

JAMA Ophthalmology Clinical Challenge

Acute Bilateral Periorbital Edema in a Psychiatric Patient

Kaela N. Acuff, BS; George A. Villatoro, MD; Sally L. Baxter, MD, MSc

A Conjunctivochalasis vs chemosis inferiorly**B** Bilateral periorbital edema

Figure 1. Clinical photographs of bilateral periorbital edema in an older patient. A, External photographs of the patient's bilateral eyes on initial evaluation showing conjunctivochalasis vs chemosis inferiorly. B, External photograph showing substantial bilateral periorbital edema present on initial ophthalmic examination.

An older patient with history of alcohol use disorder was admitted for altered mental status present since becoming incarcerated 11 days prior. The patient remained persistently delusional and psychotic despite treatment for alcohol withdrawal, including maintenance intravenous fluids, lorazepam, haloperidol, and intravenous thiamine on admission. The psychiatric service subsequently started valproic acid, 500 mg in the morning and 700 mg in the evening, and olanzapine, 5 mg in the morning and 10 mg in the evening. On hospital day 2, the patient remained afebrile but acutely developed bilateral periorbital edema. Results of metabolic laboratory tests and cell counts were remarkable for mild hyponatremia (sodium level, 152 mEq/L [reference range, 136-145 mEq/L]; to convert to mmol/L, multiply by 1) and leukocytosis (white blood cell count, 17 000/mm³ [reference range, 4000-10 000/mm³]). Ophthalmology was consulted due to concern for bilateral orbital cellulitis.

Visual acuity and extraocular movements could not be assessed due to noncompliance. There was no relative afferent pupillary defect, and intraocular pressures were 15 mm Hg OD and 16 mm Hg OS. The patient had diffuse facial edema with prominent bilateral periorbital and eyelid nonpitting edema, tense eyelid margins bilaterally, scant mucoid discharge, and conjunctivochalasis vs mild chemosis inferiorly bilaterally (Figure 1). No warmth, induration, purulence, wounds, or ecchymosis was noted. Dilated examination demonstrated normal posterior poles, but poor cooperation limited peripheral examination. The patient did not have any new rashes or swelling elsewhere.

Head computed tomography (CT) on admission was normal and did not show any acute orbital process. Orbital CT performed on day 2 showed new diffuse facial and periorbital edema with relative sparing of the intraconal fat. No intraorbital mass or hemorrhage was seen.

WHAT WOULD YOU DO NEXT?

- A. Perform orbital biopsy
- B. Correct metabolic disturbance
- C. Review administered medications for possible allergic reaction
- D. Perform lateral canthotomy and cantholysis

+ CME Quiz at jamacmelookup.com

Diagnosis

Drug reaction to olanzapine and valproic acid

What to Do Next

- C. Review administered medications for possible allergic reaction

Discussion

Given the examination, imaging, and timeline of developing edema, the most likely diagnosis was a drug reaction to the new psychiatric medications, olanzapine and valproic acid. Given this patient's taut eyelids and possible limited extraocular movement, orbital compartment syndrome was initially of concern but was ruled out by normal intraocular pressure, no relative afferent pupillary defect, and

posterior pole examination (choice D). Under the guidance of the allergy and immunology service, C1-inhibitor protein levels were obtained and hereditary angioedema was ruled out.

Bilateral periorbital edema without a history of trauma is a nonspecific finding with a broad differential diagnosis. Possible etiologies include infection, malignancy, thyroid eye disease, metabolic disorders, drug reactions, contact allergy, and vascular and rheumatologic conditions.¹ Presence of chemosis is especially concerning for infection, thyroid eye disease, or angioedema and may indicate vascular abnormalities.²⁻⁴ While ceftriaxone and vancomycin were started for possible cellulitis, they were discontinued after 2 days as the patient's afebrile status examination and CT findings (Figure 2) made this less likely. Additionally, bilateral preseptal or orbital cel-



Figure 2. Computed tomography imaging of patient's bilateral orbits showing new extensive, diffuse facial (pink arrowheads) and periorbital soft tissue swelling (yellow arrowheads), intraorbital edema within the extraconal space (upper asterisks), and new bilateral proptosis with relative sparing of the intraconal fat (lower asterisks).

lulitis would be extremely uncommon. Trauma was ruled out by the history, absence of ecchymosis and face wounds, and no evidence of orbital trauma on imaging. Metabolic factors were considered; however, the patient lacked peripheral edema or ascites, and results of metabolic laboratory tests were only remarkable for mild hypernatremia, which is not commonly associated with edematous states (choice B). The acute onset made malignancy (choice A),

thyroid eye disease, and vascular etiologies less likely. The timeline and examination findings were most consistent with localized edema resulting from iatrogenic causes, at which time the new psychiatric regimen was considered.

