

Bilateral optic disc edema associated with cryptococcal meningitis in a young diabetic male

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INITIAL PRESENTATION

Chief Complaint: A 26-year-old male presents with acute horizontal binocular diplopia.

History of Present Illness: A 26-year old male with type 1 diabetes mellitus presented for evaluation of severe headache and double vision. His symptoms started 3 weeks prior to presentation with recurrent febrile episodes, nausea with emesis, a severe progressive headache, back pain, and neck pain. He initially sought care in local emergency departments several times and was treated for diabetic ketoacidosis (DKA) due to presumed viral illness. He reported that his blood sugars had been very difficult to control for the last several months despite being compliant with medications.

In the days prior to his presentation to ophthalmology, he developed binocular horizontal diplopia in addition to his other symptoms, which prompted further evaluation. He had no known exposure to mosquitos or tick bites, no transient visual obscurations or pulsatile tinnitus, and no history of sleep apnea. Magnetic resonance imaging (MRI) of the brain prior to presentation was obtained for the patient's severe headache and lumbar back pain. This incidentally revealed a concave sella and posterior globe flattening of both eyes (Figure 1).

Past Ocular History: Refractive error, both eyes (OU)

Past Medical History:

- Type 1 diabetes mellitus with uncontrolled blood glucose complicated by multiple recent episodes of DKA
- Hypertension

Medications:

- Insulin glargine
- Insulin aspart
- Lisinopril

Allergies: None

Family History: Unremarkable

Social History:

- Lives and works locally with no recent sick contacts. No recent travel. No history of incarceration.
- Social EtOH consumption, no tobacco or illicit substance use

Review of Systems: Unremarkable other than that noted in HPI

OCULAR EXAMINATION

- **Visual Acuity with Correction (Snellen method)**

- Right eye (OD): 20/25, no improvement with pinhole
- Left eye (OS): 20/20

- **Ocular Motility/Alignment:**

- OD: -2 abduction deficit consistent with a cranial nerve six palsy
- OS: Full

- **Intraocular Pressure (Tonopen)**

- OD: 22 mm Hg
- OS: 22 mm Hg

- **Pupils**

- OD: 7 mm in dark, 4 mm in light, 0.3 log units relative afferent pupillary defect (RAPD)
- OS: 5 mm in dark, 3 mm in light

- **Confrontation Visual Fields Fields (Count fingers)**

- OU: Full

- **Slit Lamp Exam**

- Lids/lashes: Normal OU
- Conjunctiva/sclera: Clear and quiet OU
- Cornea: Clear OU
- Anterior chamber: Deep and quiet OU
- Iris: Normal architecture OU
- Lens: Clear OU

- **Dilated fundus examination (DFE)**

	OD	OS
Vitreous	Clear	Clear
Disc	Grade IV optic disc edema, peripapillary flame hemorrhages	Grade IV optic disc edema, peripapillary flame hemorrhages
Macula, vessels, and periphery	Nasal macula with retinal folds, tortuous veins	Nasal macula with retinal folds, tortuous veins

