LEADING ARTICLE

THE NEUROLEPTIC MALIGNANT SYNDROME

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The term "Neuroleptic Malignant Syndrome" was coined by Delay and Deniker in 1968 [1] to describe a rare and potentially fatal complication of neuroleptic medication. Until recently, it was not widely recognized and was hence a relatively unknown condition. There was no specific mention of the syndrome in recent standard textbooks like the Goodman and Gillman 1980 [3], Oxford Textbook of Psychiatry 1983 [4], and Postgraduate Psychiatry 1986 [5]. The core features of the syndrome are fever, extrapyramidal symptoms, autonomic dysfunctions and mental confusion.

The first case of Neuroleptic Malignant Syndrome (NMS) was described in 1960 [2]. After that, the disorder was rarely reported until the 1970's when many isolated cases appeared in the literature. In the 1980's, there have been several reviews on the subject involving large number of cases. The first large series was by Caroff (1980) [6] who reported on 60 cases from the literature followed by Kurlan et al (1984) [7] who collected and analysed 52 cases from English literature. Levinson and Simpson (1986) [8] studied 39 out of 63 cases from 40 English publications between 1972 and 1984, and found that 16 cases had concurrent medical problems. The largest series was by Shalev and Munitz (1986) [9] who analysed 120 out of 150 case reports from 80 publications covering the period 1956 to 1985. Addonizio et al (1987) [10] analysed 115 cases from the English literature for 43 variables and made recommendations for research. First case from Singapore was reported by Tian and Tsoi (1988) [11].

INCIDENCE

From the reviews of literature, the estimated incidence was around 0.4% or 0.5% [6,9]. The incidence would be higher if mild, incomplete and atypical cases were included. In their analysis on 120 cases, Shalev and Munitz (1986) [9] found that it was twice more commonly reported in males than females. It can affect any age (3 to 78 years, mean 35) and the age range was similar to the distribution of the usual psychiatric population, but the majority of the patients were below age 40 years. The youngest patient was a 3 year old child who was treated with an intramuscular injection of trimeprazine 72 mg. as a pre-operative medication and who became febrile in 15 minutes followed by rigidity and peripheral vasoconstriction and ending in death from pneumothorax [12]. Addonizio et al (1987) [10] in their analysis of 115 cases, found that the main primary diagnoses were schizophrenia 44%, mania 26%, major depression 12% and schizoaffective psychosis 6%.

PATHOGENESIS

The exact pathogenetic mechanism causing the Neuroleptic Malignant Syndrome (NMS) was unclear. Various conceptual models have been developed to mainly explain the presence of hyperthermia which is unique in this disorder. Levinson and Simpson (1986) [8] found that their 39 cases belonged to a heterogenous group of disorders which included those with concurrent medical problems with fever, those with concurrent medical problems without fever, and those without concurrent medical problems. The most well accepted mechanism was the central dopaminergic blockade theory postulated by Henderson and Wooten 1981 [13]. May et al (1983) [14] who found an increased oxygen consumption in skeletal muscle that was reduced after treatment with dantrolene concluded that a hypermetabolic state in skeletal muscle similar to malignant hyperthermia was the fundamental cause of NMS. However, unlike malignant hyperthermia, muscle tissue from NMS patients did not respond abnormally to halothane. In NMS, the primary disturbance is probably central. Neuroleptic drugs probably cause the rise in body temperature by acting centrally through the blockage of dopamine receptors of the hypothalamic thermoregulatory mechanisms causing vaso-contriction, and peripherally through the blockage of dopamine receptors on the striatal muscles causing muscular contraction (rigidity) which in turn produces excessive heat [6-8]. Concurrent febrile illness also contributes to the hyperthermia [8]. Shalev and Munitz (1986) [9] who found that the rate of neuroleptic loading was correlated with the development of NMS, postulated that NMS is a consequence of "sudden and massive

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downregulation of dopaminergic transmission". Hermesh et al [15], who reported on 2 cases of recurrent NMS caused by tiapride and haloperidol suggested the involvement of dopamine D2 receptors.

