Neuroleptic-Induced Extrapyramidal Symptoms With Fever

Heterogeneity of the 'Neuroleptic Malignant Syndrome'

Douglas F. Levinson, MD, George M. Simpson, MD

• **From 39 reported cases of the "neuroleptic malignant syndrome," three groups were identified: those with concurrent medical problems that could cause fever that accompanied the extrapyramidal symptoms; those with medical problems less clearly related to fever; and those without other medical disorders. Dehydration, infection, pulmonary embolus, and rhabdomyolysis were the common complications of untreated extrapyramidal symptoms. Three patients died, all with medical complications. In 14 cases, no medical cause of fever was identified. Hypotheses about mechanisms for fever include psychiatric illness, disruption of dopaminergic aspects of thermoregulation, and peripheral and central effects on muscle contraction leading to excess heat production. Neuroleptic-induced rigidity should be treated vigorously, with prompt discontinuation of neuroleptic therapy and administration of dopamine agonists in severe cases with or without fever. The cases of extrapyramidal symptoms with fever are too heterogeneous to justify the assumption of a unitary and "malignant" syndrome.**

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Delay and Deniker[1] first described a syndrome characterized by severe parkinsonian symptoms accompanied by fever and autonomic lability during the course of neuroleptic treatment. They characterized it as a "malignant" syndrome because of its sometimes fatal outcome. Over the past ten years, published reports of such cases have become increasingly frequent, and the existence of a "neuroleptic malignant syndrome" (NMS) has become widely accepted as fact. Recent reviews[2,3] have emphasized the similarities among these cases.

We suggest, however, that detailed case reports published in English are extraordinarily diverse, with complicating medical, psychiatric, and pharmacologic features in the majority. When these questionable cases are removed, a small group of reports remains in which severe parkinsonism attributable to neuroleptic drugs was accompanied by otherwise unexplained fever, with defervescence sometimes closely following aggressive treatment with anticholinergics, dopamine (DA) agonists, and/or muscle relaxants. The few deaths were associated with known intervening illness. In this review, we question the assumption of a unitary NMS and suggest greater attention to identification of medical contributing factors in reports submitted for publication. Severe extrapyramidal symptoms (EPS), with or without fever, may predispose to potentially lethal medical complications and should be treated vigorously. Appropriate medical workup and treatment options will be reviewed, and questions will be discussed concerning the relationship of the unexplained fever to psychiatric agitation, central DA blockade, and muscle contraction.

SELECTION OF CASE REPORTS

Material was restricted to case reports published in English with sufficient detail to permit identification of neuroleptic drugs as at least a potential contributing factor to a syndrome of rigidity and fever. Forty reports between 1972 and 1984 were reviewed, with a total of 67 cases.[3-42] These cases were either described by the authors as NMS or had been cited in other reviews of the syndrome. Nineteen of these cases were omitted from further analysis as follows: all five cases from one report[4] and 12 of 14 cases from another[26] were not individually described, and two patients had received nonneuroleptic drugs either as sole treatment (dothiepin)[5] or during the period prior to fever (lithium carbonate and chlordiazepoxide).[6]

An additional nine cases were excluded because the patients clearly had different syndromes or medical conditions. One patient had Huntington's chorea treated with nonneuroleptic DA-depleting agents, with sudden onset of dyspnea, fever, and intermittent dystonia (without parkinsonian rigidity), spontaneous resolution, and later uneventful treatment with haloperidol.[7] Three cases in two reports[8,9] were presented not as NMS but as examples of the potentially life-threatening medical complications of prolonged drug-induced rigidity and immobility (dehydration and possible pneumonia in one case[8] and pulmonary embolus and pneumonia in

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From the Department of Psychiatry, Medical College of Pennsylvania at Eastern Pennsylvania Psychiatric Institute, Philadelphia.

Reprint requests to 3200 Henry Ave, Philadelphia, PA 19129 (Dr Levinson).

Table 1.—Reported Cases of Neuroleptic-Induced

Case	Source, y (Case)	Age, y	Psychiatric Diagnosis†	Temperature, °C	Blood Pressure >140/90 mm Hg	Agitation/ Confusion	Creatine Kinase, U/mL
							Ill Patients (Medical Factors Significant
1	Dillon, 1972[13]	61	Paraphrenia	39.4	?	−/−	?
2	Bernstein, 1979[14]	36	Acute psychosis	41.7+	−	+/?	Normal
3	Henderson and Wooten, 1981[15]	59	Mania vs SA	40.5	+	+/?	6000
4	Coons et al, 1982[16]	25	BP vs SCHIZ	41.7	+	+/−	?
5	Eiser et al, 1982[17] (1)	60	? (IP)	41.2	−	?/?	1530
6	Eiser et al, 1982[17] (2)	29	Delusions	41.0	−	+/+	FG2000+
7	Eiser et al, 1982[17] (3)	43	DEP	39.2	−	−/+	1590
8	Lotstra et al, 1983[18]	49	Psychotic DEP	39.7	−	+/+	588
9	McCarron et al, 1982[19]	39	SCHIZ, ALC	39.6	−	+/+	1295
10	Chayasirisobhon et al, 1983[20]	32	NARC, AMP	40.0	+	−/+	1560
11	Fricchione et al, 1983[21]	67	Organic affective syndrome	38.1	+	+/+	Normal
12	Jessee and Anderson, 1983[22] (1)	30	SCHIZ	41.2	−	?/?	?
13	Mueller et al, 1983[23] (1)	28	Catatonic SCHIZ	38.3	−	−/?	Normal
14	Mueller et al, 1983[23] (2)	49	BP	38.1	+	+/+	1500
15	Scarlett et al, 1983[24] (2)	50	BP, ALC	38.0	?	−/−	2438
16	Knezevic et al, 1984[25] (1)	60	Agitated DEP	39.0	+	+/−	Normal
							Possibly Ill Patients (Medical
17	Itoh et al, 1977[26] (1)	18	Confusion, insomnia	39.0	?	?/+	Normal
18	Itoh et al, 1977[26] (2)	32	SCHIZ	?	?	+/?	Normal
19	Geller and Greydanus, 1979[27] (1)	15	?(INSTIT)	40.6	−	?/+	?
20	Goekoop and Carraat, 1982[28]	28	Mania	39.0	+	+/+	14 309
21	Dosani, 1983[29]	26	Delusions	40.5	−	+/+	Normal
22	Fricchione et al, 1983[21] (1)	43	Mania	38.1	+	+/+	Normal
23	May et al, 1983[30]	56	SCHIZ	39.0	−	−/−	2829
24	Knezevic et al, 1984[25] (3)	64	Paranoid	38.6	+	−/−	485
25	Kurlan et al, 1984[3]	24	Suicide attempt	39.0	−	+/+	Normal
							Not Ill Patients (No Known
26	Allan and White, 1972[31]	24	Hallucinations, delusions	37.5	−	−/+	?
27	Meltzer, 1973[32]	21	SA	39.4	+	+/+	1100
28	Moyes, 1973[33]	3	None (preop)	40.0	−	−/+	9800
29	McAllister, 1978[34]	34	SCHIZ	39.0	+	+/?	3250
30	Geller and Greydanus, 1979[27] (2)	12	SCHIZ	40.0	+	?/?	?
31	Grunhaus et al, 1979[35]	19	Acute psychosis	38.5	−	+/+	?
32	Morris et al, 1980[36]	31	MR, ?SCHIZ	40.0	−	+/−	1050
33	Tollefson, 1982[37]	41	Mania	39.4	+	+/+	?
34	Caroff et al, 1983[38]	35	?(Psych Pt)	?	?	?/?	?
35	Granato et al, 1983[39]	33	SCHIZ, MR, CP	39.4	+	?/+	4286
36	Jessee and Anderson, 1983[22] (2)	31	SCHIZ	42.0	Prior	+/+	1660
37	Scarlett et al, 1983[24] (1)	30	MR	38.9	−	+/−	3417
38	Zubenko and Pope, 1983[40]	24	SA	37.8	+	+/−	347
39	Knezevic et al, 1984[25] (2)	55	Mania	39.0	−	+/−	Normal

