

Neuroleptic malignant syndrome after the addition of lithium to risperidone treatment: a case report and review of the literature

利司培酮治療加入鋰後的抗精神失常藥惡性綜合徵：個案報告及文獻審查

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Neuroleptic malignant syndrome (NMS) is a rare but life-threatening complication of antipsychotic therapy. The classic features of NMS include muscular rigidity, altered mental status, autonomic instability and hyperthermia. NMS is most often associated with conventional antipsychotic usage. It has also been reported with lithium and antidepressants especially when combined with antipsychotics. Herein, we report a case involving a 35-year-old man with schizoaffective disorder in whom signs and symptoms consistent with NMS developed after lithium was added to his therapy of risperidone. A firm diagnosis of NMS was made on the basis of his history, physical, laboratory and neuroimaging findings. He was then followed up and treated in the intensive care unit with supportive care measures including aggressive cooling, intravenous fluid hydration, nutrition by nasogastric tube and therapy with bromocriptine. The patient had an uneventful clinical course and was discharged from the intensive care unit after three weeks with no complications related to the NMS. (*Hong Kong j.emerg.med.* 2010;17:289-292)

抗精神失常藥惡性綜合徵是精神安定藥治療的一個罕有但威脅生命的併發症。抗精神失常藥惡性綜合徵的典型徵狀包括肌肉僵硬、神志不清、自主神經不穩及高熱。抗精神失常藥惡性綜合徵最常與使用傳統精神安定藥有關，亦有報導與鋰及抗抑鬱藥有關，尤其是當聯同精神安定藥。本文在此報告一個涉及有分裂情感性精神病的35歲男子的個案，當他的利司培酮治療加入鋰後，出現符合抗精神失常藥惡性綜合徵的徵狀。基於其病歷、身體檢查、化驗室及神經造影的結果，確診為抗精神失常藥惡性綜合徵。他隨後在深切治療部以支援性護理方法治理及跟進，包括積極降溫、靜脈內輸液、鼻胃管供營養及以溴麥角隱亭治療。病人臨床過程順利，3星期後離開深切治療部，沒有與抗精神失常藥惡性綜合徵有關的併發症。

Keywords: Bromocriptine, lithium, neuroleptic malignant syndrome, risperidone

關鍵詞：溴麥角隱亭、鋰、抗精神失常藥惡性綜合徵、利司培酮

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Introduction

Neuroleptic malignant syndrome (NMS) is a rare, unpredictable and potentially lethal disease that results from the adverse side effects of antipsychotic medication.¹ The syndrome often develops after a sudden increase in dose of neuroleptic medication or in states of dehydration. The frequency of NMS with typical neuroleptic drugs ranges from 0.02 to 3.3%. The pathophysiology of NMS is not clearly understood. It has been suggested that the potential of neuroleptics to induce NMS is parallel to the potency of dopamine blockade in the nigrostriatal tract,

mesocortical pathway and hypothalamic nuclei.² Clinically, it is characterised by hyperthermia (i.e. core temperature greater than 38°C), muscle rigidity, autonomic instability, altered mental status and an elevated creatine kinase level. Although NMS was initially associated with the use of classical (typical) high-potency neuroleptics, cases have started to emerge with atypical neuroleptics.³ Haloperidol and fluphenazine have been the most commonly cited drugs, probably because of their widespread use and higher potency. Other agents including tricyclic antidepressants, monoamine oxidase inhibitors and lithium have also been reported to cause NMS, perhaps through synergistic interactions or as yet undefined mechanisms.^{4,5} Risperidone is an antipsychotic drug used for the treatment of schizoaffective disorders. It was hoped that this atypical neuroleptic agent would not cause dystonia or neuroleptic malignant syndrome owing to its unique mechanism of action with attenuated antidopaminergic activity and more potent antiserotonergic activity.⁶ However, this was found to be untrue. Lithium has been known to precipitate NMS when it is used in combination with other psychotropic medication, particularly clozapine, which is mainly characterised by its low affinity to dopaminergic receptors as an atypical antipsychotic.^{5,7,8} There have been comparatively few cases of NMS related to concomitant lithium and risperidone use reported in the literature.⁹⁻¹² In this report, we present a patient with a history of schizoaffective disorder who precipitously developed NMS after lithium was added to a regimen of risperidone.