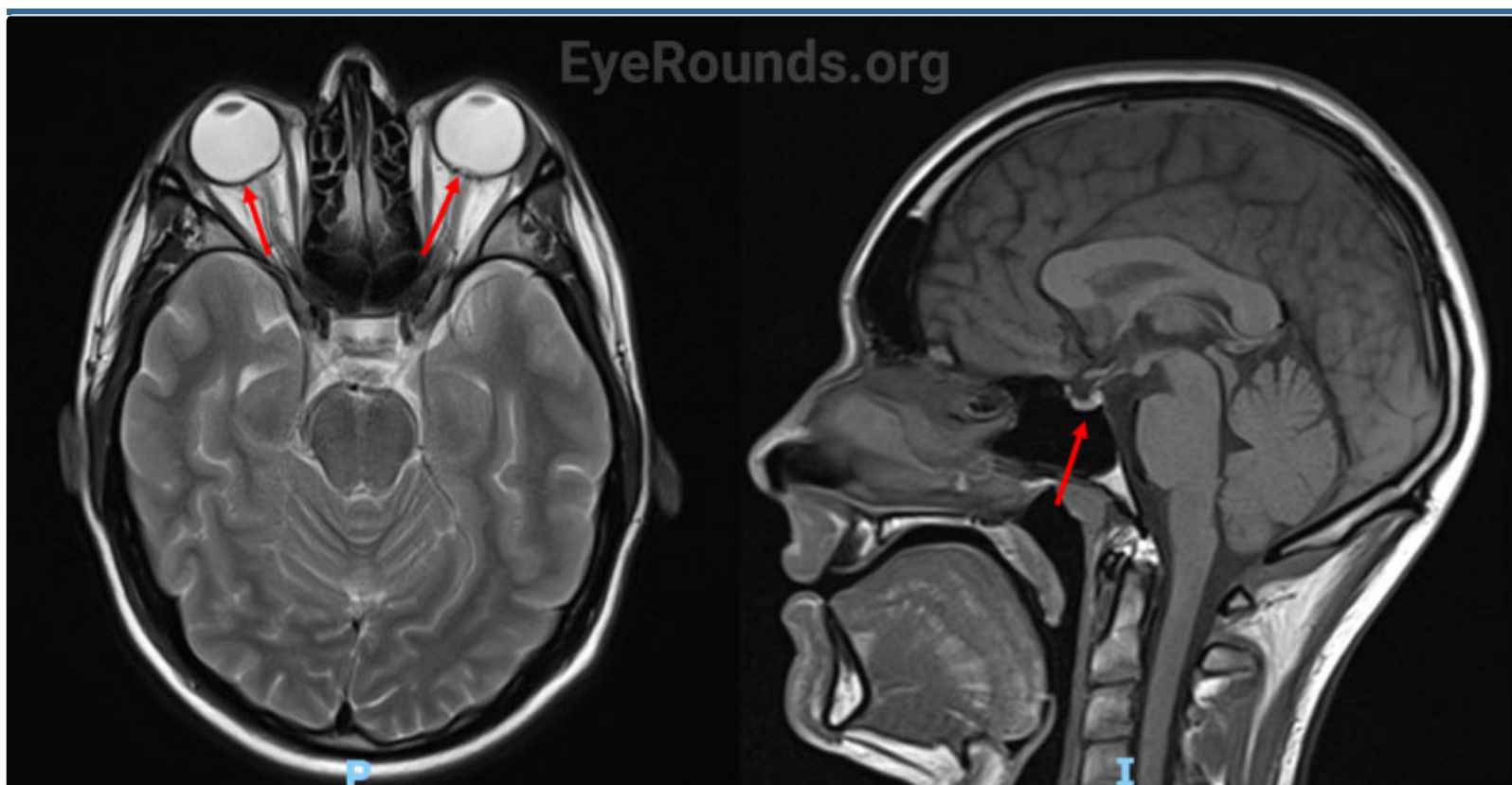


Figure 1: MRI of the brain without contrast. Prior to presentation, MRI revealed globe flattening in an axial view (*left panel, red arrows*) and a partially empty sella in sagittal view (*right panel, red arrow*).