*Plus indicates present; minus, absent; question mark, not known or questionable.

†ALC indicates alcoholic; AMP, amphetamine psychosis in past; BP, bipolar; CP, cerebral palsy; DEP, depression; INSTIT, history of long-term institutionalization; IP, psychiatric inpatient (only information given); MR, mental retardation; NARC, narcolepsy; preop, patient received neuroleptics preoperatively; Psych Pt, psychiatric patient (details not reported); SA, schizoaffective; SCHIZ, schizophrenia.

Parkinsonism With Fever ('Neuroleptic Malignant Syndrome')*

Dehydration	Treatment (Prompt?)‡	Outcome (d)	Medical Problems/Comment§
Enough to Obscure Cause of Fever/Morbidity)			
–	Procyclidine (yes)	Recovered (7)	Pneumonia (at fever outset)
–	None	Recovered (?)	MI, pulmonary embolus
+	Trihexyphenidyl (no)	Recovered (?)	Dehydration, hypernatremia, hypoxia, Parkinson's disease
?	Anticholinergic series, dantrolene (no)	Recovered (?)	Seizures, increased LFS values (enzymes)
+	None	Died	Hypernatremia, ARF, myoglobinuria
+	None	Impaired	Hypernatremia, ARF, myoglobinuria
+	None	Impaired	ARF, myoglobinuria
+	None	Recovered (7)	Dehydration
–	Diphenhydramine, benztropine, amantadine (no)	Recovered (8)	Previous trauma and infection, ARF, increased LFS values (enzymes)
+	Amantadine (no)	Recovered (?)	Hypernatremia, dehydration, increased CSF protein and γ-globulins
–	Lorazepam (yes)	Recovered (<1)	Pneumonia, decreased pituitary, steroids
?	ECT (no)	Recovered (19)	Bilateral pneumonia
?	Benztropine, diazepam (no)	Impaired	Fever with stridor and hypoxia
–	Diphenhydramine, benztropine, bromocriptine (no)	Recovered (10)	Fever with foot infection
+	Diazepam, benztropine (no)	Recovered (2-7)	Hypernatremia, dehydration, increased WBCs (urine), increased CSF protein
+	Benztropine (yes)	Recovered (13)	Dehydration
Factors With Unclear Significance)			
?	Periciazine (yes)	Recovered (1-5)	"Exhaustion and dehydration"
+	Periciazine (yes)	Recovered (3)	Dehydration, emaciation
+	Trihexyphenidyl (no)	Recovered (?)	Dehydration
–	Dantrolene (yes)	Recovered (<1)	"Lung infiltrate," timing?
+	None	Recovered (7-17)	Self-starvation, dehydration
–	Benztropine, diphenhydramine, lorazepam (yes)	Recovered (1)	Postoperative
–	Dantrolene (yes)	Recovered (5)	Fever before neuroleptics
+	Benztropine, levodopa (no)	Impaired	Dehydration, fracture, frontal lobe symptoms
?	Dantrolene, benztropine, levodopa (no)	Recovered (15)	Postop (abdomen)
Illness Prior to Fever)			
?	Procyclidine (no)	Recovered (7)	Stiff 1 wk, then slight fever
–	Benztropine (yes)	Recovered (2)	No myoglobinuria
–	None	Died	Died after respiratory therapy complications
–	None	Recovered (8)	2-wk fever before drug treatment stopped
–	None	Recovered (6)	. . .
?	Trihexyphenidyl (no)	Recovered (?)	1 wk untreated EPS, then fever
–	Anticholinergic series diazepam, levodopa	Died	Pneumonia after 47 d afebrile
–	Benztropine (yes)	Recovered (?3-4)	. . .
?	None	Recovered (?)	. . .
?	Dantrolene, bromocriptine	Recovered (10)	Dantrolene reduced fever, bromocriptine treated EPS
–	ECT (no)	Recovered (7)	Fever 7 d after neuroleptics given
–	Diazepam (no)	Recovered (21)	. . .
–	Bromocriptine (yes)	Recovered (3)	Agitated after fever
–	Benztropine, levodopa	Slight rigidity	. . .

