Case 21-2019: A 31-Year-Old Woman with Vision Loss

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Patient and Chief Complaint

31 y.o woman was admitted to emergency department of Massachusetts General Hospital due to vision loss
Which of the following is the most common cause of vision loss in the United States of America?

A. Age-related macular degeneration, cataracts, diabetic retinopathy, and glaucoma
B. Benign or malignant tumor formation in the primary visual cortex
C. Corneal damage
D. Drug-induced optic neuropathy by drugs such as Naproxen, oral contraceptives, tamoxifen, and corticosteroids
E. Eye damage from repeated substantial and/or prolonged exposure to UV light
Patient History

- No history of ocular trauma
- History of Vitamin D and Iron deficiencies
- No surgeries
- No known allergies to medications
- No current prescribed medication
- Patient lived alone in a suburb of New England
- Limited alcohol consumption
- No history of smoking or recreational drug usage
- No recent travel, insect/tick bites
- Grandfather has hyperlipidemia
- Mother has history of glaucoma
History of Current Illness

1. 3 weeks prior to presentation, left eye gradually developed blurry vision
2. 1 week prior to presentation, patient reported near total vision loss in left eye, with a “dark shadow” located in the center of vision
   a. Peripheral vision unaffected
   b. Colors were increasingly “washing out” (images appearing gray)
   c. Intermittent floaters in left eye
3. Symptoms progressed and then the patient sought care at ophthalmology specialist hospital associated with MGH
Presentation upon admission

- Central vision loss in left eye
- Intermittent dull pain under left eye
- No double vision
- No pain with eye movement
- No fevers, chills, numbness, tingling, weakness, lack of coordination, hearing loss, shortness of breath, vomiting, diarrhea, or rash
Central vision loss is indicative of what condition?

A. Degeneration of rods
B. Vitreous detachment
C. Degeneration of fovea stemming from macular degeneration
D. Retinal vein occlusion caused by high blood pressure
E. Excessive use of specific androgen receptor modulators (SARMs)
Patient Optic Information

Left Eye
- Visual acuity- 20/400
- Ishihara Color Test- 0/13
- Intraocular pressure- 17 mm Hg
- Central scotoma noted
- Relative afferent pupillary defect was noted

Right Eye
- Visual acuity- 20/30
- Ishihara Color Test- 8/13
- Intraocular pressure- 18 mm Hg

Both Eyes
- Slit-lamp examination revealed normal adnexa, lids, lashes, conjunctivae, sclerae, and corneas
- Normal anterior chambers, irises, lenses, and vitreous bodies
- Normal blood vessels
- Normal bilateral extraocular movement
Patient Vitals

- Body Temperature- 36.1C
- Pulse- 72 bpm
- Blood Pressure- 118/81 mm Hg
- Respiratory rate- 16 breaths per minute
- Oxygen saturation- 99% SpO2 on RA
- BMI- 20.4
- Normal electrolyte, glucose, vitamin B12, C-reactive protein, thyrotropin, and angiotensin-converting enzyme levels
- Normal renal and liver function, complete blood count, differential count, and erythrocyte sedimentation rate
Probable mild hazy enhancement in the left optic nerve.

No evidence of a mass lesion compressing the optic nerve or evidence of cerebral white matter lesions.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Reference Range†</th>
<th>Tube 1</th>
<th>Tube 2</th>
<th>Tube 4</th>
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<td>Glucose (mg/dl)</td>
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<td>Lymphocytes</td>
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<td>Atypical or reactive lymphs</td>
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<td>Venereal Disease Research Laboratory test</td>
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<td>Oligoclonal bands</td>
<td>No banding seen in CSF concentrated by a factor of 80</td>
<td>No banding seen in CSF concentrated by a factor of 47</td>
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</table>

* To convert the values for glucose to millimoles per liter, multiply by 0.05551. CSF denotes cerebrospinal fluid.
† Reference values are affected by many variables, including the patient population and the laboratory methods used.
The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.
Illness progression

1. 9 days after initial admission, increased blurriness in the nasal visual field of the left eye
   a. 3-day outpatient course of intravenous glucocorticoids
   b. Subsequent 14-day tapering course of prednisone prescribed

2. 34 days after initial admission to emergency dept and 2 months after development of blurry vision in the left eye, vision loss in the right eye developed.
   a. Reported brief and transient improvement of vision loss after glucocorticoid treatment
   b. Right eye visual acuity- 20/200
   c. Left eye visual acuity- 20/400
   d. Total color blindness in both eyes
Steroids are administered to treat a variety of different ailments. Prolonged and/or large usage of steroid compounds increase the chances and severity of side effects. In this case, steroidal compounds are used to treat vision loss over a period of 3 days. Which of the following compounds could have been used for treatment of the individual’s vision loss?

