Eur Arch Psychiatry Clin Neurosci (1994) 243:299–303

European Archives of Psychiatry and Clinical Neuroscience

Original articles

Neuroleptic malignant syndrome and catatonia

A report of three cases

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Received 20 June 1993

Summary. In a series of 1007 consecutively admitted patients, 3 cases of neuroleptic malignant syndrome (NMS) were identified (0.3%). All three patients were affected by mood disorders with congruent psychotic features, had shown catatonia just before the onset of NMS, and had been treated with low neuroleptic doses. All of them presented low serum iron levels. The relationship between NMS and catatonia and possible therapeutic decisions are discussed.

Key words: Neuroleptic malignant syndrome – Catatonia

Introduction

Neuroleptic malignant syndrome (NMS) is a rare and life-threatening complication of neuroleptic treatment characterized by fever, altered consciousness, rigidity and autonomic instability (Delay and Deniker 1968).

There is no consensus about its relationship to catatonia, including the acute lethal subtype, and to borderline cases where some typical symptoms are absent or soft.

Several sets of diagnostic criteria have been proposed (Caroff 1980; Levenson 1985; Guze and Baxter 1985; Addonizio et al. 1986; Pope et al. 1986; Kellam 1987; Adityanjee et al. 1988; Keck et al. 1989) and different incidence rates among patients treated with neuroleptics have been reported [range: 2.4% (Addonizio et al. 1986) – 0.02% (Neppe 1984)].

Kellam (1990), in a recent review, estimates that even this lower limit is far higher than that seen in the UK and stresses the necessity of accurately controlling the actual incidence of NMS outside the USA.

As regards the boundaries and the pathogenesis of NMS, Castillo et al. (1989) claimed to have been able to reliably distinguish NMS from "lethal catatonia" (LC). They consider the former a reaction to drugs, characterized specifically by sudden and progressive muscle hypertonicity, and the latter an exhaustion syndrome, caused and sustained by relentless psychomotor excitement which results in autonomic dysfunction, general deterioration, and organic-like delirium and coma. On these grounds Castillo et al. recommend neuroleptic withdrawal in NMS but suggest neuroleptic treatment in LC.

In their opinion, only in the final stage, when the symptomatology resembles almost any near-death acute confusional state of organic etiology, the two syndromes are indistinguishable.

In contrast, Mann et al. (1986), Kellam (1987), and White and Robins (1991) questioned the distinction between NMS and LC considering the former a drug-induced type of the latter.

We reviewed the records of the patients admitted to our psychiatric emergency service of a general hospital between May 1989 and December 1990, prospectively examined the patients admitted between January 1991 and March 1993, and found three cases of NMS. To make the diagnosis according to the most strict diagnostic criteria of NMS (Adityanjee et al. 1988), we required the presence of the four essential clinical components: altered sensorium, muscular rigidity, hyperpyrexia of unknown origin, and autonomic dysfunction.

Altogether, 1007 of 1201 admitted patients were treated with neuroleptics in our ward, 256 (of 327) in the retrospectively examined period (1 case of NMS) and 751 of 874 in 1991–1993 (2 cases of NMS) yielding an estimated 0.3% frequency for this syndrome among patients exposed to neuroleptics.

Case reports

Case 1

A 23-year-old woman, developed a major depressive episode with mood congruent psychotic features for which she was admitted in autumn 1990 and started on haloperidol (4 mg i.v. + 2 mg p.o. daily) and on diazepam (10 mg i.v. daily). Her medical history was unremarkable. Drug

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treatment before admission is not mentioned in the charts. Upon arrival in the hospital, she was perplexed, mute, akinetic with tonic contraction of muscle groups causing opisthotonus, but her eyes showed vigilance and attention. Oral nourishment was poor. Sphincteric incontinence was present.

Since no improvement was noted and psychotic features were prominent, 3 days later, haloperidol was increased to 8 mg i.v. daily. On her 8th day in hospital, while the catatonic stupor worsened, hyperthermia (38.5° C) and overall body rigidity were noted. Diagnostic investigations were carried out, intensive supportive therapy was kept, antibiotic therapy was started and nourishment was assured with a nasogastric tube since the patient was unable to swallow. However neuroleptics were not withdrawn. The results of head CT scan, head NMR scan, EEG (2), chest X-ray (3), esophagogastroduodenoscopy, echocardiography, blood cultures (4) and thyroid function tests were normal. Creatine phosphokinase (CPK) rose up to 2700 U/l (normal range: 10–70 U/l, lactate dehydrogenase (LDH) to 473 U/l, serum glutamic oxo-acetic transaminase (SGOT) to 330 U/l and serum glutamic pyruvic transaminase (SGPT) to 134 U/l. The serum iron level was 22 mg/dl on day 9 and 31 mg/dl on day 11 (normal range: 40–100), whereas RBC, Hb, Ht and platelet count were normal. The WBC revealed a maximum value of 11.500/mm^3. The patient's blood pressure varied between 120 and 160 mmHg, systolic, and 60 and 100 mmHg, diastolic; pulse rate varied between 130/min and 145/min and temperature between 37.5°C and 38.5°C.