‡ECT indicates electroconvulsive therapy; in parentheses: yes, prompt specific antiparkinsonism treatment after onset of rigidity with fever; no, treatment delayed.

§ARF indicates acute renal failure; CSF, cerebrospinal fluid; EPS, extrapyramidal symptoms; LFS, liver function studies; MI, myocardial infarction; WBCs, white blood cells. The term *postoperative* indicates that syndrome developed during recovery from major surgery.

the second and third,[9] with prior deep venous thrombosis also in the third[9]), with these complications clearly the cause of fever. One patient had an unnamed familial degenerative neurologic disorder and had onset of pneumonia prior to fever,[10] and another case was convincingly presented as a drug allergy, with fever, rash, lymphocytopenia, increased liver enzyme levels, hyponatremia, and hypokalemia.[11] One patient had methaqualone and barbiturate withdrawal with generalized seizures, multiple fractures, shock, renal failure, hepatic failure, hypoglycemia, disseminated intravascular coagulation, gastrointestinal tract bleeding, and pneumonia obscuring the proposed relationship between his temperature instability and haloperidol treatment.[12] In one case, addition of haloperidol to a lithium carbonate regimen that had previously been well tolerated was followed by a picture of toxic encephalopathy with generalized slowing on electroencephalography (EEG), confusion, and lasting cognitive and motor impairment, with brief fever initially.[13] A similar syndrome has previously been reported and attributed to the lithium carbonate–haloperidol combination[41] or primarily to the lithium carbonate[43,44] but, in any case, represents a picture quite different from NMS. Another borderline mentally retarded and schizophrenic patient developed severe rigidity, mutism, incontinence, labile blood pressure, and fever (temperature, 39°C) after receiving intramuscular (IM) neuroleptics for two days as an outpatient. She was severely dehydrated on admission (sodium level, 155 mEq/L [155 mmol/L]; serum urea nitrogen level, 100 mg/dL [35.7 mmol/L] (normal, 1.8 to 8.9 mmol/L); serum creatinine level, 1.5 mg/dL [130 μmol/L] (normal, 63 to 126 μmol/L)), and within three days she also developed *Klebsiella* pneumonia and a urinary tract infection that were treated with antibiotics. She recovered fully but subsequently had another episode, with similar symptoms (temperature to 41.3°C), after taking oral haloperidol at home; she developed EPSs and became even more dehydrated (sodium level, 167 mEq/L [167 mmol/L]; serum urea nitrogen level, 176 mg/dL [62.8 mmol/L]) and subsequently developed staphylococcal sepsis. This latter case exemplifies a problem encountered in many[42] of the reports in the literature in that the time course of medical complications, such as dehydration and infection, is seldom entirely known, so that the alleged relationship of fever to neuroleptic treatment cannot be established.

RESULTS

The remaining 39 cases[3,13-40] are summarized in Table 1. Selected clinical features of these 39 cases are summarized in Table 2. In each of these cases, fever appeared during a period of severe EPS and signs apparently resulting from administration of neuroleptic drugs, and either there were no known complicating medical factors or (more often) the relationship of these factors to the fever was not clear.

Relationship of Fever to Change in Treatment

In most of these cases, EPS appeared early in the course of neuroleptic treatment or soon after dosage increase, change to a new medication, or discontinuation of anti-EPS medication (eg, by the patient after discharge), with fever appearing several hours to eight days (usually one to five days) after the new or changed treatment. However, in four of the 39 cases with longer intervals (30 to 60 days) between initiation of treatment and EPS with fever,[13,25,35] treatment was with fluphenazine decanoate every two weeks, so that increasing fluphenazine levels might be suspected due to this drug's long half-life (particularly in the three of these patients over age 55 years, in whom the drug may have an even longer half-life). Neuroleptics administered immediately prior to onset of rigidity included fluphenazine (hydrochloride, decanoate, and enanthate), haloperidol, chlorpromazine, thioridazine, trifluoperazine, thiothixene, loxapine, trimeprazine, promazine, and methotrimeprazine (levomepromazine).

Nonneuroleptic Drugs

In seven of the 39 cases, lithium carbonate was being administered at therapeutic levels in addition to neuroleptics. In six cases, typical neuroleptic-induced EPS were present, but a contribution of lithium carbonate to the toxic reaction could not be excluded.[15,24,28,37,38,40] (These patients were nevertheless classified as "not ill" in the discussion below, unless there were other medical factors.) In the seventh case, the timing of neuroleptic treatment in relation to fever onset was unclear, and there was also a concurrent medical explanation (infection) for initial fever, as noted below.[28] Two patients were receiving concurrent antidepressants,[17] one of whom was also receiving both neuroleptics and lithium carbonate. Most of these patients received anticholinergic (antiparkinsonism) agents, which can contribute to fever by reducing sweating, but typical atropinic signs were not described and diaphoresis was generally present.

