Acute onset of bilateral mydriasis, headache, and vomiting: a challenging diagnosis

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Abstract

Bilateral fixed mydriasis is a rare condition that can arise from a variety of causes (neurological, pharmacological, toxic or metabolic, para-infectious/autoimmune conditions, and traumatic injuries). We report a 65-year-old woman presenting to the emergency department with bilateral mydriasis and complaining of acute severe headache associated with blurry vision, photophobia, vomiting, and a recent history of fever with respiratory symptoms. All preliminary medical investigations aimed at identifying possible causes of endocranial hypertension as well as intracranial lesions or expansive processes, while focusing on findings consistent with meningoencephalitis. The diagnosis of acute bilateral angle-closure glaucoma was established through a wide range of radiological and laboratory exams, and with the help of different consultants. This unusual case highlights two interesting aspects: the importance of a multidisciplinary diagnostic work-up for challenging clinical presentations, and the critical relevance of a re-evaluation diagnostic strategy to avoid clinical mistakes.

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Introduction

Mydriasis is defined as dilation of the pupil, caused by sympathetic stimulation of the iris dilator muscle fibres.[1] Bilateral fixed mydriasis, whether or not associated with headache and other symptoms, may result from a wide array of causes[2] including neurological (*e.g.*, brainstem impairment, serotonin syndrome, third cranial nerve palsy), pharmacological (*e.g.*, antidepressants, sympathomimetics, anticholinergics, serotonergic agents), toxic or metabolic (*e.g.*, cocaine, lysergic acid diethylamide, MDMA, methanol-induced optic neuropathy, post-anoxic brain damage), para-infectious or autoimmune conditions, traumatic injuries (e.g., direct ocular contusion with iridoplegia, loss of pupillary reflex following brain injury), and other causes (e.g., emotional sympathetic overdrive, incidental exposure to mydriatic agents, ophthalmological disorders, bilateral congenital mydriasis). The main causes of bilateral mydriasis are summarized in Table 1.[1-18] Several uncommon aetiologies of bilateral mydriasis have also been reported as isolated clinical findings: i) Sato *et al.* reviewed a case series of atypical post-infectious and autoimmune causes, including botulism, syphilis, Guillain-Barré syndrome (a rare post-inflammatory progressive polyradiculopathy), Fisher syndrome (a variant of Guillain-Barré syndrome), and Bickerstaff brainstem encephalitis (a rare inflammatory disorder of the central nervous system);[8] ii) Baki *et al.* described an unusual case of bilateral mydriasis as a presenting symptom of Hodgkin's lymphoma, likely caused by sympathetic pathway compression around the carotid artery;[19] iii) Du *et al.* reported a rare intraoperative onset of bilateral mydriasis during transcatheter aortic valve replacement, triggered by air embolism to the basilar artery, detectable by CT imaging and resolved with immediate aspiration;[20] iv) Kang *et al.* presented a case of bilateral mydriasis induced by Ma Huang (Ephedra), a traditional herbal remedy containing pseudoephedrine and ephedrine, commonly used as an energy booster and weight-loss aid.[4]

Case Report

A 65-year-old woman presented to our Emergency Department (ED) with a sudden onset of severe headache, blurred vision, and vomiting. She was afebrile, fully alert, and reported a recent episode of fever with respiratory symptoms, for which she had self-administered over-the-counter antitussive medication containing dextromethorphan in the preceding days. Her past medical history was unremarkable. On physical examination, bilateral mydriasis was observed (Figure 1), with poor reactive pupils to light stimulation, but no focal neurological deficits or signs of meningeal irritation. Vital signs were within normal limits, except for a single systolic blood pressure spike of 170 mmHg, which was managed with intravenous labetalol (10 mg). ECG showed no ischemic changes. Arterial blood gas analysis revealed no respiratory abnormalities (pH 7.46, pCO_2 31 mmHg, pO_2 62 mmHg, HCO_3^- 24 mmol/L, lactate 0.7 mmol/L). A contrast-enhanced cranial CT scan ruled out acute lesions or intracranial haemorrhage. Chest X-ray showed nonspecific interstitial markings. Blood tests revealed mild leucocytosis and elevated C-reactive protein (15.43 mg/dL), but no electrolyte alterations. Given the constellation of symptoms, an infectious disease specialist was consulted. Lumbar puncture revealed Clear Cerebrospinal Fluid (CSF) with mild pleocytosis (57 WBC/mm³, predominantly polymorphonuclear), normal glucose (77 mg/dL), and protein levels (45 mg/dL). A multiplex PCR panel (FilmArray) tested negative for neurotropic pathogens. Empiric antimicrobial therapy was initiated with intravenous ceftriaxone (2 g), ampicillin (4 g every 6 hours), and acyclovir (1 g three times daily). This treatment was subsequently discontinued once CSF results were confirmed negative. Blood and urine cultures remained sterile. A repeat neurological evaluation was requested. Given the negative CT findings, a cerebral and spinal MRI was recommended. An Artificial Intelligence-based clinical decision support tool suggested considering serotonin syndrome or dextromethorphan intoxication based on her recent use of this latter drug to sedate cough, although classical features (such as hyperreflexia, clonus, or altered mental status) and laboratory