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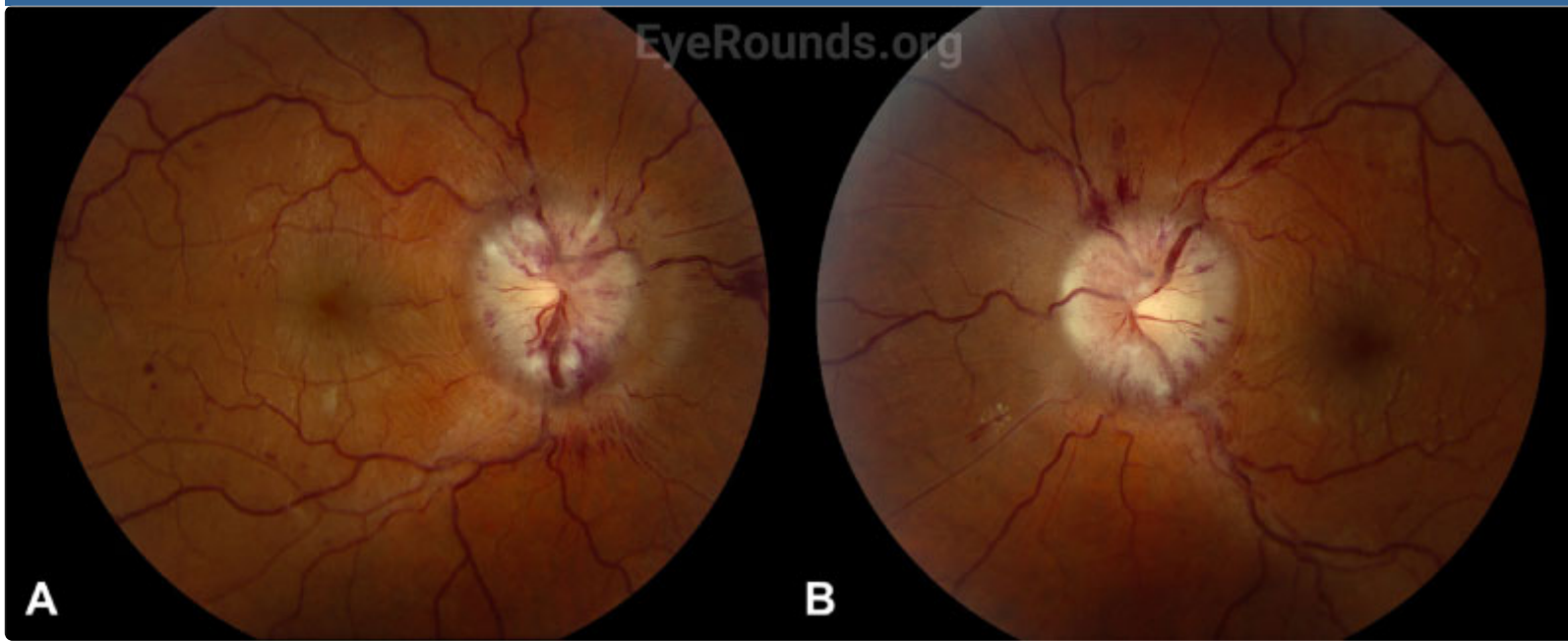


Figure 2: Color fundus photography, right (A) and left (B) eyes. Both eyes demonstrated grade IV optic disc edema with cotton wool spots, peripapillary hemorrhages, and retinal folds. In addition, scattered flame and dot-blot hemorrhages were seen in both eyes.

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- **Additional testing**

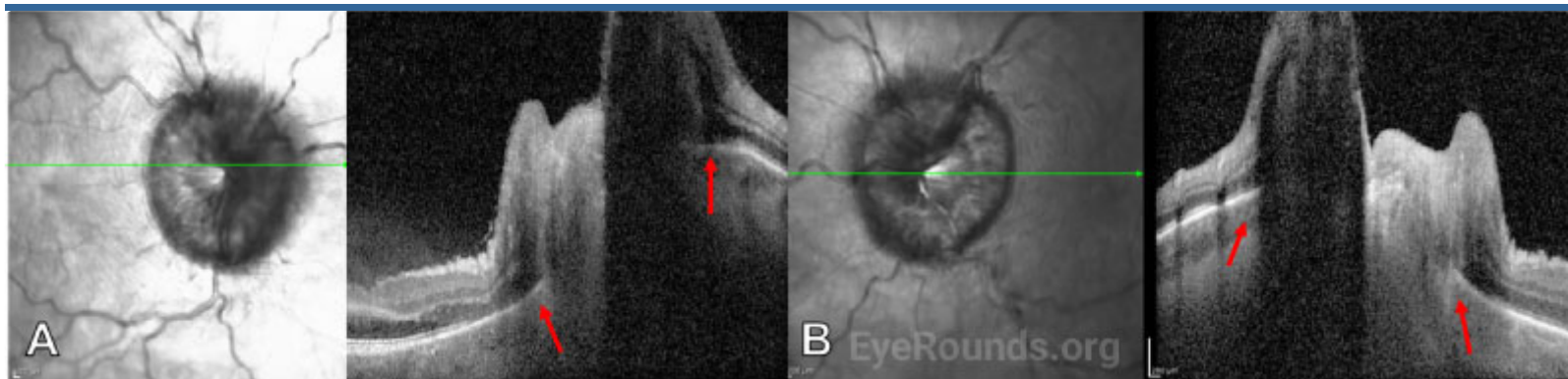


Figure 3: Optical Coherence Tomography (OCT) of the optic nerve head in the right (A) and left (B) eyes. Both eyes demonstrate an inward positive angulation of the peripapillary retinal pigment epithelium (RPE) and Bruch's membrane layers (red arrows), which is indicative of a pressure gradient between the retrobulbar space and vitreous.

