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 and subsequently named the "syndrome malin des neuroleptiques," this nomenclature suffered in translation to the neuroleptic malignant syndrome; this term has endured, in the face of continued debate. Neuroleptic malignant syndrome is an uncommon but potentially fatal idiiosyncratic reaction characterised by the development of altered consciousness, hyperthermia, autonomic dysfunction, and muscular rigidity on exposure to neuroleptic (and probably other psychotrope) medications. Yet, despite its notoriety and a now replete medical literature, 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. The core features of neuroleptic malignant syndrome, as enumerated, are common to established sets of diagnostic criteria. 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. 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. Prominent increases have been found in upwards of 70% of patients taking neuroleptics who become pyrexial due to infection, and some 30% of medically ill patients (not receiving neuroleptics) show a similar, albeit less exaggerated, rise in CK. 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.

The newly available Diagnostic and Statistical Manual of Mental Disorders—fourth edition (DSM-IV) has now incorporated research criteria for neuroleptic malignant syndrome, 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. 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.

The incidence of neuroleptic malignant syndrome over the last 20 years has shown considerable variation. Initially thought to be a rare idiiosyncratic disorder, increased interest among psychiatrists, retrospective chart reviews, and widening of diagnostic criteria to include the "spectrum concept," with incipient and atypical or partial forms of neuroleptic malignant syndrome, led to reported incidence rates of 1-4%–12-2%. 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. The spectrum concept of neuroleptic malignant syndrome has been vigorously and eloquently criticised, 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.

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. Although many of these reports are consistent with the concept of an acute
dopamine depletion syndrome,28 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 sug-
gested as being more provocative include the rate of
introduction of neuroleptics, the use of depot prepa-
rations, 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 malig-
nant 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.18 Malignant hyperthermia, which shares many
of the clinical characteristics of neuroleptic malig-
nant 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 pathophysi-
ological 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 malig-
nant syndrome and malignant hyperthermia, Hermesh
and colleagues found no increase in anaesthetic compli-
cations either in patients with neuroleptic malignant
syndrome or any of their first degree relatives.33 The calcium
channel dysfunction in the serosal reticulum has been
attributed to abnormalities in the ryanodine recep-
tor complex, a receptor system that has been linked to
ryanodine receptor gene on chromosome 19.32 Preliminary
association studies in animals on the rele-
vance of this gene for neuroleptic malignant syndrome
have proved unremarkable so far.34 Moreover, electro-
convulsive therapy has been given to patients with neuro-
leptic 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 hypo-
thalamus, the centre for thermoregulation. Blockade may
result in a higher "set point" of core temperature in tan-
dem with increased heat production (from rigidity) and
impaired heat dissipation.34 37 Although postmortem and
neurochemical findings in neuroleptic malignant syn-
drome 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 Con-
comitant, but less dramatic, reductions in 5-hydroxy-
indoleacetic 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 sero-
tonin syndrome, a drug induced hyperthermic agitated
state seen most often with monoamine oxidase and selec-
tive serotonin re-uptake inhibitors,40 closely parallel those
of neuroleptic malignant syndrome. Similarly, others
have noted that the toxic effects of ecstasy (3,4-methyl-
enedioxy-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 nega-
tively with CK and subsequently returned to normal
concentrations with resolution of neuroleptic malignant
syndrome.42 They and others have postulated that hypo-
ferraemia, possibly due to an acute phase reaction, may
result in a reduction in dopamine D2 receptors and thus
contribute to the "idiiosyncratic" basis of neuroleptic
malignant syndrome with neuroleptic treatment.43 44
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 neuro-
leptic malignant syndrome.

In the management of neuroleptic malignant syn-
drome the most effective measures include prompt recog-
nition, withdrawal of neuroleptic medication, and
transfer to an intensive care unit, with attention to hydra-
ation, 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 neurole-
ptic malignant syndrome episode and the risk of mor-
ality.45 46 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 receiv-
ing pharmacological intervention and the non-ran-
domised 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 malig-
nant syndrome. In a review, Davis and colleagues noted
that 83% of patients improved with this treatment.50
Four patients developed cardiac complications, although
in each case neuroleptics were continued despite mani-
fest neuroleptic malignant syndrome.

The long term management and outcome in patients
after neuroleptic malignant syndrome is considerably less
bleak than originally envisaged.48 Although there have
been some scant reports of subtle neurological sequela
or cognitive impairment, in general these patients do not
decline after neuroleptic malignant syndrome once their
pharmacotherapy is adequate.48 49-51 About a third of
patients will develop another neuroleptic malignant syn-
drome, 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 prefer-
able 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, but on present evidence (particularly some inconclusive reports that clozapine may cause neuroleptic malignant syndrome) this seems inappropriate; however, this agent should be considered in the face of continued intolerance to conventional neuroleptics.

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.

The secretarial assistance of Ms A Miles is greatly appreciated.

PETER F BUCKLEY
Department of Psychiatry,
Case Western Reserve University,
Cleveland, Ohio, USA

MICHAEL HUTCHINSON
Department of Neurology,
St. Vincent's Hospital, Ireland

Correspondence to: Dr Peter Buckley, Department of Psychiatry, CWRU University Hospitals of Cleveland, 2040 Abington Road, Cleveland, Ohio, USA.
Neuroleptic malignant syndrome.

P F Buckley and M Hutchinson

*J Neurol Neurosurg Psychiatry* 1995 58: 271-273
doi: 10.1136/jnnp.58.3.271

Updated information and services can be found at:
http://jnnp.bmj.com/content/58/3/271.citation

These include:
Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/