

Lithium-induced Neuroleptic Malignant Syndrome: a Case Report

鋰中毒導致抗精神病藥惡性綜合症的病例報告

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Abstract

Lithium is known to cause neuroleptic malignant syndrome in the presence of antipsychotics. Many other risk factors are also known to cause neuroleptic malignant syndrome. Lithium alone has not been reported as a risk factor for the development of neuroleptic malignant syndrome before. We report a case involving a patient with bipolar affective disorder maintained on lithium, who developed lithium toxicity followed by neuroleptic malignant syndrome in the absence of antipsychotics.

Key words: Lithium/toxicity; Neuroleptic malignant syndrome; Risk factors

摘要

醫學界已確知，在施用抗精神病藥物時，鋰能引起抗精神病藥惡性綜合症。事實上，其他危險因素也能引起此綜合症。但並沒有報告指鋰本身單獨會成為致病的危險因素。本文描述一位患上雙極情感性疾病的患者，須定時服用含鋰藥物，但患者在沒有服用抗精神病藥物的情況下，仍然出現鋰中毒，繼而引發抗精神病藥惡性綜合症。

關鍵詞：鋰中毒、抗精神病藥惡性綜合症、危險因素

Introduction

Neuroleptic malignant syndrome (NMS) was first described by Delay et al in 1960 in the French psychiatric literature.¹ The incidence of NMS in neuroleptic-treated patients ranges from 0.02 to 3.23%.² Although NMS is rare, it is a life-threatening and idiosyncratic reaction to antipsychotic medication. The male-to-female ratio is reported to be 2:1.³ The syndrome is characterised by fever, muscular rigidity, altered mental status, and autonomic dysfunction. The potential for a drug to induce NMS seems to parallel its dopamine blockade activity.¹ Its onset is usually early in neuroleptic treatment. It has been reported that NMS occurs in 67% of patients within 1 week; and 96% of patients within 30 days following the administration of neuroleptics.² Early reviews reported a mortality rate of 11 to 30%^{4,5} but with the advent of supportive treatment and development of new-generation antipsychotic medication, these rates have been lowered.

It is hypothesised that NMS is precipitated by a wide variety of risk factors including hyponatraemia, hypokalaemia,

mania, organic brain syndrome, large and rapidly escalated doses of neuroleptics and other drugs like metoclopramide.⁶⁻⁹ All antipsychotic agents are known to cause NMS. Lithium and lithium toxicity are known to precipitate NMS when lithium is given along with antipsychotics.¹⁰ Lithium toxicity, in the absence of antipsychotics, is a lesser known risk factor for NMS. In the report below, lithium and lithium toxicity alone were the precipitating factors for the development of NMS.

Case Report

A 40-year-old male divorced electrician who belonged to an urban Hindu nuclear family had been managed for bipolar affective disorder since 1976. He had no significant medical or psychiatric illnesses prior to 1976 but a family history of schizophrenia (subtype could not be classified) affecting his brother and an uncle. From 1976, he had episodes suggestive of mania with psychotic symptoms (International Classification of Diseases, 10th Revision) characterised by over-talkativeness, overspending, increased motor activity, irritability, increased appetite, reduced need for sleep, increased energy, and occasional delusions of grandiose ability and identity. There were no depressive episodes. He was usually treated with antipsychotics (typical antipsychotics included chlorpromazine up to 800 mg/day, haloperidol up to 20 mg/day; atypical antipsychotics included olanzapine up to 20 mg/day) with full recovery from the episode. His treatment adherence was poor and the psychotic episodes