Case report

A 35-year-old man with a history of schizoaffective disorder presented to the emergency department (ED) in February 2009 with the complaints of high fever and muscle rigidity in all extremities. He had been taking oral risperidone 4 mg/day, 3 months prior to presentation to the ED. Three weeks earlier he had been prescribed oral lithium carbonate 900 mg/day (450 mg bid) by his psychiatrist due to an exacerbation of severe mania. There was no prior history of neuroleptic malignant syndrome, electroconvulsive therapy, use of anticholinergic agents or

antidepressants, rapid increase in neuroleptic dose, depot injectable neuroleptic use or malnutrition. Upon physical examination, the patient was dehydrated and lethargic. His pulse rate was 102 beat/min and respiratory rate was 20 breath/min. His axillary temperature was elevated (41.5°C), although he was normotensive (blood pressure 115/75 mmHg). The pupils were equal and reactive. His tongue was dry and skin turgor was decreased. Muscle rigidity could be elicited in all extremities and the jaw. Laboratory studies taken on admission showed markedly elevated serum creatine kinase (CK) level of 7185 U/L with normal CK-MB fraction. The leukocyte count was 4900/uL with haemoglobin 11.3 g/dL and haematocrit 39.5%. The patient's serum sodium level was elevated (169.08 mmol/L), potassium was 4.52 mmol/L and chloride was 140.74 mmol/L. The patient's serum lactic dehydrogenase level was 1384 U/L, lithium level was 0.82 mEq/L and erythrocyte sedimentation rate was 18 mm/h. Arterial blood gas showed pH 7.36, PaCO₂ 46.6 mmHg, PaO₂ 84.7 mmHg, SaO₂ 94.2%, HCO₃ 17.8 mmol/L and anion gap 10.54 mEq/L (normal 6-14 mEq/L). Urine myoglobin result was 0.9 mg/L (normal 0-1 mg/L). Liver and thyroid function tests were normal and there was nothing else of significance in his medical history. An electrocardiogram revealed no acute ischemic changes. The results of analyses on the cerebrospinal fluid gathered by lumbar puncture were normal. Computed tomography of the brain was unremarkable. All blood cultures, urine cultures and cerebrospinal fluid cultures were negative for growth. No obvious focus of sepsis was detected. Following consultations with a range of clinicians, the patient was diagnosed with NMS related to concomitant use of lithium and risperidone on the basis of his history, physical, laboratory and neuroimaging findings, and on consideration of current consensus definitions of this syndrome. Risperidone and lithium treatment was immediately cut-off with the recommendation of psychiatry and neurology consultations. After emergency room evaluation of the patient's airway, breathing, and circulation, controlled intravenous fluid infusion with 5% dextrose and external cooling by tepid sponging were started. Nasogastric tube and urine catheter were inserted. He was then followed up and

treated in the intensive care unit with supportive care measures including aggressive cooling and therapy with bromocriptine (5 mg tid) via nasogastric tube. By the third day, the patient's symptoms improved and his CK and serum sodium level returned to normal and subsequently he was mobilised. Over a period of three weeks, the patient recovered and he was discharged without further complications.

