Neuroleptic malignant syndrome in adolescents: Four probable cases in the Western Cape

Terri Henderson

Background. Neuroleptic malignant syndrome (NMS) is a rare side-effect of neuroleptic medication. Most NMS reports have been on adults, and the incidence in children and adolescents is unknown.

Objective. This report reviews cases of NMS to highlight possible risk factors for the development of NMS in adolescents.

Method. Four cases of probable NMS in adolescents diagnosed in the Western Cape between February 2009 and March 2010 are presented.

Results. Risk factors in the development of the syndrome in adolescents in the Western Cape may be male gender, polypharmacy,

the use of zuclopenthixol acetate (clopixol acuphase), a previous history of extra-pyramidal side-effects or NMS, and a history of substance misuse – in particular methamphetamine.

Conclusion. Caution must be applied in the apparent overuse of intramuscular antipsychotics, and especially zuclopenthixol acetate (clopixol acuphase), in neuroleptic-naïve and agitated psychotic adolescents where the short-term use of benzodiazepines is more appropriate.

S Afr Med J 2011;101:405-407.

Neuroleptic malignant syndrome (NMS) represents a cluster of adverse effects of antipsychotic medications including: hypertonicity, autonomic instability, fever, and cognitive disturbance.[1] It is a rare but potentially life-threatening complication of neuroleptic (antipsychotic) drug therapy, with a mortality rate of 5 - 25%[2] and an incidence of 0.01 - 0.02% in adults.[3] The incidence rates in children and adolescents are uncertain. Precipitation of NMS may occur within hours of the first dose or after a period of maintenance treatment if there has been an increase in dose. All antipsychotics, including the newer atypical ones, have been associated with the development of NMS. Morbidity and mortality are predominantly the result of cardiopulmonary and renal complications.[4]

Presentations of NMS vary, and many diagnostic criteria have been proposed.[2,3] The DSM-1V-TR diagnostic criteria[3] require both core symptoms (fever, rigidity) and 2 or more additional symptoms (diaphoresis, dysphagia, tremor, incontinence, altered mental status, mutism, tachycardia, labile blood pressure, leukocytosis and evidence of muscle damage, e.g. raised creatine phosphokinase CK level).[3] Therefore, a raised CK level is not a mandatory diagnostic sign but one of many possible additional features. Diagnostic criteria used in adults are applied to children and adolescents and, with a few exceptions, NMS presents similarly in children and in adults.[1]

Table I presents data from 4 cases of probable NMS seen between February 2009 and March 2010; all were eventually referred to, and managed at, a rehabilitation unit for adolescents with psychosis at Lentegeur Hospital. They represent 3.6% of admissions over that time. While reference is made to a diagnosis of NMS, it is acknowledged that the evidence is circumstantial and, while fairly strong, is nevertheless presumptive.

Discussion

The cases suggest that male gender and polypharmacy (including the use of 2 or more antipsychotics), a past history of EPSE/NMS

Lentegeur Hospital, Mitchell's Plain, Cape Town, and the Department of Psychiatry, University of Cape Town

Terri Henderson, MB ChB, FCPsych (SA)

Corresponding author: T Henderson (thenders@pgwc.gov.za)

and agitation are important possible risk factors for NMS. Although intellectual disability and affective disorders are considered to increase vulnerability to NMS, these cases occurred in adolescents with normal intellectual functioning and without an overwhelming association with affective disorder. Other features include large variations in CK levels and a favourable outcome. Other key risk factors for NMS include: use of physical restraint to control psychomotor agitation, recent commencement of an antipsychotic regime, use of intramuscular antipsychotics, and excessive psychomotor agitation resulting in higher levels of dehydration.[5] This raises the dilemma about appropriate, yet safe, use of antipsychotics in youths who need antipsychotics to control their behaviour, in particular those receiving high doses in short time periods.[5] Zuclopenthixol acetate (clopixol acuphase) is a common denominator in 3 cases (2, 3 and 4), and oral haloperidol was co-prescribed in 3 cases (1, 2 and 4). The Cochrane systematic review database found limited efficacy data for claims that zuclopenthixol acetate would rapidly calm or sedate aggressive patients with schizophrenia.[6] Therefore, the use of zuclopenthixol acetate in neuroleptic-naïve adolescents with a first-presentation psychotic illness, and for the specific purpose of rapid tranquillisation, must be carefully considered.