On day 20, haloperidol was reduced to 4.5 mg p.o. daily and chlorimipramine was gradually introduced (up to 125 mg p.o. daily), without remarkable clinical changes. On day 34, the patient's temperature spiked to 39.5°C, without any evidence of infection. NMS was then suspected; neuroleptics and antidepressants were suspended. Six days later, the clinical picture gradually improved with no further complications.

Ten days after neuroleptic withdrawal, the patient was treated with sulpiride (50 mg p.o.) for her psychotic symptoms (delusions and hallucinations consistent with depressive themes), without difficulty. During the next 20 days, she became progressively symptom free and was discharged.

In February 1993, we had the opportunity to verify the patient's excellent state of health.

Case 2

A 61-year-old man with a 10-year history of bipolar affective disorder was admitted in May 1992 with severe psychotic crisis.

Table 1. Two syndromes

Catatonia	Neuroleptic malignant syndrome
Clinical setting: Mood disorders, schizophrenia, (rarely) neurologic, metabolic, or autoimmune diseases	*Clinical setting:* Use of dopamine-receptor antagonists, or withdrawal of L-dopa or dopamine agonists
Clinical course: Usually develops over a short period of time (a few days)	*Clinical course:* Usually begins abruptly, over a few hours
Prodromal phase: Behavioural disorders, personality changes	*Prodromal phase:* Poor response to neuroleptics, severe side extrapyramidal effects, confusion
Initial symptoms: Delusions, prominent hallucinations, incoherence or marked loosening of associations, catatonic behavior (rigidity, severe excitement, intense anxiety, posturing, stupor, negativism); possible fever, tachycardia, and acrocyanosis	*Initial symptoms:* Fever (in the absence of infection), parkinsonism, autonomic instability, clouding of consciousness
Full syndrome: Severe psychomotor agitation and destructive behavior may alternate with mutism, rigidity and stupor; autonomic disorders (tachycardia, fluctuating fever, hypo-hypertension, tachypnea, diaphoresis)	*Full syndrome:* Hyperpyrexia, severe muscular rigidity, autonomic disturbances (hypo-hypertension, tachycardia, tachypnea, diaphoresis); altered mental state (confusion, drowsiness, stupor); the patient may appear unresponsive but may be physiologically awake
Associated features: Stereotypies, mannerisms, waxy flexibility; elevated CPK, leucocytosis, sphincteric disturbances, dehydration	*Associated features:* Elevated CPK, leucocytosis, dehydration, possibly hypoferremia
Complications: Rhabdomyolisis, myoglobinuria, renal failure, intravascular thrombosis, pulmonary embolism, pneumonia or urinary tract infections, decubitus ulcers	*Complications:* Rhabdomyolisis, myoglobinuria, renal failure, intravascular thrombosis, pulmonary embolism, pneumonia or urinary tract infections, decubitus ulcers
Final stage: Extreme exhaustion, delirium, coma, death	*Final stage:* Extreme exhaustion, delirium, coma, death

The distinction between the two syndromes is difficult because of the great variability of the main symptoms and signs and the inconstancy of the timing of their presentation. In the final stages the two syndromes are clinically indistinguishable

In 1977, the patient, affected by cholangitis caused by an obstructed common bile duct, had required emergency surgery. Otherwise his medical history was unremarkable. Past psychiatric crises had been successfully treated with neuroleptics and antidepressants. He had had multiple psychiatric hospitalizations and years of oral and parenteral neuroleptic medications.

