

## A case of risperidone-associated neuroleptic malignant syndrome in a patient receiving long-term haloperidol treatment

一名長期接受氟哌啶醇治療的病人，與利司培酮有關的抗精神失常藥惡性綜合徵的個案

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We report a case of risperidone-associated neuroleptic malignant syndrome. A 53-year-old gentleman with mental retardation, psychosis and hypertension who was on long term haloperidol, lorazepam and atenolol treatment presented to the Department of Emergency Medicine of the Singapore General Hospital with hyperthermia, generalised rigidity, impaired consciousness and diaphoresis five weeks after adding on risperidone. Biochemical investigations revealed hyponatremia, raised creatine kinase levels and myoglobinuria. Chest X-ray showed consolidative changes in the right upper and middle zones and left middle zone. He was diagnosed as neuroleptic malignant syndrome with rhabdomyolysis, and aspiration pneumonia. He was discharged well after 13 days. (*Hong Kong j.emerg.med.* 2010;17:285-288)

本文報告一個與利司培酮有關的抗精神失常藥惡性綜合徵的個案。一名53歲有精神病、弱智及高血壓的男士，長期以氟哌啶醇、勞拉西泮及阿替洛爾治療，因加入利司培酮5星期後出現高熱、全身僵硬、神志不清及冒汗而到新加坡全科醫院的急症室求診。生化檢驗顯示低血鈉、肌酸激酶水平提升及有肌紅蛋白尿。胸部X光顯示右上及右中區及左中區有實變，診斷為抗精神失常藥惡性綜合徵、橫紋肌溶解及吸入性肺炎。他13天後情況良好出院。

**Keywords:** Antipsychotic agents, case reports, drug therapy

**關鍵詞:** 精神安定藥、個案報告、藥物治療

### Introduction

Neuroleptic malignant syndrome (NMS), first described in 1960,<sup>1</sup> is an uncommon but potentially fatal complication of antipsychotic therapy. We report a case of NMS which was the complication of the

addition of risperidone in a patient on long-term haloperidol therapy.

### Case

The patient was a 53-year-old gentleman with hypertension, mental retardation and psychosis on long-term haloperidol at 5 mg every night and lorazepam at 0.5 mg twice daily. He was started on risperidone 1 mg every night since 21st May 2009. He presented to the Department of Emergency Medicine of the Singapore General Hospital on 28th June 2009 with drowsiness, generalised stiffness, fever of 40 degrees Celsius, diaphoresis and one episode of vomiting on the day of admission.

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He had a blood pressure of 161/77 mmHg and a pulse rate of 86/min. His Glasgow Coma Scale score was E2V2M4. He was generally stiff and tachypnoeic. Systemic review was unremarkable.

Blood investigations showed: serum sodium 118 mmol/L, creatine kinase (CK) 4029 U/L, CK-MB 21.2 ug/L and urine myoglobin 62 ug/L. The corrected serum calcium was 2.18 mmol/L. The arterial blood gas on FiO<sub>2</sub> of 28% revealed respiratory alkalosis: pH 7.511, pCO<sub>2</sub> 24.8 mmHg, pO<sub>2</sub> 86.3 mmHg, HCO<sub>3</sub> 22.7 mmol/L. The total white cell count was 8.56 x 10<sup>9</sup>/L with absolute neutrophil count of 7.27 x 10<sup>9</sup>/L (84.9%). His coagulation profile, thyroid function and creatinine were normal. The chest X-ray showed consolidative changes in the right upper, right middle and left middle zones. The electrocardiogram showed sinus rhythm of 86/min. Blood cultures were taken and subsequently showed no growth.

Computed tomography of his brain showed ischaemic changes with no acute intracranial haemorrhage. Magnetic resonance imaging of his brain revealed no features suggestive of meningo-encephalitis.

He was diagnosed as NMS with rhabdomyolysis and aspiration pneumonia. He was managed in the high dependency unit and his antipsychotics were stopped. He was started on intravenous hydration, ice packs, paracetamol, parenteral ceftriaxone and metronidazole. He recovered with remission of his symptoms and his CK gradually declined to 260 U/L on the day before discharge on the 9th July 2009, after 12 days.

## Discussion

Neuroleptic malignant syndrome is a potentially life threatening complication of treatment with antipsychotics. NMS is characterised by hyperthermia, rigidity, autonomic instability and impaired consciousness.<sup>2</sup> The incidence of NMS ranged from 0.167 to 35.258 cases per 1000 patients on antipsychotics.<sup>3</sup> Although traditionally NMS has been associated with haloperidol, more recent cases reported an association with the newer atypical antipsychotics

e.g. risperidone.<sup>4-6</sup> The pathophysiology of NMS is believed to be the result of antidopaminergic action in the brain, with direct action on the skeletal muscles playing an additional role.<sup>2</sup> Acute blockade of the nigrostriatal and hypothalamic dopamine pathways is believed to be the cause of NMS. This is supported by several evidences: withdrawal of dopaminergic drugs can precipitate a NMS-like syndrome, all the drugs associated with NMS produce dopamine blockade, the risk of NMS depends on the affinity of the drug to the dopamine receptors.<sup>7</sup> Muscle biopsies showed a spectrum of fibre oedema from focal swelling through diffuse vacuolation to necrosis, and associated with severe endomysial oedema.<sup>8</sup>

