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LETTER TO THE EDITOR

Contributing factors in trimethoprim-sulfamethoxazole-induced tremor in Pneumocystis jirovecii pneumonia

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Trimethoprim-sulfamethoxazole (TMP-SMX) is the first-line antibiotic for the treatment of opportunistic infections, including Pneumocystis jirovecii pneumonia (PJP), in immunocompromised patients.[1,2] Most patients tolerate the treatment well, particularly in lower doses, but dose-related dermatological, renal, and hepatic reactions are the most common adverse events (AEs).[1,2] Although neurological AEs are rare, TMP-SMX-induced tremor has been infrequently reported since 1988 as a reversible neurotoxic AE at higher doses, mostly in immunocompromised patients.[3-6] Herein, we presented a patient with tremor induced by both mild hypoxia and TMP-SMX during PJP treatment.

A 67-year-old male presented with a high fever and dyspnea. Mild hypoxia was evident at admission, and a chest computed tomography revealed bilateral ground-glass opacities. Following clinical, laboratory, and imaging findings, PJP was diagnosed. Microbiological investigations for respiratory pathogens were negative. The patient was diagnosed with multiple myeloma in 2019 and received four cycles of cyclophosphamide, bortezomib, and dexamethasone. In 2022, the patient underwent hematopoietic stem-cell transplantation, which was followed by ongoing treatment with lenalidomide. The patient had a history of irregular use of inhaled pentamidine for PJP prophylaxis. The patient had coronary artery disease.

The patient was administered 960-4,800 mg/day of TMP-SMX (TMP: 11.3 mg/kg/day). Tremor appeared in both hands within 72 h of initiating TMP-SMX and subsequently deteriorated over the next day. It was a postural tremor with a high frequency, more pronounced in the upper limbs and predominantly affecting the right side. The patient reported dyspnea, dizziness, exacerbation of the tremor, and balance problems with minimal effort. The patient's mother had a history of essential tremor. Metabolic causes of tremors were excluded through laboratory tests, including electrolytes and renal, liver, and thyroid function tests. Laboratory findings at admission indicated elevated levels of C-reactive protein at 39.7 mg/L (reference range: <5 mg/L). On the day of the tremor, the laboratory results for the patient with anemia of chronic disease showed a decrease in hemoglobin levels from 9.4 to 8.2 g/dL and a decrease in C-reactive protein levels to 12.6 mg/L. Other laboratory parameters remained within normal limits. There was no evidence of hemolytic anemia in the clinical and laboratory findings. A marked reduction in the patient's tremor was observed following an infusion of 2 units of erythrocyte suspension. After reducing the TMP-SMX dosage (TMP: 5.6 mg/kg/day) on the seventh day, a more significant reduction in the tremor was noted. The patient's hemoglobin level increased to 11.5 g/dL. The patient completed a three-week course of TMP-SMX treatment without any AEs.

This case report suggests that TMP-SMX can cause tremors, particularly in individuals who are

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genetically susceptible to tremors, when combined with mild hypoxia caused by pneumonia and anemia. Tremors occur most frequently on the third day of treatment[3-6] and typically resolve within a few days of discontinuing the medication[3,4,6] or with a reduction in dosage.[5] Our patient presented with clinical features consistent with previously documented reports. Despite a family history of essential tremor, the tremor in this case was not exacerbated by voluntary movements, a feature that distinguishes it from typical essential tremor. This familial predisposition suggests a possible genetic component to the patient's susceptibility to tremors, including those induced by TMP-SMX.

Slavik et al.[5] observed a decrease in tremor with a decrease in TMP dose from 19.4 mg/kg/day to 15.1 mg/kg/day. They suggested that this AE was dose-related and stated that the use of low-dose TMP-SMX would be both effective and reduce the possibility of tremor. In this case, tremor was observed despite the low dose of TMP and exacerbated by minimal physical activity along with the dyspnea, providing further insight into the relationship between TMP-SMX-induced tremor and hypoxia. In the case of Slavik et al.,[5] despite hypoxia during the first few days of the treatment, no tremor was observed; hemoglobin decreased to 8.1 g/dL on the day of tremor and increased to 9.4 g/dL on the day of recovery, as in our patient. In our case, the tremor showed a remarkable reduction following the correction of anemia. These observations suggest that hypoxia due to anemia and pneumonia may increase the incidence and severity of TMP-SMX-induced tremor, even if mild. Anemia-related factors, such as reduced oxygen delivery to the brain and its effect on neuronal excitability, may contribute to the pathophysiology of these tremors.[7]

In conclusion, this case report emphasizes that hypoxia-promoting conditions, such as anemia and pneumonia, and genetic predisposition should be considered in the occurrence of tremor, a rare AE of TMP-SMX treatment.

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Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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