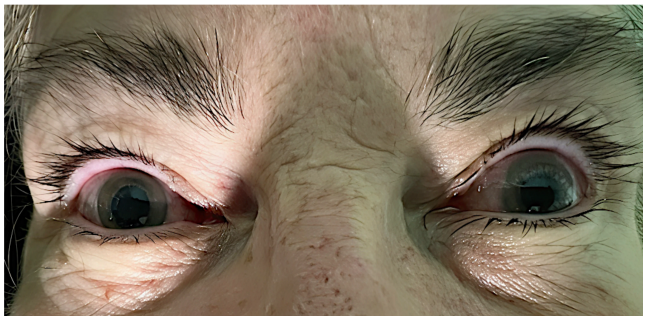

Figure 1. Acute bilateral angle-closure glaucoma. This image shows a case of bilateral mydriasis, a clinical finding which can arise from a variety of causes. In this case a definitive diagnosis of acute bilateral angle-closure glaucoma was established only following the manifestation of overt ocular signs such as conjunctival hyperaemia (evident in this image), corneal oedema, and a significant elevation in intraocular pressure.

Table 1. Differential diagnosis of bilateral mydriasis and relevant pathophysiological mechanisms

Aetiology	Specific Causes	Mechanism / Notes
Neurological [2,3]	• Brainstem impairment • Serotonergic syndrome • Third cranial nerve palsy • Ophthalmoplegic migraine	Disruption of pupillary Reflex pathways Serotonin excess
Pharmacological [1,2,4,5]	• Antidepressants • Sympathomimetics • Anticholinergics • Serotonergic agents	Direct receptor-mediated pupillary dilation
Toxic / Metabolic [2,4,6,7]	• Cocaine • LSD, MDMA • Herbal medicine (e.g., Ma Huang) • Methanol-induced optic neuropathy • Post-anoxic brain damage	Sympathetic overdrive Direct toxicity Optic nerve injury
Para-infectious / Autoimmune [2,8-13]	• Herpes zoster, VZV • Botulism • Syphilis • Guillain-Barré syndrome • Fisher syndrome • Bickerstaff brainstem encephalitis • Vogt-Koyanagi-Harada syndrome	Post-infectious neuropathies Autoimmune inflammation of CNS pathways
Traumatic Injuries [2,14,15]	• Ocular contusion with iridoplegia • Brain injury with pupillary reflex loss • Urrets-Zavalia syndrome post-keratoplasty • Postganglionic mydriasis after blow-out fracture repair	Disruption of iris innervation or muscle damage
Ophthalmological Disorders [2,16]	• Bilateral angle-closure glaucoma	Pupillary block Sudden IOP increase may impair iris function
Other Causes [2,17,18]	• Emotional sympathetic overdrive • Malignant glaucoma after cataract surgery *(e.g.,* capsular tension ring) • Congenital bilateral mydriasis	Functional or structural disruption of parasympathetic tone or iris anatomy

CNS, central nervous system; IOP, intra-ocular pressure; LSD, lysergic acid diethylamide; MDMA, 3,4-methylenedioxymethamphetamine; VZV, varicella zoster virus.

signs of organ dysfunction were absent. Approximately 19 hours after admission, the patient developed progressive binocular conjunctival redness, periorbital swelling, and worsening blurred vision. An ophthalmologic consult was obtained. Examination revealed conjunctival hyperaemia, corneal oedema with folds, and narrowing of the anterior chamber. Intraocular pressure measured by tonometry was markedly elevated (57 mmHg), leading to a diagnosis of acute bilateral angle-closure glaucoma. The patient was transferred to the ophthalmology unit following administration of intravenous mannitol (18%, 250 mL) and topical therapy with timolol 0.5%, brimonidine, and pilocarpine eye drops. Emergency treatment in the ED also included oral acetazolamide (250 mg) and intravenous furosemide (40 mg). Two additional boluses of mannitol (18%, 500 mL each) were administered and YAG laser peripheral iridotomy was performed once the corneal oedema had resolved. The patient was discharged in good condition four days after admission.