A few days before admission to our ward, the patient had become agitated, logorrhoeic, pale, confused and, later on, akinetic and mute for which he had consumed a low dose of clothiapine (50 mg p.o. daily) for 3–4 days. On admission the patient showed paleness, catatonic stupor and negativism, echolalia, akinesia and rigidity. His bladder was distended and there were involuntary "overflow" voidings. Blood pressure was 170/110 mmHg, pulse rate was 104/min, and temperature was 37.7°C. Neurologic examination and chest X-ray were normal. A provisional diagnosis of bipolar disorder, mixed, with catatonic features and urinary tract infection was made. A catheter for bladder drainage was applied, intensive supportive care was provided and treatment with cefotaxime (2 g i.m. daily), haloperidol (4 mg i.v. daily) and diazepam (20 mg i.v. daily) was begun.

The next day, the patient was disoriented, dehydrated and extremely akinetic, however, rigidity was notably absent. He looked anguished. His thought processes included perseveration and verbigeration. He mentioned ideas of guilt and alluded to acquaintances of his as "traitors".

Two h later, his temperature suddenly increased to 39.6°C. His clinical course was now felt to be most consistent with NMS. Haloperidol was immediately discontinued. Catatonic stupor, negativism and posturing persisted in the following days. In addition, on day 5, muscular rigidity with cogwheel phenomenon, coarse tremor, and sweating became evident. Temperature varied between 37.0°C and 40.2°C, blood pressure varied between 90 and 170 mmHg, systolic, and 60 and 100 mmHg, diastolic. Pulse rate varied between 90/min and 110/min. Chest X-ray (4), pancreas and liver echography, blood cultures, urine cultures and other laboratory investigations were normal except for elevation of serum CPK (up to 1905 U/l), SGOT (50), SGPT (49), amylase (441) and for decrease of serum iron [36 mg/dl, on day 5 (normal range: 50–120)] while RBC, WBC, Hb, Ht and platelet count were normal.

The patient was kept well hydrated, intensive supportive care was provided, antipyretics and antibiotics were given.

On day 8, fever lessened and a rapidly progressive clinical improvement began until the patient was discharged without psychotic symptoms, with very slight akinesia and muscular hypertonia, and irregular postural hand tremor. In March 1993, patient's health was excellent.

Case 3

A 59-year-old lady, known to have had a major depressive episode treated with electroconvulsive therapy (ECT) (after her second daughter's birth), manifested again depressive symptoms with mood-congruent psychotic features after her husband's death for which she was twice admitted, treated with chlorimipramine (200 mg p.o. daily), haloperidol (3 mg p.o. daily) and diazepam (20 mg p.o. daily) with only moderate benefit, and discharged.

Two months later she was again admitted because of abnormal behavior (she had thrown heavy objects out of her window, stating trivial reasons for this action). Severe psychomotor retardation, diminished ability to think or concentrate, loss of interest, apathy and a strange indifference were evident. Since her symptoms looked atypical, an alternative diagnostic hypothesis of pseudodepressive dementia was considered, but excluded. Neurologic examination was normal, Wechsler's adult intelligence scale (WAIS) test gave a 98 IQ and TC provided normal cerebral imaging (except a little localized atrophic area in left parieto-occipital region).

The patient was treated with (daily dose) chlorimipramine (200 mg p.o.), trifluoperazine (6 mg p.o.), flurazepam (30 mg p.o.), propanolol (20 mg p.o.) (for a mild akathisia) and discharged with moderate improvement. She refused ECT.

Six weeks later, the patient was newly admitted for complex partial seizures (characterized by elementary visual sensations, loss of vision and right motor involvement of the face and limbs) which evolved in secondarily generalized seizures. Her mental status was not changed compared to the former admission. Therapy was begun with fluoxetine (20 mg p.o.), haloperidol (2 mg p.o.), diazepam (16 mg p.o.), propanolol (20 mg p.o.). Neurologic examination was normal, TC confirmed the presence of a little (unchanged) atrophic area in left parieto-occipital region, EEG showed 3.5–4 Hz slow waves in temporal regions, but no epileptiform discharges. On day 15, serum iron level was 38 mg/dl (normal range: 40–100).

On day 22, the patient presented dysphagia with consequent poor oral intake. The day after, muscular rigidity with cogwheel phenomenon became unexpectedly evident. She was able to converse but exhibited long latencies in response. Her mental status was unchanged and she was aware and fully oriented. A diagnosis of impending NMS was entertained and haloperidol was immediately discontinued. That night, high fever (39.5°C) suddenly developed, with diaphoresis, dyspnea, and wheezing. The patient became lethargic. Fluoxetine and diazepam were stopped. Antibiotics and intensive support therapy, including maintenance of adequate hydration and physiologic monitoring, were started. Results of chest radiographies, lumbar puncture, physical examination and blood cultures were negative.

