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Psychosis resulting from trimethoprim-sulfamethoxazole treatment for preseptal cellulitis

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Abstract:

Trimethoprim-sulfamethoxazole (TMP-SMX) is a commonly used antimicrobial agent because of its low cost, diverse antimicrobial profile, and minimal severe adverse effects. A rare side effect is psychosis, a complication that has not been published in the ophthalmology literature. A 53-year-old female presented to the ophthalmology office with left upper eyelid erythema, focal tenderness, and discharge. She was diagnosed with preseptal cellulitis of the left upper lid and started on TMP-SMX. The next day, the patient's condition improved with reduced swelling and no discharge. However, 2 days later, she experienced visual hallucinations whereby worms were growing out of her left eye accompanied by theme-congruent tactile hallucinations. TMP-SMX was discontinued and substituted for clindamycin, and she reported resolution of her symptoms 8 h later. TMP-SMX has extensive cerebrospinal fluid penetration and causes a folic acid deficiency, which may explain the rare occurrence of neuropsychiatric side effects. This patient had a substance-induced psychosis, in which visual and tactile hallucinations began 3 days after taking TMP-SMX and resolved 8 h after discontinuation, a timeline consistent with the literature. Central nervous system toxicity is rare in nonelderly immunocompetent patients, with only three such cases reported in the literature. While visual and auditory hallucinations have been described previously, this is the first reported case of TMP-SMX-induced tactile hallucinations and unilateral visual hallucinations. Moreover, because TMP-SMX is a first-line agent commonly used to treat orbital and preseptal cellulitis, it is important for ophthalmologists to be aware of this atypical side effect, as it can be life threatening.

Keywords:

Cellulitis, hallucinations, psychosis, trimethoprim-sulfamethoxazole

Introduction

Trimethoprim-sulfamethoxazole (TMP-SMX) is a combination of two antimicrobial agents that are effective against a wide range of bacteria and some protozoa. The medication is used to treat aerobic Gram-positive bacteria and Gram-negative bacteria in urinary tract infections, gastrointestinal infections, pneumonia, and cellulitis; it is also a first-line agent in prophylaxis against toxoplasmosis and *Pneumocystis jirovecii* pneumonia (PCP). TMP-SMX is generally well-tolerated except in the elderly and

immunocompromised, and common side effects include nausea, vomiting, rash, pruritus, and hypersensitivity reactions; less common side effects include nephrotoxicity, hepatitis, megaloblastic anemia secondary to reduced folate availability, and Stevens-Johnson syndrome.^[1] An uncommon and lesser known side effect is psychosis. There are case reports in the literature that have implicated an association between TMP-SMX and psychosis; however, it is very rare in immunocompetent younger patients, has not been published in the ophthalmology literature, and is not recognized by most physicians. It is important for physicians to be aware of the drug's neurological adverse effects, which consist not only

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of hallucinations but also of delusions, depression, agitation, confusion, and suicide attempts because resolution requires immediate discontinuation of the medication.^[2,3] This paper presents a unique case of a middle-aged immunocompetent patient who developed visual and tactile hallucinations after treatment with oral TMP-SMX for preseptal cellulitis, also known as periorbital cellulitis.

Case Report

A 53-year-old female presented with left upper eyelid pain, erythema, and swelling. She had a past medical history of thyroid cancer status postthyroidectomy in 2017, major depressive disorder, fibromyalgia, and chronic pain syndrome. After being discharged from the urgent care with gentamicin drops, she presented to our ophthalmology practice 1 day later. Her examination revealed left upper lid erythema, swelling, focal tenderness, and discharge upon palpation. Visual acuity without correction showed right eye 20/30 and left eye 20/40. Intraocular pressures were within normal limits. Anterior segment examination was significant for early nuclear sclerotic cataracts. The patient was diagnosed with preseptal cellulitis of the left upper lid and started on 80 mg TMP/400 mg SMX PO twice daily for 10 days, given her allergy to amoxicillin. She was also prescribed erythromycin and tobramycin/dexamethasone ophthalmic ointment to the left upper lid, as well as preservative-free artificial tears. She was instructed to discontinue the gentamicin eye drops.

The patient's medication list was extensive, which included topiramate, suvorexant, calcitriol, citalopram, fentanyl transdermal patch, hydromorphone, ketoconazole cream, lidocaine topical ointment, potassium chloride, levothyroxine, warfarin, tizanidine, and venlafaxine.

