Editorial

Neuroleptic malignant syndrome

Few conditions have attracted such widespread attention among both neurologists and psychiatrists in recent years as the neuroleptic malignant syndrome. First described in 1960 by French clinicians in a study of haloperidol[1] and subsequently named the "syndrome malin des neuroleptiques",[2] this nomenclature suffered in translation to the neuroleptic malignant syndrome; this term has endured, in the face of continued debate.[3-6]

Neuroleptic malignant syndrome is an uncommon but potentially fatal idiosyncratic reaction characterised by the development of altered consciousness, hyperthermia, autonomic dysfunction, and muscular rigidity on exposure to neuroleptic (and probably other psychotropic) medications. Yet, despite its notoriety and a now replete medical literature,[3 5 7] the pathobiology of neuroleptic malignant syndrome remains disappointingly enigmatic. The over-representation of single or brief series of case studies and the application of variable diagnostic criteria for neuroleptic malignant syndrome have hampered rigorous scientific enquiry into the nature of this condition.

The lack of universally accepted diagnostic criteria is, perhaps, the most serious drawback to understanding.[8 9] The core features of neuroleptic malignant syndrome, as enumerated, are common to established sets of diagnostic criteria.[9] Yet the relative weight of each component, in the face of an apparent spectrum of clinical severity, remains unclear. For instance, some researchers have advocated that a pyrexia in excess of 38°C or 39°C is necessary for the diagnosis of neuroleptic malignant syndrome.[7 10] Because raised temperature in such cases often occurs with dehydration or concomitant sepsis, the relevance of this sign is confounded and the potential for diagnostic error is heightened. Moreover, there has been a general over-reliance on the estimation of creatine kinase (CK) as a potential diagnostic marker for neuroleptic malignant syndrome.[11-13] Prominent increases have been found in upwards of 70% of patients taking neuroleptics who become pyrexial due to infection,[12] and some 30% of medically ill patients (not receiving neuroleptics) show a similar, albeit less exaggerated, rise in CK.[13] Given such poor specificity, claims for the use of CK values as a marker for the diagnosis and course of neuroleptic malignant syndrome appear injudicious.[11]

The newly available *diagnostic and statistical manual of mental disorders—fourth edition (DSM-IV)* has now incorporated research criteria for neuroleptic malignant syndrome,[14] placing prominence on signs of increase in temperature and muscle rigidity; these must be accompanied by two or more of: diaphoresis, dysphagia, tremor,

incontinence, altered consciousness, tachycardia, blood pressure changes, leucocytosis, and raised CK concentrations. It will be important to compare the diagnostic validity of these against other established criteria. The manual also emphasises the difficulty in distinguishing neuroleptic malignant syndrome from other medical conditions that cause pyrexia or mimic neuroleptic malignant syndrome (for example, infection, heat stroke, status epilepticus, endocrine disorders, toxic poisoning). Some guidelines are also offered to help differentiate lethal catatonia from neuroleptic malignant syndrome. These conditions may be indistinguishable clinically, although the relatively late emergence of muscle rigidity and a prior history of catatonic states in the absence of neuroleptic treatment favour the diagnosis of catatonia.[15 16] Others have proposed that neuroleptic malignant syndrome and catatonia represent a single entity and that a misrepresentation of forms of catatonia as neuroleptic malignant syndrome accounts for the apparently low incidence of catatonia in recent years.[16 17]

The incidence of neuroleptic malignant syndrome over the last 20 years has shown considerable variation.[5 7] Initially thought to be a rare idiosyncratic disorder, increased interest among psychiatrists, retrospective chart reviews, and widening of diagnostic criteria to include the "spectrum concept",[10] with incipient and atypical or partial forms of neuroleptic malignant syndrome,[18-20] led to reported incidence rates of 1·4%–12·2%.[5 21] Well planned prospective studies of neuroleptic malignant syndrome are relatively rare, considering the frequency of neuroleptic use, but give incidences of 0·07%–0·15%, which probably accord closer to reality.[22-24] The spectrum concept of neuroleptic malignant syndrome has been vigorously and eloquently criticised,[10] and the extensive use of such a concept could contribute considerably to the mismanagement of extrapyramidal disorders due to neuroleptics. There is a suggestion from epidemiological studies that the incidence is falling, a phenomenon that may be due to more conservative neuroleptic use, earlier recognition of premonitory symptoms, and decreased use of intramuscular neuroleptic depot preparations.[22 23]