CLINICAL PRESENTATION

The main symptoms of neuroleptic malignant syndrome (NMS) are:

1) fever (as high as 42°C or 108°F),
2) muscular rigidity and other extrapyramidal movement disorders,
3) coma, stupor, agitation and confusion, with fluctuating level of consciousness, and
4) autonomic dys-regulation characterized by hypertension, tachycardia, dysphoresis and dehydration.

Important laboratory findings are:

1) polymorphonuclear leucocytosis (12,000-30,000 / mm^3),
2) creatine phosphokinase elevation (up to 30,000 units/ ml) in 92% of the cases,
3) rhabdomyolysis causing myoglobinaemia in 75% of the cases,
4) elevated liver enzymes and electrolyte imbalance, and
5) lysis and necrosis of muscle biopsy specimen.

According to Kurland et al (1984) [7] only 72% of his 52 cases had the first three symptoms of fever, movement disorder and confusion. A typical or incomplete NMS may not have fever or rigidity. Signs reported in 52 cases of neuroleptic malignant syndrome (adapted from Table 1 of Kurlan et al 1984) [7] are:

Fever		52	100%
Parkinsonism		51	98%
	rigidity	48	92%
	tremor	29	56%
	sialorrhoea	16	31%
	dystonia	17	33%
Dysphagia		21	40%
Akinetic mutism		20	38%
Aphonia		10	19%
Dysarthria		10	19%
Chorea		8	15%
Tachycardia		41	79%
Excessive perspiration		31	60%
Libile blood pressure		28	54%
Tachypnoea		13	25%
Urinary incontinence		8	15%
Coma		14	27%
Stupor		14	27%
Confusion		4	8%

About 80% of the cases occurred within the first 2 weeks after administration of a new neuroleptic (mode = 5 days), but in extreme cases it could vary from 45 minutes to 65 days. The symptoms may start with elevated blood pressure. They progressed rapidly within the next 24 to 72 hours and lasted for 12-14 days. The duration was longer for those caused by depot injection. Two important complications that contributed to mortality were:

1) pulmonary insufficiency - due to dysphagia and aspiration, and
2) renal failure - due to myoglobinuria.

The mortality rate was between 15% to 22% [6,8,9]. It appeared to be decreasing probably due to earlier recognition, the inclusion of milder cases in the later reports, better understanding of the condition and more appropriate treatment. It was estimated to be only 4% of the last 50 cases reported by Pearlman (1986) [16]. It was low when associated with haloperidol (5%), and high with sulpiride and in patients with organic brain disease like mental retardation and alcoholic psychosis.

THE IMPORTANT DIFFERENTIAL DIAGNOSES INCLUDE:

1) lethal catatonia which is characterized by excitement, agitation, fever and rigidity and was commonly reported before the introduction of neuroleptics;
2) malignant hyperthermia which is a genetically determined condition commonly associated with halothane anaesthesia which causes severe muscle contraction, heat production uncoupling of oxidative phosphorylation, increased glycogen metabolism, increased carbon dioxide and lactate production and diminished heat loss due to peripheral vasoconstriction;
3) neurotoxicity from lithium which may be combined with a neuroleptic agent giving rise to delirium and rigidity;
4) heat stroke which may be precipitated by neuroleptics causing disruption of central nervous system thermoregulation, leading to excessive heat production. Its main feature is hyperthermia without rigidity;
5) side-effect of MAO inhibitor combined with tricyclic antidepressant; and
6) other conditions causing muscular rigidity and fever like encephalitis, head injuries, epilepsy, tetanus, hysterical rigidity, and decerebrate rigidity.

RELATIONSHIP TO DRUG TREATMENT

NMS can result from many different types of drugs or combination of drugs. By far the most common precipitating agents were haloperidol (35%), fluphenazine decanoate (18%), chlorpromazine [8], other neuroleptics (9%), and non-neuroleptics (11%) [9]. Many cases had more than one drug. Less common neuroleptics included levopromazine, thioridazine, trifluoperazine, promazine, thiothixene, loxapine, and sulpiride [9]. Other drugs which contributed to one or a few cases include phenothiazines without antipsychotic activity eg. trimeprazine, other agents like tiapride, lithium and tetrabenazine. Sudden withdrawal from dopamine agonist (antiparkinsonian drugs) like carbidopa/levodopa, amantadine and bromocriptine can also give rise to the syndrome. NMS usually occurred when the dose was increased rapidly eg. during the initial stage of treatment. The onset of NMS correlated with the rate of increase rather than total dose. Less commonly it occurred without any increase in dosage.