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Together with the retinal folds, this suggests elevated intracranial pressure as the etiology of the optic disc edema.

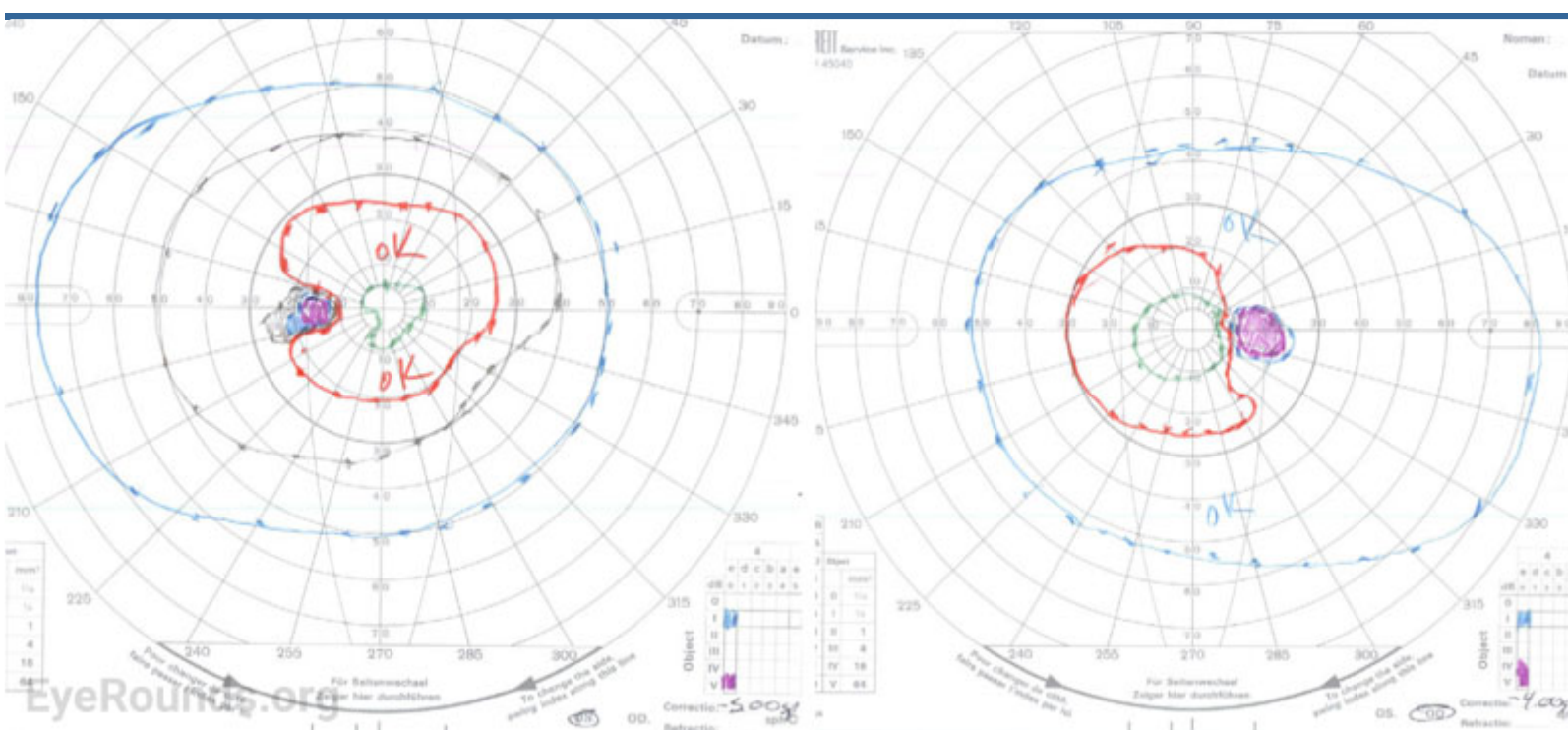


Figure 4: Goldmann Visual Field testing demonstrated an enlarged blind spot in both eyes.