Concurrent Medical Problems

Ill Patients.—In a group of 16 of the 39 cases (the ill group), known medical factors appeared to explain the fever satisfactorily (cases 1 through 16 in Table 1). In many of these cases, the implicated medical factors were probably related to prolonged and severe EPS. In three cases, initial dehydration was severe, and fever appeared to have resolved due to rehydration therapy (cases 8, 10, and 16); two of these patients also had hypernatremia (cases 8 and 10). A fourth patient showed increased sodium, serum urea nitrogen, and creatinine levels initially, with an unexplained increase in cerebrospinal fluid protein (52 mg/dL [0.52 g/L]) and lymphocyte levels; fever resolved within two days of starting rehydration (case 15). Three cases were reported because of the discovery of myoglobinuria with acute renal failure (with hypernatremia in two cases) presumed to be due to EPS-induced rhabdomyolysis (cases 5 through 7); renal failure appeared simultaneously with fever, which may accompany myoglobinuria.[45] In a fourth case, a patient received neuroleptics just after discontinuation of therapy with unnamed antibiotics (but presumably including a gentamicin-type drug) for abdominal abscess following multiple abdominal trauma and surgery; fever accompanied onset of acute renal failure (creatinine level was 3.0 mg/dL [270 μmol/L], with a serum urea nitrogen level of only 24 mg/dL [8.6 mmol/L]; the phosphate level increased to 7.7 mg/dL [2.49 mmol/L]), but since no test for myoglobinuria was reported, the cause of renal failure is undetermined (case 9). In three cases, pneumonia was discovered coincident with fever, and fever was brief in relation to the more prolonged accompanying EPS (cases 1, 11, and 12). One patient had a myocardial infarction and pulmonary embolus at the time of fever onset (case 2). In one patient with idiopathic parkinsonism, therapy with antiparkinsonism agents had been discontinued when neuroleptic administration was begun; he developed dehydration with hypernatremia and severe unexplained hypoxemia with fever after a period of severe EPS (case 3). Another patient had severe hypoxia, possibly related to EPS, producing stridor simultaneously with brief fever (temperature only to 38.3°C) (case 13). One patient was discovered wandering and stuporous, with temperature to 41.7°C, and proved to be having generalized seizures (although he developed slight fever [temperature to 37.8°C] with subsequent increase in haloperidol dose) (case 4). One patient had a foot infection at the time of fever onset to a temperature of only 38.1°C, and fever was not mentioned subsequently (case 14). We conclude that in most of these cases, fever occurred concurrently with EPS but was due to other medical factors and that in all of these cases the prominence of medical factors was too great to permit any conclusions about the relationship between neuroleptics and fever.

Possibly Ill Patients.—In nine additional cases (the possibly ill group), there were complicating medical factors initially (dehydration in five cases [cases 17 through 19, 21, and 24], postoperative status in two [cases 22 and 25], pneumonia in one [case 20], and fever prior to initiation of neuroleptic treatment in one [case 23]), but fever appeared to have been prolonged, disproportionate, poorly responsive to the measures that relieved EPS, or recurrent with later neuroleptic rechallenge. The role of dehydration in such cases is particularly difficult to establish. Many authors have asserted that dehydration and other forms of debilitation represent predisposing factors for a specifically neuroleptic-related syndrome, but it can be equally well argued that severe rigidity and immobilization in such cases led to reduced oral intake and that the dehydration itself was the cause of fever. Typically, the exact time course of dehydration has not been known, usually because

Table 2.—Clinical Features

Group	Mean Age, y	Mean Temperature, °C	No. (%) of Patients*				
			High BP	Increased CK	Agitation	Confusion	Dehydration
Ill (n = 16)	44.8	39.7	6 (38)	9 (56)	9 (56)	7 (44)	8 (50)
Possibly ill (n = 9)	34.0	39.2†	3 (33)	3 (33)	5 (56)	6 (67)	4 (44)
Not ill (n = 14)	30.0‡	39.3†	6 (43)§	9 (64)	9 (64)	7 (50)	0 (0)
Total (N = 39)	37.2	39.5	**15** (38)	**21** (54)	**23** (59)	**20** (51)	**12** (31)

*Proportions include only cases with the feature specifically mentioned in report; other cases may have been positive. BP indicates blood pressure (>140/90 mm Hg); CK, creatine kinase. Dehydration was described in report or strongly indicated by laboratory values.
†No temperature included in one case.
‡Does not include one 3-year-old patient.
§Previously existing hypertension noted in one additional case.

the patient was initially out of the hospital. We have separated these cases from the next group because the role of medical factors (while possibly unrelated or only predisposing) is so unclear that the role of neuroleptic treatment in causing fever cannot be determined.

Not Ill Patients.—There remain 14 cases (cases 26 through 39) in which a syndrome of severe parkinsonian rigidity and otherwise unexplained fever appeared in the course of neuroleptic treatment, with a time course of onset and resolution such that neuroleptic-related effects cannot be excluded. These patients included a 3-year-old child, a 12-year-old child, and 12 adult patients aged 19 to 55 years (mean age for the adults, 28.9 years). Three patients (cases 33, 34, and 40) were receiving concurrent lithium carbonate treatment. In four cases, onset followed high doses of neuroleptics: 150 mg of fluphenazine decanoate over one week (case 26), 75 mg of haloperidol per day at age 12 years (case 30), 72 mg of trimeprazine at age 3 years (*Physician's Desk Reference* recommended dose is 2.5 mg) for preoperative medication (case 28), and IM thiothixene (20 mg) plus haloperidol (30 mg by mouth [po]) in one day (case 29). As noted in Table 1, all had psychiatric diagnoses except the 3-year-old child, who received preoperative medication. Dehydration was apparently not present in nine of these cases and was undetermined from the case report (but probably absent) in five cases. The EEG was normal in seven cases and not reported in seven.

Clinical Findings

Fever.—In eight of the 39 cases, temperature reached in excess of 40°C. Six of these cases were from the ill group, one was from the possibly ill group, and only one was from the not ill group. The not ill group had maximum temperature ranging from 37.5 to 42°C, with 11 of 14 exceeding 38.9°C. In the not ill group, six patients reportedly had high white blood cell counts. Duration of fever was variable and often difficult to determine from the report.

Hypertension.—Elevated blood pressure coincident with EPS and fever was noted in six of the 14 not ill patients, seven of the 16 ill patients, and three of nine possibly ill patients. One of the ill patients (case 2) with myocardial infarction and pulmonary embolus had hypotension.

Creatine Kinase (CK).—Elevated CK levels (from 347 to 4286 U/mL) were reported in nine (64%) of the 14 not ill patients, perhaps indicative of the severity of EPS-induced muscle contraction. In four of the not ill patients, no CK measurement was reported, while in one it was reported as normal. Twelve of the 25 cases from the ill and the not ill groups also reportedly had elevated CK levels, up to 14 309 U/mL, with four not reporting on CK.

Dehydration.—Signs of dehydration (physical examination results and/or elevated serum urea nitrogen level) were reported in eight of 16 ill patients, with three other possible cases. Among the possibly ill patients, four were reported to be dehydrated and in two it was uncertain.

