Incidence of Extrapyramidal Syndromes in AIDS Patients and a Comparison Group of Medically Ill Inpatients

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The authors retrospectively reviewed the charts of 29 inpatients with AIDS and 24 medically ill inpatients, all of whom were exposed to neuroleptics. Results adjusted for age, gender, type and dosage of neuroleptic, and extrapyramidal prophylaxis indicated that inpatients with AIDS were 7 times more likely to develop extrapyramidal syndromes (EPS) from neuroleptics than the comparison group of medically ill inpatients. Possible neuroanatomic, neuropathologic, and neurochemical reasons for the vulnerability of patients with AIDS to EPS are reviewed.

(The Journal of Neuropsychiatry and Clinical Neurosciences 1997; 9:579–583)

Patients with AIDS appear to be especially susceptible to the extrapyramidal side effects (EPS) of neuroleptics[1,2] and to neuroleptic malignant syndrome (NMS).[3–7] However, these patients are prone to agitation and delirium by virtue of their treatment with multiple medications, the predilection of the human immunodeficiency virus (HIV) for the central nervous system, and the predisposition to various opportunistic infections.[8] Thus, management of behavioral manifestations of AIDS patients is problematic.

In 1991, Hriso et al.[9] retrospectively reviewed the charts of 31 patients with acquired immunodeficiency syndrome (AIDS) and 32 patients with medical illnesses and found that the likelihood of developing EPS was 2.4 times higher in the AIDS group, although this difference did not reach statistical significance. The authors suggest that neuroleptics should be used cautiously and in lower doses in AIDS patients because they are more sensitive than non-AIDS patients to the dopamine-blocking effects of these agents. Ayd[10] also recommends using low doses of neuroleptics in the AIDS population because of the higher sensitivity of these patients to neuroleptic-induced EPS. Sewell et al.[11] performed a rater-blinded clinical trial of haloperidol and thioridazine in 13 patients with AIDS and new onset of psychosis. Even with a low mean daily dose of 124 mg

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(chlorpromazine equivalents), 11 of the 13 patients, including everyone on haloperidol, developed EPS as determined by rating scales.

We hypothesized that patients with AIDS would be significantly more sensitive than a comparison group of medically ill inpatients to the extrapyramidal side effects of neuroleptics. In our study we conducted a retrospective review of inpatient charts to determine if AIDS patients had a statistically significant higher incidence of EPS and NMS. We also reviewed the charts to investigate the effect of dosage of neuroleptic on the incidence of EPS in our patients. In addition, we reviewed relevant neuropathological, neurophysiological, and neurochemical literature on AIDS patients in order to identify factors that may increase their susceptibility to the extrapyramidal side effects of neuroleptics.

METHODS

We retrospectively examined the occurrence of EPS and NMS in hospitalized patients in the adult medical and surgical wards of our 1,200-bed hospital complex over an arbitrarily chosen 3-month period. All patients were admitted with a primary medical or surgical diagnosis. Psychiatric consults were called by the primary physicians when indicated. Reasons for consultation were generally for the assessment and management of agitation and psychosis or for the evaluation of competence. The consultation-liaison (C-L) team (six psychiatrists, three psychiatric residents, and one psychiatric fellow) then evaluated these patients.

We reviewed the notes by the psychiatric consultant and the medical chart notes for all patients seen by our C-L team from December 1, 1990, through February 28, 1991. All patients in the AIDS group met the Centers for Disease Control surveillance case definition for AIDS.[12]

As a comparison group, we chose an age-matched population of patients with a primary medical or surgical diagnosis who were seen by the C-L team during the same period. These patients were placed on neuroleptic treatment by the C-L service, usually for control of agitation. None of these patients had had testing for HIV, since there was no clinical indication to do so.

In our study, we selected those patients who either had never been on neuroleptics, had been off neuroleptics for at least 2 months, or had had their neuroleptic dose increased within the previous week. Patients in these groups are known to be more prone to EPS and NMS due to neuroleptics.[13]

The following variables were determined from the chart review: age, gender, computed tomography (CT) scan of the brain, extrapyramidal prophylaxis, neuroleptic type, route, dose of neuroleptics, changes in dosage or route of administration of neuroleptic, use of adjunctive neuroleptics such as metoclopramide, and the presence of EPS and NMS.