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recurred every 2 to 3 years. On one occasion, he was prescribed a depot preparation of fluphenazine decanoate 25 mg/month and on another occasion he was also prescribed lithium for maintenance, but he exhibited poor adherence. In 1996, he developed generalised tonic-clonic convulsions and was given carbamazepine 600 mg/day. He again showed poor drug adherence but was seizure-free until an episode in 2002, for which he was prescribed sodium valproate 500 mg/day. He stopped taking the valproate several days later with no seizure recurrence. In August 2004, he developed an episode of mania without psychotic symptoms and was treated with lithium 1200 mg/day (blood levels up to 0.8 mmol/l) and olanzapine 20 mg/day. He became asymptomatic by October 2004 so the olanzapine was tapered off and he was maintained on lithium 1200 mg/day. He remained well on lithium till 3 January 2005 when he was away from home for 2 days. He began vomiting and had loose stools (4-5/day) from 4 January 2005. He continued taking lithium 1200 mg/day and, 2 days later developed fine hand tremors, intermittently slurred speech and reduced appetite. On his return home, he took fluids and passed urine normally but had a poor appetite. The next day, he had 2 episodes of incontinence, of both urine and faeces. Because his caregiver (grandmother) considered him very ill, she gave him 2000 mg of lithium on 7 January 2005. On 8 January 2005, he visited the psychiatry outpatient department of the Government Medical College and Hospital, Sector 32, Chandigarh and was admitted.

On examination, he was oriented in time, place and person, and reported no sadness or euphoria. On central nervous system examination, he had slurring, coarse hand tremors, and very brisk deep tendon reflexes. No signs of dehydration were seen. It was considered likely that he was suffering lithium toxicity so all medications were stopped. Conservative management was started and intake and output charting was maintained. Lithium levels done on admission were 3.6 mmol/l. He developed a fever, rising to 104°F, rigidity in his limbs and autonomic instability (blood pressure fluctuated from 60/40 to 130/90 mm Hg, pulse fluctuated from 80 to 104 beats/min), tachypnoea, excessive sweating, one episode of dark-coloured urine, intermittent disorientation in time, place and person, visual hallucinations and leukocytosis (white blood cell count, 18,000/mm³). Neuroleptic malignant syndrome was considered a possible diagnosis. His creatine phosphokinase-MM (CPK-MM) was 2310 µ/l, blood urea 95 µ/l, serum creatinine 1.2 mmol/l, serum potassium 6.3 mmol/l, and serum sodium 144 mmol/l. His liver function tests, complete blood count, and urinalysis were normal. Blood and urine cultures sent on 9 January 2005 grew no organisms. From 10 January 2005, second daily haemodialysis was commenced. He was also prescribed bromocriptine 2.5 mg/day. After 1 week, his CPK-MM decreased to 59 µ/l and serum lithium decreased to less than 0.12 mmol/l. He became asymptomatic within 7 days and over the next 7 days, the bromocriptine was stopped and sodium valproate 250 mg/day commenced then increased to 750 mg/day during the next 3 weeks. The patient remained well for the next 6 months but failed to attend for follow-up after that.

Discussion

This man had a clear triad of hyperthermia, rigidity, and autonomic instability, diagnostic of NMS developing after lithium toxicity. Lithium toxicity coupled with antipsychotic use is a known predisposing risk factor for NMS but in this case NMS developed without the concomitant use of antipsychotics. It is difficult to find any valid reason for the development of NMS although the presence of an underlying illness like epilepsy and being a middle-aged male may have been predisposing factors. Lithium has diverse mechanisms of action and affects all neurotransmitter systems. A sudden, massive blockade of dopaminergic receptors is the most favoured theory explaining the development of NMS.¹ The effect of lithium on dopamine neurotransmitters is still debatable but there is some evidence that lithium antagonises the dopamine action via the AKT/glycogen synthase kinase 3 signalling cascade.¹¹ Thus, an excess of lithium may antagonise the action of dopamine. Our patient was given an overdose of lithium when already developing lithium toxicity. It is possible that such a heavy dose of lithium may have resulted in sudden and massive depletion/antagonism of dopamine. He had also been using antipsychotics earlier, thus prior sensitisation to an idiosyncratic reaction like NMS might have occurred. A further insult from the lithium toxicity alone might have then precipitated the development of NMS. The research data supporting lithium alone as a risk factor for NMS are negligible. Whatever the reason may be for the development of NMS, this case serves as a warning that NMS may develop in the presence of lithium toxicity.

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