As well as neuroleptic drug use, other causes of neuroleptic malignant syndrome exist including withdrawal of dopaminergic stimulations in parkinsonian patients either inadvertently or as part of a planned drug holiday, and treatment with metoclopramide, desipramine, dothiepin, lithium and phenelezine, tetrabenazine, and reserpine.[24-28] Although many of these reports are consistent with the concept of an acute

dopamine depletion syndrome,[24] the cases with other drugs cannot be so explained; the tricyclic antidepressants may act by increasing the noradrenaline:dopamine ratio, a mechanism of the pathogenesis of neuroleptic malignant syndrome suggested by Schibuk and Schachter.[29] All neuroleptics have been implicated in the genesis of the syndrome and factors that have been suggested as being more provocative include the rate of introduction of neuroleptics, the use of depot preparations, a preceding attack of neuroleptic malignant syndrome, and the concomitant use of other drugs, in particular, lithium.[7 18 22-24 30 31] Predisposing features that may lead to increased vulnerability to neuroleptic malignant syndrome include severe agitation and restlessness, dehydration, organic cerebral disease, and a diagnosis of affective disorder.[7 18 24 30 31]

Other medication induced hyperthermic states and neuroleptic malignant syndrome precipitated by drugs other than antipsychotics have provided useful insights into the putative pathogenesis of neuroleptic malignant syndrome.[7 18] Malignant hyperthermia, which shares many of the clinical characteristics of neuroleptic malignant syndrome, is a disorder of calcium regulation within skeletal muscle and it occurs in genetically susceptible patients receiving halogenated inhalation anaesthetics or depolarising muscle relaxants.[32] A common pathophysiological basis for malignant hyperthermia and neuroleptic malignant syndrome was originally proposed but this now seems unlikely. In a clinical study evaluating the potential for genetic overlap between neuroleptic malignant syndrome and malignant hyperthermia, Hermesh and colleagues found no increase in anaesthetic complications either in patients with neuroleptic malignant syndrome or any of their first degree relatives.[33] The calcium channel dysfunction in the seroplasmic reticulum has been attributed to abnormalities in the ryanodine receptor complex, a receptor system that has been linked to ryanodine receptor gene on chromosome 19.[32] Preliminary association studies in animals on the relevance of this gene for neuroleptic malignant syndrome have proved unremarkable so far.[34] Moreover, electroconvulsive therapy has been given to patients with neuroleptic malignant syndrome without either the emergence of malignant hyperthermia or a worsening of neuroleptic malignant syndrome.[35 36] By contrast with a "peripheral" explanation for neuroleptic malignant syndrome, findings from patients with basal ganglia disorders who develop the disorder after abrupt cessation of antiparkinsonian drugs or treatment with dopamine depleting agents (for example, reserpine, tetrabenazine) or neuroleptics are consonant with the prevailing notion that neuroleptic malignant syndrome results in a sudden and profound reduction—a "crash"—in central dopaminergic function.[24 28 37] This effect is thought to be mediated by neuroleptic blockade of dopamine receptors in the hypothalamus, the centre for thermoregulation. Blockade may result in a higher "set point" of core temperature in tandem with increased heat production (from rigidity) and impaired heat dissipation.[24 37] Although postmortem and neurochemical findings in neuroleptic malignant syndrome are inconsistent, some indirect support for this dopaminergic hypothesis comes from the findings of reduced CSF homovanillic acid (HVA) in two patients who died from hyperthermic conditions and from a study showing decrements in CSF HVA in patients during an episode of neuroleptic malignant syndrome.[38 39] Concomitant, but less dramatic, reductions in 5-hydroxyindoleacetic acid were also noted in this study,[39] raising the possibility that some combined dopamine-serotonin perturbation may be of importance. In this regard, it is noteworthy that many of the clinical features of the serotonin syndrome, a drug induced hyperthermic agitated state seen most often with monoamine oxidase and selective serotonin re-uptake inhibitors,[40] closely parallel those of neuroleptic malignant syndrome. Similarly, others have noted that the toxic effects of ecstasy (3,4-methylenedioxy-methamphetamine; a 5HT2 agonist), bear a close resemblance to neuroleptic malignant syndrome.[41] This potential serotonergic involvement in neuroleptic malignant syndrome warrants further research.

