International Journal of Research in Medical Sciences
Gupta M et al. Int J Res Med Sci. 2024 Mar;12(3):985-989
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20240553

Case Report

Reversible blindness in cryptococcal meningitis with human immunodeficiency virus infection

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Received: 13 January 2024
Accepted: 08 February 2024

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ABSTRACT

Ocular complications in cryptococcal meningitis (CM) are commonly attributed to elevated intracranial pressure (ICP). We report a case of reversible vision loss complicating acquired immunodeficiency syndrome (AIDS) related to CM with a normal ICP. The patient had sudden onset painless blindness during the anti-retroviral therapy (ART) and anti-fungal therapy. On evaluation, clinical and radiological findings of optic neuritis were present. While reviewing the literature for causes of blindness in CM, we concluded the cause was optic neuritis due to immune reconstitution inflammatory syndrome (IRIS) because of concomitant ART intake by the patient. We witnessed dramatic visual improvement after the use of systemic corticosteroids. The potential significance of this case report is to highlight the possible role of corticosteroids in the prevention of blindness due to CM.

Keywords: Cryptococcal meningitis, Anti-retroviral therapy, Immune reconstitution inflammatory syndrome, Steroids

INTRODUCTION

Cryptococcal meningitis (CM) is a severe opportunistic central nervous system fungal infection. It is primarily seen in patients with human immunodeficiency virus (HIV) infection which leads to an immune-compromised state. Around 10% of acquired immunodeficiency syndrome (AIDS) patients have associated other co-infections like cryptococcus meningitis and cytomegalovirus retinitis.[1] Ocular involvement is seen in nearly 40% of patients with CM. However, visual loss as a presenting complaint is rarely present in AIDS patients secondary to cryptococcal meningitis.[2] The pathophysiology of the vision complications associated with CM remains unclear. Possible explanations include direct invasion of the optic nerve or optic tracts by the fungus or perineuritic arachnoiditis leading to vision loss.[3] Other mechanisms include inflammatory compression of the optic nerve, intracranial hypertension, cerebral vasculitis, and amphotericin B toxicity. Although raised intracranial pressure (ICP) leading to visual loss is considered one of the most common mechanisms, very rarely visual loss can also occur with normal ICP.[4] Despite antifungal therapy's availability, eradicating the infection can be challenging. Aggressive interventions may be necessary to prevent permanent vision loss in cases where antifungal treatments are insufficient to reduce visual complications.[5]

CASE REPORT

A 36-year-old male presented in the emergency room with complaints of low-grade fever, cough, nausea, loss of appetite, and significant loss of weight in 3-month duration. He was diagnosed with human immunodeficiency virus (HIV) infection from an outside hospital 1 month back and was started on anti-retroviral therapy (ART) for the last 10 days. His CD4 count reported

1 month back was 70 cells/mm^3. On presentation, his clinical evaluation revealed altered sensorium and, presence of meningeal signs i.e. neck rigidity, Kernig's sign, and photophobia. The patient was febrile with a body temperature of 101.6 ˚F. His pulse rate was 108/minute and his blood pressure was 104/70 mmHg. Chest had bilateral normal vesicular breath sounds and cardiac examination revealed tachycardia with no murmur or any added sounds. The rest of the general and systemic examination was normal.

Post admission his routine blood investigations along with CSF were sent to the laboratory (Table 1) and the patient was started on empirical antibiotics and antipyretics. CSF examination showed clear fluid with normal opening pressure of 90 mm H_2O, protein 218 mg/dl, glucose 15 mg/dl, and white blood cell count 29/mm^3 with 100% lymphocytes and 12/mm^3 red blood cell count. CSF also revealed budding cryptococcus with a capsule on India Ink preparation (Table 1). Subsequently, he was started on injection of amphotericin B 50 mg IV OD (1 mg/kg/day) along with a tablet of flucytosine 1250 mg/day. With good improvement in the next 3 days, the same treatment was continued further.

On the fourth day, the patient complained of decreased vision. Upon examination, his vision was found to be diminished, with the right eye being worse than the left, and without peripheral sparing. There was no light perception in the right eye and visual acuity was limited to counting fingers in the left eye. His right pupil was unresponsive to direct light, but his consensual light reflex was intact. His left pupil was responsive to light and consensual light reflex. A rapid afferent papillary defect was also noted in the right eye. He denied diplopia, vomiting, headache, or any surge in fever. He was afebrile, awake, and alert with no evidence of confusion or focal neurological deficit. An immediate funduscopic examination showed no papilledema, vitritis, or chorioretinal lesions. There was no evidence of retinal artery occlusion. Extraocular movements were intact bilaterally. There was no other neurologic abnormality. The remaining physical exam was unremarkable.