Discussion

This report illustrates a rare and challenging case presentation characterized by bilateral Acute Angle-Closure Glaucoma (AACG), an ophthalmologic emergency that typically occurs unilaterally. Bilateral involvement is uncommon and often misleading, as it can mimic life-threatening neurological or systemic conditions.[16] In our patient, the initial symptoms (sudden-onset severe headache, vomiting, blurred vision, and bilateral fixed mydriasis) were suggestive of intracranial pathology rather than of a primary ocular disorder. The absence of ocular pain and conjunctival hyperaemia at presentation further complicated the diagnostic process.

Bilateral fixed mydriasis raises concern for several critical differential diagnoses, including brainstem lesions, elevated intracranial pressure, bilateral third cranial nerve palsy, toxic or metabolic encephalopathies, and post-infectious or autoimmune neuropathies.[2] In this case, the diagnostic approach appropriately prioritized urgent neurological and infectious causes. A stepwise exclusion of these possibilities (through neuroimaging, lumbar puncture, and laboratory investigations) was essential, albeit initially inconclusive. Only after the onset of overt ocular signs (*i.e.*, conjunctival hyperaemia, corneal oedema, and elevated intraocular pressure) did the underlying aetiology become evident. The delayed appearance of ophthalmologic features underscores the importance of serial reassessment in evolving clinical scenarios, especially when the initial presentation is non-specific or atypical. Acute angle-closure glaucoma is usually unilateral and associated with ocular pain, photophobia, and visual loss.[17] In contrast, bilateral AACG is rare and may present predominantly with headache, nausea, vomiting, and even altered mental status, mimicking conditions such as intracranial hypertension, subarachnoid bleeding, or serotonin syndrome, particularly when pupillary abnormalities are prominent, as in the reported case.[16]

Various factors can trigger bilateral AACG, including medications (e.g., decongestants containing sympathomimetics),[1,2,4,5] systemic diseases such as Vogt-Koyanagi-Harada disease,[9] anatomical predispositions like microspherophakia,[17] and postoperative complications of intraocular procedures, such as cataract surgery with capsular tension ring implantation.[14,18] In our case, the recent use of dextromethorphan (a serotonin reuptake inhibitor with mild anticholinergic properties) may have precipitated or worsened angle closure in a predisposed individual. Although serotonin syndrome was initially considered, the absence of hallmark features such as hyperreflexia, clonus, or organ dysfunction made this diagnosis unlikely. This case underscores several key clinical messages: i) bilateral mydriasis should not prompt a neurological work-up alone; although rare, ophthalmologic causes must be considered, especially when the clinical picture evolves; ii) bilateral AACG, while uncommon, should be part of the differential diagnosis in patients presenting with unexplained headache, visual symptoms, and pupillary abnormalities, even in the absence of classic ocular pain; iii) a multidisciplinary approach is essential when initial investigations prove inconclusive and the clinical condition continues to evolve; iv) timely ophthalmologic evaluation and appropriate medical and surgical interventions are crucial to prevent irreversible visual impairment. This management strategy is supported by current European and international guidelines, which advocate prompt laser peripheral iridotomy and individualized pharmacological treatment based on anterior chamber anatomy, intraocular pressure profile, and patient-specific risk factors.[21,22]

Conclusions

In this case, the final diagnosis of bilateral AACG was achieved through repeated clinical assessments and a multidisciplinary approach. The initial presentation was misleading, as it lacked classical ocular signs and instead mimicked neurological and infectious conditions. This emphasizes the need to maintain a broad differential diagnosis when faced with non-specific symptoms, such as bilateral mydriasis, headache, and vomiting. The evolution of the clinical picture, marked by the appearance of ocular signs and elevated intraocular pressure, ultimately guided to the correct diagnosis. Prompt ophthalmological evaluation enables both medical and surgical treatment, preventing potentially severe complications. This case highlights the importance of considering atypical and rare presentations of vision-threatening diseases in the emergency setting and underscores the value of dynamic reassessment and interdisciplinary collaboration in managing challenging cases.