One further pathogenic model merits attention. In a prospective study, Rosebush and Mazurek noted a low serum iron in 96% of patients, which correlated negatively with CK and subsequently returned to normal concentrations with resolution of neuroleptic malignant syndrome.[42] They and others have postulated that hypoferraemia, possibly due to an acute phase reaction, may result in a reduction in dopamine D2 receptors and thus contribute to the "idiosyncratic" basis of neuroleptic malignant syndrome with neuroleptic treatment.[42 43] Indeed, it is plausible that the psychomotor agitation often seen in advance of neuroleptic malignant syndrome and now thought to be a risk factor, may be attributable to a low iron concentration. It may be prudent, then, to perform baseline iron studies in those agitated patients who will require "aggressive" neuroleptic therapy, or at least, in those patients at higher risk to develop neuroleptic malignant syndrome.

In the management of neuroleptic malignant syndrome the most effective measures include prompt recognition, withdrawal of neuroleptic medication, and transfer to an intensive care unit, with attention to hydration, fever reduction, sedation with benzodiazepines—if indicated—and control of rigidity with bromocriptine or dantrolene. The adjunctive use of bromocriptine has been reported to reduce the duration of the neuroleptic malignant syndrome episode and the risk of mortality[18 20 44]; similar claims have been made for dantrolene, which may also have a central action in addition to its effects on calcium transmission in the sarcoplasmic reticulum.[44 45] Based on current evidence, these agents should be instituted in most cases of neuroleptic malignant syndrome. One recent report claiming that these agents delayed resolution of neuroleptic malignant syndrome stands as an exception.[46] These findings are most likely explained, however, by the higher rates of concomitant medical illness in the patient group receiving pharmacological intervention and the non-randomised manner in which these agents were used. The possibility of a prospective randomised trial to minimise the effects of selection bias in this relatively rare disorder seems unlikely. Electroconvulsive therapy is probably an underutilised, effective treatment in neuroleptic malignant syndrome. In a review, Davis and colleagues noted that 83% of patients improved with this treatment.[36] Four patients developed cardiac complications, although in each case neuroleptics were continued despite manifest neuroleptic malignant syndrome.

The long term management and outcome in patients after neuroleptic malignant syndrome is considerably less bleak than originally envisaged.[47] Although there have been some scant reports of subtle neurological sequelae or cognitive impairment, in general these patients do not decline after neuroleptic malignant syndrome once their pharmacotherapy is adequate.[18 47-50] About a third of patients will develop another neuroleptic malignant syndrome, and this is particularly likely if neuroleptics are reinstituted within two weeks of the cessation of an episode.[48] Conventional wisdom suggests that it is preferable to delay rechallenge until after two weeks, to give a

low potency neuroleptic, and to titrate the dosage gradually in accordance with close clinical and biochemical (CK) monitoring. Clozapine has been advocated as the treatment of choice after neuroleptic malignant syndrome,[50] but on present evidence (particularly some inconclusive reports that clozapine may cause neuroleptic malignant syndrome)[51] this seems inappropriate; however, this agent should be considered in the face of continued intolerance to conventional neuroleptics.[52]

Further research is needed to identify risk factors for neuroleptic malignant syndrome more clearly, with the aim of determining a biochemical or trait marker for susceptibility to this condition. It is possible, however, that the rapid development of newer antipsychotic drugs which possess a low liability for extrapyramidal side effects (and hopefully also neuroleptic malignant syndrome) may overtake these efforts.

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1 Delay J, Pichot P, Lemperier MT, Ellisalde B, Peigne F. Un neuroleptique majeur non phenothiazineque et non reserpinique, l'halidol, dans le traitement des psychoses. Ann Med Psychol (Paris) 1960;118:145–52.

2 Bourgeois M, Tignol J, deBouchard D. Le syndrome malin des neuroleptiques. Bordeaux Medicine 1971;4:1115–28.

3 Kellam AM. The neuroleptic malignant syndrome, so-called—a survey of the world literature. Br J Psychiatry 1987;150:752–9.