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Differential Diagnosis:

- Infectious Etiologies
 - Meningitis
 - Meningoencephalitis
 - Brain or spinal abscess
- Neoplastic Etiologies
 - Intracranial tumor (i.e. meningioma)
 - Elevated cerebrospinal protein from other malignancy
- Intracranial hemorrhage
- Hydrocephalus
- Migraine variants
- Idiopathic intracranial hypertension ([Article](#) | [Case](#))
- [Cerebral venous sinus](#)
- Elevated central venous pressure (i.e. congestive heart failure)

DIAGNOSIS: Cryptococcal Meningitis With Secondary Intracranial Hypertension

CLINICAL COURSE

Given the patient's clinical exam findings of new onset cranial nerve six palsy and severe optic disc edema in both eyes, he was promptly referred to the Emergency Department. A lumbar puncture was performed, with CSF opening pressure measured at 36 cm H₂O, which immediately improved the patient's headache and back pain. The cerebrospinal fluid (CSF) was sent for comprehensive infectious analysis, which was positive for Cryptococcal antigen with a titer of 1:320. He had testing for syphilis and HIV, which were both negative. The patient was initially started on treatment with Acetazolamide. Infectious Disease was consulted for initiation of treatment for Cryptococcal meningitis, and they recommended prompt antifungal treatment with Amphotericin B and oral Fluconazole. The patient was admitted and monitored during treatment. He developed an acute kidney injury with mild acidosis that was self-limited, but otherwise tolerated the treatment well.

Subsequent examination two days after initial LP and initiation of antifungal treatment showed improvement of the optic disc edema to grade III in both eyes. On OCT, Bruch's membrane configuration changed from angled into the eye to angled out, indicating a decrease in the pressure gradient between the retrobulbar space and the vitreous (Figure 5). The patient continued antifungal therapy for three weeks along with serial LPs, during which time his symptoms continued to improve. His extraocular motility returned to normal and within 1 month, and the optic disc edema was reduced to grade II in both eyes at that time. Over subsequent weeks of follow-up, he reported no recurrence of symptoms of increased ICP. Visual function and perimetry remained stable, and optic disc edema continued to improve. After completing induction therapy, his antifungal regimen was changed to fluconazole monotherapy for a treatment duration of one year.

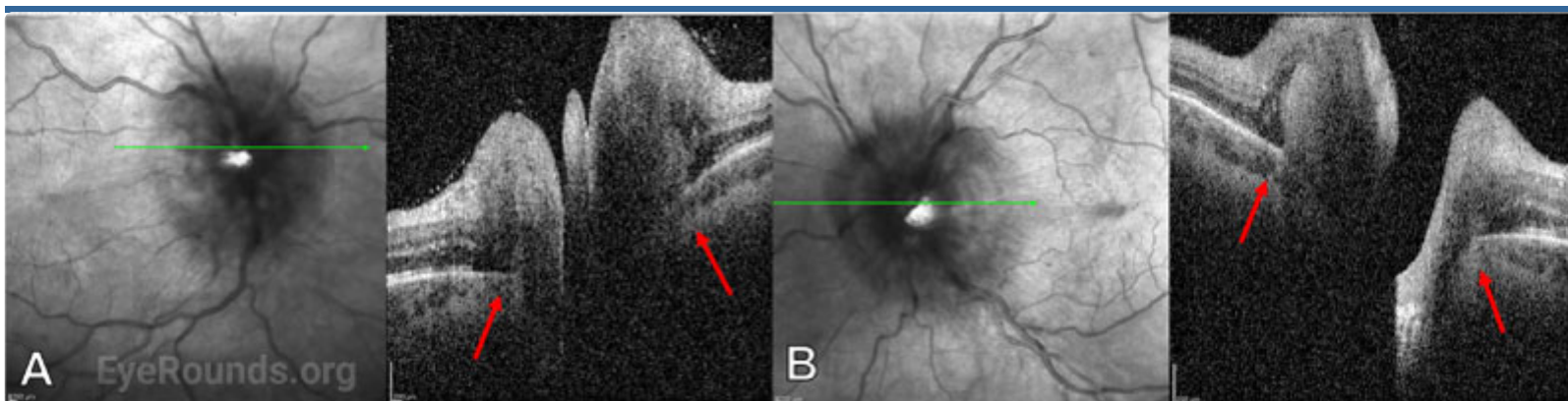


Figure 5: OCT of the right (A) and left (B) eyes following lumbar puncture and initiation of treatment for Cryptococcal meningitis. In both eyes there is downward displacement of Bruch's membrane towards its normal anatomical plane. This is improved compared to prior tests (Figure 3)