Discussion

NMS is believed to result from central dopaminergic receptor blockade or dopamine depletion in the central nervous system, including the hypothalamus, the corpus striatum, the basal ganglia, and spinal areas with wide-ranging effects.¹³ Theoretically, central dopaminergic blockade explains the clinical tetrad of symptoms (muscular rigidity, altered mental status ranging from confusion to coma, autonomic instability such as elevated or labile blood pressure, tachypnoea or tachycardia and elevated temperature) seen in NMS.^{13,14} Other frequently seen symptoms in NMS regardless of antipsychotic medication include diaphoresis, dysphagia, tremor, incontinence, leukocytosis, myoglobinuria and elevated CK concentration.¹⁰ A summary of the well supported risk factors for NMS includes the followings: high-potency and high-dose neuroleptic use, rapid increase in neuroleptic dose, depot injectable neuroleptic use, episodes of neuroleptic malignant syndrome, age younger than 40 years, male sex, dehydration, malnutrition, past history of electroconvulsive therapy, and warm and humid environments. Other risk factors for NMS include stress, and concomitant use of lithium, anticholinergic agents or some antidepressants.^{15,16} The differential diagnosis of NMS is often confusing and may initially lead to diagnostic delay with other, more common diagnoses including central nervous system infection, heat illness, heavy metal poisoning, lithium toxicity, sepsis, serotonin syndrome, tetanus, thyrotoxicosis, drug interaction (e.g. between monoamine oxidase inhibitors and antidepressants or narcotics) and withdrawal of alcohol, benzodiazepine or barbiturate. Thorough history taking, physical examination and laboratory investigations, should be performed.^{13,17}

In the present case, the lithium level was found to be therapeutic (0.82 mEq/L) and within the desirable level of 0.6-1.2 mEq/L.¹⁸ Although risperidone can cause NMS by itself, we believe that the NMS in our patient was caused by the addition of lithium to risperidone, basing on the temporal sequence of the event.

Neurotoxic encephalopathy induced by the lithium-risperidone combination treatment in a patient with schizoaffective disorder has been reported in the literature. The authors suggested that neurotoxicity related to lithium-risperidone combination treatment is the result of the interaction of different etiopathogenetic mechanisms.¹⁹ It was previously stated that fever and rigidity (which occurred in 97-98% of patients) were essential clinical signs of NMS in some but not all articles.^{20,21} Recent literature suggests that the frequency of NMS without fever or muscle rigidity has increased with the use of novel (atypical) antipsychotics due to their lower affinity for the dopamine D₂ receptor in comparison to traditional (typical) agents.^{11,16,22} Bourgeois and Kahn reported the case of a 30-year-old white male with an acute onset of tachycardia, hypertension and hyperthermia, but without muscle rigidity, described as NMS associated with concomitant lithium and risperidone use.¹⁰ Our patient presented with four signs of NMS which were high fever, muscle rigidity, elevated CK level, and altered consciousness. The patient's admission laboratory values such as high CK level and hypernatremia were consistent with dehydration.

Complications of NMS are numerous. The most universal complication is rhabdomyolysis resulting from sustained muscle rigidity and consequent muscle breakdown. Other common complications include renal failure, aspiration pneumonia, pulmonary embolism, pulmonary oedema, adult respiratory distress syndrome, sepsis, disseminated intravascular coagulation, seizures, and myocardial infarction.^{14,17,23} Kosehasanogullari et al reported a case of NMS which was probably caused by the combination of risperidone and lithium and further complicated by coexisting thalassaemia minor, deep vein thrombosis, hyperthyroidism, pneumonia, anaemia and myoglobinemia.¹² There were no complications related to the NMS encountered in the present case during

the follow-up period in the intensive care unit. For the treatment of NMS, it is essential to recognise the symptoms and to stop the neuroleptic therapy immediately. Supportive therapy, such as fever reduction, hydration and nutrition, is important.¹⁴ Bromocriptine at a dose of 2.5-5 mg, 3-4 times daily for at least 2-3 weeks appears to be effective for improving muscle rigidity.^{13,14} Dantrolene is also an effective drug but it is not available in Turkey.¹⁴ In the present case, bromocriptine at a dose of 5 mg, 3 times daily was continued for two weeks. For the present case whose clinical signs and symptoms improved, laboratory measures also returned to normal within a few days.

Conclusions

Management of NMS is an important task for emergency physicians because of its acute onset and its severity. Physicians should consider the possibility of NMS particularly in patients who have been treated with combinations of antipsychotics and lithium. Early diagnosis and prompt therapeutic approach can substantially reduce morbidity and mortality of this potentially fatal syndrome.

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