Psychiatric medications have been known to cause adverse ocular effects. Well-known effects include the induced myopic shift associated with topiramate,⁵ while others are less recognized. Prior reports have shown atypical antipsychotics such as olanzapine to be associated with edematous reactions, blepharospasm, oculogyric crisis, and retinal vein occlusion.⁶ However, while peripheral edema is a well-documented adverse effect of certain psychiatric medications, facial and periorbital edema is rare and has only been reported in nonophthalmology journals. Reports of periorbital edema with olanzapine have been limited to a few psychiatry and pharmacology publications.^{7,8} Additionally, only 1 report of valproate-induced periorbital edema exists.⁹ While we could not discern if only 1 or both agents caused the adverse reaction, both medications have been associated with periorbital edema. Ophthalmologists should be aware of this and other potential ocular adverse effects from psychiatric medications and consider it as part of their differential diagnosis in patients with bilateral periorbital and facial edema.

Patient Outcome

The patient started receiving methylprednisolone and diphenhydramine, and the psychiatric regimen was switched to mirtazapine, 7.5 mg in the evening, resulting in resolution of the periorbital edema without recurrence.

ARTICLE INFORMATION

Author Affiliations: Viterbi Family Department of Ophthalmology and Shiley Eye Institute, University of California, San Diego, La Jolla (Acuff, Villatoro, Baxter); Division of Biomedical Informatics, Department of Medicine, University of California, San Diego, La Jolla (Baxter).

Corresponding Author: Sally L. Baxter, MD, MSc, Viterbi Family Department of Ophthalmology and Shiley Eye Institute, University of California San Diego, 9415 Campus Point Dr, MC 0946, La Jolla, CA 92093 (slbaxter@health.ucsd.edu).

Published Online: August 1, 2024.

doi:10.1001/jamaophthalmol.2024.2815

Conflict of Interest Disclosures: Dr Baxter reported grant UL1TR001442 from the National Institutes of Health and an unrestricted departmental grant from Research to Prevent Blindness; personal fees from Topcon; and nonfinancial support from Optomed. No other disclosures were reported.

REFERENCES

1. Dyken JR, Pagano JP, Soong VY. Superior vena caval syndrome presenting as periorbital edema. *J Am Acad Dermatol*. 1994;31(2, pt 1):281-283. doi:10.1016/S0190-9622(08)81981-0
2. Scott IU, Siatkowski MR. Thyroid eye disease. *Semin Ophthalmol*. 1999;14(2):52-61. doi:10.3109/08820539909056064
3. Hung MH, Kuo JR, Wang CC. Chemosis: traumatic carotid cavernous fistula. *ANZ J Surg*. 2011;81(6):486-487. doi:10.1111/j.1445-2197.2011.05780.x
4. Mueller A. Allergic conjunctivitis: an update. In: Traidl-Hoffmann C, Zuberbier T, Werfel T, eds. *Allergic Diseases—From Basic Mechanisms to Comprehensive Management and Prevention*. Handbook of Experimental Pharmacology. Springer International Publishing; 2022:95-99.
5. Mechrgui M, Kanani S. The ophthalmic side effects of topiramate: a review. *Cureus*. 2022;14(8):e28513. doi:10.7759/cureus.28513
6. Umar MU, Abdullahi AT. Self-limiting atypical antipsychotics-induced edema. *Indian J Psychol Med*. 2016;38(3):182-188. doi:10.4103/0253-7176.183089
7. Kuppli PP, Nebhinani N, Jain S, Singhai K. Olanzapine associated palpebral edema. *Asian J Psychiatr*. 2018;36:60-61. doi:10.1016/j.ajp.2018.06.010
8. Zink M, Kuwilsky A, Knopf U. Olanzapine-associated bilateral eyelid edema. *J Clin Psychopharmacol*. 2007;27(2):214-215. doi:10.1097/01.jcp.0000264968.69958.28
9. Hatahet S, Khalaf K, Elhamamsy S. Valproate-induced periorbital edema. *R I Med J (2013)*. 2021;104(10):10-11.