Neurological Abnormalities in Schizophrenic Patients and Their Siblings

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Objective: The aim of this study was to investigate the prevalence and type of neurological abnormalities in schizophrenic patients and their nonpsychotic siblings. Method: A comprehensive neurological assessment, including evaluation of both hard and soft signs, was performed for 60 schizophrenic patients, 21 siblings, and 75 normal comparison subjects. Results: None of the comparison subjects scored higher than 6 on the neurological assessment scale, but a score of 7 or higher was given to 67% of patients and 19% of siblings. Both patients and siblings scored significantly higher than comparison subjects on total neurological abnormalities, hard signs, soft signs, primitive reflexes, integrative sensory functions, and motor functions. The most conspicuous abnormalities were motor coordination problems and involuntary movements in the patients and cranial nerve deviations and mirror movements in their siblings. Levels of neurological abnormality were positively correlated within patient-sibling pairs. The total battery and hard signs best discriminated patients from comparison subjects. Conclusions: High levels of neurological abnormality characterize both schizophrenic patients and their siblings. The constellation of abnormalities and absence of overt psychopathology in siblings may represent the mildest form of disturbance within the schizophrenia spectrum. Levels of neurological abnormality covary positively in patients and siblings within the same family, suggesting common genetic and/or environmental pathogenic factors. An extended assessment battery provides optimal discrimination of patients from normal subjects, and hard signs are more differentially associated with schizophrenia than are soft signs. The neurological abnormality has no consistent localizing profile, and nearly all functional domains are involved.

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for abnormality (1), while others either have defined neurological abnormality as the presence of deviation on any item (9, 14, 15) or have used a predetermined arbitrary cutoff (6).

Third, a major unresolved conceptual issue is the classification, prevalence, and meaning of "soft" and "hard" neurological signs. There is a lack of agreement as to whether certain neurological abnormalities represent soft signs or hard signs. By definition, soft signs are neurological abnormalities that are not readily localizable to a specific brain region, while hard signs provide some indication of the underlying brain systems or regions that are affected (1). The early studies in schizophrenia focused on both types of abnormalities, but more recent studies have come to focus on soft signs, possibly because they are expected to have a higher than normal frequency in the siblings of the patients. On the other hand, Woods et al. (7) argued that hard signs are more reliable and "etiologically relevant" than soft signs, as the former are more specific and less likely to be consequences of medication. Inclusion of both hard and soft items in the same study of patients, their nonpsychotic siblings, and normal comparison subjects might shed more light on their relative prevalence and discriminating ability across different groups.

Fourth, the possible lateralization of neurological abnormalities in schizophrenia is unresolved. In two studies (7, 8) right-sided sensory errors were more common than left-sided errors, but these studies used a sensory battery consisting of only two items.

Fifth, the nature of the underlying neuropathology remains unclear. Basic sensory and motor mechanisms appear not to be generally disturbed in schizophrenia, while higher-order functional areas, such as integrative sensory function, motor coordination, and the sequencing of motor actions, appear to be impaired. Some authors have suggested that specific subcortical structures, such as the basal ganglia and brainstem or the limbic system, might be involved (2). Further investigation of the functional domains implicated by the neurological abnormalities associated with schizophrenia might increase our understanding of the neuropathological processes in schizophrenia.

Last, the etiology of the neurological abnormalities associated with schizophrenia remains unclear. The investigation of familiarity based on nonpsychotic siblings may provide information concerning whether a familial component of neurological abnormality exists independent of overt psychopathology and its various consequences (including both the disease process and treatment). Siblings are an especially interesting group as they share much of the patients' early environment. Investigation of neurological abnormalities in nonpsychotic siblings and, especially, the similarity of neurological abnormality levels within the same family may further clarify the genetic and/or early environmental contributions to neurological abnormalities.

