Extrapyramidal Motor Abnormalities Associated With Late-Life Psychosis

by Michael P. Caligiuri, James B. Lohr, Diane Panton, and M. Jackuelyn Harris

Abstract

Studies of extrapyramidal motor function in patients with schizophrenia have contributed to our understanding of the phenomenology and therapeutic outcome associated with neuroleptics. An increasing body of literature suggests that extrapyramidal motor abnormalities associated with schizophrenia may be linked to the pathophysiological mechanisms responsible for schizophrenia. Similarly, it has been documented that the extrapyramidal system may be involved in motor abnormalities in patients with Alzheimer's disease (AD). The present study was undertaken to examine motor function in schizophrenia and AD patients with psychosis. Quantitative instrumental procedures were used to examine rigidity, tremor, and bradykinesia in 13 neuroleptic-naive patients with schizophrenia, 13 AD patients with psychosis, and 26 age-comparable controls. Both schizophrenia and AD patients had significantly higher tremor and rigidity scores than did normal subjects. This comparative study of schizophrenia and AD patients with psychosis suggests that the effect of dementia in patients with psychosis is to prolong movement time, whereas abnormal parkinsonian postural tremor tends to be associated with psychosis in the absence of dementia.

Previous studies of motor function in neuropsychiatric patients have contributed to our understanding of the phenomenology and therapeutic outcome associated with neuroleptics. There is evidence from studies of neuroleptic-naive patients suggesting that parkinsonian motor disturbances may be directly related to schizophrenia. Extrapyramidal disorders such as tremor, rigidity, and akinesia were observed in many of the patients described by Kraepelin (1919/1921) in his treatise on dementia praecox. Subsequent clinical (Reiter 1926; Mettler and Crandell 1959a, 1959b) and laboratory (Caligiuri et al. 1993) investigations have found that a sizable proportion of drug-free schizophrenia patients exhibited parkinsonism. The presence of extrapyramidal involvement in patients with Alzheimer disease (AD) is well established (Mayeux et al. 1985; Ditter and Mirra 1987; Hansen et al. 1990; Tyrell et al. 1990). It remains unclear, however, whether the extrapyramidal motor disturbances found in AD are similar to those found in schizophrenia.

The presence of extrapyramidal motor signs in schizophrenia and AD patients suggests abnormal nigrostriatal dopaminergic neurotransmission. Anatomic and physiologic evidence implicating this region of the basal ganglia in schizophrenia comes from functional imaging studies (Owen et al. 1978; Wong et al. 1986) and postmortem neurochemical studies (Bird et al. 1979, 1984; Seeman et al. 1984; Bracha and Kleinman 1986). Neuropathological studies of AD have implicated the substantia nigra and substantia innominata as the subcortical sites involved in producing extrapyramidal motor...
signs (Hansen et al. 1990), whereas functional imaging studies showed abnormal activity within the putamen and caudate (Tyrrell et al. 1990) and ventricular enlargement (Burns et al. 1991) in AD patients with parkinsonism.

The neuropathological and neurochemical similarities between AD and schizophrenia patients with extrapyramidal syndromes suggest the need for closer examination of these groups. Yet because schizophrenia and AD are commonly associated with persons of disparate ages (AD patients are considerably older than schizophrenia patients in most studies), it has been difficult to attribute differences in motor function between the two groups that cannot be explained by an age factor. The degree of psychosis among schizophrenia patients may represent an important variable associated with extrapyramidal motor disturbances. Comparative studies of AD and schizophrenia patients must consider the contribution of psychosis in patients with extrapyramidal involvement. To our knowledge, previous studies examining motor function in AD and schizophrenia patients have not adequately controlled for the presence of psychosis. We hypothesized that if extrapyramidal motor involvement is a fundamental component of psychosis, older neuroleptic-naïve schizophrenia patients will not differ from psychotic AD patients on measures of extrapyramidal motor function.

**Methods**

**Subjects.** Fifty-two subjects were studied; 26 were patients with psychosis that began during late life (after age 45) and 26 were age-matched normal comparison (NC) subjects. The patients either had no past exposure to neuroleptic medication or had been neuroleptic-free for at least 10 years. Psychiatric diagnoses were made according to DSM-III-R criteria (American Psychiatric Association 1987) by board-certified staff psychiatrists (M.J.H. and D.P.). Thirteen patients were diagnosed as having either schizophrenia or delusional disorders, and 13 patients were diagnosed as having probable AD. All patients were candidates for neuroleptic treatment and were examined before beginning treatment. All AD patients exhibited at least mild psychosis as judged by clinical assessment (see below).