There are a number of conditions that can present similarly. Meningo-encephalitis must be excluded as its management is different from NMS. Acute lethal catatonia can present with hyperthermia, akinesia and rigidity but usually is preceded by behavioural change a few weeks before. Neuroleptic-induced heat stroke is usually seen in the elderly and can have seizures but often with an absence in rigidity, in contrast to NMS. Malignant hyperthermia is associated with halogenated anaesthetic agents and depolarising muscle relaxants. Serotonin syndrome can mimic NMS, but it tends to have additional features such as ataxia, shivering, myoclonus, hyperreflexia and gastrointestinal symptoms such as vomiting and diarrhoea.<sup>2</sup> Other conditions such as tetanus, strychnine poisoning and rabies must be considered as differentials. Often, careful history taking, including drug history, is essential.

Although no correlation between NMS and duration of exposure to an antipsychotic has been found, Caroff and Mann reported that about 16% of cases of NMS develop within 24 hours after initiation of antipsychotics, 66% within the first week, and most cases within 30 days unless the dose was increased or an additional antipsychotic was administered.<sup>9</sup> Our patient was started on risperidone 1 mg ON about five weeks before his presentation, in addition to being on long-term haloperidol. Risperidone inhibits the postsynaptic dopaminergic receptors with some antagonistic effects on 5HT (5 hydroxytryptamine) receptors.

Several risk factors have been correlated to NMS such as agitation, dehydration, restraint, pre-existing abnormality of central nervous system dopamine activity or receptor function, and iron deficiency.<sup>7</sup> In our patient, there was none of the above.

In one analysis of 340 patients, 82% of them had rigidity or mental status changes as the only presenting sign.<sup>10</sup> NMS may present variably and many diagnostic criteria have been established but each has its limitations. One commonly used criterion is from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). In our case report, the patient had all four features (fever, rigidity, impaired consciousness and autonomic instability), however it may seem unusual that there was no tachycardia but it may be because he was on atenolol.

CK elevation is common in NMS although not required for a DSM-IV diagnosis of NMS. Although NMS associated with atypical antipsychotics tends to have less rigidity and less marked CK elevation,<sup>2</sup> Ladds et al reported a case of NMS associated with atypical antipsychotics with very markedly elevated CK levels of 392,623 U/L.<sup>11</sup> In our patient, his initial CK level was 4029 U/L, probably reflecting mild rhabdomyolysis from muscle rigidity. Higher levels of CK have been suggested to have poorer prognosis, although Ladds' patient<sup>11</sup> recovered with no renal impairment despite very high CK levels.

Woodbury et al has proposed a treatment algorithm for NMS spectrum-related symptoms based on the severity of the disease.<sup>12</sup> The principles of treatment are to stop the offending agent, supportive measures, pharmacological treatment and electroconvulsive therapy in refractory cases. Most importantly the offending agent must be stopped or if NMS is precipitated by stopping dopaminergic therapy, it should be restarted immediately.

Supportive measures include aggressive volume resuscitation, correcting electrolyte imbalances, bicarbonate infusion and temperature reduction. The higher the peak and duration of temperature elevation, the higher the morbidity and mortality.<sup>7</sup> Artificial

ventilation may be required in patients with respiratory failure from chest wall rigidity. Haemodialysis can be instituted in renal failure. Prevention of secondary complications such as deep venous thrombosis must be considered.

There is still no general consensus on the optimal pharmacological treatment for NMS. The most commonly used agents include bromocriptine and dantrolene. Bromocriptine is a central dopamine agonist whereas dantrolene causes skeletal muscle relaxation via inhibition of calcium release from the sarcoplasmic reticulum. Bromocriptine is available only orally and is administered via a nasogastric tube in most cases, thus it is suitable in mild to moderate NMS. Dantrolene can be given intravenously for severe cases and can be administered together with bromocriptine. Treatment needs to be continued for at least 10 days after the resolution of symptoms as early withdrawal can precipitate recurrence of NMS. Evidence remains conflicting regarding the use of bromocriptine and dantrolene whether in combination or separately and it is uncertain if pharmacotherapy has any effect on the mortality of NMS.<sup>2</sup> Most consider it as a secondary measure to supportive treatment. Other pharmacological agents have been considered e.g. amantadine, clonidine, anticholinergic drugs and benzodiazepines but more evidence is needed before their use can be recommended as standard treatment.

Electroconvulsive therapy is found to be effective even after failed pharmacotherapy.<sup>13</sup> Six to ten treatments is typically required for NMS and is relatively safe. It is indicated specifically in patients who have failed medical treatment after 48 hours, when it is not possible to differentiate NMS from acute lethal catatonia, in patients with residual catatonia or psychosis in the immediate post NMS period and if the underlying psychiatric diagnosis is psychotic depression or catatonia.<sup>2</sup>

In conclusion, this case documented that atypical antipsychotics when used with traditional antipsychotics can cause NMS even after five weeks and must be monitored closely. It is important as emergency physicians to be able to obtain a quick and

accurate diagnosis so that supportive and pharmacological treatment can be instituted as soon as possible to decrease mortality and morbidity in patients with NMS.

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