A. Oxandrolone (Offset side effects of prolonged corticosteroid usage)
B. Dexamethasone (stronger binding than cortisol to same receptors)
C. Methandienone (brand name: Dianabol)
D. Estradiol Benzoate (Commonly used for hormone therapy in women)
E. Clenbuterol (Structurally similar to epinephrine)
Second admission

- Mild anisocoria and a trace relative afferent pupillary defect in the left eye
- Left optic-nerve disk was pallid (pale)
- Normal results from funduscopic examination of both eyes
- Normal levels of folate, thiamine, and copper in blood
- Antibodies anti-Ro and anti-La were not detected in blood
  - Associated with an earlier disease onset, glandular dysfunction and extraglandular manifestations as well as with other B cells activation markers
- MRI showed mild asymmetric increase in signal without definite abnormal enhancement in the retrobulbar segment of the right optic nerve
- Lumbar puncture yielded opening pressure of 17 cm of water
- Gram stain of CSF showed moderate amount of mononuclear cells
  - No neutrophils or organisms were identified
- CSF cytological examination revealed no malignant cells.
- Intravenous glucocorticoids were administered for 3 days but vision loss persisted.
- On 5th hospital day, patient was discharged home.
- 4 days after discharge, patient was evaluated in neurology clinic of MGH:
  - No improvement in her vision.
  - Results of examination were unchanged from prior admission.
- Diagnostic test was performed.
Differential Diagnosis
Summary So Far...

- Healthy, 31-year-old women presented with subacute, sequential bilateral vision loss
- No other neurologic abnormalities
- Patient initially delayed seeking treatment because she thought she was just in need of new glasses
Step 1- Anatomical Localization

- Patient has monocular vision loss
  - Implies issue is anterior to the optic chiasm (either eye structures or the anterior portion of the optic nerve)

- Binocular vision loss is typically cerebral in origin
Which is the correct order of structures involved in the visual pathway starting when light enters the eye?

a. Retina → optic nerve → optic tract → optic chiasm → lateral geniculate body (LGN) → primary visual cortex
b. Retina → optic nerve → optic chiasm → optic tract → LGN → primary visual cortex
c. Retina → optic tract → optic chiasm → LGN → optic nerve → primary visual cortex
d. Retina → LGN → optic tract → optic nerve → optic chiasm → primary visual cortex
e. Retina → optic tract → optic nerve → LGN → optic chiasm → primary visual cortex
Anatomical Localization

- Patient has relative afferent pupillary defect (RAPD)
  - Pupils respond differently to light shown in one eye at a time
  - Normally both pupils should constrict when light is shown to either eye

- Dysfunction of the optic nerve anterior to the optic chiasm
  - Show light to unaffected eye → both pupils constrict
  - Show light to affected eye → decreased response to light → mild constriction only

- Pupils will appear to dilate when light is moved from the unaffected to the affected eye
Anatomical Localization

- Ocular diseases (corneal abnormalities, cataracts, retinal disorders, etc.) do not cause a relative afferent pupillary defect (RAPD)
- Color desaturation and central vision deficits also point to an issue involving the optic nerve
- Severity of the vision loss suggests optic neuropathy
Optic Neuropathy

- Patient has painless, subacute optic neuropathy
- Possible causes...
  - Ischemic/traumatic
    - Hyperacute and therefore unlikely
  - Chronic causes
    - Cancer, vitamin deficiencies, toxin exposure unlikely
    - Not suggested by labs, scans, etc.
  - Infection/autoimmune disease
    - Most likely
Infection

- **Bartonellosis**
  - Group of diseases caused by Bartonella genus (bacteria), transmitted by vectors such as fleas
  - Zoonotic diseases that can be passed from animal to human through bite or scratch
  - No/mild symptoms in healthy adults, severe symptoms in immunocompromised patients including neuroretinitis

- **Tuberculosis**
  - Caused by mycobacterium tuberculosis, primarily affects the lungs
  - 5-15% of individuals infected show symptoms, much higher risk if immunocompromised
  - Can affect the eye, including uveitis (inflammation of the middle layer of the eye)

- **Cytomegalovirus**
  - Common virus that shows no/mild symptoms in healthy adults
  - Can affect the eye in patients with weak immune system causing retinitis, blind spot, loss of peripheral vision, etc.
Infection- Fitting Diagnosis?