On day 24, the patient's status was unchanged, blood pressure varied between 110 and 160, systolic, and 80 and 100, diastolic. Pulse rate varied between 100 and 110/min, CPK was elevated at 2000 U/l. Arrangements were made for transfer to the medical intensive care unit.

Upon arrival in the intensive care unit in the evening, there was a noted improvement of her mental status, also decreased rigidity, lowering of body temperature (37.5°C) and of CPK (869 U/l, 711 U/l).

On day 25, the patient was afebrile, fully oriented, but still akinetic and rigid and CPK level was 939 U/l. No

psychotropic drug was given. Two days later, fever (38.8° C), confusion and drowsiness suddenly reappeared, without any evidence of infection. Antibiotic therapy with ceftriaxone and gentamicin was started. In the following 2 days temperature varied between 38°C and 39.8°C, blood pressure between 130 and 170, systolic, and 80 and 90, diastolic, pulse rate between 100 and 110/min, CPK was elevated at 530 U/l and LDH at 402 U/l.

The patient became comatose until death for cardiac arrest supervened. Autopsy results were unremarkable.

Discussion

To our knowledge this is the second italian study on the incidence of NMS. In the first one, Amore and Montanari (1992) found 7 cases of NMS in a series of 1500 consecutive patients treated with neuroleptics. In our patients we estimated a NMS incidence of 0.3% quite similar to the incidence rate (0.47%) reported by Amore and Montanari. These rates appear consistent with the results of studies where strict diagnostic criteria were used and so-called "incomplete", "atypical" or "milder variant forms of NMS" were excluded [Caroff 1980 (0.5%), Shalev and Munitz 1986 (0.4%)]. Even assuming that NMS cannot be reliably diagnosed in the absence of even one of the four essential clinical components, (namely hyperpyrexia of unknown origin, altered sensorium, muscular rigidity and autonomic dysfunction), its occurrence is not exceptionally rare.

Although it seems to us unreliable a definite diagnosis of NMS according to the wide criteria suggested by some authors (Addonizio et al. 1986; Pope et al. 1986), we are aware that high level of diagnostic suspicion must be kept, in order to detect the early appearance of NMS, and that even single symptoms may be sufficient to consider a diagnosis of possible impending NMS. In our case 3 we retrospectively consider dysphagia the first sign of the syndrome, while the unexpected appearance of severe rigidity in absence of any drug treatment change (without fever, altered sensorium and vegetative dysfunction) prompted us to suspect the diagnosis and to stop neuroleptics.

Adityanjee (1988) criticises the spectrum concept of NMS according to which the syndrome is seen as an extension of extrapyramidal symptoms induced by neuroleptics. Since drug-induced extrapyramidal effects are frequent in neuroleptic treated patients, he suspects that such an approach could lead to an excessively high false-positive rate of diagnoses and to initiation of treatment with anticholinergics and dopamine agonists; whereas the risk of starting with anticholinergics (which may worsen or precipitate hyperpyrexia) in NMS cases and with dopamine agonists (which may exacerbate psychosis) in patients without NMS, is alarming, alternative safer therapeutic options (e.g. reduction or withdrawal of neuroleptics, benzodiazepines, ECT) are available.

There are many reasons to suppress extrapyramidal symptoms during neuroleptic treatment and the danger of a possible impending NMS is certainly one of these.

If a high level of diagnostic suspicion is advisable to detect borderline or initial NMS cases (and even soft or isolated symptoms must be regarded cautiously), we doubt whether it is possible reliably distinguishing between NMS and LC. Castillo et al. (1989), who claim it is possible, acknowledge that there is variability of signs and symptoms in both disorders and overlap in the timing of their appearance.

In our opinion evidence is lacking for selecting safely opposite therapeutic strategies (administration or withdrawal of neuroleptics) and it is preferable to defer the diagnostic dilemma, suspend (or do not initiate) neuroleptics, provide supportive therapy, and consider other therapies as benzodiazepines or ECT.

Even in never treated catatonic patients, when NMS can be firmly excluded, neuroleptics are not riskless since NMS and catatonia may be both produced by a disturbance in the dopaminergic systems of the brain (Kellam 1987) sharing the same underlying pathophysiology (Kaufmann and Wyatt 1987). Catatonic symptoms often precede drug treatment in cases of NMS (White and Robins 1991) and many other factors typically present in catatonia (deydration, psychomotor agitation, physical exhaustion, psychiatric affective diagnosis, concurrent medical illness) are risk factors of NMS (Rosebush and Stewart 1989; Rosenberg and Green 1989).