TREATMENT OF NEUROLEPTIC MALIGNANT SYNDROME

This consists of early recognition and immediate

withdrawal of the offending agent. Non-specific supportive treatment which may be carried out in an intensive care unit, consists of (a) reduction of temperature with antipyretics and if necessary with cooling blankets and ice packs and (b) supplement oxygen (if necessary) with mechanical ventilation, and (c) treatment of renal complication. Because of the rarity and severity of the condition, there were no controlled trials with specific drug treatment. The sum total of experiences from most reports have divided the drugs into three groups: (a) ineffective drugs which were the anticholinergic and anti-parkinsonian drugs, (b) partially effective drugs which were the benzodiazepines like diazepam and lorazepam which gave temporary relief without enduring effect, and (c) effective drugs which included dopamine agonists like bromocriptine, amantadine, and carbidopa/levodopa (Simeret) and the muscle relaxant dantrolene [9]. The most effective drug was bromocriptine with or without dantrolene [17]. In most studies, bromocriptine had no failure. The recommended dose range was 2.5-60mg/day. The typical oral dose was 2.5-10mg t.d.s, increasing up to 60mg/day. It was sometimes combined with dantrolene. Dhib-Jalbut et al (1987) [18] treated 5 patients with bromocriptine mesylate 7.5-45mg/day in three divided doses for at least 10 days. Four of 5 cases reported had a rapid drop in serum creatine phosphokinase. All the 5 patients showed improvement within 24-72 hours, but resolution of extrapyramidal rigidity took one week. Early discontinuation of bromocriptine in two cases resulted in a relapse which responded to reinstitution of the bromocriptine. The effective oral dose of dantrolene was 50 mg b.d. to 100 mg q.d.s. for up to 5 days. The initial treatment would be intravenous dantrolene 1-3mg/kg over 10-15 minutes. The dosage should not exceed 10 mg/kg/day because of hepatotoxicity. Dantrolene was reported to reduce the duration of NMS in 10 cases which was given in doses of i/v 0.8mg-1.25mg/kg, oral 50 mg q.d.s., and in four cases oral 50 mg b.d. Dantrolene is potentially hepatotoxic and its long term use has not been established. Other dopamine agonists which were used much less frequently and were reported to be effective included:

1) amantadine which has 3 successes, 3 failures, and one uncertain. It was given in doses of 200-400mg/day [9];
2) carbidopa/levodopa (Simeret) which had 4 successes and one failure. It was given in doses of from 25/100mg t.d.s to 50/200mg q.d.s. [9].

Electroconvulsive therapy (ECT) was reported to be effective in 3 cases, but was known to cause brain damage in one case (due to cardiac arrest during ECT). Generally ECT is not advisable, unless lethal catatonia is suspected [9]. Many cases of NMS have been known to resolve completely with supportive treatment alone. ie. withdrawing neuroleptics without specific drug treatment.

REINTRODUCTION OF NEUROLEPTICS

Most patients (50%) with NMS were schizophrenics and may require further neuroleptic treatment. Rechallenge with the same or higher potency drugs at the same or higher doses was most likely to cause a recurrence of NMS which may be fatal. Experience from past reports showed that rechallenge with same drug in 8 cases had recurrence in 6 cases, but rechallenge with low potency drug (thioridazine) in 10 cases had recurrence in only one case [9]. In a review of all known cases of recurrent NMS by Susman and Addonizio 1988 [19], 20 patients were safely restarted on neuroleptics. Of these 11 received thioridazine. There were 5 recurrent cases each of NMS receiving haloperidol and chlorpromazine, but there was a wide range of dosage from a single dose of haloperidol 0.5 mg to chlorpromazine 4400 mg given over one week. Lithium heightened the risk of NMS. Five of 15 patients with recurrent NMS were on lithium at nontoxic range [19]. Lithium may decrease dopaminergic function [20]. High risk factors for recurrent NMS were administration of high-potency neuroleptics and reintroduction of neuroleptics before the initial episode of NMS had completely resolved. Neuroleptics were recommended to be given after complete resolution of the NMS usually between 2-8 weeks as recurrence was likely if neuroleptic was resumed within a few days [19]. Low doses of low-potency neuroleptics are probably the safest approach and the concomitant use of lithium should be avoided. In non-schizophrenic patients neuroleptics should be avoided. Benzodiazepines should be used for agitation.