Laboratory data revealed negative blood and urine cultures for bacteria, mycobacteria, and fungi. Cytomegalovirus antigen testing of peripheral blood and serum toxoplasma immunoglobulin were negative. The absolute CD4 count was 6 cells/µl, with a plasma HIV viral load of 619 copies/ml. A repeat lumbar puncture on day 4 of his hospitalization revealed normal ICP. Magnetic resonance imaging findings revealed leptomeningeal enhancement and dilated perivascular Virchow-Robin spaces with gelatinous pseudocysts, all classic findings in neuro cryptococcosis (Figure 1).

At this stage, the patient was taking tenofovir/lamivudine/efavirenz as ART, which was temporarily withheld. Intravenous (IV) methylprednisolone 1 gm/day was started. It was continued for the next 3 days followed by an oral taper of prednisone over twenty days from 40 mg daily to 5 mg daily, then discontinued. After receiving the first dose of steroids, the patient's vision dramatically improved. On day 4 of glucocorticoid therapy, vision testing revealed 20/40 OD (right eye) and 20/25 OS (left eye) with good pupillary response bilaterally. Amphotericin B and 5-flucytosine were continued for 2 weeks and transitioned to fluconazole 400 mg/day. The patient continues to do well clinically and has preserved vision to date.

Table 1: Relevant laboratory investigations.

Parameter	Value	Reference Range	Unit
Haemoglobin	12.6	12.5-15	gm/dl
Total leucocyte count	8970	4000-11000	Cells/mm^3
	Neutrophils-67	Neutrophils: 40-75	**%**
	Lymphocytes-31	Lymphocytes: 20-40	**%**
	Eosinophils-2	Eosinophils: 1-6	**%**
Platelets	321000	150000-400000	Cells/mm^3
Blood urea	36	20-40	mg/dl
Serum creatinine	1.3	0.7-1.3	mg/dl
AST	48	<40	U/l
ALT	37	<41	U/l
ALP	95	<128	U/l
Serum sodium	144	136-145	mEq/l
Serum potassium	4.4	3.5-5.1	mEq/l
Serum calcium	9.8	8.6-10	mg/dl
Fasting blood glucose	98	70-110	mg/dl
TSH	3.5	0.27-4.2	µIU/ml
T4, total	9.8	5.1-14.1	µg/dl
T3, total	1.4	0.8-2	ng/ml
ANA/ANCA/APLA	Negative		

Continued.

Parameter	Value	Reference Range	Unit
CSF	Opening pressure – 90	Opening pressure – 60-200	mmH_2O
	Cells-29	Cells: 0-8	WBC/mm^3
	Protein-218	Protein: 15-45	mg/dl
	Glucose-15	Glucose: 50-80	mg/dl
	Gram stain and bacterial culture - Negative		
	India ink preparation – Budding cryptococcus		
HbsAg/ Leptospira/ HSV 1,2/ Japanese encephalitis/ dengue profile			Negative
Autoimmune encephalitis panel			Negative

AST-Aspartate transaminase, ALT- alanine transaminase, ALP- alkaline phosphatase, TSH- thyroid stimulating hormone, T3-triiodothyronine, T4- thyroxine, ANA- antinuclear antibodies, ANCA- antineutrophil cytoplasmic antibodies, APLA- antiphospholipid antibodies, CSF - cerebrospinal fluid, HIV- human immunodeficiency virus, HbsAg- hepatitis B surface antigen, HSV- herpes simplex virus, NT-proBNP- N-terminal pro-B type natriuretic peptide

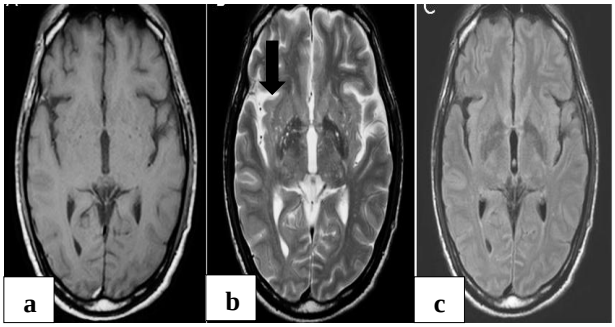

Figure 1: Magnetic resonance imaging (MRI) of the brain (a) T1W, (b) T2W, and (c) FLAIR sequences showing dilated perivascular Virchow-Robin spaces with gelatinous pseudocysts (black arrow) suggestive of neurocryptococcosis.

DISCUSSION

There are two different types of vision loss in CM. The first type is a rapid loss that is associated with a clinical syndrome that suggests optic neuritis. The second type is a slower and more progressive loss, which may be caused by the effects of increased intracranial pressure or intraocular pressure. A literature review was performed for cases of CM infection with ophthalmic manifestations since 1984. Cases of vision loss without elevated ICP and the role of corticosteroids in treating cryptococcal vision loss were also reviewed. Out of 5 patients treated with corticosteroids, 4 patients showed good clinical improvement in their vision (Table 2). A retrospective analysis done by Beardsley et al of 26 patients showed a significant improvement in visual deterioration in patients of CM treated with corticosteroids (12.5% versus 70%, p=0.007).[6]