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DISCUSSION

Etiology/Epidemiology

Cryptococcal meningitis (CM) is the world's most common cause of fungal meningitis and extrapulmonary cryptococcus.[1-3] There are over 220,000 annual cases, more than 181,000 annual deaths worldwide, and around 3,000 cases in the United States each year.[1] The two most prominent species that cause human pathogenesis are *Cryptococcus neoformans* and *Cryptococcus gatti*. [2] Cryptococci are encapsulated fungi that survive mainly in the environmental reservoirs of bird feces, soil, and decaying organic matter. [2] These capsules are then inhaled by humans, allowing the fungi to colonize the lungs and disseminate across the blood-brain barrier to cause meningitis. [2] Cryptococcal capsules have high virulence and genetic variability that allows them to evade the macrophage-led host immune response. [2]

CM is a high-risk infection which requires prompt diagnosis and intervention. Mortality rate varies drastically between high- and low-income countries, with high-income areas averaging 9% and low-to-middle income areas averaging 55%. [2] Sub-Saharan Africa, which accounts for 70% of the world's cryptococcal meningitis cases annually, reports an average mortality rate of 70%. [2]

The incidence of CM is significantly associated with compromised immune system function due to various causes including human immunodeficiency virus (HIV), autoimmune disease, diabetes mellitus (DM), cancer, organ transplant, chronic kidney disease, alcohol and drug abuse, other disease leading to immune deficiency, or immunosuppressive drugs. HIV is associated with 95% of CM cases in low-to-middle income countries and 80% of cases in high-income countries. [3] However, the incidence of CM among non-HIV-infected persons is rising in developed countries with access to antiretroviral therapy. [2] Incidence of CM is lower in HIV-negative individuals, however mortality in these patients tends to be higher due to delayed diagnosis. [4]

In patients with underlying disease who contract cryptococcal infection, individuals with DM comprise 10-20% of cases. [5] Within this group there is a mild male predominance and a median age of 60.5 years. [5,6] Uncontrolled DM can precipitate an immunocompromised state, and is one of the most common predispositions for opportunistic infections such as cryptococcosis in HIV-negative individuals. [5]

Pathophysiology/Signs/Symptoms

Cryptococcal infection can remain temporarily asymptomatic in immunocompetent individuals, but often leads to more rapidly disseminated and symptomatic disease in immunocompromised patients. Initial signs and symptoms of CM vary in timing of onset and in severity and include fever, headache, neck stiffness, photophobia, change in or loss of vision, papilledema, cranial nerve palsies, focal neurological deficits, and altered mental status or depressed level of consciousness. [7,8] The most common clinical presentations in patients that have underlying DM with cryptococcal meningitis are headache, fever, altered mental status, nausea, and vomiting. [2]

Elevated ICP in cryptococcal meningitis can arise from interstitial edema, hydrocephalus, or from impaired CSF drainage. [9] Higher CSF fungal concentration is associated with higher ICP, which in turn is associated with mental status changes and mortality. [7] CM can affect the optic nerve either through increased intracranial pressure (ICP) or, more rarely, direct invasion of the optic nerve. [7] Infiltration of the optic nerve or nerve sheath tends to present with a relatively rapid onset of vision loss compared to papilledema, which tends to present with a slower, more progressive onset. In addition, optic nerve infiltration will often show enhancement on an MRI scan performed with fat suppression. [7,8]

Depending on the underlying etiology of ICP and a patient's immune status, vision loss has a variable time course and presentation in CM. Around 50% of CM patients experience some degree of vision loss, with papilledema underlying up to 30% of these cases. [10] Papilledema due to increased ICP can cause severe permanent vision loss. Symptoms and manifestations of papilledema may include blurry vision, sixth nerve palsy, transient visual obscurations, or pulse synchronous tinnitus. Patients rarely can present with severe papilledema and rapid vision loss. Less commonly, central vision can be affected by papilledema-induced changes including submacular fluid or hemorrhages, however these changes are often reversible.