Agitation.—Agitation was reported to be part of the pre-neuroleptic psychiatric picture in six of 14 not ill patients (cases 27, 29, 32, and 37 through 39), with three others uncertain. In two additional cases (cases 31 and 36), severe agitation occurred prior to rigidity rather than coincident with fever that appeared later, and in one case agitation was described only after the fever (case 38). Among the ill and possibly ill patients, 14 were described as agitated, while five histories were unclear.

Confusion.—Confusion, ranging from mild to stuporous, was clearly described in eight of the 14 not ill patients after onset of the rigidity and fever, in six of the nine possibly ill patients, and in seven of the fourteen ill patients.

Incontinence.—Urinary or fecal incontinence was noted in one not ill subject (case 39) and three ill subjects (cases 2, 8, and 10).

Tests for Malignant Hyperthermia.—Two patients in the not ill group (cases 33 and 37) and one in the ill group (case 15) had negative tests for malignant hyperthermia (MH) (measurement of contraction induced by halothane and caffeine in muscle biopsy specimens). One patient in the not ill group had contraction of muscle specimens to lower concentrations of halothane and of fluphenazine (this patient became rigid on a haloperidol, thiothixene, and lithium carbonate regimen) compared with control subjects.[34]

Myoglobinuria.—Myoglobinuria associated with renal failure was reported in three cases (cases 5 through 7) from one hospital, while negative urinary tests for myoglobin were reported in one not ill and one ill patient (cases 27 and 15, respectively). No such tests were reported in the other cases, although there was renal failure in another ill patient (case 9) who had also suffered multiple trauma.

Time to Improvement.—Case reports varied in providing precise information about timing of onset, treatment, and recovery. In general, the not ill patients who recovered did so two to eight days after onset of the associated fever, which usually began some days after onset of severe rigidity. In a number of cases, fever resolved more quickly than the rigidity (when no effective antiparkinsonism treatment was given). Longer courses (ten to 28 days) were reported in some cases, including three patients who had received fluphenazine and four patients who received oral neuroleptics.

Rechallenge With Neuroleptics.—Subsequent administration of neuroleptics without recurrence of rigidity and fever was reported in five cases (cases 12, 13, 15, 27, and 36). Recurrence of fever was reported in one case treated with both chlorpromazine plus lithium carbonate and with haloperidol plus lithium carbonate (case 2) and in one case treated with methotrimeprazine (case 18). In one case fever recurred after a single dose of haloperidol was given nine days after admission (after resolution of initial fever) but not later with administration of "both oral and parenteral" neuroleptics (case 17).

Treatment

It was striking that in 26 of these 39 cases, aggressive efforts to treat the EPS were either never made or were delayed for more than several days of rigidity and fever. Standard anticholinergic drugs were described as ineffective in at least eight cases and may have been tried in others. Improvement (in most of these cases rapid) appeared to be specifically related to a treatment in 20 cases (summarized in Table 3), including eight with anticholinergic drugs (cases 1, 3, 16, 18, 26, 27, 31, and 33), two with bromocriptine (cases 14 and 38), three with dantrolene (cases 4, 20, and 23), one with a combination of dantrolene (which lowered fever) and bromocriptine (which reduced rigidity) (case 35), three with levodopa and car-

Table 3.—Treatment Reported Effective in Cases of Extrapyramidal Symptoms With Fever

Treatment	Dosage	No. of Cases	
		Treated	Successes
Anticholinergic agents	. . .	20	8
Bromocriptine	7.5-60 mg/d po	3	3
Dantrolene	0.8-1.25 mg/kg IV; 50-mg po up to qid	5	4
Levodopa	100 mg bid	1	1
Carbidopa-levodopa	25/100 mg tid to 50/200 mg qid po	3	2
Amantadine	200 mg/d po	2	2
Lorazepam	1.5 to 2 mg IV, then po	2	2

*IV indicates intravenously; qid, four times daily; bid, twice daily; tid, three times daily; po, by mouth.

Table 4.—Deaths in 39 Cases of Extrapyramidal Symptoms With Fever

Case	Age, yr	Medical Problem Before Fever?	Cause of Death
28	3	No	Pneumothorax; technical problems in respiratory therapy
32	31	No	Initially had tracheostomy, then developed pneumonia after 4 wk afebrile with continued rigidity
5	60	Yes	Myoglobinuria with renal failure, pneumonia, shock

Table 5.—Possible Mechanisms for Fever With Drug-Induced Extrapyramidal Symptoms

- Psychiatric illness ("lethal catatonia" [excitement, calcium abnormalities?])
- Medical complications
  - Dehydration, electrolyte imbalance
  - Infection (especially pneumonia)
  - Pulmonary embolus
  - Rhabdomyolysis, myoglobinuria, renal failure
  - Seizures
  - Allergy
- Proposed neuroleptic effects on temperature
  - Central disruption of dopaminergic thermoregulatory mechanisms
  - Direct (malignant hyperthermialike) effect on muscle contraction with secondary heat production
  - Muscle contraction due to extrapyramidal symptoms with secondary heat production

bidopa (cases 24, 25, and 39), and two with amantadine (cases 9 and 10). Bromocriptine was administered in dosages of 7.5 to 60 mg/d (case 35), 15 to 25 mg/d (case 38), and 15 to 30 mg/d (case 14) orally. Dantrolene was given in doses of 0.8 mg/kg intravenously (IV) (case 35), 1.25 mg/kg IV (case 20), 50 mg po up to four times daily (qid) (case 4), and 50 mg po twice daily (case 23). Levodopa preparations were reported as effective in one case with dosage not given (case 39), in one case with a dosage of 100 mg of levodopa twice daily (case 25), and in one case with levodopa-carbidopa given from 100/25 mg three times daily to 200/50 mg qid (case 25). The latter combination was ineffective in one case at 100/10 qid (case 32). Amantadine, 200 mg po daily, was reported as gradually effective in one case (case 10) and immediately effective in another (case 9). Electroconvulsive therapy was reported as effective in two cases (cases 11 and 22).