The next day, the patient returned feeling better. Her examination revealed reduced swelling of the left upper lid with no further discharge expressed upon palpation. She was to continue the current treatment and return 1 week later for follow-up. However, the patient returned 2 days later severely distressed about seeing worms appear out of her left eye. She described seeing worms grow out of the left eye and being able to pull them out with her fingers, after which more would appear. The patient denied having any auditory hallucinations, previous psychotic episodes, or suicidal/homicidal ideation and was alert, oriented, and attentive. She has a history of major depressive disorder, but she denied a family history of psychiatric illnesses. Furthermore, she denied the use of tobacco, alcohol, or other substances that may precipitate hallucinations.

The decision was made to discontinue TMP-SMX and switch treatment to an alternative antibiotic, clindamycin. Eight hours later, the patient reported to us that she no longer saw worms and had resolution of her psychosis. Because her symptoms resolved soon after discontinuing the medication and because she denied having a history of hallucinations, neuropsychiatry evaluation was not necessary and would have been considered if symptoms persisted.

Discussion

TMP-SMX is a widely used medication because of its low cost, diverse antimicrobial profile, and minimal severe adverse effects. In a study consisting of 1121 hospitalized patients, serious drug toxicity was rare and no episodes of delirium were reported.^[4] The mechanism of action of TMP-SMX-induced psychosis and central nervous system (CNS) toxicity is not definitively known, but biochemical pathways have been implicated,^[3] and it is known that it has excellent cerebrospinal fluid penetration.^[5,6] TMP is also an irreversible dihydrofolate reductase inhibitor and thus reduces the conversion of dihydrofolate to tetrahydrofolate, the active form of folic acid that is essential in the formation of deoxythymidine monophosphate for DNA synthesis. Folic acid deficiencies have been linked to diverse neuropsychiatric sequelae such as dementia, depression, and cognitive impairment.^[7] Folate thus has an essential role in thymidine and thus nucleic acid synthesis, especially in CNS growth and metabolism, suggesting that deficiencies caused by TMP can lead to neurological toxicity.

In this patient, visual and tactile hallucinations began 3 days after taking TMP-SMX and from the new medications given to treat the preseptal cellulitis; it was the most likely medication causing the symptoms. It was presumed that the patient had a substance-induced psychosis, and resolution of the psychiatric symptoms 8 h after discontinuing the medication further affirmed the diagnosis. Diagnostic criteria include a delusion or hallucination that occurs during or soon after the intoxication or withdrawal of a medication, without occurring in the context of another psychotic disorder or delirium, and causes extreme distress or impairment.^[8]

The mean half-life of both drugs has been reported to be between 8 and 10 h, and thus, steady state concentrations are reached by 3 days, suggesting that levels of TMP-SMX increased to steady state to cause mental status changes in the patient presented here.^[9] Symptoms abated 8 h or about one-half life after the drug was stopped; this timeline is consistent with the literature as most cases of TMP-SMX-induced psychosis begin within 3 days of drug initiation and resolve within 24 h.^[10]

TMP-SMX quickly enters the bloodstream after gastrointestinal absorption, is broken down by the liver into inactive metabolites by the cytochrome P450 system, and is renally excreted.^[1] Patients with impairments in hepatic or renal function, such as the elderly or those with chronic kidney disease or liver failure, are at greater risk of accumulating TMP-SMX and metabolites and thus drug toxicities. The 53-year-old patient presented here had no history of renal or hepatic disease or insufficiency, suggesting that TMP-SMX was adequately metabolized and excreted such that she was never exposed to a toxic dose.

Given that TMP-SMX is a commonly prescribed medication targeted for a wide range of microbes, associated CNS toxicities are uncommon and extremely rare in younger and immunocompetent patients. There are studies describing TMP-SMX-induced psychosis, which was initially thought to occur mostly in the elderly^[2,11] or immunocompromised.^[10,12,13] Three cases have been reported in healthy adults' ages 18, 19, and 46 with no psychiatric history who developed visual and auditory hallucinations in response to TMP-SMX, leading one of them to shoot himself in the face.^[1,3,14] Two of them were taking oral double-strength tablets (160 mg TMP/800 mg SMX) BID, whereas the patient described in this case took half that dose and still developed CNS side effects. Given these historical reports of TMP-SMX-induced psychosis in nonelderly immunocompetent patients, there is an increased likelihood that the woman in this case developed hallucinations secondary to TMP-SMX. Notably, none of the aforementioned studies have described tactile hallucinations associated with the drug. Moreover, it is fascinating that the tactile and visual hallucinations appeared only from the left eye, the location of the preseptal cellulitis, an atypical psychotic presentation that has not been associated with TMP-SMX. In addition, no cases of TMP-SMX-induced psychosis have been mentioned in the ophthalmology literature, as almost all cases have arisen from treatment for UTI in immunocompetent patients or from treatment for PCP in immunocompromised patients.