These issues were addressed as a part of a multifaceted study of schizophrenia in Malmö, Sweden, in which etiological factors and signs of prenatal dysmorphogenesis were explored in relation to neurological and neuropsychological abnormalities. The purpose of the current study was to investigate the prevalence and nature of neurological abnormalities in a group of schizophrenic patients, their nonpsychotic siblings, and a group of normal comparison subjects by using an extended, composite assessment battery. The following hypotheses were tested: 1) neurological abnormality is more common in schizophrenic patients than in their nonpsychotic siblings and normal comparison subjects and also is more common in the siblings than in comparison subjects; 2) there is a positive correlation between the degrees of neurological abnormality in the patient and his or her sibling; and 3) right-sided neurological abnormality is more common than left-sided abnormality, especially in the integrative sensory domain (7, 8). Furthermore, special attention was directed to the influence of varying cutoff scores on the prevalence of neurological abnormality in the subject groups.

METHOD

Subjects

The subjects were 60 patients with schizophrenia, 21 healthy siblings from the families of 21 of these patients, and 75 normal comparison subjects. The 60 patients (44 men and 16 women) were recruited from the centralized psychiatric facilities in Malmö, Sweden, if they fulfilled the following criteria: 1) DSM-III-R diagnosis of schizophrenia based on psychiatric case records; 2) birth in Scandinavia during 1941 or later; 3) absence of psychoactive substance abuse as defined by DSM-III-R criteria; and 4) no history of head trauma, major neurological disorder, or somatic disorder with neurological components (e.g., multiple sclerosis). The mean duration of illness since the first psychotic episode was 14.8 years (SD = 7.2, range = 1–29). The mean age at the time of the study was 38.2 years (range = 19–55 years). The mean kappa coefficient of agreement on the DSM-III-R diagnosis of 11 other patients independently diagnosed before the study by four experienced psychiatrists (including B.I.) was 0.77 (range = 0.75–0.88).

The project's goal was to study one nonpsychotic sibling for each patient. Siblings were to be excluded if they had a history of 1) psychotic or affective disorder; 2) head trauma, neurological disorder, or somatic disorder with neurological components; or 3) psychoactive substance abuse according to DSM-III-R criteria. Within each family, an attempt was made to involve the nonpsychotic sibling of the same sex who was nearest in age to the patient. Twenty patients had no nonpsychotic siblings available for study, while the siblings of nine other patients declined to participate and 10 did not respond to the invitation. In the remaining 21 families, one sibling per family agreed to participate, and each was screened through interviews regarding the exclusion criteria (no siblings were excluded). The participating siblings were interviewed with the Structured Clinical Interview for DSM-III-R Personality Disorders (SCID-II) (20) to determine the presence of schizotypal personality disorder. While a few siblings had isolated symptoms of that disorder, no sibling fulfilled the complete DSM-III-R criteria for the disorder. The mean age of the participating siblings was 37.9 years (range = 17–51).

The normal comparison subjects who were selected 1) were similar to the patient group with respect to educational level, age, and gender ratio but 2) did not themselves have a psychosis, a schizophrenia-related personality disorder, or a family history of mental disorder. Thus, 75 comparison subjects (59 men, 16 women) were recruited from among several occupational categories (i.e., firefighters, laboratory assistant trainees, and hospital service personnel other than those in the psychiatric facilities). The exclusion criteria were the same as criteria 1–3 for the siblings plus 4) a history of psychosis or affective disorder in a first- or second-degree biological relative and 5) the presence of schizotypal personality dis-
order according to the SCID-II. Only one comparison subject was excluded on the basis of these exclusion criteria (because of treatment for affective disorder), and no potential subject fulfilled exclusion criterion 4. While a number of comparison subjects showed signs of schizophrenia, no subject fulfilled the complete DSM-III-R criteria for the disorder.

The mean age of the 75 participating normal comparison subjects was 35.9 years (range=20–54). There was no significant difference in age between the schizophrenic, sibling, and normal comparison groups in current age or educational level.

After complete description of the study to the subjects, written informed consent was obtained.