4 Myers FH. Benign type of malignant syndrome. Lancet 1989;i:50.

5 Kellam AMP. The (frequently) neuroleptic (potentially) malignant syndrome. Br J Psychiatry 1990;157:16–7.

6 Bristow MF, Kohen D. How "malignant" is the neuroleptic malignant syndrome? BMJ 1993;307:1223–4.

7 Caroff SN, Mann SC. Neuroleptic malignant syndrome. Med Clin North Am 1993;71:185–202.

8 Levinson DF, Simpson GM. Neuroleptic-induced extrapyramidal symptoms with fever: heterogeneity of the neuroleptic malignant syndrome. Arch Gen Psychiatry 1986;43:839–48.

9 Gurrera RJ, Chang SS, Romero JA. A comparison of diagnostic criteria for neuroleptic malignant syndrome. J Clin Psychiatry 1992;53:56–62.

10 Adityan Jee, Sing S, Singh G, Ong S. Spectrum concept of neuroleptic malignant syndrome. Br J Psychiatry 1988;153:107–11.

11 Goldwasser HD, Hopper JF, Spears NM. Concomitant treatment of neuroleptic malignant syndrome and psychosis. Br J Psychiatry 1989; 154:102–4.

12 O'Dwyer A, Sheppard P. The role of creatine kinase in the diagnosis of neuroleptic malignant syndrome. Psychol Med 1993;23:323–6.

13 Cohen O, Liebovici L, Mor F, Wysenbeek AJ. Significance of elevations of elevated levels of serum creatinine phosphokinase in febrile diseases: a prospective study. Reviews of Infectious Diseases 1991;13:237–42.

14 Diagnostic and statistical manual for mental disorders. Fourth edition (DSM-IV). Washington DC: American Psychiatric Press, 1994:739–42.

15 Mann SC, Caroff SN, Bleier HR, Welz WKR, Kling MA, Hayashida M. Lethal catatonia. Am J Psychiatry 1986;143:1374–81.

16 Woodbury MM, Woodbury MA. Neuroleptic-induced catatonia as a stage in the progression toward neuroleptic malignant syndrome. J Am Acad Child Adolesc Psychiatry 1992;31:1161–4.

17 White DAC. Catatonia and the neuroleptic malignant syndrome—a single entity? Br J Psychiatry 1992;161:558–60.

18 Shalev A, Munitz H. The neuroleptic malignant syndrome: agent and host interaction. Acta Psychiatr Scand 1986;73:337–47.

19 Velamoor VR, Fernando MLD, Williamson P. Incipient neuroleptic malignant syndrome? Br J Psychiatry 1990;156:581–4.

20 Schneiderhan ME, Marken PA. An atypical course of neuroleptic malignant syndrome. J Clin Pharmacol 1994;34:325–34.

21 Addonizio G, Susman VL, Roth SD. Symptoms of neuroleptic malignant syndrome in 82 consecutive inpatients. Am J Psychiatry 1986;143: 1587–90.

22 Gelenberg AJ, Bellinghausen B, Wojcik JD, Falk WE, Sachs GS. A prospective survey of neuroleptic malignant syndrome in a short-term psychiatric hospital. Am J Psychiatry 1988;145:517–8.

23 Keck PE, Pope HG, McElroy SL. Declining frequency of neuroleptic malignant syndrome in a hospital population. Am J Psychiatry 1991; 148:880–2.

24 Henderson VW, Wooten GF. Neuroleptic malignant syndrome: a pathophysiologic role for the dopamine receptor blockade? Neurology 1981; 1331:132–7.

25 Friedman LS, Weinrauch LA, D'Elia JA. Metoclopramide-induced neuroleptic malignant syndrome. Arch Intern Med 1987;147:1495–7.

26 Heyland D, Sauve M. Neuroleptic malignant syndrome without the use of neuroleptics. Can Med Assoc J 1991;145:817–9.

27 Keyser DL, Rodnitzky RL. Neuroleptic malignant syndrome in Parkinson's disease after withdrawal or alteration of dopaminergic therapy. Arch Intern Med 1991;151:794–6.

28 Haddad PM. Neuroleptic malignant syndrome may be caused by other drugs. BMJ 1994;308:200.

29 Schibuk M, Schachter D. A role for catecholamines in the pathogenesis of neuroleptic malignant syndrome. Can J Psychiatry 1986;31:66–9.

