Contribution of methotrexate in precipitation of manic episode in bipolar affective disorder explored: a case report

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Abstract: Bipolar affective disorder is characterized by recurring episodes of mania with or without, but commonly with, episodes of depression. It usually begins in adolescence and can cause enduring and substantial impairment if left untreated. It needs a long-term treatment with mood stabilizers to prevent relapses. Elevated or depressed mood relapses can be either primary or secondary. However, primary mood relapses can occur without a significant precipitating factor, more often tending to occur following stressful life events or discontinuation of mood stabilizer medications. Secondary mood relapses can be caused by many conditions, such as physical illnesses, substance misuse and medications. When a mental illness coexists with another physical illness and the treatment of one complicates the other, it adds complexity to the selection of appropriate pharmacological regime for either condition. In this paper, the authors present a case of bipolar affective disorder who had two episodes of mania likely precipitated by methotrexate, which were reversed by the withdrawal of the offending drug (methotrexate). To the best of the authors' knowledge, to date there have been no published reports in the literature in which methotrexate, an immunosuppressive and a cytotoxic drug, precipitated a manic episode in a patient with bipolar affective disorder.

Keywords: bipolar affective disorder, depression, mania, manic depressive illness, methotrexate, mood disorder

Introduction

Bipolar affective disorder is a chronic enduring mental illness characterized by periods of elation and depression in mood. The modern conceptualization of this phenomenon as a distinct illness dates back to the 19th century when Falret first described the concept of folie circulaire [Saunders and Goodwin, 2010]. Mania can occur by a chance association during drug treatment, particularly in patients predisposed to mood disorder. Drugs that are probably capable of inducing mania, but for which the evidence is less scientifically secure, include the dopaminergic anti-Parkinsonian drugs such as levo dopa, thyroxine, baclofen, alprazolam, captopril, amphetamine, phencyclidine [Peet and Peters, 1995], steroids and antidepressant medications. To the best of the authors' knowledge, to date there have been no published reports in the literature in which methotrexate, an immunosuppressive and a cytotoxic

drug, precipitated a manic episode in a patient with stable bipolar affective disorder. We present a case who had two episodes of mania likely precipitated by methotrexate, which were reversed by the withdrawal of the offending drug in addition to the usual antimanic treatment.

Case history

The patient, Mr V, is a Chinese Singaporean who suffered from bipolar mood disorder and psoriasis. He first presented to psychiatric services in 1984, at the age of around 27. He has had multiple admissions to hospital for recurrent relapses, mostly manic in nature. He was vulnerable to frequent relapses after experiencing work-related stress that affected his sleep pattern and a few times due to partial compliance to his prescribed medications. He has been hospitalized on more than 20 occasions since his first admission in

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1994. Over the years, he was treated with various combinations of mood stabilizers such as either lithium or carbamazepine or valproate with various antipsychotic medications, typical and atypical. Following worsening of his psoriasis, his lithium was temporarily discontinued in 2003 but he was put back on it once his psoriasis improved. Later in 2010, he developed hypothyroidism requiring thyroxine replacement therapy and he was taken off lithium once again. During a few of his severe relapses, he also underwent electroconvulsive therapy (ECT) whilst his condition remained resistant to combination pharmacotherapy.

He was noted to be suffering from psoriasis since 2003, at the age of 46. His psoriasis has been treated by the National Skin Centre with tropical medications such as betamethasone, aqueous, coal Tar 15% in aqueous and hydrocortisone 1%–CLIOQUINOL 3% creams along with betamethasone scalp lotion and coal tar shampoo.