The mean age of the schizophrenia patients was 60.7 (standard deviation [SD] = 8.8) years; that of the AD patients was 77.7 (±10.5) years. Because schizophrenia patients were significantly younger than AD patients (t = 4.28, p < 0.01), normative data from an ongoing data base were selected to attain age comparability for the two groups. NC subjects had been recruited over the previous 4 years from among San Diego Department of Veterans Affairs Medical Center volunteers, staff, patients' spouses, and conservators. All NC subjects were over the age of 45 years. Data from some of the NC subjects and schizophrenia patients have been reported previously in studies validating the quantitative procedures (Caligiuri et al. 1993; Caligiuri and Galasko 1992).

**Procedures.** All subjects underwent laboratory assessment for parkinsonism. Patients received the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962) to rate the overall severity of psychopathology and the positive and negative symptom severity on the basis of subscale scores (Jeste et al. 1984; McGlashan and Fenton 1992). Positive symptoms included disorganized speech, suspiciousness, hallucinatory behavior, hallucinatory statements, and unusual thought content. Negative symptoms included emotional withdrawal, motor retardation, and blunted affect. Group characteristics and mean BPRS scores for the three groups are shown in table 1. Group comparisons for the total and for positive and negative subscale scores revealed no significant differences.

Parkinsonism was examined with an established instrumental procedure for quantifying rigidity, postural tremor, and aspects of bradykinesia. Quantitative motor assessment offers the advantage of sensitivity to mild abnormalities. With these laboratory procedures, relatively mild parkinsonian signs, which would remain undetected by an observer, can be identified on the basis of statistical criteria. Electromechanical devices have been shown to be sensitive to mild rigidity and parkinsonian tremor, making them particularly useful in studies of psychopathology and aging.

Hand rigidity was quantified by means of a device that transduces displacement and force simultaneously (Caligiuri and Galasko 1992). Stiffness slope coefficients were obtained from resting and activated conditions. The ratio of the activated coefficient to the resting coefficient was used as the index to score severity of parkinsonian rigidity. Postural tremor was quantified using a hand force transducer. We have previously demonstrated that sustained force is a sensitive procedure for quantifying postural tremor phenomena.
Table 1. Demographic characteristics and BPRS scores for the schizophrenia and Alzheimer's disease patient groups and a group of normal comparison subjects

<table>
<thead>
<tr>
<th>Group</th>
<th>Sex (Male:Female)</th>
<th>Age (years) (Mean ± SD)</th>
<th>BPRS scores (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>13:10:3</td>
<td>60.7 ± 8.8</td>
<td>57.7 ± 15.0</td>
</tr>
<tr>
<td>Alzheimer's</td>
<td>12:1</td>
<td>77.7 ± 10.51</td>
<td>53.4 ± 10.5</td>
</tr>
<tr>
<td>Normal</td>
<td>11:15</td>
<td>67.1 ± 10.1</td>
<td>11.3 ± 4.6</td>
</tr>
</tbody>
</table>

Note.—BPRS = Brief Psychiatric Rating Scale (Overall and Gorham 1962); SD = standard deviation.

1Significantly higher than the ages of both other groups as determined by analysis of variance (F = 9.91, p < 0.001).

associated with parkinsonism (Caligiuri et al. 1991). Analysis consists of applying Fourier methods to the force signal and obtaining the peak amplitude of the power spectra within the 3- to 7-hertz (Hz) frequency band. The movement time component of parkinsonian bradykinesia was quantified by measuring the time, in milliseconds, associated with rapid alternating flexion and extension movements of the wrist.

Data derived from the instrumental procedures were subjected to statistical analyses to examine their concurrent validity with traditional clinical rating scales, their test-retest reliability under stable drug treatment regimens, and their sensitivity to the presence of pathology. Previously published validity, reliability, and sensitivity data demonstrated high concurrent validity (r = 0.85), test-retest reliability (r = 0.80-0.97), and more than 89 percent sensitivity to the presence of clinically observable motor pathology (Caligiuri et al. 1991; Caligiuri and Galasko 1992). Also, analyses of the interrelationships among the three instrumental procedures indicated that these three procedures yield data that reflect independent motor functions.

Data Reduction. Individual motor scores for each hand were obtained and the more severe score for rigidity and postural tremor was used for statistical analyses. For movement time, the faster of the two times, usually reflecting hand dominance, was used for statistical analyses. An analysis of variance (ANOVA) was used to examine group differences for tremor, rigidity, and bradykinesia, and, where appropriate, t tests were used for specific post hoc comparisons. Individual scores exceeding two SDs of the normal comparison mean for each motor measure were considered abnormal. Chi-square analyses were used to evaluate the significance of the proportions of schizophrenia and AD patients who exhibited abnormal motor function on these tests. Pearson correlational analyses were conducted to examine the relationships between motor function and psychiatric profiles (based on BPRS subscale scores).