Body temperature recording in this series was often taken haphazardly and in difficult circumstances such as marked agitation and restlessness, when it is unsafe to use the oral method. Temperature readings were obtained from the axilla. In one case the temperature was never recorded, one patient had no pyrexia, and 2 patients showed only a mild elevation. A core feature of NMS is pyrexia; therefore it could be argued that at least 2 patients did not conform to a 'true' NMS. However, the additional signs and symptoms noted in all the subjects were consistent with a *probable* diagnosis of NMS.

Important differential diagnoses in adolescents with probable NMS are malignant hyperthermia, heat stroke, anticholinergic delirium, serotonin syndrome, central nervous system infection and neuroleptic-induced dystonia. The latter occurs within 7 days of initiating drug treatment or following a rapid increase in the dose and is an involuntary contraction of muscle groups forcing certain parts of the body into abnormal, sometimes painful, postures. It is not associated with fluctuations in blood pressure, pyrexia, tachycardia or any other additional signs or symptoms seen with NMS.

Silva *et al.*[1] emphasise that, in children and adolescents, NMS presents in a form and course similar to adults. A fatal outcome is associated with age <12 years, although the number of fatal outcomes

Table I. Patient data related to 4 probable cases of NMS

	Case 1	Case 2	Case 3	Case 4
Age, gender	17, male	16, male	16, male	16, male
Diagnosis	Schizophrenia	Bipolar mood disorder	Schizophreniform disorder	Schizophrenia
First presentation	No, known schizophrenic, previous EPSE, treated on clozapine	Yes	Yes	No, known schizophrenic, previous diagnosis of NMS
Intellectual functioning	Normal	Normal	Normal	Normal
History of substance abuse	Negative	Crystal methamphetamine, cannabis	Negative	Crystal methamphetamine, cannabis, alcohol
Presenting history	Psychotic, aggressive, disruptive	Psychotic	Psychotic	Psychotic, restlessness
Agitation prior to NMS	Yes	Yes	No	Yes
Medication (incl. route of administration and dose)	Haloperidol 2.5 mg 20h00, flupentixol 10 mg IMI × 2	Zuclopenthixol acetate 25 mg, haloperidol 1.5 mg twice daily, diazepam 20 mg thrice daily	Zuclopenthixol acetate 50 mg IMI, risperidone 0.5 mg twice daily	Zuclopenthixol acetate 50 mg IMI × 2, haloperidol 5 mg twice daily, lorazepam 4 mg thrice daily
Latency period	5 days	11 days	1 day	4 days
Highest recorded temperature	36.7°C	37.5°C	37.4°C	37.4°C
Rigidity	Present	Present	Present	Present
BP fluctuation	No	No	No	Not recorded
Tachycardia	120 bpm	120 bpm	126 bpm	Not recorded
Tremor	NN	NN	No	No
Dystonia	Yes	NN	No	No
Diaphoresis	NN	Yes	No	No
Incontinence	NN	NN	Yes	No
Dysphagia	NN	NN	NN	Yes
WCC	15.9 cells/mm³	NN	7.86 cells/mm³	3.86 cells/mm³
CK (highest)	5 307 IU/l	783 IU/l	10 000 IU/l	1 173 IU/l
Na, liver enzymes, EEG, CT scan, MRI, CSF	Negative	Negative	Negative	Negative
Treatment	Antipsychotics were stopped. Treated with diazepam.	Antipsychotics were stopped. Treated with lorazepam.	Antipsychotics stopped. IVI rehydration and benzodiazepines given.	Antipsychotics were stopped.
Outcome	Full recovery from NMS. Discharged on clozapine.	Full recovery from NMS. Discharged on quetiapine.	Full recovery from NMS. Discharged on clozapine.	Full recovery from NMS. Discharged on risperidone.

