Case-Control Study of Neuroleptic Malignant Syndrome

Perminder Sachdev, M.B.B.S., M.D., Ph.D., F.R.A.N.Z.C.P., Catherine Mason, M.B.B.S., F.R.A.N.Z.C.P., and Dusan Hadzi-Pavlovic, B.Sc., M.Psychol.

Objective: The authors performed a case-control study of neuroleptic malignant syndrome to identify potential risk factors. Method: Twenty-five patients with neuroleptic malignant syndrome were matched with 50 comparison subjects on age, sex, primary psychiatric diagnosis, and time of admission to the hospital. The records of all subjects were reviewed independently by two researchers for information on postulated risk factors. Exploratory direct comparisons of the two groups were followed by a conditional logistic regression analysis. Results: Patients with neuroleptic malignant syndrome were more likely to be agitated or dehydrated before the development of neuroleptic malignant syndrome, often needed restraint or seclusion, and received larger doses of neuroleptics soon after hospitalization. Previous treatment with ECT increased vulnerability. Conclusions: The prevalence of neuroleptic malignant syndrome may be reduced by avoiding large doses of neuroleptics over short periods in the management of acute psychosis and by paying adequate attention to the patient's hydration and electrolyte status.

(Am J Psychiatry 1997; 154:1156–1158)

Of the various neurological side effects of neuroleptic medication, neuroleptic malignant syndrome is the most serious and is potentially fatal (1). The identification of risk factors for its development is therefore of great interest, since this may lead to its prevention in a number of cases. The published literature, which has been previously reviewed (1, 2), has drawn attention to numerous putative risk factors, but the data have deficiencies because of inconsistency in the diagnostic criteria used and dependence on small case series.

Since neuroleptic malignant syndrome is a rare syndrome, the best epidemiological method to study its risk factors is a case-control study. One such study of 18 patients with neuroleptic malignant syndrome has been previously published (2). In this article, we report the results of a relatively large study that used a methodology similar to that of the previous study, with the intention of replicating and extending the findings.

METHOD

In this chart-based study, 25 patients with neuroleptic malignant syndrome were identified between 1989 and 1994 from 11 psychiatric units in New South Wales. They met the following criteria for the diagnosis: 1) fever (oral temperature higher than 37.5°C on at least two occasions); 2) extrapyramidal features (at least one): a) moderately severe rigidity or b) at least two of the following: mild rigidity, dysphagia, short shuffling gait, resting tremor, dystonia, dyskinesia, and creatine kinase level more than 400 U/liter; or c) creatine kinase level more than 1,000 U/liter; 3) either a) altered consciousness or catatonia or b) autonomic instability characterized by two or more of the following: systolic (30 mm above baseline) or diastolic (20 mm above baseline) hypertension, labile blood pressure (variability more than 30 mm systolic or more than 20 mm diastolic at different readings), tachycardia (30 bpm above baseline), intense diaphoresis, incontinence, and tachypnea (more than 25 breaths/minute); and 4) absence of another identifiable physical illness.

The subjects with neuroleptic malignant syndrome also met the operational criteria of Keck et al. (2) for a definite (N=23) or probable (N=2) diagnosis of neuroleptic malignant syndrome (with oral temperature of 37.5°C as the cutoff).

Each patient with neuroleptic malignant syndrome was matched with two comparison patients also treated with neuroleptic medication in the same psychiatric unit, on the following variables: age (within 2 years), sex, primary psychiatric diagnosis, and time of admission (within 1 month of index patients), in that order.

Case records were independently reviewed, through use of a standard data form, by two research assistants. Any discrepancy was dealt with by a consensus decision involving the first author (P.S.). The variables on which information was recorded are listed in table 1. The operational definitions of some relevant variables were as follows: psychomotor agitation (excessive and purposeless motor activity recorded on two separate occasions and requiring additional medication or restraint or seclusion), dehydration (necessitating "pushing" of fluids orally or by intravenous administration and indicated by laboratory indices such as urine volume less than 500 ml/day, urine/plasma creatinine ratio more than 40, or urine osmolality higher than 500 mosmol/kg). All neuroleptic drug doses were converted into milligrams of chlorpromazine equivalents (given orally) through use of the data presented by Davis (3).