### Neurological Examination

All examinations were performed by one physician (B.I.). An extended, standardized assessment instrument (consisting of 44 items, 26 of which permitted bilateral assessment) was used. This included 21 items from Woods et al. (7), all 19 items (seven of which permitted bilateral assessment) of Rossi et al. (8), two items (right-left confusion and finger/thumb opposition) from Quitkin et al. (5), and two items (finger-nose test and crossing body midline) from McNeil et al. (21).

The items used by Rossi et al. were operationally regarded as representing hard signs, while the remaining items were regarded as representing soft signs. The neurological examination encompassed the following functional domains.

- Motor functions. The assessment covered 1) motor coordination problems (e.g., dysdiadochokinesia), 2) involuntary movements (e.g., choreiform movements), 3) mirror movements, 4) deviant muscle power, 5) deviant muscle tone, and 6) cranial nerve deviations (oculogyric, trigeminal, and facial).
- Sensory functions. Problems in this domain involved abnormalities in 1) integrative sensory function (e.g., astereognosis) and 2) central sensory function (unilateral sensory loss).
- Reflexes. These disorders related to 1) primitive reflexes (e.g., snout reflex) and 2) deep tendon reflexes (unilateral reflex hyperactivity).
- Cognitive functions. This domain included such items as imaginary acts, two-objects test, and right-left confusion.

### Statistical Analysis

Owing to the distribution of scores, group comparisons of the neurological abnormality scores for the three groups were done by the Mann-Whitney U test, while pairwise comparison of 21 patients with their 21 siblings was done by the Wilcoxon matched-pairs signed-ranks test (22). Relative (receiver) operating characteristic curves (23) were used to describe the relationship of the specificity and sensitivity of the assessment instrument, contrasting the patients' and normal comparison subjects' scores for total neurological abnormality, soft signs, and hard signs. Statistical significance was defined as p<0.01, two-tailed.

### RESULTS

**Group Scores for Neurological Abnormalities**

Table 1 shows the total neurological abnormality scores, scores grouped according to the hard/soft dichotomy, and scores grouped according to functional domain. The scores for specific items that may be useful in the localization of neurological deficits (2) are also...
given. The distributions of the total scores for the schizophrenic, sibling, and comparison groups are shown in figure 1. The mean item score and percentage of subjects showing abnormality on each item for the three subject groups are available from the last author (T.F.M.).

All of the patients, 81% of the siblings, and 45% of the normal comparison subjects had at least one abnormal neurological sign each. The patients had a significantly higher mean score than the comparison subjects on each of the scales except the one for mirror movements (the lack of significance was due to high scores for the comparison group rather than low scores for the patient group). The siblings had significantly higher scores than the normal comparison subjects on all scales except motor coordination and mirror movements. The differences between the patients and normal comparison subjects in the total abnormality and motor function scores remained highly significant even after filtering for signs that can represent a medication effect.

Furthermore, the 21 patients with participating siblings had significantly higher scores than their own siblings for the total and filtered abnormality assessments, hard signs, soft signs, motor functions, and motor coordination. The degree of neurological abnormality tended to be familial in that there was a significant positive correlation between patients and their own siblings in the scores for motor functions ($r_s = 0.62, N = 21, p = 0.003$) and moderately high correlations for total neurological abnormality ($r_s = 0.49, N = 21, p = 0.02$) and soft signs ($r_s = 0.44, N = 21, p = 0.04$). There were no significant differences in the scores on the aforementioned measures between the patients with participating siblings and those without such siblings. The median total abnormality scores for the patients with and without siblings were 9.0 and 10.0, respectively (Mann-Whitney U test: $z = 0.73, p = 0.46, N = 60$). In contrast, neither the patients nor the siblings showed a significant difference (Wilcoxon matched-pairs signed-ranks test) between the right and left sides of the body in total neurological abnormality score (patients: $z = 0.18, p = 0.86, N = 60$; siblings: $z = 0.65, p = 0.51, N = 21$) or the integrative sensory function subscore (patients: $z = 0.17, p = 0.86, N = 60$; siblings: $z = 1.13, p = 0.27, N = 21$).

