

## Short report

# Cerebellar syndrome following neuroleptic induced heat stroke

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**SUMMARY** We report a patient in whom extreme hyperthermia, rhabdomyolysis, acute renal failure and a residual pancerebellar syndrome occurred while taking a combination of perphenazine and amitriptyline. We postulate that impaired thermoregulation due to psychotropic drugs was responsible for the development of heat stroke and that the cerebellar syndrome resulted directly from the elevated temperature.

Residual neurological deficits after recovery from hyperthermia, particularly heat stroke, are well known<sup>1</sup> and probably result directly from elevated body temperature.<sup>2</sup> Impaired thermoregulation in patients taking neuroleptic drugs may lead to hyperthermia. We present a case in which hyperthermia with rhabdomyolysis, renal failure, and a persistent cerebellar syndrome developed during therapy with perphenazine and amitriptyline.

### Case report

A 50-year-old woman was found in her home one hour after having collapsed. When discovered, she was alert, sweating, and unable to walk without assistance. She repeatedly became sweaty and subsequently collapsed again without losing consciousness, but was confused and was admitted to hospital. She had been taking a perphenazine and amitriptyline combination 4-25 and diazepam 10 mg each four times a day for seven years. On physical examination rectal temperature was 42.5°C and

blood pressure was 100/80 mm Hg. She was drowsy with eye deviation downward and to the left. Initial laboratory evaluation revealed a serum glucose of 0.6 g/l and abnormal liver function tests. Chest radiographs showed interstitial oedema. Computed cranial tomography (CT) and spinal fluid examination were normal. The patient required ventilatory support and was treated with aspirin suppositories and a cooling blanket. Progressive deterioration of renal function necessitated dialysis.

After initial improvement in mentation, she deteriorated unexpectedly and was transferred to North Carolina Baptist Hospital. Examination on admission revealed diffuse ecchymoses, bilateral basal rales and hepatomegaly. She was unresponsive to pain and hyporeflexic with flexor plantar responses. The BUN was 0.92 g/l, creatinine 0.105 g/l, potassium 6.3 moles/l, CK 362 U/l (n/50-160 U/l), LDH 816 U/l, and aldolase 29 U/l (nl 7-24 U/l). Serum myoglobin was 1687 µg/l (nl 6-85 µg/l). Haematocrit was 32% with normal red cell indices. Prothrombin and partial thromboplastin times were normal. Fibrin degradation products were present in a concentration between 0.32 and 0.64 g/l. Repeat lumbar puncture was normal. CT showed cerebral atrophy.

With supportive care and dialysis, mental status and renal function improved. As the patient improved, her neurological deficit became apparent. There was ataxic, dysarthric speech and marked ocular dysmetria. Mild, generalised weakness was more marked proximally. There was truncal ataxia, hypotonia, and marked dysmetria of all four extremities. Sensation was normal. Muscle stretch reflexes were symmetrically brisk. Plantar responses were flexor. CT, CSF protein electrophoresis, plasma, zinc, urine for heavy metals, serum copper and ceruloplasmin levels were normal. Peripheral nerve conduction velocities, EMG and brainstem auditory responses were normal.

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## Discussion

This patient developed extreme hyperthermia, rhabdomyolysis, acute renal failure and a residual cerebellar syndrome while taking perphenazine and amitriptyline. We speculate that hyperthermic cerebellar damage resulted from heat stroke related to psychotropic medications. To our knowledge, a permanent cerebellar syndrome following neuroleptic-induced heat stroke has not been previously described.

Heat stroke occurs when an individual's ability to dissipate heat is overwhelmed by heat absorbed from the environment or produced by the body. Severe neurological symptoms such as coma and delirium are associated with multiple organ system dysfunction and elevated body temperatures, usually above 41°C. The onset is abrupt in 71% of cases, but nonspecific prodromal symptoms including nausea, dizziness, confusion, restlessness, drowsiness, and exertional "faints" may occur.<sup>2,3</sup> Other neurological manifestations of acute heat stroke include hallucinations, seizures, oculogyric crises, tremor, dystonia, pupillary abnormalities, decerebrate rigidity and hemiplegia.<sup>3,4</sup> Although these findings are generally reversible, neurological abnormalities may be permanent. A cerebellar syndrome is the most common persistent abnormality.<sup>1,5-7</sup> Residual pyramidal signs and mental status changes commonly have been reported.<sup>5</sup> Dysarthria, dysphagia, hemiplegia and lower motor neuron findings may also persist after heat stroke.<sup>1,3,8</sup> Patients with heat stroke are generally hypotensive, tachypnoeic and tachycardic on presentation. Haemorrhagic complications are common. Heat-induced endothelial injury may precipitate disseminated intravascular coagulation.<sup>4</sup> Renal failure can result from direct thermal injury to the kidneys, hypoperfusion or myoglobinuria. Although classic descriptions of heat stroke stress the lack of sweating, patients often continue to sweat profusely. When present, anhidrosis may be due to direct thermal injury or exhaustion of sweat glands.<sup>9</sup>