The two groups were compared by using the t test for continuous variables, the Wilcoxon signed rank test for nonnormal continuous and noncontinuous discrete variables, and Fisher's exact test for

Received May 3, 1996; revisions received Dec. 12, 1996, and Feb. 11, 1997; accepted Feb. 18, 1997. From the School of Psychiatry, University of New South Wales, and the Neuropsychiatric Institute, Prince Henry Hospital, Sydney, Australia. Address reprint requests to Dr. Sachdev, NPI, Prince Henry Hospital, Little Bay, New South Wales 2036, Australia; P.Sachdev@unsw.edu.au (e-mail).

Supported in part by the National Health and Medical Research Council of Australia.

The authors thank Jane Kruk and Shubha Srinivasan for data collection and a number of psychiatrists and other physicians, in particular Dr. David Burke, F.R.A.N.Z.C.P.

TABLE 1. Differences in Putative Risk Factors for Neuroleptic Malignant Syndrome Between Patients With the Syndrome (N=25) and Comparison Patients (N=50)[a]

Variable	Patients With Neuroleptic Malignant Syndrome		Comparison Patients		Analysis		Odds Ratio		Effect Size (d)[b]
					Test Value	p	Unconditional	Conditional	
	Mean	*SD*	*Mean*	*SD*					
Continuous									
Age (years)[c]	37.5	17.9	36.9	18.2	0.12[d]	0.90			
Maximum dose of neuroleptics[c,e]	958.3	821.1	488.1	334.4	–2.39[f]	0.02	4.33	4.30	0.86
Total dose of neuroleptics in first 24 hours[e]	529.2	425.8	362.1	351.3	–1.72[f]	0.09	2.88	3.33	0.44
Number of intramuscular injections	2.1	6.9	1.3	3.6	–1.20[f]	0.23	1.14	1.19	0.13
Time to maximum dose (days)	3.9	7.2	4.2	5.7	–1.40[f]	0.16	0.69	0.68	–0.06
Time in restraint/seclusion (days)	2.3	—[g]	0.6	—[g]	–3.96[f]	0.0001	28.2	314.1	0.39
	N	*%*	*N*	*%*					
Categorical									
Sex[c]						1.0[h]			
Male	16		32						
Female	9		18						
Diagnosis[c]						0.86[h]			
Schizophrenia	17	68	31	62					
Bipolar disorder	5	20	14	28					
Major depression	2	8	4	8					
Organic mental syndrome	1	4	1	2					
Pre-neuroleptic malignant syndrome condition in hospital									
Agitation	22	88	32	64		0.03[h]	3.50	4.26	1.91
Dehydration	6	24	4	8		0.07[h]	3.67	3.53	1.56
Dystonia	7	28	11	22		0.57[h]			
Other related to treatment									
Neuroleptics at admission	14	56	21	42		0.33[h]			
High-potency neuroleptics	15	60	29	58		0.71[h]			
Previous exposure to neuroleptics	20	80	41	82		1.00[h]			
Past history of ECT	8	32	5	10		0.03[h]	4.53	5.89	2.05

[a]The following variables were not significant: history of extrapyramidal side effects (six patients with neuroleptic malignant syndrome and 12 comparison patients), akathisia (N=4 and N=3, respectively), withdrawal of anticholinergic drugs (N=2 and N=0), mental retardation (N=3 and N=7), medical illness (N=4 and N=3), neurological illness (N=1 and N=3), alcohol (N=3 and N=13) and other substance (N=4 and N=16) abuse, and medication before development of neuroleptic malignant syndrome (lithium: N=8 and N=10, anticholinergics: N=12 and N=26, and benzodiazepines: N=14 and N=25).
[b]Effect sizes were calculated by using the formula in Dupont and Plummer's report (6) for case-control studies. All calculations were based on the unconditional odds ratios and on the codings used in the regression analyses (see text), with the exception of restraint/seclusion, which was entered as a binary variable.
[c]Matched variable.
[d]Student's t test; df=73.
[e]Chlorpromazine equivalents per day.
[f]Wilcoxon signed ranks test; z value.
[g]Ranges for patients with neuroleptic malignant syndrome and comparison patients were 0–15 and 0–30 days, respectively.
[h]Fisher's exact test.

dichotomous variables. The association between the risk factors and caseness was examined by using conditional logistic regression analysis for case-control studies with one case matched to more than one control subject. This was carried out in generalized linear interactive modeling (4) by using the commands given by Adena and Wilson (5). The effect sizes presented in table 1 were based on the unconditional odds ratios calculated by using the formula for d in matched case-control studies (6).