NN = nil noted; EPSE = extra-pyramidal side-effects.

has dropped sharply in all age groups in recent years. A milder course of NMS associated with atypical antipsychotics, a greater resilience in children, earlier detection, prompt antipsychotic discontinuation and more aggressive management of NMS are additional moderating factors.[3] The latency period in these 4 cases refers to the time elapsed between the administration of an intramuscular antipsychotic and the diagnosis of possible NMS. Signs of NMS develop within 24 hours in 16% of patients initiating antipsychotic medication, 66% by 1 week and 90% within 30 days, and NMS is less likely to occur after 30 days.[9] Treatment of NMS includes referral to a medical unit, fever reduction, intravenous rehydration, dantrolene and bromocriptine, and sedation with benzodiazepines. Electroconvulsive therapy is an effective treatment option both for the NMS and the underlying psychiatric illness.[3] After resolution of NMS and normalisation of CK level, a 2-week waiting period is recommended before re-exposure to antipsychotics.

In 2 of the 4 cases, crystal methamphetamine, a street drug manufactured from ephedrine or pseudo-ephedrine that is smoked or injected and popularly known as 'tik' in the Western Cape, was one of the substances used prior to illness. Its use has accelerated

in the Western Cape since 2003, particularly among the youth. This observation suggests a possible relationship between substance abuse and the development of NMS. Methamphetamine causes the release of dopamine and noradrenaline (and, to a lesser extent, serotonin) into the synaptic cleft and inhibits their reuptake. This creates very high intrasynaptic dopamine concentrations that probably accelerate or exacerbate the psychotic process. Chronic use of stimulants such as methamphetamine or cocaine may predispose the individual to NMS.[11] A hypothetical mechanism is that the initial dopamine stimulation induced by methamphetamine is followed by a depletion of neuronal dopamine reserves with continuing use of the agent. The resulting dopamine deficiency would be aggravated by the therapeutic administration of antipsychotics that further compound the hypodopaminergic state by their blockade of post-synaptic receptors. These events establish a setting of reduced dopamine activity, which is probably the aetiological basis for NMS.

Ethics approval

Ethics approval was given by the University of Cape Town Research and Ethics Committee, and the Tygerberg Hospital and Lentegeur Hospital authorities provided permission to extract data from patient folders.

References

1. Silva R, Dinohra M, Alpert M, Perlmutter R, Diaz J. Neuroleptic malignant syndrome in children and adolescents. J Am Acad Child Adolesc Psychiatry 1999;38(2):187-194.
2. Erermis S, Bildik T, Tamar M, Gockay A, Karasoy H, Sabri Ercan E. Zuclopenthixol-induced neuroleptic malignant syndrome in an adolescent girl. Clinical Toxicology 2007;45:277-280.
3. Croarkin P, Emslie G, Mayes T. Neuroleptic malignant syndrome associated with atypical antipsychotics in paediatric patients: a review of published cases. J Clin Psychiatry 2008;69(7):1157-1165.
4. Kahn H, Syed N, Sheerani M, Khealini B, Kamal A, Wasay M. Neuroleptic malignant syndrome: need for early diagnosis and therapy. Journal Ayub Med Coll Abbottabad 2006;18:1.
5. Viejo L, Morales V, Punal P, Perez J, Sancho R. Risk factors in neuroleptic malignant syndrome. A case-control study. Acta Psychiatr Scand 2003;107:45-49.
6. Gibson R, Fenton M, Campbell C. Zuclopenthixol acetate for acute schizophrenia and similar serious mental illnesses. Cochrane Database of Systematic Review 2004:3: Art no CD 000525.
7. Cohen O, Leibovici L, Mor F, Wysenbeek A. Significance of elevated levels of serum creatine phosphokinase in febrile diseases: a prospective study. Reviews of Infectious Diseases 1991;13:237-242.
8. Meltzer H, Cola P, Parsa M. Marked elevations of serum creatine kinase activity associated with antipsychotic drug treatment. Neuropsychopharmacology 1996;15(4):395-404.
9. Mahendran R, Winslow M, Lim D. Recurrent neuroleptic malignant syndrome. Aust N Z J Psych 2000;34(4):699-700.
10. Batki S, Harris D. Quantitative drug levels in stimulant psychosis: relationship to symptoms severity, catecholamines and hyperkinesias. Am J Addict 2004;13:461-470.
11. MaCauly J, Ruiz P. Neuroleptic malignant syndrome: A complication of neuroleptics and cocaine abuse. Psychiatric Q 1991;62(4):299-309.