Morbidity and Mortality

Full recovery was reported in 11 of 14 not ill patients, eight of nine possibly ill patients, and 12 of 16 ill patients (total, 31 [79%]). In eight (21%) of 39 cases, full recovery was not observed. Nonlethal adverse outcomes (five cases) included the following: minimal rigidity at discharge in a not ill patient (case 39), residual myoclonus in a possibly ill patient who had frontal release signs prior to neuroleptic treatment and an abnormal EEG during the episode (case 24), two patients who recovered from myoglobinuria and acute renal failure with dysarthria and dysphagia in one and slight tremor and decreased deep tendon reflexes in another (cases 6 and 7), and residual hand and foot dystonia in one ill patient (case 13).

There were three deaths (8% of the entire series), including two not ill patients (14%) and one ill patient (6%) (summarized in Table 4). One death was reported in the 3-year-old child treated with trimeprazine 72 mg IM as preoperative medication; the child became febrile in 15 minutes, with rigidity and peripheral vasoconstriction. Atropine, 0.3 mg IM, was given after fever onset. Respiratory therapy was begun on the first day (although the reasons for its institution are unclear in the report), and death resulted from pneumothorax and reduced lung compliance believed to be secondary to high respirator pressures, with "technical problems in the management of artificial respiration" (case 28). A second death occurred in a 31-year-old mentally retarded man ("schizophrenic" by history) (case 32) who became severely rigid after three weeks of chlorpromazine therapy, 1600 mg daily, and febrile after two additional weeks (with dosage reduced to 1000 mg daily for the last week). Anticholinergics (maximum dose, 2 mg of IV benztropine) and IV diazepam had little effect, nor did carbidopa-levodopa 10/100 mg qid. A tracheostomy was performed on the first day for excess secretions. Nevertheless, he became afebrile by the 19th day, although he remained rigid, and no further anti-EPS treatment was reported. Pneumonia developed in the seventh week (he remained rigid), and he died in the tenth week. The third death was in a 60-year-old woman with a psychiatric illness (not described), treated with amitriptyline, diazepam, and haloperidol, and mild hypertension, treated with hydrochlorothiazide (case 5). On the third day of the haloperidol regimen, she developed fever, acute renal failure, and myglobinuria, with the CK level reaching 1530 U/mL and the lactate dehydrogenase level (muscle origin) reaching 1200 mIU/mL, presumed to be due to rhabdomyolysis. During a 23-day course, she remained in renal failure, developed pneumonia and septic shock, and died.

COMMENT

This review suggests that a heterogeneous group of cases of neuroleptic-induced EPS with concurrent fever have been described erroneously as representing a unitary "malignant syndrome." Of the 48 well-documented case reports in English, nine were judged to represent cases of primary medical illness and were excluded from further analysis. Of the remaining 39 cases, 16 were judged to have such significant concurrent medical problems that neuroleptics could not be clearly implicated as the cause of fever, nine had concurrent medical problems that were judged not to have accounted entirely for the fever course, and 14 had no obvious medical cause of fever. There is also no evidence of mortality due to any specific neuroleptic-related mechanism in these cases. Mortality was less than 10% (three cases), resulting from known medical complications in two cases (prolonged untreated EPS with tracheostomy and pneumonia in one case[36] and pneumothorax during respiratory therapy with "technical problems" in another[33]) and from renal failure secondary to rhabdomyolysis,[17] a potential complication of any type of muscle contraction or injury, in a third. Fever was unimpressive, with only one not ill

patient[22] having a maximum temperature over 40°C. It must further be assumed that most or all fatal cases, but not all nonfatal cases, have been reported.

The 14 not ill patients demonstrate that prolonged fever may accompany severe drug-induced EPS in the absence of any apparent medical explanation. Four major hypotheses are that this fever may be due to (1) psychiatric illness with severe agitation ("lethal catatonia"[46]) regardless of drug treatment; (2) the effects of dopaminergic blockade in central thermoregulatory systems; (3) excess heat production due to peripheral induction of muscle contraction similar to the MH syndrome; and (4) excess heat production due to muscle rigidity caused by central dopaminergic blockade. Proposed mechanisms are summarized in Table 5.

Lethal Catatonia

The concept of lethal catatonia was introduced by Stauder[46] in 1934 to describe a type of fulminant psychiatric illness not uncommonly accompanied by fever and death. Since six of the 14 not ill patients described above had documented severe agitation in the context of psychiatric illness prior to onset of fever, an etiologic factor associated with psychiatric illness itself must be considered. We found 17 additional reports of 270 cases of lethal catatonia in the literature.[47-63] Although the term *catatonia* is associated today primarily with rigidity, most of the patients in the older case reports appear to have suffered from what was known as catatonic excitement, a state of extreme agitation most common during acute mania. It is difficult to determine from the older literature whether the lethal form ever occurred in the absence of medical complications. Most of the reports summarized large numbers of cases as a group, and many predated modern understanding of laboratory tests and fluid and electrolyte measurements. The typical patient appears to have been a manic who, after a period of anorexia and sleeplessness, became "exhausted" and died of undiagnosable causes. Shulack was the first to implicate dehydration and electrolyte imbalance as a major factor: after reviewing 376 cases[52] in 1944, he successfully treated seven consecutive cases with volume expansion (saline and adrenocortical extract).[54] There are also autopsy reports of hemorrhagic petechiae[50,51] in several of these cases suggestive of the type of superficial brain vessel injury often seen in cases of hypernatremia.

Most individual case reports suggest a mixed group of medical disorders. Some were probably psychiatric disorders with intercurrent dehydration and/or infection.[55,57,60] Others appear to have been central nervous system infections producing psychiatric symptoms, including probable eastern equine encephalitis,[62] acute increased intracranial pressure with good recovery suggestive of encephalitis,[49] and a patient who developed dehydration, hypertension, and perseveration followed by nuchal rigidity, papilledema, coma, and death.[59]

More recently, Carmen and Wyatt[63] described a patient with episodic agitation and fever related to pharmacologic manipulations of calcium. This 47-year-old man had a history of recurrent brief episodes of severe agitation followed by a stuporous, delirious appearance with rigidity and temperature over 40°C. While participating in a National Institute of Mental Health study of calcium metabolism in psychosis, a febrile episode was apparently exacerbated during treatment with calcium and vitamin D, and two subsequent episodes were promptly terminated by administration of calcitonin. This result suggested a role of calcium in the etiology of his behavioral disturbance, muscle contraction, and fever, but he was also dehydrated during these episodes and this may also have contributed to the fever. This case supports the notion that there may be undetermined pathologic factors in some psychiatric cases that may cause fever with or without rigidity.