Sensitivity and Specificity

Table 2 shows the effect on the prevalence of neurological abnormality in the three subject groups when different cutoff scores for total neurological abnormality are used. At an extreme value of 100% specificity for schizophrenia (i.e., 0% of the comparison subjects with abnormality scores of $\geq 7$), neurological abnormality was found in 67% of the patients and 19% of their siblings. This frequency is at the upper end of the range given by Heinrichs and Buchanan (i.e., 50%–65%) in their overview (2). Furthermore, with a specificity of 95% for schizophrenia (i.e., 5% of comparison subjects having $\geq 5$ points), fully 82% of the patients and 38% of their siblings were categorized as neurologically abnormal.

Relative operating characteristic curves demonstrate the relationship between sensitivity and specificity at different cutoffs and are helpful in evaluating the relative discriminative properties of the total battery, hard signs, and soft signs (23). An optimally discriminative technique would be characterized by a forward-tipped L-shaped curve, showing a high level of sensitivity even at a high level of specificity. In contrast, a technique that did not discriminate between the groups would show a 45° diagonal line, with a low level of sensitivity at high specificity and specificity decreasing stepwise as sensitivity increases.

The relative operating characteristic curve for discrimination of patients from normal comparison subjects in total neurological abnormality score showed an approximation of the optimal L-shaped curve, a pattern that was similar to that for the hard signs score by itself. In contrast, the curve for soft signs indicated lower sensitivity at high

![Figure 1. Distribution of Total Neurological Abnormality Scores of Schizophrenic Patients, Nonpsychotic Siblings, and Normal Comparison Subjects](image)

TABLE 2. Effect of Different Cutoff Scores on Prevalence of Neurological Abnormalities in Schizophrenic Patients, Nonpsychotic Siblings, and Normal Comparison Subjects

<table>
<thead>
<tr>
<th>Total Score on Neurological Assessment</th>
<th>Sensitivity (rate in patients)</th>
<th>Specificity (1.00 minus rate in normal subjects)</th>
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<tr>
<td></td>
<td>N</td>
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<tr>
<td>0</td>
<td>0</td>
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<tr>
<td>≥1</td>
<td>60</td>
<td>100</td>
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<tr>
<td>≥2</td>
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<td>≥7</td>
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The results showed, as expected, that the basal neurological functions were intact, at least within the scope of the examination methods used in this study. The abnormal neurological signs were scattered over a wide range of higher functional systems and demonstrated no particular pathognomonic profile, although the subdomains of motor coordination abnormalities and involuntary movements were most prominent in the patient group, and cranial nerve deviations and mirror movements were most prominent in their siblings (table 1).

DISCUSSION

The patients showed high levels of neurological abnormality across nearly all domains, particularly motor coordination abnormalities and involuntary movements. As such, these findings add to the growing body of literature suggesting that neurological abnormalities may be generally characteristic of schizophrenia. Moreover, the differences between the patients and the comparison subjects remained even after filtering for neurological abnormality items that may represent effects of neuroleptic medication. In addition, as compared with the comparison subjects, the neuroleptic-naive siblings showed significantly higher levels of neurological abnormalities, including both soft and hard signs and, notably, involuntary movements. Taken together, these findings suggest that the neurological abnormalities found in schizophrenic patients are a genuine neurological disturbance that perhaps can be augmented by neuroleptic medication in some cases but is unlikely to be solely a toxic medication effect.

The profile of the neurological dysfunction in the siblings was somewhat different from that of the patients, as cranial nerve deviations and mirror movements were more prominent than other domains in the siblings. The high score on cranial nerve deviation was mainly due to an eye movement disturbance, i.e., nystagmus. This finding is in accordance with previous findings of disturbances in eye movements in schizophrenic patients (24). Furthermore, no sibling met the full criteria for schizotypal personality disorder, and the configuration seen in the siblings (i.e., some degree of neurological abnormality and the absence of full-syndrome schizotypal psychopathology) may well represent the mildest form of disturbance within the schizophrenia spectrum. Whether this configuration is the effect of genetic factors solely (either pathogenic or protective) or is due to a different constellation of genetic and environmental risk factors is as yet unknown and remains one of the most challenging questions for future research. Furthermore, the degree of severity of the neurological abnormality appears to be familial, suggesting the existence of some shared features in the patients and their siblings. Whether these shared features are due to genetic or environmental effects cannot be determined from the current analyses.