**YES:**
- Bartonellosis, TB and Cytomegalovirus can affect the eye and cause vision loss

**NO:**
- Primarily affect the retina and cause neuroretinitis, not isolated neuropathy
- Tests for Lyme disease, syphilis and HIV were negative
Isolated Optic Neuritis

- Immune-mediated disease that causes inflammation and demyelination of the optic nerve
- Leads to pain with eye movements, likely resulting from the inflammatory process acting on the sensitive meningeal sheath of the optic nerve and extraocular muscles
- Visual acuity typically improves over time, but color vision deficits and brightness sensitivity often remain
- Common precursor to other diseases such as multiple sclerosis (MS), neuromyelitis optica
Isolated Optic Neuritis- Fitting Diagnosis?

**YES:**
- Most common form of optic neuropathy

**NO:**
- Patient does not have pain with eye movements
Multiple Sclerosis

- Chronic disease of the central nervous system where the immune system attacks the myelin that covers nerve fibers
- Results in communication problems between the brain and body and can lead to permanent nerve damage
- Symptoms include weakness of limbs, electric shock sensations, tremors, partial/complete vision loss and pain with eye movements
Multiple Sclerosis- Fitting Diagnosis?

YES:

- Vision loss from optic neuritis often first symptom of MS

NO:

- Typically only mild-moderate loss of visual acuity and color perception
- Does not explain lack of response to glucocorticoids
  - Most MS patients recover their vision after given glucocorticoids
- MRI of the head normal and no oligoclonal bands in CSF
Neuromyelitis Optica

- Inflammatory disease of the central nervous system especially affecting the optic nerves, spinal cord and parts of the brain stem
- Like MS, the immune system attacks the myelin covering nerve fibers
- Symptoms include vision loss, pain in the eyes, and weakness/paralysis in the extremities
Neuromyelitis Optica - Fitting Diagnosis?

YES:

- Worse visual prognosis than associated with MS
- 80% of patients have visual acuity worse than 20/200

NO:

- Inflammation of optic nerve not seen on MRI
- Tested negative for specific antibodies to aquaporin-4 water channels
  - These antibodies are found in 80% of neuromyelitis optica patients
Isolated optic neuritis, MS and neuromyelitis optica are all disorders in which the immune system attacks the myelin covering nerve cells. Which is NOT true of myelin?

a. Myelin is formed by Schwann cells in the PNS
b. Myelin is formed by oligodendrocytes in the CNS
c. Myelin allows action potentials to travel at greater velocities
d. Myelin allows ions to move through channels throughout the neuron
e. Myelin is mostly made of lipid
Myelin oligodendrocyte Glycoprotein-mediated optic neuritis

- Uncontrolled production of antibodies that target myelin oligodendrocyte glycoprotein
- MOG (myelin oligodendrocyte glycoprotein) is essentially just a protein found on the outermost surface of myelin sheaths on an oligodendrocyte
- MOB antibodies was once thought to be a biomarker of MS but this is no longer true

However...

- This patient tested negative for antibodies to MOG
- Therefore, we cannot completely rule out this diagnosis but it makes it very unlikely.
Paraneoplastic Syndromes

- A group of disorders that sometimes develops in people with cancer
- These disorders occur because cancer-fighting agents of the immune system begin to attack the CNS, PNS, or muscles
- Symptoms are neurologic
  - Ataxia, dementia, neuromuscular-junction disorder
  - Lambert-Eaton myasthenic syndrome
- Bilateral optic neuropathy can be the initial stages of a paraneoplastic process

However...

- This patient showed no neurologic symptoms so this can be ruled out
- Patient does not have cancer
Paraneoplastic syndromes affect the nervous system. Which of the following signs and symptoms would you expect to see in a patient with this condition?

A. Seizures
B. Hallucinations
C. Loss of muscle tone
D. Stuttering
E. All of the above
Sarcoidosis

- An inflammatory granulomatous condition with associated symptoms such as:
  - Chest pain, erythema, lymphadenopathy
  - Specifically optic neuritis is also a symptom, although rarely
- Patient showed mild pain and slow disease progression which are characteristic of sarcoidosis

However...

- This type of optic neuropathy would present with:
  - dural thickening
  - enlarged optic nerves
  - An MRI that shows leptomeningeal enhancement on gadolinium-enhanced MRI
What is a granuloma?