RESULTS

Since the two groups were matched on age, sex, psychiatric diagnosis, and time of year of admission, the risks associated with these variables could not be examined. Patients with neuroleptic malignant syndrome were distributed evenly through the year (for each quarter, N=7, N=7, N=5, and N=6). A comparison of the two groups on the different variables is presented in table 1. Six variables that were significant ($p<0.10$) were used in a conditional logistic regression analysis: 1) past ECT, 2) agitation before neuroleptic malignant syndrome, 3) dehydration before neuroleptic malignant syndrome, 4) total neuroleptic dose in first 24 hours (coded as 600 mg or less versus over 600 mg), 5) maximum neuroleptic dose (coded as 600 mg or less versus over 600 mg), and 6) days in restraint or seclusion (recoded as 0 days=0, 1–2=1, 3–5=2, 6 or more=3 and treated as a 0–3 score). One patient with neuroleptic malignant syndrome and two comparison subjects were excluded from this analysis because of incomplete data.

We first considered a model (model A, improvement in fit: χ^2=25.0, df=6, p<0.001) in which all six variables were entered in the most likely chronological order (i.e., a history of ECT through to the maximum dose given), and this gave four significant variables (past history of ECT, agitation before neuroleptic malignant syndrome, time in restraint/seclusion, and neuroleptic dose on day 1). Removing the two nonsignificant variables (model B, improvement in fit: χ^2=24.4, df=4, p<0.001) made only a trivial difference to the model. Model B correctly assigned 15 of 24 patients with neuroleptic malignant syndrome and 45 of 48 comparison subjects. The removal of past ECT at this stage would have only a small effect. Of greater concern was the possibility that restraint/seclusion was distorting the results. For this reason, we examined a third model (model C, improvement in fit: χ^2=20.0, df=4, p<0.001) in which this variable was excluded; the variables included were past ECT, agitation before neuroleptic malignant syndrome, dehydration before neuroleptic malignant syndrome, and maximum neuroleptic dose. This was also useful because restraint and seclusion are events that, in part, reflect such factors as staffing levels and ward policy and are therefore more variable across institutions. We did not include interaction terms because of the small group sizes.

DISCUSSION

Our study suggests that neuroleptic malignant syndrome is more likely to occur in a patient who is in an agitated or dehydrated state, often needing restraint or seclusion, who receives large doses of neuroleptic medication soon after admission to the hospital, and who continues to receive high doses over the next few days. Our findings are in agreement with the trends reported in the previously published literature (2, 7, 8). Our data suggest that agitation and dehydration make independent contributions to the risk.

The emergence of some neuroleptic drug-related risk factors is also consistent with the suggestions from previous literature. Most commonly used neuroleptics were implicated, and drug potency did not emerge as an important factor. The administration of a large neuroleptic dose in a short period, leading to a marked escalation of the daily dose, received some support from our study as a risk factor. The subjects with neuroleptic malignant syndrome also received more intramuscular injections, but the effect size for this variable was small.

A surprising risk factor to emerge from our analysis was a past history of ECT. We could not determine the implications of this finding. Noteworthy was our finding that lithium, medical or neurological illness, and mental retardation were not risk factors; however, we acknowledge that this finding could be due to certain methodological limitations such as small group size, especially in relation to some variables, diversity of sources, retrospective design, lack of blind conditions, and the limitations of heuristic model building that used a large number of variables. Future studies with larger groups and prospectively gathered information may be able to overcome some of these shortcomings.

REFERENCES

1. Addonizio G, Susman VL, Roth SD: Neuroleptic malignant syndrome: review and analysis of 115 cases. Biol Psychiatry 1987; 22:1004–1020
2. Keck PE, Pope HG Jr, Cohen BM, McElroy SL, Nierenberg AA: Risk factors for neuroleptic malignant syndrome: a case-control study. Arch Gen Psychiatry 1989; 46:914–918
3. Davis JM: Comparative doses and costs of antipsychotic medication. Arch Gen Psychiatry 1976; 33:858–861
4. Numerical Algorithms Group: GLIM 3-77 Reference Manual. Oxford, England, Numerical Algorithms Group, 1985
5. Adena MA, Wilson SR: Generalised Linear Models in Epidemiological Research: Case-Control Studies. Sydney, Australia, Instat Foundation, 1982, pp 11.1–11.10
6. Dupont WD, Plummer WD: Power and sample size calculations: a review and computer program. Control Clin Trials 1990; 11: 116–128
7. Harsch HH: Neuroleptic malignant syndrome: physiological and laboratory findings in a series of nine cases. J Clin Psychiatry 1987; 48:328–333
8. Naganuma H, Fujii I: Incidence and risk factors in neuroleptic malignant syndrome. Acta Psychiatr Scand 1994; 90:424–426