Extrapyramidal syndrome (other than NMS) was diagnosed when tremor, rigidity, bradykinesia, dystonia, or akathisia began after a subject was started on neuroleptics and either resolved or improved upon neuroleptic discontinuation or upon commencing antiparkinsonian medication.[13] NMS was diagnosed in the presence of at least two major criteria (fever, rigidity, elevated creatine phosphokinase level) and four minor criteria (tachycardia, tachypnea, abnormal blood pressure, altered consciousness, diaphoresis, leukocytosis).[14]

Our C-L psychiatric team routinely checked patients started on neuroleptics for any evidence of EPS or NMS and noted this in progress notes. No rating scales were used. In our chart review, the presence of EPS and NMS was determined by the psychiatrists' notes. The absence of any record of EPS was taken to indicate absence of EPS.

The data were analyzed by the use of SPSS (version 6) software. Demographic variables were evaluated with the Student's two-tailed *t*-test and the chi-square test, as appropriate. For the purpose of analysis, we included NMS as a variant of EPS.[15] The outcome variable of EPS was evaluated as a categorical variable by using logistic regression analysis in patients with AIDS and the comparison group both before and after adjusting for age, gender, drug type, dosage, and EPS prophylaxis. All drug doses were converted into chlorpromazine equivalents by using standard conversion algorithms.[13] Patients who were on time-contingent intravenous infusions were estimated to have had the full dose prescribed over a 24-hour period, although, in most circumstances, dosages were less than this because medication was withheld when the patient was sedated. Accurate estimation of dosage received through this method would have required measurement of the fluid remaining in the intravenous bag, a cumbersome procedure on wards. In cases where a patient was exposed to more than one dose and route of medication, the highest dose was used in the analysis, even if this was not the dose the subject was on when EPS was noted.

RESULTS

Data on subject and neuroleptic characteristics among groups are presented in Table 1. There were 29 patients with AIDS (20 men, 9 women) and 24 patients in the comparison group (12 men, 12 women; $P = 0.16$). Patients with AIDS were older than those in the comparison group (mean age $\pm$ SD = 34.3 $\pm$ 5.1 vs.

TABLE 1. Characteristics of neuroleptic variables in patients with AIDS and comparison group

Variable	AIDS Patients		Comparison Group		
	n	EPS/NMS[a]	*n*	EPS/NMS[a]	*P*
Drug type					=0.46
Chlorpromazine	5	2	7	0	
Thioridazine	3	0	1	0	
Haloperidol	21	10	16	2	
Drug route					=0.28
Oral	18	8	16	1	
Intravenous	6	2	2	0	
Combination[b]	5	2	6	1	
Dosage change					=0.14
New	22	9	16	2	
Rechallenge	2	1	5	0	
Increase	5	3	3	0	
EPS prophylaxis					<0.01*
Benztropine	2	0	6	0	
Amantadine	15	8	3	0	
Both	1	0	0	0	
None	11	4	15	2	

Note: AIDS = acquired immunodeficiency syndrome; EPS = extrapyramidal syndrome; NMS = neuroleptic malignant syndrome.

[a]Number of subjects who developed EPS or NMS.

[b]Subjects on combination route of medication received parenteral and oral neuroleptics either simultaneously or at separate times.

*Statistically significant.

29.9 ± 7.7 years; $F = 6.07$, df = 1, $P = 0.02$). The neuroleptics used were haloperidol, chlorpromazine, and thioridazine; haloperidol was the neuroleptic most frequently used (72.4% in AIDS patients; 66.7% in comparison group patients). The route of drug administration was most commonly oral, with the intravenous route being second. There was no difference in the mean neuroleptic dosage (chlorpromazine equivalent) between AIDS patients and the comparison group (1,550 ± 2,569 mg vs. 1,400 ± 1,990 mg; $F = 0.05$, df = 1, $P = 0.82$). Patients with AIDS were significantly more likely than the patients in the comparison group to be on prophylaxis against EPS (AIDS patients, 62.0%; comparison group, 37.5%; $P < 0.01$). AIDS patients were more often on amantadine (patients, 51.7%; comparison group, 12.5%) rather than benztropine for EPS prophylaxis.