In this case, the patient had rapid vision loss with a normal opening CSF pressure. There were no papilledema or funduscopic abnormalities on examination, suggesting optic neuritis or arachnoiditis as possible mechanisms. MRI findings (presence of leptomeningeal enhancement with enhancing nerve sheaths) also suggest inflammation as a likely etiology of vision loss. Our patient had a dramatic improvement in visual acuity after receiving IV methylprednisolone because he was suffering from the effects of rapid immune reconstitution. Immune reconstitution inflammatory response (IRIS) is a hyper-inflammatory response to previously or recently treated infections or the unmasking of subclinical infections when patients regain the ability to mount a suitable immune response. Worsening of cryptococcal disease after ART initiation, is a reasonable explanation of sudden blindness in our patient. A recent randomized clinical trial conducted in sub-Saharan Africa showed increased mortality rates when initiating ART treatment early.[7] Hence, in the context of early ART initiation, IRIS may be an important contributing factor despite the lack of objective data on IRIS-related mortality.

Table 2: Review of the literature of vision loss in cryptococcal meningitis.

Author	Age /sex	Durati-on of antifung-al therapy	Progres-sion of vision loss	Visual acuity	CSF opening pressu-re	Imaging/autopsy	Treatment	Outcome
Ofner et al[8], 1987	43/ M	6 months	Gradual (6 months)	NPL BE	350	CT: Enlarged optic nerve BE, biopsy: cryptococcal neoformans invasion in optic nerve	IV AMB + dexametha-sone	CF BE, died
Rex et al[9], 1993	30/ M	1 week	Subacu-te (2 months)	NPL BE	NR	MRI: Mild hydrocephalus, normal optic nerves	IV and IT AMB + 5-FC	CF BE

Continued.

Author	Age /sex	Durati-on of antifung-al therapy	Progres-sion of vision loss	Visual acuity	CSF opening pressu-re	Imaging/autopsy	Treatment	Outcome
Torres et al[10], 1999	28/ F	9 days	Acute (6 days)	NPL BE	NR	MRI: Bilateral hyperintense signal of optic nerves	IV AMB + fluconazole + dexametha-sone	NPL BE
Corti et al[11], 2010	34/ M	10 days	Sudden	NPL BE	Elevate d	Autopsy: cryptococcal neoformans invasion in optic nerve	IV AMB	NPL BE, died
De Socio et al[12], 2011	35/ M	7 days	Acute (<1 week)	CF LE	60	MRI: LE ectasia of the optic nerve sheath with contrast enhancement, retrobulbar optic neuritis	IV AMB + IV acyclovir + IV methylprednis-olone	Rapid improve-ment of vision, 9/10 LE
Pooja et al[13], 2014	34/ M	7 days	Acute (1 week)	CF LE, NPL RE	40	MRI: Hyperintense enhancement of optic nerve sheaths and internal auditory canals bilaterally	IV AMB + 5-FC + fluconazole + IV methylprednis-olone	Rapid improve-ment of vision, 20/40 RE, 20/25 LE
Chen et al[14], 2016	45/ F	3 months	Acute	NPL BE	180	MRI: High-signal change and mild atrophy of both optic nerves. Cryptococcal antigen titer in CSF 1:128, and staining of CSF with India ink-positive.	IV AMB + 5-FC + fluconazole	NPL BE
McCabe et al[15], 2022 Case 1	20/ F	7 days	Acute (<1 week)	6/9 BE	Normal	MRI: T1 ring-enhancing lesion, CSF culture: cryptococcal growth	Liposomal AMB + 5-FC	6/5 BE
McCabe et al15, 2022 Case 2	61/ M	5 days	Sudden	CF RE, 6/15 LE	50	MRI: generalized mild hydrocephalus and abnormal leptomeningeal enhancement	IV AMB + 5-FC + dexametha-sone	Died
McCabe et al[15], 2022 Case 3	41/ M	3 weeks	Acute (<1 week)	6/18 BE	25	MRI: multiple cerebral cryptococcomas. CSF culture: cryptococcal growth	IV AMB + 5-FC + fluconazole	6/4.5 BE

5-FC: 5-fluorocytosine; AMB: amphotericin B; CSF: cerebrospinal fluid; CF: count fingers visual acuity; CT: computerized tomography; IT: intrathecal; IV: intravenous; LP: light perception; MRI: magnetic resonance imaging; NPL: no perception of light; NR: not reported; RE: right eye; LE: left eye; BE: both eyes

CONCLUSION

Here is a case report of vision loss in a patient with CM and normal ICP. Early initiation of ART has shown increased incidences of IRIS and mortality. Systemic and ophthalmic complications of cryptococcal infection are diverse and potentially devastating. ART plays an important role in causing IRIS and glucocorticoids play a crucial role in its management. Also, proper screening of other opportunistic infections in an HIV patient before starting ART is advised to avoid such complications.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Gupta M, Kumar A, Kumar A, Mathur V. Reversible blindness in cryptococcal meningitis with human immunodeficiency virus infection. Int J Res Med Sci 2024;12:985-9.