Medical conditions that might have triggered this patient's hallucinations include hypothyroidism following thyroidectomy, delirium secondary to infection, and major depressive disorder. Psychiatric manifestations in hypothyroidism typically include lethargy and mental slowness, but visual hallucinations have been reported; moreover, psychosis usually appears several months or years after the onset of physical symptoms.^[15] History and physical examination were unremarkable in regards to signs of hypothyroidism, and the patient has been compliant and stable with her levothyroxine for years. Delirium is a common cause of psychosis; however, the patient was fully alert and

oriented during appointments and it is typically the elderly who are at increased risk of becoming delirious during an infection.^[16] The patient's depression had also been stable and compliant with her citalopram and venlafaxine and has never reported episodes of psychosis or other psychiatric illnesses in the past. In addition, psychosis seen in major depressive disorder (MDD) is typically auditory and mood congruent (depressive themes of deserved punishment or hopelessness) and rarely consists of mood incongruent frank visual and tactile hallucinations as seen in this patient.^[8]

The patient's medication regimen may be linked to the patient's symptoms. Among them, tobramycin/dexamethasone ophthalmic ointment was the only newly introduced drug that is possibly but unlikely related to her psychosis. It is widely known that oral steroids commonly cause psychiatric symptoms, in contrast to topical steroids which rarely do so; only two reports have been cited in the literature, neither of which were caused specifically by dexamethasone.^[17,18]

Hydromorphone and fentanyl, as well as opiate withdrawal in general, can cause psychosis.^[19] In addition, psychosis associated with topiramate, venlafaxine, tizanidine, and citalopram has been cited in the literature but is scarce.^[20-23] Furthermore, the patient has been taking these drugs consistently over years, so they are unlikely to have caused the sudden transient psychiatric symptoms in this patient, which resolved immediately after TMP-SMX cessation. Furthermore, this patient had been using her pain medication as indicated and had not experienced other withdrawal symptoms at the time of her hallucinations.

Her medication regimen was inputted into a drug interaction checker to analyze for pharmacodynamic and pharmacokinetic interactions and changes in hormone levels, which did not demonstrate significant adverse effects contributing to the patient's presentation. However, it is possible that taking TMP-SMX in the context of her medical history and medication schedule may have caused a cumulative effect that contributed to the patient's symptoms.

Delusional infestation, also known as delusional parasitosis, is a delusional disorder (somatic subtype) in which patients have a fixed, false belief that they are infected by living organisms such as parasites, fungus, or worms, and typically have excoriations from trying to remove the bugs. Ocular manifestations of delusions of parasitosis have been reported.^[24,25] However, the patient does not satisfy the criteria for delusional infestation because the delusion did not last for more than 1 month and the condition cannot be attributed to a medical condition or medication.^[8] Furthermore, this case did

not have any evidence of self-inflicted trauma, which is typical of delusional infestation.

Conclusion

The timeline of TMP-SMX administration and cessation and of the onset and resolution of psychiatric symptoms, in the absence of renal/hepatic insufficiency or history of hallucinations, strongly affirms that the drug was the primary cause of the patient's symptoms. Taking TMP-SMX in the setting of medical illnesses and medications potentially contributing to her psychosis may have an additive effect that ultimately resulted in her visual and tactile hallucinations. It is thus essential that physicians have a thorough understanding of a patient's medical and psychiatric history as well as medication schedule when prescribing TMP-SMX, and closely monitor their mental status while taking the drug, as substance-induced psychosis, although rare, can be life threatening. The case is also unique in that tactile hallucinations and unilateral visual hallucinations have never been associated with this drug. Moreover, because TMP-SMX is a first-line agent commonly used to treat orbital and preseptal cellulitis, it is important for ophthalmologists to be aware of this atypical side effect.

Declaration of patient consent

The patient has given informed oral consent for her clinical information to be reported in the journal. The patient understands that her name, initials, or other identifiable information will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

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Conflicts of interest

The authors declare that there are no conflicts of interest of this paper.

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