Factors predisposing to the development of heat stroke include advanced age, obesity, cardiovascular disease, lack of acclimatisation to heat and poor physical conditioning.<sup>3</sup> Alcohol and certain drugs, notably antipsychotics, may also increase the risk. Neuroleptics all have varying degrees of anticholinergic and anti-alpha-adrenergic effects. Both impair heat dissipation; anticholinergic properties decrease sweating and alpha-adrenergic blockade causes vasodilation, which may enhance heat absorption from the environment.<sup>10</sup> Use of high potency antipsychotics such as haloperidol and fluphenazine, which have lower peripheral alpha-adrenergic and cholinergic blocking activity, may

lessen this problem.<sup>10</sup> Concurrent administration of anticholinergic agents or tricyclic antidepressants, which also have anticholinergic properties, may further increase the risk to heat exposed individuals.

Antipsychotic induced heat stroke must be differentiated from the neuroleptic malignant syndrome, the cardinal features of which are hyperthermia, autonomic dysfunction, and extrapyramidal rigidity. Generally, the clinical picture develops over one to two days and follows shortly after initiation of antipsychotic therapy or dosage adjustment.<sup>11</sup> Extrapyramidal symptoms such as tremor, bradykinesia, and rigidity predominate. Altered mental status varies from alert mutism to coma. Autonomic manifestations include pallor,<sup>12</sup> hyperhidrosis,<sup>11</sup> hypotension<sup>13</sup> or hypertension,<sup>14-16</sup> dysuria, sialorrhoea and tachycardia.<sup>11,17</sup> Leukocytosis, rhabdomyolysis, renal and hepatic failure may all occur.<sup>11,13</sup> Hyperthermia in this syndrome probably results from dopamine receptor blockade simultaneously in the basal ganglia (leading to rigidity and thermogenesis) and in the hypothalamus (impairing heat dissipation and autonomic function).<sup>12</sup> A recent report incriminating alpha-methyltyrosine and tetrabenazine as a cause of the neuroleptic malignant syndrome suggests that dopamine depletion may play a similar role.<sup>18</sup> There is evidence, however, that in addition to its other pharmacologic properties, tetrabenazine may be a dopamine receptor antagonist.<sup>19</sup> Probably any dopamine blocker may cause this syndrome, but most cases have occurred with haloperidol and fluphenazine.<sup>17</sup> The risk with lower potency antipsychotics may increase when they are given in combination.<sup>11</sup> High antipsychotic doses are not necessary. Dehydration, exhaustion<sup>11</sup> or pre-existing organic brain disease<sup>17</sup> appear to increase risk. An identical clinical picture, known as Stauder's lethal catatonia, has been described in untreated manic and catatonic patients.<sup>20</sup> Differentiation from the drug induced syndrome hinges on the persistence of psychosis.<sup>21</sup>

Non-neuroleptic drugs which may cause hyperthermia include amphetamines,<sup>22</sup> glutethimide,<sup>23</sup> LSD,<sup>24</sup> phencyclidine,<sup>25</sup> and the combination of tricyclic antidepressants and monoamine oxidase inhibitors.<sup>26</sup> Hyperthermia and permanent neurological deficits, mostly cerebellar, may occur with lithium alone<sup>27</sup> or combined with haloperidol.<sup>28</sup> Other hyperthermic states including malignant hyperthermia, thyrotoxic crises, Luft's disease, and neurogenic hyperthermia can be excluded on clinical and paraclinical grounds.

Thermal injury to mammalian tissues begins at temperatures of 42°C. Extreme heat liquifies membrane lipids, denatures enzymes, uncouples oxidative phosphorylation and alters molecular

binding.<sup>3,29</sup> The cerebellum is the part of the nervous system most susceptible to hyperthermia, followed by cerebral cortex, brainstem, and spinal cord.<sup>2</sup> Purkinje cell loss occurs within 24 hours of heat stroke.<sup>2</sup> Malamud asserts that the extent of neuronal degeneration in heat stroke correlates better with the degree and duration of hyperthermia than with hypoxia. Studies in passively heated animals indicate that neither lactic acidosis nor hypoxia limits the degree of hyperthermia tolerated by the central nervous system.<sup>3</sup>

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