REFERENCES

1. Delay J, Pichot P, Lemperiere T, Elizzalde B, Peigne F: Un neuroleptique majeur non phenothiazinique et non reserpinique, l'haloperidol, dans le traitement des psychoses. Ann Med Psychol 1986; 118: 145-52.
2. Delay J, Deniker P. Drug-induced extrapyramidal syndromes. In: Vinken D, Gruyu G. eds: Handbook of Clinical Neurology. New York: Elsevier North Holland Inc. 1968: 248-66.
3. Baldessarini RJ. Drugs and the treatment of psychiatric disorders. In: Goodman LS, Gillman A. eds. The Pharmacological Basis of Therapeutics, 6th ed. New York: Macmillan, 1980: 406-14.
4. Gelder M, Gath D, Mayou R. Oxford Textbook of Psychiatry. Oxford: Oxford University Press, 1983.
5. Hill P, Murray R, Thorley A: Essentials of Postgraduate Psychiatry. London, New York: Grune & Stratton, Inc. 1986.
6. Caroff SN. The neuroloptic malignant syndrome. J Clin Psychiatry 1980; 79-83.
7. Kurlan R, Hamill R, Shoulson I: Neuroleptic malignant syndrome. Clin Neuropharmacol 1984; 7: 109-20.
8. Levinson DF, Simpson GM: Neuroleptic-induced extrapyramidal symptoms with fever. Arch Gen Psychiatry 1986; 43: 39-48.
9. Shalev A, Munitz H: The neuroleptic malignant syndrome: agent and host interaction. Acta Psychiatr Scand 1986; 337-47.

10. Addonizio G, Susman VL, Roth SD: Neuroleptic malignant syndrome: review and analysis of 115 cases. Biol Psychiatry 1987; 22: 1004-20.
11. Tian CS, Tsoi WF: Neuroleptic malignant syndrome - report of a case. Singapore Med J 1988; 29: 80-2.
12. Moys D: Malignant hyperpyrexia caused by trimeprazine. Br J Anaesthesiol 1973; 45: 1163-4.
13. Henderson VW, Wooten GF: Neuroleptic malignant syndrome: a pathogenetic role for dopamine receptor blockage. Neurology 1981; 31: 132-7.
14. May DC, Morris WS, Stewart RM, et al: Neuroleptic malignant syndrome: response to dantrolene sodium. Ann Intern Med 1983; 183-4.
15. Hermesh H, Huberman M, Radvan H, Kott E: Recurrent neuroleptic malignant syndrome due to tiapride and haloperidol: the possible role of D-2 dopamine receptors. J Nerv Ment Dis 1984; 172; 692-5.
16. Pearlman CA: Neuroleptic malignant syndrome: A review of the literature. J Clin Psychopharmacol 1986; 6: 257-73.
17. Lazarus A: Therapy of neuroleptic malignant syndrome. Psychiatr Dev 1986; 4 19-30.
18. Dhib-Jalbut S, Hesselbrock R, Mouradian MM, Means ED: Bromocriptine treatment of neuroleptic malignant syndrome. J Clin Psychiatry 1987; 48: 69-73.
19. Susman VL, Addonizio G: Recurrence of neuroleptic malignant syndrome. J Nerv Ment Dis 1988; 176: 234-41.
20. Spring G, Frankel M: 1981. New data on lithium and haloperidol incompatibility. Am J Psychiatry 1981; 138: 818-21.