Following discharge from hospital after a week's stay as an inpatient for a manic relapse in August 2010, he remained well on a combination of quetiapine 400 mg daily and carbamazepine 400 mg twice daily doses up until December 2011. His psoriasis, however, became worse necessitating a trial of once a week methotrexate with folic acid in August 2011. He suffered a relapse to manic state in December 2011. Since his earlier relapse in August 2010, he was not working and his family members reported that they supervised his medication intake. Therefore, work-related stress and noncompliance were unlikely to explain the relapse in December 2011. He was hospitalized and his mental state improved quickly with discontinuation of methotrexate with an increase in dose of quetiapine from 200 to 600 mg daily along with same dose of carbamazepine. His mood state returned to euthymic state in hospital. Unfortunately, just a week prior to discharge on 16 January 2012, his psoriasis flared up again despite the regular use of the topical applications, therefore he was recommenced on methotrexate a few days prior to trial home leave before discharge. He was advised to keep a closer watch for re-emergence of his manic symptoms. As suspected by the clinical team, this rechallenge with methotrexate resulted in relapse of his mental state to a severe manic episode within a week of rechallenge, much severer than that of the previous likely methotrexate-precipitated relapse in December 2011 and required prolonged

rehospitalization. This second severe relapse, likely precipitated by methotrexate rechallenge, also remained resistant to his usual combination medications treatment. ECT was once again explored by the team due to the resistant nature of the second relapse likely precipitated by methotrexate rechallenge, but the patient and also his family refused to consent for ECT. Methotrexate was discontinued but his symptoms did not resolve fully despite the combinations of maximum dose of quetiapine and olanzapine with carbamazepine. Later, he recovered with re-initiation of lithium after meeting with his dermatologist in addition to the above combinations whilst the condition of his psoriasis has been observed closely by regular monitoring by dermatologists. Fortunately his psoriasis remained under control, thyroid status remained under control and he has been maintaining well on a combination of quetiapine, carbamazepine and lithium since his discharge from hospital in April 2012.

Discussion

This case illustrates the difficulties in managing a patient who has both a psychiatric illness and a comorbid medical condition. This patient has bipolar affective disorder and medical conditions such as hypothyroidism and psoriasis. The treatment or absence of the treatment of one condition can potentially exacerbate/worsen the other condition. Mania can be precipitated by hyperthyroid states [Lishman, 2004] and rarely with hypothyroidism [Stowell and Barnhill, 2005]. Lithium, which is a mood stabilizer with bimodal action, is well known to cause hypothyroidism in at least 20% of patients [Taylor *et al.* 2009]. Although this patient had been diagnosed with hypothyroidism and was on thyroxine replacement, clinical and laboratory evidences indicated that he was euthyroid, thus providing minimal or no contribution to the current clinical picture. While treatment with lithium can exacerbate the psoriasis [Taylor *et al.* 2009], the treatment of psoriasis with methotrexate could precipitate a manic episode in a patient with bipolar disorder, as in this case, posing a huge challenge in the management. Unfortunately his folate levels were not checked during his the admission in December 2011, his methotrexate was discontinued for 2 weeks and folate levels measured during the readmission in January 2012 after a week of rechallenge with methotrexate was found to be well within the normal range (21 nmol/l).

Methotrexate is an antimetabolite analog of folate that is used for a variety of conditions including psoriasis, rheumatoid arthritis and other autoimmune diseases [Vezmar *et al.* 2009]. The main action of methotrexate is inhibition of the enzyme dihydrofolate reductase, which is necessary for the reduction of dihydrofolate to tetrahydrofolate (THF), a key intracellular compound. THF deficiency leads to depletion of intracellular folate and, thereby, decreased synthesis of purines and pyrimidines [Quinn and Kamen, 1996], the nucleotide bases which form DNA and RNA. It also markedly interferes with transmethylation reactions, which are crucial for the formation of proteins, lipids and also myelin, presumably leading to demyelination [Harila-Saari *et al.* 1998] of nervous tissues. Cytotoxic agents including methotrexate are potent neurotoxins, which are reported to cause widespread cortical, subcortical, hippocampal and white matter pathologies [Rzeski *et al.* 2004]. Although psychiatric side effects are rare with methotrexate [Levenson, 2006], cognitive and psychiatric disturbances, but not mania, have been reported with methotrexate [Copeland *et al.* 1996].