Of all the patients, 72% (38/53) were newly started on neuroleptics, 13% were restarted on neuroleptics after at least 2 months off neuroleptics (7/53), and 15% had had a neuroleptic dosage increase in the prior week (8/53). There was no significant difference in exposure patterns between the patients with AIDS and the comparison group ($P = 0.14$). None of the patients had received adjunctive neuroleptics.

The prevalence of abnormal computed tomography (CT) scans was significantly greater among AIDS patients ($P = 0.004$). Of the 29 patients with AIDS, 25 had CT scans: 5 were normal scans, 16 showed atrophy, and 4 showed focal lesions. Of the 24 patients in the comparison group, 9 had CT scans: 5 were normal scans and 4 showed focal lesions. However, the presence of abnormalities on the CT scans did not predict the development of EPS or NMS ($P = 0.92$). Among patients with AIDS, the focal CT findings were as follows: left hemisphere encephalomalacia, right temporal toxoplasmosis, diffuse toxoplasmosis, and left internal capsule hemorrhage. Among the patients in the comparison group who had lesions, 1 had a right frontal contusion, 1 had a right frontal hematoma, 1 had a right basal ganglia infarction, and 1 showed bilateral chronic subdural hematomas and left subfrontal contusion.

We found the likelihood of developing of EPS or NMS among AIDS patients was significantly higher than among patients in the comparison group (odds ratio [OR] = 7.76; 95% confidence interval [CI] = 1.52–39.65). After adjusting for age and prophylaxis, we found that AIDS patients continued to have significantly more EPS than patients in the comparison group (OR = 9.99; 95% CI = 1.32–75.19). We then controlled additionally, separately for gender, type, dosage, route of neuroleptic, and type of exposure to neuroleptic (new exposure, recent increase in dosage, or rechallenge after noncompliance with neuroleptic for at least a 2-month period) and found that the increased risk for EPS among AIDS patients remained at least sevenfold. We found that there was no correlation between the neuroleptic dosage and the development of EPS and NMS ($P = 0.93$). NMS occurred in 2 (male) AIDS patients, both on prophylactic amantadine. One of these 2 patients had no side effects on 3,000 mg (chlorpromazine equivalents) of intravenous haloperidol but developed NMS upon being switched to oral haloperidol (937 mg chlorpromazine equivalents per day). The other instance of NMS was in an AIDS patient on 250 mg per day of chlorpromazine.

Within the AIDS group, 18 of the patients (62%) were on EPS prophylaxis, with 15 of the 18 being on amantadine alone. Eight of the AIDS patients on amantadine and 4 patients without prophylaxis developed EPS or NMS. In the comparison group, 9 of the patients (37.5%) were on EPS prophylaxis, and none of these patients developed EPS or NMS. Two of the 15 patients in the comparison group who were not on prophylaxis developed EPS.

DISCUSSION

In our retrospective chart analysis of inpatients with AIDS and a medically ill comparison group, we found

that patients with AIDS were significantly more susceptible to neuroleptic-induced EPS and NMS. There was at least a sevenfold increased risk for EPS and NMS among AIDS patients, and this difference was maintained after adjusting for possible confounding variables. Our data support the results of the studies by Hriso et al.[9] and Sewell et al.[11] as well as numerous anecdotal reports suggesting increased susceptibility of AIDS patients to the extrapyramidal side effects of neuroleptics. In our review, approximately 45% of the AIDS patients on prophylactic amantadine or benztropine went on to develop EPS or NMS. Furthermore, neuroleptic dose did not appear to increase the risk for EPS in patients.

There may be several reasons for the increased susceptibility of patients with AIDS to neuroleptics. Data from autopsy, neurochemical, neurophysiological, and neuroimaging studies suggest that the HIV virus has a predilection for the basal ganglia. Arendt et al.[16] performed motor tests in 50 HIV-infected patients without any clinically apparent neurologic disease and found the morphology of the test pattern to be similar to that of patients with basal ganglia pathology such as that in Parkinson's disease.

