Can low-dose methotrexate cause seizures?

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Introduction:

Methotrexate is commonly used in low doses (up to 30 mg once weekly) for the treatment of psoriasis, rheumatoid arthritis and psoriatic arthritis. Methotrexate is generally well tolerated although monitoring is required for any signs of renal, liver or haematological toxicities.

Objective:

To describe a rare case of seizures associated with low-dose methotrexate.

Clinical Features:

A 20-year-old Caucasian woman with generalised epilepsy was started on methotrexate 10 mg weekly for the treatment of psoriatic arthritis. Five days after the second dose of methotrexate she had a generalised seizure. Prior to this episode, she had not had a seizure for five years.

Past medical history

Generalised epilepsy (probably juvenile myoclonic epilepsy) diagnosed at age of 14 years.

Psoriatic arthritis diagnosed in 2017

Medications

Topiramate 75 mg daily (started April 2017)

Methotrexate 10 mg once weekly (started mid June 2017)

Levlen ED 1 daily

Medication history

Date	Medication	Comments
2011-2012	Lamotrigine	Stopped as had 4 seizures in 2012
2012-2016	Sodium valproate	Ceased due to adverse effects
2016 - end May 2017	Levetiracetam 500 mg bd	Woman wanted to stop as thought it caused her psoriatic arthritis. Dose tapered over two months before ceasing

Case progress and outcome:

Her antiepileptic medication was changed from topiramate back to levetiracetam 500 mg twice daily. She continued methotrexate 10 mg weekly for her psoriatic arthritis. Twenty-four days later, she had a second generalised seizure. The neurologist contacted QMAIS to investigate whether low-dose methotrexate has been associated with seizures.

The decision was made jointly with the woman to cease the methotrexate. She continued taking levetiracetam 500 mg twice daily. Eight weeks later she had another generalised seizure and her dose of levetiracetam was increased to 1000 mg twice daily. No further seizures had occurred when last seen in July 2018.

Interventions:

A literature search was conducted to investigate if low-dose methotrexate has been associated with seizures. Epilepsy is not listed as a warning or precaution to the use of methotrexate. The Australian product information (PI) states convulsions have been reported following intravenous and intrathecal use for chemotherapy. However, the US PI states convulsions have occurred during treatment for rheumatoid arthritis and psoriasis.

There are four published case reports of seizures from low dose methotrexate in patients being treated for rheumatoid arthritis.[1-3] Both patients had no previous history of seizures. A 44-year-old woman had been treated with methotrexate 10 mg weekly for five months when the dose was increased to 15 mg weekly due to persistent inflammation. She had three seizures over three weeks, one month after her dose of methotrexate was increased. She was treated with sodium valproate 1000 mg daily and the methotrexate was continued at 15 mg weekly.[1]

In the second case, a 62-year-old man developed seizures six weeks after starting methotrexate 7.5 mg weekly. Methotrexate was ceased and no other cause for the seizures was found. He remained seizure free after follow-up for three years.[2] This report referenced another case of new onset seizures in a patient with diabetes mellitus who was in a study of 183 patients taking alternate day methotrexate for rheumatoid arthritis.[2]

There are two case reports of seizures from low-dose methotrexate for the treatment of rheumatoid arthritis in patients with a history of epilepsy.[3] A 60-year-old woman had been well controlled with phenytoin therapy and seizure free for three years. She was started on methotrexate 5 mg weekly which was increased over six months to 15 mg weekly. Two months later she experienced three seizures over a four week period. Her phenytoin level was therapeutic and had not changed compared to levels prior to starting methotrexate. Methotrexate was ceased and no further seizures had occurred at the time of the report, 15 months later.[3]

A 41-year-old woman was being treated with phenytoin 400 mg daily for generalised epilepsy and had no seizures for 13 months. She had steroid dependent rheumatoid arthritis and was administered two intravenous injections of methotrexate 10 mg at weekly intervals. Within 24 hours after receiving the second dose she had a generalised tonic clonic seizure. Methotrexate was discontinued and she remained free of seizures three years thereafter.[3]

Summary of case reports of low-dose methotrexate (MTX) induced seizures

Patient	(MTX) dose	Onset (after current dose MTX)	Number seizures	History Epilepsy & seizure free period	Outcome
F, 44 yr	15 mg po weekly	1 mth	3 in 3 weeks	No	Valproate 1 g daily added MTX 15 mg weekly continued
M, 62 yr	7.5 mg po weekly	6 wk	1 episode	No	MTX ceased No seizures 3 yr later
F, 60 yr	15 mg po weekly	2 mth	3 in 4 weeks	Yes 3 yr	MTX ceased No seizures 15 mth later
F, 41 yr	10 mg IV weekly	2 wk	1 (24 hr after 2nd dose)	Yes 13 mth	MTX ceased No seizures 3 yr later

Discussion:

This woman's seizures were possibly related to the use of low-dose methotrexate for psoriatic arthritis according to the Naranjo[4] scale and the WHO-UMC[5] causality rating. Her history is complicated as levetiracetam therapy was stopped one month prior to her seizure. She had two seizures within 24 days while taking methotrexate; one while taking topiramate and the other while on levetiracetam. However, a third seizure occurred two months after methotrexate was ceased requiring the dose of levetiracetam to be increased to 1000 mg twice daily before no further seizures occurred.

Methotrexate is thought to lower the seizure threshold but the mechanism is unknown. One proposed mechanism is that methotrexate's inhibition of tetrahydrofolate may decrease the production of gamma amino butyric acid (GABA) in the brain reducing it's effect as an inhibitory neurotransmitter.[1]

Conclusion:

This case highlights that low-dose methotrexate which is commonly used for the treatment of rheumatoid arthritis and psoriasis may rarely cause seizures. The pharmacist had an important role in confirming the neurologist's suspicions to ensure optimal medication management for this woman.

References:

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Acknowledgement:

Kahlya Simpson for assistance in designing the poster.

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