Mechanisms of precipitation of manic symptoms by methotrexate could be hypothesized. One possible cause is the interference of folate metabolism as folic acid is used in the body to manufacture of serotonin and other neurotransmitters and there is some evidence that patients diagnosed with mania are also more likely to have folate deficiencies than healthy controls [Hasanah *et al.* 1997]. Some studies, however, have found that folic acid deficiency was not more common in bipolar patients taking lithium than in healthy people [McKeon *et al.* 1991] adding to the controversy regarding the above association. Other studies have also found that of people who take lithium long term, those with high blood levels of folic acid, responded better to lithium [Lee *et al.* 1992], strengthening the association of folate deficiency and mania. Interestingly a double-blind study of patients receiving lithium therapy showed that the addition of 200 µg of folic acid per day resulted in clinical improvement whereas placebos did not [Coppen and Abou-Saleh, 1982]. Other postulations include interferences in serotonin and dopamine neurotransmitters by methotrexate as it interferes with the biopterin pathway of monoamine metabolism and interference in glutaminergic neurotransmission (increased release in glutamate and aspartate) by high levels of homocysteine and sulfur-containing amino acids which is resulted by

the interference in folate metabolism [Vezmar *et al.* 2003]. Glutaminergic neurotransmission is implicated in the pathophysiology of bipolar affective disorder [Sanacora *et al.* 2003] and some studies report patients with manic episode show elevated glutamate and glutamine [Michael *et al.* 2003].

In this case, there was a time lag between the initiation of methotrexate in August 2011 and the onset of relapse in December 2011. To err on the side of caution, the earlier relapse in December 2011 could well be a natural relapse of his bipolar mood disorder without any etiological implication from methotrexate given the past history of frequent relapses and that a dose increase in quetiapine could have alone been sufficient to cause recovery. However, the rechallenge with methotrexate and the immediate precipitation of severe and resistant manic relapse again suggests somewhat definitive contribution from methotrexate as well. Intriguingly, a case report of another immunomodulator, chloroquine, in combination with sulfasalazine caused a mixed affective psychotic episode [Gulcan *et al.* 2009], necessitating hospital admission, with a similar pattern of reaction of developing psychiatric symptoms only on rechallenge but not at the initial course of chloroquine given for 9 months. Therefore, in this case, it is likely that methotrexate might have played a lesser role during December 2011 episode but a major role in the relapse during the rechallenge.

While significant improvement of neurological symptoms due to methotrexate has been achieved with combined administration of aminophylline, an adenosine antagonist, and high-dose folic acid [Jaksic *et al.* 2004], no studies have been performed to prove the similar efficacy to the psychiatric symptoms with the above medications. Thus, to date, the most effective means of dealing with a manic episode precipitated by methotrexate is withdrawal of the drug with use of alternative treatment strategies for the medical condition and the control of the manic symptoms with the antimanic psychotropic agents.

The authors would like to emphasize and improve the awareness of all clinicians of this potentially plausible psychiatric manifestation of methotrexate and the challenges faced when a patient presented with psychiatric and medical comorbidity requiring the administration of methotrexate. As the management of one condition potentially exacerbates the other: in this case, lithium

exacerbated his psoriasis whilst the psoriasis treatment methotrexate was likely to have contributed to a manic relapse. We would like to stress the finding of the resolution of mania with removal of methotrexate with a slight increase in quetiapine dose and the reappearance of mania on rechallenge and recommend caution and a close monitoring in bipolar affective disorder sufferers when methotrexate has been prescribed for a co-existing medical condition. Research focusing on the measurement of the rate of prevalence of mood symptoms in patients on methotrexate prescription and comparing between the individuals with and without the history of pre-existing mood disorder will help us to better understand the likely association.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