Results

Extrapyramidal Motor Findings. The ANOVA revealed a significant main effect for group for parkinsonian tremor (F = 7.75, p < 0.01), rigidity (F = 5.39, p < 0.01), and movement time (F = 10.84, p < 0.001). Table 2 shows the results of the quantitative motor testing and post hoc analyses for specific comparisons for the schizophrenia and NC subjects. Significant differences were observed between NC and schizophrenia subjects for postural tremor (t = 5.62, p < 0.01) and rigidity (t = 2.71, p < 0.05) but not for movement time (t = 0.23, p < 0.10). Analysis of individual scores revealed that 46 percent of the schizophrenia patients exhibited elevated postural tremor amplitudes and 46 percent exhibited increased rigidity, whereas only 8 percent exhibited prolonged movement times. Thus, schizophrenia patients as a group exhibited significantly elevated tremor amplitudes and greater activated rigidity in the absence of bradykinesia.

Schizophrenia patients were compared with AD patients to examine the added effects of demen- tia on motor function. Table 2 shows the descriptive statistics. Significant differences were ob- served between schizophrenia and AD patients for movement time only (t = 2.69, p < 0.01); schizo- phrenia and AD patients exhibited similar degrees of postural tremor.
Table 2. Results of quantitative motor testing: Tremor, rigidity, and bradykinesia (movement time) for schizophrenia, Alzheimer's disease, and normal healthy comparison subjects

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Tremor (decibels) (Mean ± SD)</th>
<th>Rigidity (%) (Mean ± SD)</th>
<th>Movement time (ms) (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
<td>13</td>
<td>54.4 ± 20.4</td>
<td>54.9 ± 19.9</td>
<td>221.5 ± 66.2</td>
</tr>
<tr>
<td>Alzheimer's</td>
<td>13</td>
<td>53.5 ± 9.1</td>
<td>61.2 ± 36.2</td>
<td>385.2 ± 198.9</td>
</tr>
<tr>
<td>Normal</td>
<td>26</td>
<td>40.1 ± 8.62</td>
<td>38.8 ± 7.82</td>
<td>216.4 ± 48.02</td>
</tr>
</tbody>
</table>

1Significantly higher than schizophrenia and normal subject groups as determined by analysis of variance (ANOVA) (p < 0.01).
2Significantly lower than the schizophrenia and Alzheimer's patient groups as determined by ANOVA (p < 0.01).

(t = 0.14, p > 0.10) and rigidity (t = 0.54, p > 0.10). Analysis of individual scores revealed that 23 percent of the AD patients exhibited elevated postural tremor amplitudes, 38 percent exhibited increased rigidity, and as many as 62 percent exhibited prolonged movement times. Chi-square statistics revealed that although twice as many schizophrenia patients as AD patients exhibited abnormal tremor amplitude, this difference was not significant. However, the difference in the proportions of schizophrenia and AD patients exhibiting prolonged movement times was significant ($x^2 = 8.32$, $p < 0.01$). Comparable proportions of schizophrenia and AD patients exhibited abnormal rigidity. The proportions of schizophrenia and AD patients exhibiting abnormal tremor, rigidity, and bradykinesia are shown in figure 1. These proportions suggest that the effect of dementia in patients with psychosis was to prolong movement time, whereas abnormal parkinsonian postural tremor tended to be associated with psychosis in the absence of dementia.

Figure 1. The proportions of schizophrenia (SZ) and Alzheimer's disease (AD) patients exhibiting abnormal rigidity, tremor amplitudes, and movement (M.) times

Abnormality was operationally defined as a score greater than two standard deviations above the normal mean. P value indicates results of posthoc specific comparison t test.
each of the three subject groups. Thus, the significant patient subgroup differences in motor function could not be explained on the basis of age alone, despite the significant difference in age between the AD and schizophrenia patients.

Discussion

The present study represents one of the first quantitative studies of extrapyramidal motor function in older neuroleptic-naive neuropsychiatric patients. We hypothesized that schizophrenia patients would not differ from the AD patients with psychosis on instrumental measures of extrapyramidal motor dysfunction. This hypothesis was based on clinical observations that some untreated schizophrenia patients exhibit parkinsonism and that there exists a subgroup of AD patients with parkinsonism for whom the suspected neuropathological findings resemble those of Parkinson’s disease. In the present study, schizophrenia and AD patients exhibited similar degrees of severity of tremor and rigidity, whereas AD patients exhibited more severe bradykinesia than did schizophrenia patients. The finding that more schizophrenia patients than AD patients exhibited postural tremor is consistent with previous studies in our laboratory on schizophrenia (Caligiuri et al. 1993) and with the findings of others who have demonstrated that tremor is relatively infrequent in AD (Mayeux et al. 1985; Tyrell et al. 1990; Burns et al. 1991).