Testing/Laboratory Work-Up/Imaging

CSF or blood culture is considered the gold standard for diagnosis and monitoring response to treatment. Routine culture does not differentiate between *C. gatti* and *C. neoformans*, although canavanine-glycine-bromothymol blue agar culture can be used to further distinguish species. [10] Microscopy using india ink staining provides a more rapid test result with result times ranging from a few hours to three days. [11]

Currently, the World Health Organization recommends cryptococcal antigen (CrAg) detection assays of serum or CSF using latex agglutination or lateral flow assay, as these methods provide high sensitivity (98.2%) and high specificity (96.8%). [11] CrAg assays are the preferred method for diagnosis of CM. If access to CrAg is not available, then the preferred diagnostic approach is lumbar puncture with CSF India ink. [11]

Elevated ICP occurs in more than 50% of cases with CM, and therefore, LP is recommended even in minimally symptomatic patients to assess ICP and need for serial LPs. [8,10] In addition to LP, a visual field test should be administered and often shows enlargement of the blind spot due to papilledema, with or without arcuate pattern loss. In the setting of CM or suspected CM, neuroimaging is used to distinguish papilledema due to raised intracranial pressure from other causes of optic nerve elevation such

as intracranial mass.[8] Magnetic resonance imaging (MRI) of the head can show radiographic findings of increased ICP. OCT findings including anterior retinal projection, total retinal thickness, and RNFL thickness may correlate with ICP.[12] Ultrasonography can also be sometimes be used to identify sheath distension in patients with increased ICP.

Treatment/Management/Guidelines

In addition to visual, auditory, and other neurological damage, uncontrolled ICP contributes to the high rate of mortality in patients with CM.[13] Treatment for ICP and coincident papilledema due to CM often involves intermittent, temporary or permanent CSF diversion.[7] Lumbar puncture can provide immediate symptomatic relief and either reverse or prevent neurological outcomes such as headache, vision loss or blindness, and mental status changes. Early lumbar puncture (<24 hours) following admission or diagnosis is associated with decreased mortality.[14,15] Current guidelines for management of CM and elevated ICP include up to daily serial LPs until ICP normalizes, with follow-up LPs after antifungal therapy to monitor CSF sterility and ICP.[4] A temporary lumbar drain or extraventricular drain may be necessary in patients with extremely elevated ICP. The merits of surgical placement of a CSF shunt during an active infection is debated among physicians but may be appropriate for patients whose ICP fails to normalize with serial LPs.[10]

Current guidelines recommend a combination therapy of amphotericin B (0.7–1.0 mg/kg per day) intravenously with flucytosine 100mg/kg/day for 14 days.[15] Historically, flucytosine availability has been limited in many parts of the world, and its high cost creates a barrier to treatment in areas where it is available. In cases where flucytosine is unavailable, combination therapy with amphotericin B 0.7–1.0 mg/kg per day and fluconazole 800 mg/day is recommended.[11, 15] Voriconazole has also been studied as an alternative to fluconazole in combination with amphotericin B with similar results at both 800 mg/day and 1,200 mg/day.[15] If amphotericin B availability is limited or a 14 day course is not feasible, a 5-7 day course of amphotericin B with fluconazole 1,200 mg/day is recommended as an alternative. Lastly, if amphotericin B is unavailable, fluconazole monotherapy at 1,200 mg/day for 10-12 days is recommended.[15]

<p>EPIDEMIOLOGY</p> <ul style="list-style-type: none"> • > 220,000 annual cases worldwide • ~ 3,000 United States cases annually • 10-20% CM cases with underlying disease are individuals with DM • CM cases in DM patients have a slight male predominance • Median age of CM in DM individuals is 60.5 years 	<p>SIGNS</p> <ul style="list-style-type: none"> • Fever, vomiting • Increased opening pressure on LP • Papilledema, cranial nerve palsies, focal neurological deficits • DKA in patients with DM, especially after nausea and vomiting
<p>SYMPTOMS</p> <ul style="list-style-type: none"> • Headache, neck stiffness • Change in/loss of vision, photophobia • Nausea • Confusion/altered mental status 	<p>TREATMENT/MANAGEMENT</p> <ul style="list-style-type: none"> • LP to assess/lower opening pressure, drain CSF, relieve symptoms • Amphotericin B and flucytosine/fluconazole antifungal therapy • Caution with acetazolamide as it may potentiate acidosis and renal dysfunction from Amphotericin B

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