References

1. Koss MC. Pupillary dilation as an index of central nervous system α2-adrenoceptor activation. J Pharmacol Methods 1986;15:1-19.
2. Caglayan HZB, Colpak IA, Kansu T. A diagnostic challenge: dilated pupil. Curr Opin Ophthalmol 2013;24:550-7.
3. Simonetto M, Zanet L, Capozzoli F, et al. Unilateral headache with bilateral internal ophthalmoplegia. Neurol Sci 2012;33:1185-7.
4. Kang YE, Chae J, Nguyen TT, et al. A Case Report of Acute Bilateral Mydriasis Induced by Herbal Medication. Neuro-Ophthalmol 2024;48:193-7.
5. Chean CS, Ali AIAH, Malick H. Bilateral simultaneous acute angle closure glaucoma triggered by an over-the-counter cold and influenza medication. BMJ Case Rep 2024;17:e260950.
6. Adegoke S, Alo L. Datura stramonium poisoning in children. Niger J Clin Pract 2013;16:116.
7. Cheng KL, Chan YC, Mak TWL, et al. Chinese herbal medicine-induced anticholinergic poisoning in Hong Kong. Hong Kong Med J Xianggang Yi Xue Za Zhi 2013;19:38-41.
8. Sato H, Naito K, Hashimoto T. Acute isolated bilateral mydri-

asis: case reports and review of the literature. Case Rep Neurol 2014;6:74-7.
9. Yuan F, Zhang Y, Yan X. Bilateral acute angle closure glaucoma as an initial presentation of Vogt-Koyanagi-Harada syndrome: A clinical case report. Eur J Ophthalmol 2022;32:NP230-4.
10. Hakim W, Sherman R, Rezk T, Pannu K. An acute case of herpes zoster ophthalmicus with ophthalmoplegia. Case Rep Ophthalmol Med 2012;2012:1-3.
11. Shaw M, Handley SE, Porooshani H. A case of internal ophthalmoplegia associated with varicella zoster. J Pediatr Ophthalmol Strabismus 2012;49:0731-04.
12. Kaymakamzade B, Selcuk F, Koysuren A, et al. Pupillary involvement in miller fisher syndrome. Neuro-Ophthalmol 2013;37:111-5.
13. Monaco S, Freddi N, Francavilla E, et al. Transient tonic pupils in botulism type B. J Neurol Sci 1998;156:96-8.
14. Figueiredo GS, Kolli SSP, Ahmad S, et al. Urrets-Zavalia syndrome following penetrating keratoplasty for keratoconus. Graefes Arch Clin Exp Ophthalmol 2013;251:809-15.
15. Hamel O, Corre P, Ploteau S, et al. Ciliary ganglion afferents and efferents variations: a possible explanation of postganglionic mydriasis. Surg Radiol Anat 2012;34:897-902.
16. Zhang CL, Lai WL, Ziyar I, et al. Bilateral simultaneous primary acute angle-closure glaucoma. Precis Clin Med 2020;3:297-300.
17. Khazaeni B, Zeppieri M, Khazaeni L. Acute angle-closure glaucoma. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2025 May 26]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK430857/
18. Jin G, Hu D, Li Q, et al. A rare case of bilateral malignant glaucoma after cataract surgery with capsular tension ring implantation: a case report. BMC Ophthalmol 2024;24:427.
19. Baki E, Scheidhauer K, Schmidt-Graf F. Bilateral mydriasis as first manifestation of Hodgkin's lymphoma: a case report. BMC Neurol 2022;22:473.
20. Du Y, Qi H, Han Z. Bilateral mydriasis due to air embolism. JACC Cardiovasc Interv 2024;17:816-7.
21. European Glaucoma Society Terminology and Guidelines for Glaucoma, 5th Edition. Br J Ophthalmol 2021;105:1-169.
22. Wagner IV, Stewart MW, Dorairaj SK. Updates on the diagnosis and management of glaucoma. Mayo Clin Proc Innov Qual Outcomes 2022;6:618-35.