The question of whether fever can accompany catatonic illness without other drug-induced or medical causes thus deserves further investigation. Patients with recurrent fever, in particular, deserve careful workup and the findings deserve publication. However, little is known about such factors, and most previously reported cases of lethal catatonia appear to have lacked rigidity and to have had other, medical causes of fever. Clinically the distinction between EPS and catatonic rigidity is an important one. Neuroleptic-induced rigidity can mimic catatonia,[8] obscuring the need for anti-EPS treatment; indeed, this syndrome is undoubtedly more common than EPS with fever. We fear that the current assumption of a unitary NMS may lead to the misdiagnosis and, potentially, the mistreatment of patients with functional or drug-induced catatonia who happen to become febrile.

Disruption of Dopaminergic Thermoregulatory Mechanisms

It has been proposed that neuroleptic drugs may cause fever via the effects of dopaminergic blockade on central thermoregulatory mechanisms.[64] There is evidence that stimulation of rat hypothalamic DA receptors can decrease core temperature,[65] that DA release may be the basis for the hypothermic effects of amphetamine in the rat,[66] and that patients with Parkinson's disease may have decreased peripheral vascular responsiveness, with unilateral deficits in two patients with unilateral disease, possibly leading to decreased heat loss.[67] It is unclear whether the prompt fever-lowering effects of DA agonists in the cases reported above are due to effects on thermoregulation, muscle rigidity, or both (see discussion below).

Direct Effects on Muscle Contraction

The concurrent rigidity and fever in these cases has led many authors to suggest a similarity with cases of MH. Malignant hyperthermia is believed to result from a genetically transmitted, poorly understood vulnerability to efflux of calcium ions from sarcoplasmic reticulum in the presence of specific chemical agents, most notably the anesthetic agent halothane. During surgical anesthesia, vulnerable individuals may therefore suffer sudden severe muscle contraction, heat production, uncoupling of oxidative phosphorylation, increased glycogen metabolism, increased carbon dioxide and lactate production, and diminished heat loss due to concurrent peripheral vasoconstriction, as well as myoglobinuria and renal failure. These individuals can be identified by in vitro observation of excessive contraction of muscle biopsy specimens in the presence of halothane or caffeine. Malignant hyperthermia is treated with IV dantrolene, a muscle relaxant believed to act directly to reduce release of calcium from sarcoplasmic reticulum, and it can be prevented by administration of dantrolene preoperatively to susceptible individuals.[68,69]

A relationship between the syndrome of EPS with fever and MH is suggested by the success of dantrolene in the treatment of four cases (above) and by a report by Caroff et al[38] that muscle biopsy specimens from one patient who had recovered from EPS with fever and rhabdomyolysis showed excessive in vitro contraction in the presence of halothane and also of fluphenazine (although her fever had appeared after lithium carbonate, haloperidol, and thio-

thixene treatment). Conversely, three other cases of EPS with fever had negative tests for halothane-induced contraction (cases 15, 33, and 37), suggesting that most cases are not directly related to MH. Also, dantrolene was ineffective in one patient (case 25), and in another (case 35) fever was reduced immediately but rigidity did not resolve fully until bromocriptine was given, suggesting that while muscle contraction may have contributed to excessive heat production, at least a component of the syndrome was due to DA blockade in the basal ganglia or the hypothalamus. Thus, the involvement of peripheral neuroleptic effects on muscle contraction has not been fully explored and cannot explain all of these cases. The type of testing initiated by Caroff et al[38] would be useful to pursue in cases of EPS with unexplained fever. It also may be suggested that calcium-channel blockers (reportedly useful in MH) may have a role in the treatment of EPS-induced fever if calcium release is an important factor in some cases; such treatment has not been reported.

Muscle Contraction due to DA Blockade

It seems likely that in some cases of EPS with fever, there is excessive heat production due to muscle contraction caused by central DA blockade (ie, the EPS themselves), alone or in combination with the postulated disruption of thermoregulation. The only direct support for a peripheral heat production hypothesis comes from the success of the peripherally acting drug dantrolene in some cases. The fact that dantrolene reduced fever without completely reversing centrally induced EPS in one case (case 35) suggests that a combination of central and peripheral factors are involved, but the relative significance of peripheral heat production is not understood.

The most parsimonious hypothesis for cases of severe EPS with unexplained fever is that central DA blockade produces the EPS in typical fashion and that an unknown combination of excessive peripheral heat production due to muscle contraction and central dysregulation of thermoregulation, both presumably results of the DA blockade, produces the fever. Sympathetic activity and norepinephrine release induced by muscle contraction might also account for the autonomic symptoms observed in some patients. This hypothesis is supported by the fact that DA agonists (bromocriptine, levodopa-carbidopa, and amantadine) have most frequently been reported to ameliorate the syndrome rapidly. Zubenko and Pope[40] reported an illustrative case (case 38) in which severe EPS, fever, and exacerbation of preexisting hypertension all developed after an injection of fluphenazine. The drug had been given for several months but at ten-day intervals, which probably causes increasing tissue levels after each injection in some patients. Diphenhydramine therapy and then amantadine therapy were ineffective, but initiation of a bromocriptine regimen (5 mg po three times daily) resolved the rigidity within two doses and the fever and hypertension within two days. Reduction of bromocriptine led to renewed symptoms (presumably due to the continued presence of fluphenazine), which were again successfully treated with increased bromocriptine for four days. This case is similar to that reported by Mueller et al[23] (case 14) in which mild diastolic hypertension preceded the febrile syndrome, for both of which bromocriptine treatment was rapidly effective. It is of interest that a patient with idiopathic parkinsonism has been described who developed rigidity, incontinence, elevated CK levels, and prolonged fever after abrupt discontinuation of antiparkinsonism medications, with resolution after resumption of levodopa-carbidopa therapy.[70] Thus, it appears that in some patients, EPS induced by central reduction of DA transmission may be accompanied by fever, but the preponderance of central thermoregulatory and peripheral contraction-induced heat production remains unclear.