Because of the unpredictable nature of the syndrome and in the absence of controlled random-assignment treatment trials for the NMS the decision to provide only supportive therapy or to initiate a specific drug treatment (bromocriptine, amantadine, L-dopa, dantrolene) or ECT remains an individual clinical choice. In their recent review of 665 cases of NMS, Davis et al. (1991) found that the most commonly used treatment for NMS is the discontinuation of neuroleptics and the use of supportive therapy ($n = 438$), however they found a mortality rate of 9.7% in the specific drug treated patients, of 10.3% in the ECT-treated patients and of 21% in the patients receiving only non specific treatment. In contrast, Rosebush and Stewart (1989) do not advise specific drug treatment. Perhaps, as Scheftner and Shulman (1992) suggest, because both bromocriptine and dantrolene have mean response times of < 2 days (Rosenberg and Green, 1989), either agent may be tried for up to 48 h, while continuation beyond 2 days seems unwarranted. In the absence of a clear reduction in rigidity and temperature after this time these authors recommend ECT.

The notable features of the presently reported cases were the following:

1. all patients were affected by mood disorders with congruent psychotic features.

Other studies reported a high percentage of affective psychoses among NMS cases (Rosebush and Stewart 1989; Keck et al. 1987; Addonizio et al. 1986; Pearlman 1986). However in most of these cases, patients were manic; consequently many authors have hypothesized that agitation (or a high neuroleptic dosage used to control it), dehydration or physical exhaustion, which are NMS risk factors, can account for the higher incidence of NMS among affective patients. On the contrary our patients were severely depressed, retired and akinetic. Patient 2 had been agitated and logorrhoeic just a few days before

becoming clinically depressed akinetic and mute and we cannot exclude that early NMS signs had begun during this brief manic phase; however the full-blown syndrome developed at least after 3 days of retirement and akinesia.

2. On admission, before the NMS, each of our patients showed a catatonic stupor. Also White and Robins (1991) reported a series of 5 patients, each of them showing catatonia before the onset of NMS. These data are consistent with the hypothesis that catatonia and NMS share a common pathophysiology (deficient brain dopaminergic activity?), spontaneous in the former and neuroleptic-induced in the latter, and suggest that neuroleptics can worsen catatonia or convert it into NMS.

3. In each of our patients, at the onset of NMS, neuroleptic dosage was low (concomitant fluoxetine may have somewhat increased plasma level in case 3). Again these data are consistent with White ahd Robins report (1991) where patients are described receiving a few (or just a single) low neuroleptic doses who underwent NMS. However some important studies (Caroff 1980; Shalev and Munitz 1986; Gelenberg et al. 1988; Rosebush and Stewart, 1989; Keck et al. 1989) stress the importance of neuroleptic dosage as a NMS risk factor.

4. Serum iron levels were low in all three cases. To our knowledge low serum iron levels in NMS were reported only by Rosebush and Stewart (1989) and this is the first replication of their data.

Endogenous pyrogens produced by leukocytes in febrile infections can cause hypoferremia as well as muscular hypertonia and (probably damage) since low serum iron levels are related to muscle injury. However, in our patients, with the possible exception of case 2, no detectable infection was present and in case 3 serum iron level was low before the onset of NMS. More direct links may exist between hypoferremia and the etiopathogenesis of NMS. Actually iron is implicated in striatal dopamine receptor function (Rutledge et al. 1987). Some studies (Brown et al. 1987; Barton et al. 1990; O'Loughlin et al. 1991), found hypoferremia related to akathisia, although other studies did not (Nemes et al. 1991; Sachdev and Longeragan 1991; Barnes et al. 1992). Many hypotheses have been proposed about a significant relation between iron and dopaminergic D2 receptors, neuroleptic drugs, and motor disturbances (see Barnes et al. 1992 for a review). Hypoferremia could be an important marker for NMS.