30 Keck PE, Pope HG, Cohen BM, McElroy SL, Nierenberg A. Risk factors for neuroleptic malignant syndrome. Arch Gen Psychiatry 1989;46: 914–8.

31 Rosebush PI, Stewart TA. Prospective analysis of 24 episodes of neuroleptic malignant syndrome. Am J Psychiatry 1989;146:717–25.

32 Heiman-Patterson TD. Neuroleptic malignant syndrome and malignant hyperthermia. Med Clin North Am 1993;71:477–92.

33 Hermesh H, Aizenberg D, Lapidot M. Risk of malignant hyperthermia among patients with neuroleptic malignant syndrome and their families. Am J Psychiatry 1988;145:1431–4.

34 Gejman PV. Molecular genetic studies of neuroleptic malignant syndrome. 150th Annual Meeting of the American Psychiatric Association Philadelphia, May 1994.

35 Hermesh H, Aizenberg D, Weizman A. A successful electroconvulsive treatment of neuroleptic malignant syndrome. Acta Psychiatr Scand 1987;75:237–9.

36 Davis JM, Janicak PG, Sakkas P, Gilmor C, Wang Z. Electroconvulsive therapy in the treatment of the neuroleptic malignant syndrome. Convulsive Therapy 1991;7:111–20.

37 Buckley P, Carmody E, Hutchinson M. Wilson's disease and the neuroleptic malignant syndrome. Irish Journal of Psychological Medicine 1990; 7:138–9.

38 Kish SJ, Kleinert R, Minauf M, Gilbert J, Walter GF, Slimovitch C, et al. Brain neurotransmitter changes in three patients who had a fatal hyperthermia syndrome. Am J Psychiatry 1990;147:1358–63.

39 Nisijima K, Ishiguro T. Neuroleptic malignant syndrome: a study of CSF monoamine metabolism. Biol Psychiatry 1990;27:280–8.

40 Sternbach H. The serotonin syndrome. Am J Psychiatry 1991;148:705–13.

41 Ames D, Wirshing WC. Ecstasy, the serotonin syndrome, and neuroleptic malignant syndrome—a possible link? JAMA 1993;269:869.

42 Rosebush PI, Mazurek MF. Serum iron and neuroleptic malignant syndrome. Lancet 1991;338:149–51.

43 Garcia FM, Duarte J, Perez A, Mataix AL, Coria F, Claveria LE. Low serum iron and neuroleptic malignant syndrome. Ann Pharmacother 1993;27:101–2.

44 Sakkas P, Davis JM, Jancak PG, Wang Z. Drug treatment of the neuroleptic malignant syndrome. Psychopharmacol Bull 1991;27:381–4.

45 Nisijima K, Ishiguro T. Does dantrolene influence central dopamine and serotonin metabolism in the neuroleptic malignant syndrome? A retrospective study. Biol Psychiatry 1993;33:45–8.

46 Rosebush PI, Stewart TA, Mazurek MF. The treatment of neuroleptic malignant syndrome. Are dantrolene and bromocriptine useful adjuncts to supportive care? Br J Psychiatry 1991;159:709–12.

47 Buckley P, Freyne A, McCarthy A, Larkin C. Neuroleptic malignant syndrome—a follow-up study. Ir J Med Sci 1991;160:45–7.

48 Wells AJ, Sommi RW, Crismon ML. Neuroleptic rechallenge after neuroleptic malignant syndrome: case report and literature review. Drug Intelligence and Clinical Pharmacy 1988;22:475–80.

49 Rosebush PI, Stewart TA, Gelenberg AJ. Twenty neuroleptic rechallenges after neuroleptic malignant syndrome in 15 patients. J Clin Psychiatry 1989;50:295–8.

50 Weller M, Kornhuber J. Clozapine rechallenge after an episode of "neuroleptic malignant syndrome". Br J Psychiatry 1992;161:855–6.

51 Weller M, Kornhuber J. Does clozapine cause neuroleptic malignant syndrome? J Clin Psychiatry 1993;54:70–1.

52 Buckley PF, Meltzer HY. Clozapine and NMS. Br J Psychiatry 1993; 162:566.