CONCLUSION

The reported cases of EPS with fever represent a heterogeneous group of disorders. In the majority of cases, either fever can be attributed to diverse medical disorders or its relation to concurrent medical problems cannot be evaluated definitively. Among the individually described cases chosen for analysis here, the mortality was lower (7.7%) than has been reported previously, and each death could be explained by known intervening medical complications rather than by a specifically neuroleptic-induced mechanism.

When fever appears with severe EPS during neuroleptic treatment, workup should be initiated for common medical factors, which include dehydration with electrolyte imbalance, infection (especially pneumonia), pulmonary embolus, rhabdomyolysis with myoglobinuria, and sometimes renal failure, seizures, and drug allergy. Rhabdomyolysis in particular was seldom considered in these cases, although in one hospital with an alert renal team there were three apparently neuroleptic-related cases in one year.[17] Heme-positive urine without red blood cells, accompanied by elevated serum CK levels, establish this diagnosis. It is of interest that rhabdomyolysis has also been reported in a case of phencyclidine (PCP) psychosis.[71] Dehydration appears to be the most common complication, so that fluid and electrolyte status should always be assessed and corrected appropriately.

Patients who have became severely rigid and immobile due to EPS and whose judgment and cooperation are impaired by psychiatric illness appear to be at great risk for these potentially lethal medical complications. This is true regardless of whether fever is present. Clinical experience suggests that cases of "neuroleptic-induced catatonia" (ie, severe EPS) without fever are indeed the most common. It is most critical that severe EPS be recognized and treated vigorously. Our recommendations include the following:

1. In cases of moderate severity, it is usually sufficient to reduce neuroleptic dosage (which is often excessive in clinical practice in any case) and to institute or increase regular dosages of anticholinergic or dopaminergic drugs.
2. If a patient shows decreased ability to speak, move, eat, or breathe and if anti-EPS treatment is not immediately effective, administration of neuroleptic drugs should be discontinued and more vigorous treatment should be instituted.
3. Bromocriptine may be the most rational choice because it is a direct-acting DA agonist and thus should counteract the effects of neuroleptic-induced DA blockade. It has proved to be rapidly effective in reported cases. Although DA agonists given alone may exacerbate psychosis, this response has not proved to be a problem in cases where they are used to overcome excessive DA blockade. Thus, temporary institution of a regimen of DA agonists in cases of severe EPS should be considered safe. Other dopaminergic and muscle-relaxant drugs have also proved to be useful, as discussed above.
4. If neuroleptics are still clinically indicated after recovery from acute EPS (with or without fever), they should be reinstituted cautiously, with appropriate antiparkinsonism medication. In most of the reported cases in which re-

challenge was attempted, it was successful; even when fever recurred, prompt discontinuation of the offending drug (and antiparkinsonism treatment if necessary) was sufficient treatment, and there was no morbidity. Rechallenge with the same neuroleptic may give the most information, because if the drug is now well tolerated, exaggerated concerns may be avoided. If fever recurs despite absence of medical complications, the drug should be promptly discontinued (and any associated EPS should be treated). It may still be possible to institute therapy with a different neuroleptic.

5. There is a need for well-studied cases in which all known medical causes for fever associated with EPS have been ruled out. In addition to reporting sufficient medical information to support this conclusion, valuable data would include tests for MH, studies of thermoregulatory mechanisms and of the effects of centrally vs peripherally active drugs, and consideration of possible association of fever to psychiatric illness and associated metabolic mechanisms in the absence of neuroleptic treatment.

A group of 14 of 39 potential cases has been identified in which unexplained or prolonged fever accompanied neuroleptic-induced EPS without known medical complications. Several mechanisms have been proposed to explain such cases, including as yet undetermined pathophysiological factors related to psychiatric illness with severe agitation, peripheral effects of neuroleptics on muscle similar to the MH syndrome, and effects of central DA blockade, including disruption of thermoregulatory mechanisms and excessive heat production from EPS-related muscle contraction. Existing evidence lends the most support to the hypothesis that central DA blockade can produce both rigidity and fever through a combination of thermoregulatory and peripheral heat production (muscle contraction) effects. However, factors intrinsic to some forms of psychiatric illness and syndromes resembling MH of anesthesia deserve further attention as well. It is likely that there is heterogeneity even among these cases without medical complications.

We suggest that the term *NMS* no longer serves a useful purpose. First, it is a misnomer: available evidence suggests that predictable and preventable complications of prolonged immobility and muscle contraction produce morbidity and mortality. It does not seem justified or useful to suggest that neuroleptics themselves are "malignant." Second, in our experience, the diagnosis of NMS can have harmful effects. Patients with severe EPS urgently require the treatment approaches outlined above; if there is accompanying fever, they additionally require prompt workup for possible medical complications. The diagnosis of NMS often diverts attention from these two tasks, while the patient is observed and this mysterious syndrome is contemplated. This delay may itself be an important cause of morbidity. Further, coincidental occurrence of fever (due to viral illness or mild dehydration, for example) and severe EPS may lead to the diagnosis of NMS. Because the syndrome is alleged to be malignant, much-needed neuroleptics may be denied to the patient in the future.

Therefore, we favor the term *EPS with fever* to refer to the heterogeneous syndrome described here and suggest that in the majority of cases, a known medical cause of fever will be found. This descriptive term places emphasis on the two features requiring prompt clinical attention: severe EPS and treatable medical causes of fever. It appears that in a small number of cases no known medical cause of fever can be found. Some of these cases may represent fever associated with dopaminergic blockade, some may involve a neuroleptic-induced form of MH, and some may represent fever related to the pathophysiologic nature of specific psychiatric illnesses or of severe agitation. It seems more useful to continue to study and report on each of these important areas than to support the concept of a unitary syndrome on the basis of inadequate evidence.

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