References

Addonizio G, Susman VL, Roth SD (1986) Symptoms of neuroleptic malignant syndrome in 82 consecutive inpatients. Am J Psychiatry 143:1587–1590

Adityanjee, Singh S, Singh G (1988) Spectrum concept of neuroleptic malignant syndrome. Br J Psychiatry 153:107–111

Adityanjee (1991) The myth of elevated serum creatine phosphokinase level and neuroleptic malignant syndrome. Br J Psychiatry 158:706–707

Amore M, Montanari M (1992) La sindrome maligna da neurolettici e sindromi correlate. Minerva Psichiatr 33:259–283 (Summary in English)

Barnes TRE, Halstead SM, Little PWA (1992) Relationship between iron status and chronic akathisia in an in-patient population with chronic schizophrenia. Br J Psychiatry 161:791–796

Barton A, Bowie J, Ebmeier K (1990) Low plasma iron status and akathisia. J Neurol, Neurosurg Psychiatry 53:671–674

Brown KW, Glen SE, White T (1987) Low-serum iron status and akathisia. Lancet I:1234–1236

Caroff SN (1980) The neuroleptic malignant syndrome. J Clin Psychiatry 41:79–83

Castillo E, Rubin RT, Holsboer-Trachsler E (1989) Clinical differentiation between lethal catatonia and neuroleptic malignant syndrome. Am J Psychiatry 146, 324–328

Davis JM, Janicak PG, Sakkas P, Gilmore C, Wang Z (1991) Electroconvulsive therapy in the treatment of the neuroleptic malignant syndrome. Convulsive Therapy 7(2):111–120

Delay J, Deniker P (1986) Drug-induced extrapyramidal syndromes. In: Viken PJ, Bruyn GW (eds) Handbook of Clinical Neurology. North Holland, Amsterdam, pp. 248–266

Gelenberg AJ, Bellinghausen B, Woicik JD, et al. (1988) A prospective survey of neuroleptic malignant syndrome in a short term psychiatric hospital. Am J Psychiatry 145:517–518

Guze BH, Baxter LR (1985) Current concepts: neuroleptic malignant syndrome. N England J Med 313:163–166

Kaufmann CA, Wyatt RJ (1987) Neuroleptic malignant syndrome. In: Meltzer HY (ed) Psychopharmacology. The Third Generation of Progress. Raven Press, New York, pp. 1421–1430

Keck PE Jr, Pope HG Jr, McElroy SL (1987) Frequency and presentation of neuroleptic malignant syndrome: a prospective study. Am J Psychiatry 144:1344–1346

Keck PE Jr, Harrison GP, Cohen BM, et al. (1989) Risk factors for neuroleptic malignant syndrome. Arch Gen Psychiatry 46: 914–918

Kellam AMP (1987) The neuroleptic malignant syndrome, so-called. Br J Psychiatry 150:752–759

Kellam AMP (1990) The (frequently) neuroleptic (potentially) malignant syndrome. Br J Psychaitry 157:169–173

Levenson JM (1985) Neuroleptic malignant syndrome. Am J Psychiatry 142:1137–1145

Mann SC, Caroff SN, Bleier HR, et al. (1986) Lethal catatonia. AM J Psychiatry 143:1374–1381

Nemes ZC, Rotrosen J, Angrist B, et al. (1991) Biol Psychiatry 29: 411–413

Neppe VM (1984) The neuroleptic malignant syndrome. S Afr Med J 65:523–525

O'Loughlin V, Dickie AC, Ebmeier KP (1991) Serum iron transferrin in acute neuroleptic induced akathisia. J Neurol Neurosurg Psychiatry 54:363–364

Pearlman CA (1986) Neuroleptic malignant syndrome: a review of the literature. J Clin Psychopharmacol 6:257–273

Pope HG, Keck PE Jr, McElroy SLB (1986) Frequency and presentation of neuroleptic malignant syndrome in a large psychiatric hospital. Am J Psychiatry 143:1227–1233

Rosebush P, Stewart T (1989) A prospective analysis of 24 episodes of neuroleptic malignant syndrome. Am J Psychiatry 146:717–725

Rosenberg MR, Green M (1989) Neuroleptic malignant syndrome. Arch Intern Hed 149:1927–1931

Rutledge JN, Hilal SK, Silver AJ, et al. (1987) Study of movement disorders and brain iron by MR. Am J Radiol 149:365–379

Sachdev P, Longeragan C (1991) Acute drug-induced akathisia is not associated with low serum iron status. Psychopharmacology 103:138–139

Scheftner WA, Shulman RB (1992) Treatment choice in neuroleptic malignant syndrome. Convulsive Therapy 8(4):267–279

Shalev A, Munitz H (1986) The neuroleptic malignant syndrome: agent and host interaction. Acta Psychiatr Scand 73:337–347

White DAC, Robins AH (1991) Catatonia: harbinger of the neuroleptic malignant syndrome. Br J Psychiatry 158:419–421