Our findings on the relationship between motor function and psychopathology suggest a positive association between severity of rigidity and severity of positive symptom subscale scores on the BPRS for the schizophrenia patients. We found an association between bradykinesia and negative symptom subscale scores for the AD patients but no relationship between parkinsonism and negative symptoms among the schizophrenia or AD patients. The absence of a relationship between parkinsonism and negative symptoms for the schizophrenia patients disagrees with the results of previous studies of medicated schizophrenia patients (Andreasen 1985; Sandyk and Kay 1990). A number of methodological differences between this and previous studies may explain this discrepancy. First, we studied neuroleptic-naive patients, whereas the patients in previous studies were generally treated with neuroleptics, which could alter the relationship between parkinsonism and psychopathology. Second, we studied older schizophrenia patients exclusively, whereas previous notions of the relationship between negative symptoms and parkinsonism were formulated on the basis of data from younger schizophrenia patients. Third, our selection of the BPRS to rate negative symptoms may have caused us to underestimate the severity of pathology. Finally, our instrumental measures of extrapyramidal motor function may have been overinclusive compared with clinical ratings. It is possible that the relationship between negative symptoms and parkinsonism is valid only in the presence of overt motor signs.

This comparative study of schizophrenia and AD patients suggested that the effect of dementia in patients with psychosis was to prolong movement time, whereas abnormal parkinsonian postural tremor tended to be associated with psychosis in the absence of dementia. Older schizophrenia patients were more likely to exhibit tremor than bradykinesia, whereas AD patients were more likely to exhibit bradykinesia than tremor. Tremor is thought to be a relatively uncommon feature associated with AD (Mayeux et al. 1985; Ditter and Mirra 1987; Hansen et al. 1990; Tyrell et al. 1990). Our finding that only 23 percent of the AD patients exhibited parkinsonian postural tremor is consistent with this notion; however, the finding that the group mean tremor amplitude was significantly higher than our age-comparable control sample suggests that the presence of psychosis may have had a marked effect on the severity of tremor. The presence of tremor in approximately one-half of the neuroleptic-naive schizophrenia patients, together with the finding that schizophrenia and AD patients exhibited similar mean tremor amplitude, supports this hypothesis.

An examination of the pathophysiology of tremor and bradykinesia may enhance our understanding of potential anatomic and neuropharmacologic mechanisms that may distinguish schizophrenia from AD. According to DeLong and Georgopoulos (1981), parkinsonian motor signs may be dichotomized according to pathophysiology. Animal experimentation has shown that rigidity and bradykinesia result largely from damage to pallidal outflow circuits (DeLong 1990), whereas parkinsonian resting and postural tremor require the additional involvement of several structures within the basal ganglia, including the substantia nigra, the ventral tegmentum, and probably the red nucleus (Poirier et al. 1975). Pharmacologic findings support a similar dichot-
tive to bradykinesia among older neuroleptic-naive schizophrenia patients may indicate abnormal dopaminergic neurotransmission throughout the basal ganglia, particularly within the putamen, and the tegmental area. The observations that AD patients exhibited bradykinesia as their primary parkinsonian sign suggests that the involvement of dopamine neurotransmission may be restricted to fewer basal ganglia regions in AD patients than in schizophrenia patients. We emphasize that this discussion of anatomic mechanisms is based on a relatively small sample of patients and must be considered highly speculative. Confirmation of these ideas awaits further systematic biochemical and high-resolution imaging studies. Moreover, further study is necessary to elucidate the particular roles of dementia and psychosis in patients who present with extrapyramidal motor findings. A systematic study of AD patients with and without psychosis is necessary. Finally, studies of extrapyramidal motor function in patients with mood disorders with and without psychosis will enhance our general understanding of the relationship between psychopathology and extrapyramidal movement disorders.

References


DeLong, M.R., and Georgopoulos, A.P. Motor functions of the basal


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Announcement
The Western Psychiatric Institute and Clinic of the University of Pittsburgh Medical Center is hosting the First Conference on Bipolar Disorder to be held at the University of Pittsburgh, Pittsburgh, Pennsylvania, June 23–24, 1994. The Conference will present the most current information on treatment and modalities, both biological and psychotherapeutic, for the acute and maintenance treatment of bipolar disorders. Panel sessions will be available to answer questions and promote discussion from the audiences. Poster presentations will be displayed on June 23. The Conference will be broken into four sessions: Neurobiology and pathophysiology, vulnerability factors: psychobiology and stress, epidemiology and clinical course, and treatment.

For further information about the Conference, please contact:

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