A. A collection of macrophages that is formed during inflammation
B. A mass of tissue that is formed by the accumulation of abnormal cells
C. Plasma cells that grow abnormally and become cancerous
D. A noncancerous tumor that arises from the membranes surrounding the brain and spinal cord
Leber’s Hereditary Optic Neuropathy (LHON)

- A disease linked to mutations in mitochondrial DNA, therefore a heritable disease
- Symptoms include:
  - Severe vision loss
  - Visual acuity worse than 20/200 in both eyes
  - Administration of glucocorticoids does not lead to improvement
- MRI usually shows hyperintensity in posterior of optic nerve
- Previous family history is not required
- So how can you properly diagnose?

However...

- patient did not have a positive family history
Final Diagnosis
Which of the following is likely the final diagnosis?

A. Optic Neuropathy
B. Neuromyelitis Optica
C. Myelin Oligodendrocyte Glycoprotein-Mediated Optic Neuritis
D. Sarcoidosis
E. Leber’s Hereditary Optic Neuropathy
Final Diagnosis:

Leber’s Hereditary Optic Neuropathy

- Maternally inherited mitochondrial disorder
- Caused by mutations in mitochondrial genes that encode the NADH dehydrogenase subunits and cause decreased activity of complex 1 of the ETC → lead to decreased ATP production
- Diagnosed by testing for mitochondrial DNA in the blood
- Targeted analysis of mitochondrial DNA → presence of m.14484T → C mutation
It was mentioned that a decreased activity of Complex I leads to a decrease in ATP production. What is the role of Complex I?

A. Complex I moves electrons from NADH to FADH$_2$ to molecular oxygen
B. Complex I contributes to the proton gradient that drives the formation of ATP
C. Complex I phosphorylates ADP, making it ATP
D. Both A and B
E. All of the above
What causes Leber’s Hereditary Optic Neuropathy?

<table>
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<tr>
<th>Factors:</th>
<th>Leads to:</th>
<th>Effect on the Body:</th>
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<tbody>
<tr>
<td>Genetic Mutations</td>
<td>Increase in Free Radicals</td>
<td>Retinal Ganglion-cell</td>
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<tr>
<td>Other GeneticModifiers (mitochondrial DNA copy number, haplotype, and nuclear modifiers), Environmental Factors (tobacco, alcohol, toxin exposure), Sex hormone levels</td>
<td>Decrease in ATP Production</td>
<td>Apoptosis</td>
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<td>Disruption in Redox Balance</td>
<td>Optic-nerve Degeneration</td>
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Treatment
Treatment

● There is no Food and Drug Administration-approved therapy for LHON
● Proposed potential treatments consist of supplements and medications that:
  ○ Boost mitochondrial mass and number
  ○ Circumvent dysfunction in the respiratory chain complex
  ○ Prevent oxidative damage to retinal ganglion cells
The patient was prescribed Idebenone, which is also known as Coenzyme Q10). What does Idebenone likely do?

A. It selectively blocks mitochondrial oxidative damage and prevents cell death
B. It transfers electrons directly to complex III of the mitochondrial ETC, bypassing complex I, and restores ATP generation
C. It helps to increase the biosynthesis of glutathione, a compound essential for the control of oxidative stress
D. It inhibits mitochondrial Na\(^+\)-Ca\(^{2+}\) exchange, resulting in an increase in mitochondrial Ca\(^{2+}\) concentration and subsequent ATP production
E. None of the above
Management:

- Patient was legally blind and had visual acuity of
  - 1 ft in the left eye
  - 4 ft in the right eye
- Supportive care was established (allows her to acclimate to her home & work environment)
- Received rehabilitative and social services
- Provided with low-vision assistive devices
Resolution
Resolution

- 8 months after the onset of vision loss
  - There was no improvement seen, despite the initiation of Idebenone therapy
- Gene Therapy is a potential future treatment
Clinical Relevance
Clinical Relevance

- LHON has a mitochondrial pattern of inheritance
  - All females with an mtDNA mutation, even those without signs or symptoms, will pass the genetic change to their children
Clinical Relevance

- About 35,000 people worldwide have LHON
- 100 people in the US each year join the 4,000 Americans who are already legally blind due to LHON
Clinical Relevance

- It causes such severe and usually permanent visual loss in generally young people
  - Males peak around ages 14-16
  - No peak onset age in females
References

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