Kure and co-workers[17,18] examined the prevalence and distribution of the HIV-1 antigen (gp41) in 100 brains of HIV-positive adults and found gp41 immunoreactivity in 78% of them. Frequent gp41 immunoreactivity, especially in the basal ganglia area, was found. The gp41-positive cells (macrophages and microglia) characteristically were most numerous in the medial section of the globus pallidus and the substantia nigra of the basal ganglia. Other areas were progressively less likely to be involved, the cortex being the area with the least number of gp41-positive cells. Preferential involvement of the deep gray matter by the HIV virus has been documented on at least one other autopsy series.[19]

Magnetoelectrical stimulation of the cortex in 42 patients with HIV infection demonstrated subclinical involvement of the extrapyramidal circuits even in the absence of clinical neurologic involvement.[20] Patients with AIDS show regional hypermetabolism in the basal ganglia on positron emission tomography, suggesting differential involvement of the basal ganglia by the HIV virus.[21] Quantitative magnetic resonance imaging of patients with HIV dementia shows smaller basal ganglia volume when compared with nondemented HIV patients and with normal control subjects.[22] Finally, cerebrospinal fluid dopamine levels are reduced in HIV patients with and without neurological impairment when compared with control subjects.[23]

Thus, it appears that, given the template of previously impaired basal ganglia structure and function in patients with HIV infection with or without AIDS, the addition of typical neuroleptics may shift the precarious balance in the direction of extrapyramidal side effects. This poses a difficult predicament for the treating physician akin to the problem facing physicians in treating psychosis in Parkinson's disease.

Patients with HIV infection and AIDS are more likely than patients without HIV infection to have psychosis and agitation.[11] AIDS patients have a high incidence of dementia[24,25] and are on multiple medications that are known to induce psychosis and delirium.[26] However, treatment of these symptoms with typical neuroleptics may cause side effects such as EPS and NMS. Reduced doses of neuroleptics do not appear to decrease this risk,[11] and in our study we found no correlation between drug dosage and incidence of EPS. One short-term option might be the use of benzodiazepines instead of neuroleptics[27] in the acute management of AIDS patients with delirium and psychosis. Fernandez and Levy[28] report the successful use of molindone in the treatment of delirium and psychosis in 4 AIDS patients who had been refractory to conventional neuroleptics and had developed EPS on these neuroleptics. Use of intravenous neuroleptics has been shown to be associated with a reduced incidence of EPS and may be another treatment option to be explored.[29]

Our study has several limitations. We did not use any clinical scales to rate EPS and probably underestimated the true incidence of EPS in our subjects; however, because of the retrospective nature of our review, any errors in estimation of EPS were probably comparable across both the AIDS and comparison groups. Our patients had a variable prior exposure to neuroleptics. Although the majority were neuroleptic naive, it would have been ideal to evaluate only neuroleptic-naive patients; however, there was no significant difference in neuroleptic exposure patterns between our AIDS patients and the patients in the comparison group. In our C-L practice, we used very large total doses of neuroleptics in our patient population; however, there was no correlation between dosage and EPS.

Our study was also unusual in that a large number of patients in both groups were on medication for the prophylaxis of EPS. None of the patients in our comparison group had had HIV testing, and it can be argued that some of them may have been HIV-infected without yet having progressed to the full clinical AIDS spectrum; however, such a situation would have only strengthened our results. In those patients who had received intravenous infusions of neuroleptics, we used the prescribed dose in our statistical analysis (not the actual dosage administered, which was often somewhat less because infusions were withheld when a patient was completely sedated); however, any bias secondary to this is applicable to both the AIDS patient group and the

comparison group, since we used the same method for both groups. Finally, because of the preexisting notion that persons with AIDS were more susceptible to EPS, clinicians may have been more likely to diagnose it in these patients.

Despite these limitations, we feel that our retrospective chart review supports prior studies suggesting a vulnerability to the extrapyramidal side effects of neuroleptics in patients with AIDS. Better EPS prophylactic measures and alternative means of control of agitation and psychosis in these patients would be worthwhile areas to explore.

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