Regarding the localization of the neurological abnormalities, despite the use of an extensive assessment procedure, our study shows that the neurological abnormalities do not display a consistent pathognomonic profile and are not localized to a particular region. Nearly all functional domains are involved to some degree. The diversity in the type of neurological abnormality found in the patients parallels the large body of evidence emerging from recent neuroimaging studies, which suggests that a similarly widespread area of subtle brain abnormality is characteristic of schizophrenia (25). Further refinement of the neurological examination methods and combination of the neurological findings with neuropsychological and neuroimaging results in future studies may help to advance our understanding of the underlying pathophysiology of the neurological disturbance.

The present study demonstrates clearly how the apparent prevalence of neurological abnormality may be affected by both the scope of the instrument used and the choice of cutoff level for neurological abnormality. Given the actual distribution of the abnormalities found, it appears that using a comprehensive battery, rather than arbitrarily limiting an investigation to either soft or hard signs or a minor subset of neurological abnormality items, makes strategic sense. The relative operating characteristic analysis is a simple and effective tool, with two essential benefits in this regard. First, the cutoff level can be determined on a scientific basis, which may provide a resolution of the wide diversity among different studies regarding the definition of...
neurological abnormality. Second, it shows clearly the discriminative power of different methods. In this study, it indicated that the comprehensive battery was superior to either of the subsets of items, followed in rank by the hard signs component of the battery.

A possible limitation of this study may be that the examiner was not blind to the diagnoses of the subjects being examined. Nevertheless, it is unlikely that any systematic error in judgment occurred. Moreover, every effort was made to ensure the cooperation of the subjects, and a complete assessment of all subjects was performed. Some of the study’s limitations involve the sibling group: 1) not all of the siblings had passed through the age of risk for schizophrenia, 2) the sibling group was comparatively small, and 3) the rate of attrition in the sibling group was high. Because of this high attrition rate, the possibility that some of the siblings who chose not to participate or respond to the invitation had schizotypal disorder or other mental disturbances cannot be excluded. There are a number of other potential reasons for low compliance (e.g., geographical distance, other current activities, lack of interest, embarrassment at having a psychotic sibling). If the sibling group is (self-) selected for mental health, then the significantly higher rate of neurological abnormality in the siblings than in the normal comparison subjects is even more notable.

In conclusion, there is a high prevalence of neurological abnormality in schizophrenic patients. This abnormality seems to be a part of the disease process rather than a medication effect. The configuration of the abnormality observed in the siblings (i.e., in the absence of overt psychopathology) may be the mildest form of disturbance within the schizophrenia spectrum. While schizophrenic patients are more neurologically deviant than their siblings, levels of neurological deviation tend to be similar within the family. This suggests common genetic and/or environmental factors in the pathogenesis of these abnormalities in the two groups. The prevalence rate is affected by both the scope of the neurological assessment battery and the choice of the cutoff level. The use of an extended assessment battery helps to avoid incomplete conclusions, and as relative operating characteristic analysis shows, such a battery provides optimal discrimination of patients from comparison subjects. At the same time, hard signs are shown to be more differentially associated with schizophrenia than are soft signs. Last, the neurological abnormality has no consistent localizing profile, and nearly all functional domains are involved.

The different research centers must reach a consensus about a universally applicable neurological battery that has good reliability and that eventually can be adapted for clinical use. Prospective and longitudinal studies should be used to investigate the stability and possible progression of the neurological deficit in schizophrenia. Integrating the neurological findings with neuropsychological and neuroimaging results may facilitate understanding of the nature of the neurological deviations.

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