References

- Copeland, D., Moore, B. III, Frances, D., Jaffe, N. and Culbert, S. (1996) Neuropsychologic effects of chemotherapy on children with cancer: a longitudinal study. *J Clin Oncol* 14: 2826–2835.
- Coppen, A. and Abou-Saleh, M. (1982) Plasma folate and affective morbidity during long-term lithium therapy. *Br J Psychiatry* 141: 87–89.
- Gulcan, G., Yenilmez, C. and Ayranci, U. (2009) Sulphasalazine plus chloroquine – induced mood disorder in a patient with rheumatoid arthritis. Case report. *Iran J Med Sci* 34: 72–75.
- Harila-Saari, A., Vainionpaa, L., Kovala, T., Tolonen, E. and Lanning, B. (1998) Nerve lesions after therapy for childhood acute lymphoblastic leukemia. *Cancer* 82: 200–207.
- Hasanah, C., Khan, U., Musalmah, M. and Razali, S. (1997) Reduced red-cell folate in mania. *J Affect Disord* 46: 95–99.
- Jaksic, W., Veljkovic, D., Pozza, C. and Lewis, I. (2004) Methotrexate-induced leukoencephalopathy reversed by aminophylline and high-dose folic acid. *Acta Haematol* 111: 230–232.

- Lee, S., Chow, C., Shek, C., Wing, Y. and Chen, C. (1992) Folate concentration in Chinese psychiatric outpatients on long-term lithium treatment. *J Affect Disord* 24:265–270.
- Levenson, J. (2006) Psychiatric issues in rheumatology. *Primary Psychiatry* 13(11): 23–27.
- Lishman, W. (2004) *Organic psychiatry: The psychological consequences of cerebral disorder*, 3rd edn. Boston, MA: Blackwell Science.
- McKeon, P., Shelley, R., O'Regan, S. and O'Broin, J. (1991) Serum and red cell folate and affective morbidity in lithium prophylaxis. *Acta Psychiatr Scand* 83: 199–220.
- Michael, N., Erfurth, A., Ohrmann, P., Gossling, M., Arolt, V., Heindel, W. *et al.* (2003) Acute mania is accompanied by elevated glutamate/glutamine levels within the left dorso-lateral prefrontal cortex. *Psychopharmacology (Berl)* 168: 344–346.
- Peet, M. and Peters, S. (1995) Drug-induced mania. *Drug Saf* 12: 146–153.
- Quinn, C. and Kamen, B. (1996) A biochemical perspective of Methotrexate neurotoxicity with insight on nonfolate modalities. *J Invest Med* 44: 522–530.
- Rzeski, W., Pruski, S., Macke, A., Felderhoff-Mueser, U., Reiher, A., Hoerster, F. *et al.* (2004) Anticancer agents are potent neurotoxins *in vitro* and *in vivo*. *Ann Neurol* 56: 351–360.
- Sanacora, G., Rothman, D., Mason, G. and Krystal, J. (2003) Clinical studies implementing glutamate neurotransmission in mood disorders. *Ann N Y Acad Sci* 1003: 292–308.
- Saunders, K. and Goodwin, G. (2010) The course of bipolar disorder. *Adv Psychiatric Treatment* 16: 318–328.
- Stowell, C. and Barnhill, J. (2005) Acute mania in the setting of severe hypothyroidism. *Psychosomatics* 46: 259–261.
- Taylor, D., Paton, C. and Kapur, S. (2009) *The Maudsley Prescribing Guidelines*, 10th edition. London: Informa Healthcare.
- Vezmar, S., Becker, A., Bode, U. and Jaehde, U. (2003) Biochemical and clinical aspects of methotrexate neurotoxicity. *Chemotherapy* 49: 92–104.
- Vezmar, S., Schüsseler, P., Becker, A., Bode, U. and Jaehde, U. (2009) Methotrexate-associated alterations of the folate and methyl-transfer pathway in the CSF of ALL patients with and without symptoms of neurotoxicity. *Pediatric Blood Cancer* 52: 26–32.