocytic infiltrate in the retinal ganglion cell layer was

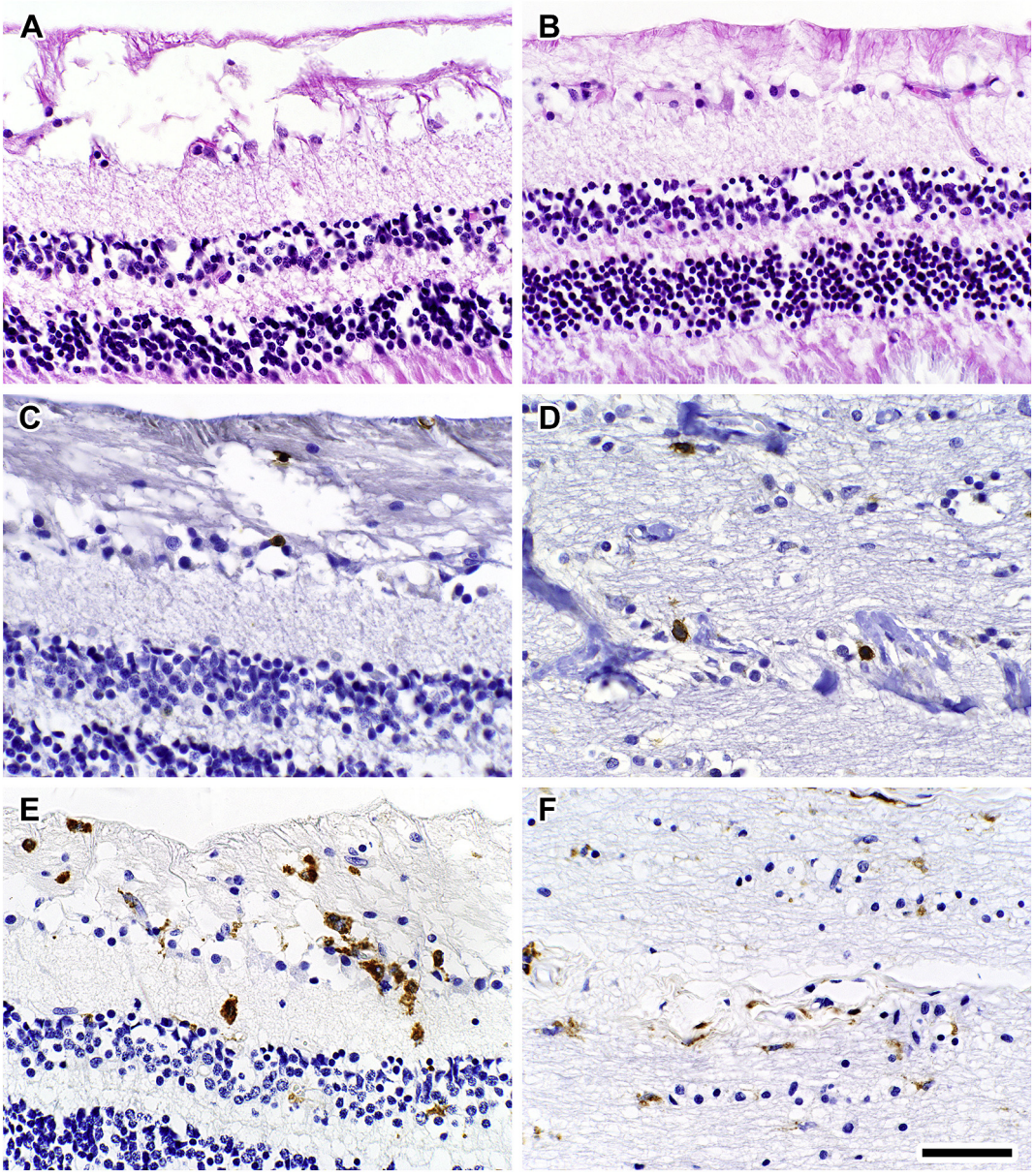

Fig. 1. Histopathology of the retina in the Eastern equine encephalitis patient and an unaffected individual.
A. Both eyes of the Eastern equine encephalitis (EEE) patient had a decreased number of ganglion cells and microcysts in the ganglion cell and nerve fiber layers of the posterior retina, simulating a retinoschisis. **B**. The posterior retina from an unaffected eye of a 76-year-old for comparison. **C, D**. A few T-lymphocytes, stained brown using anti-CD3 antibodies and 3,3′-diaminobenzidine as detection agent, are seen in the ganglion cell layer of the posterior retina (**C**) and optic nerve of the EEE patient (**D**). **E, F**. Macrophages expressing CD68 antigen were more abundant than lymphocytes in both the posterior retina (**E**) and optic nerve (**F**). All photographs were taken at the same magnification; magnification bar for all images = 50 μm. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

associated with a reduced number of ganglion cells, which is reminiscent of the central nervous system (CNS) effects of EEE virus. The brain characteristically exhibits meningoencephalitis with perivascular inflammation, microglial nodules, and neuronal death.[7] The perivascular inflammatory infiltrate is predominantly neutrophilic early in the course of the disease, but converts to mononuclear cells by 7–8 days after the onset of symptoms.[13] To exclude the possibility that the retinal inflammation and degeneration were nonspecific responses to the patient's total cerebral necrosis, we examined both eyes from two subjects with total cerebral necrosis from other causes. In none of these eyes were there any lymphocytes or histiocytes detected in the retina. This indicates that the retinal lymphohistiocytic infiltrate and loss of retinal ganglion cells were secondary to the infection by EEE virus and were not a nonspecific response to cerebral necrosis.

Although the retinal inflammation in this case of EEE was not florid, it was associated with degeneration of the neurons composing the ganglion cell layer that would undoubtedly have compromised vision had the patient survived his acute illness.

4. Conclusions

This case report reveals that EEE causes inflammatory changes in the retina that parallel those in the brain, a finding which has not been previously documented.

5. Patient consent

Consent to publish the case report was not obtained, as the family of the deceased patient could not be contacted. This report

does not contain any personal information that could lead to identification of the patient.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Conflict of interest

None of the authors had any potential conflicts of interest with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

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