# Correlates of Lateral Ventricular Size in Chronic Schizophrenia, I: Behavioral and Treatment Response Measures

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*The ventricle-brain ratio (VBR) of 28 drug-free male schizophrenic inpatients was significantly higher than that of 21 matched normal control subjects and was not related to severity of positive or negative symptoms. Response to haloperidol in an open 6-week trial using a fixed-dose schedule was not predicted by severity of positive or negative symptoms or by VBR. The nine severely deteriorated patients with chronic "Kraepelinian" schizophrenia had left lateral ventricles 28% larger than their right, whereas the control subjects and other schizophrenic patients did not show ventricular asymmetry.*

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Abnormal CAT scan findings, especially enlarged lateral ventricles, in schizophrenic individuals have generated considerable interest in identifying characteristics that distinguish patients with normal CAT scans from those without (1). Of potential etiological significance is the possibility that response to neuroleptic treatment may be limited to schizophrenic patients with normal brain images (2), implicating central dopaminergic hyperactivity in the etiology of the disease in this subgroup. Attempts to differentiate schizophrenic patients with and without enlarged ventricles on the basis of their clinical features have focused on the positive-negative symptom classification scheme (3). These studies and others have led to the proposal (4) that schizophrenia is an illness with two phenomenologically and etiologically distinct syndromes: type I syndrome—characterized by normal ventricles, central dopamine hyperactivity, positive response to neuroleptic treatment, and a predominance of positive symptoms—and type II—characterized by enlarged ventricles, structural brain damage without central dopamine hyperactivity, unresponsiveness to neuroleptics, and a predominance of negative symptoms. Furthermore, this scheme suggests that individuals with positive symptoms may or may not lose them over time and develop negative symptoms but that, once acquired, negative symptoms are irreversibly present. This paradigm has inspired a large number of studies, each examining a few aspects of the clinical or biological relationships predicted by the model. The studies reported here were intended to examine the relationships among all these etiologic and phenomenologic variables in a single cohort of rigorously diagnosed and well-characterized chronic schizophrenic patients. Specifically, the relationships among ventricular size, positive and negative symptoms, neuroleptic treatment response, and biological measures of central dopamine activity were investigated. The results of this investigation are presented in two parts. This paper reviews the relationship between ventricular size and clinical state, including symptoms in drug-free patients and treatment response, while a paper that will appear in a future *Journal* issue describes the relationship of ventricular size to biological characteristics.

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## METHOD

### *Subjects*

Otherwise healthy schizophrenic patients were selected from patients consecutively admitted to the Special Treatment Unit of the Bronx Veterans Administration Medical Center at the Mount Sinai School of Medicine. The group studied included 28 men whose mean±SD age was 36.0±10.0 years; they had been ill for 12.2±8.8 years and had spent 4.3±6.7 years in the hospital. The inclusion criterion for the study was a diagnosis of chronic schizophrenia according to either the Feighner criteria (5) or the Research Diagnostic Criteria (RDC) (6), based on the Schedule for Affective Disorders and Schizophrenia (7) to standardize the basis of diagnosis. Each diagnosis was based on a consensus rating of two experienced clinicians; the kappa scores for interrater reliability were 0.80 for the RDC and 0.91 for the Feighner criteria. Candidates for admission to the Special Treatment Unit came from several different sources. Chronic patients with acute exacerbations generally came from the emergency room, while clinically stable patients were usually being followed in the outpatient clinic. A few subjects were transferred from a chronic neuropsychiatric care unit specifically for participation in research studies. According to the RDC, 26 subjects had chronic schizophrenia and two subjects had schizoaffective, mainly schizophrenic, disorders, while 23 subjects received Feighner diagnoses of chronic schizophrenia. Nineteen subjects were experiencing acute exacerbations of their chronic psychotic conditions, which required hospitalization. Five subjects were studied while clinically stable, defined as not needing hospitalization for the 6 months before admission to the study and having total Brief Psychiatric Rating Scale (BPRS) (8) scores of 40 or less with a range of less than 10 points for 4 consecutive weeks. The most severely deteriorated patients, the "Kraepelinian" group, consisted of four subjects meeting the following additional criteria for the past 5 years: 1) either continuous hospitalization or, if living outside the hospital, complete dependence on others for necessities such as food, clothing, and shelter and 2) no useful work or employment. An additional five subjects meeting the requirements for "Kraepelinian" schizophrenia were available only for the CAT studies. These five subjects were somewhat older than the rest of the schizophrenic patients; their mean±SD age was 48.2±10.3 years. Since these subjects participated only in the CAT studies, presentation of their data will be limited. Informed consent was obtained from the patient or from a first-degree relative if an otherwise assenting patient was unable to give true informed consent.

Normal male control subjects were recruited by newspaper advertisements. These individuals had normal psychiatric and medical histories, had no known family history of psychiatric illness, and denied significant drug or ethanol use. Twenty-one normal men were selected for the CAT studies; they ranged in age from 22 to 54 years old and the mean±SD age was 34.2±10.0 years. The age distribution of the normal subjects did not differ significantly from that of the schizophrenic patients.

### *Clinical Assessments*

The patients were kept drug free for at least 2 weeks (mean=22 days) before participating in the various protocols. All clinical ratings were performed after a minimum of 2 weeks without medications, except those conducted as part of the neuroleptic treatment protocol (described later). The 18-item BPRS was administered in the morning on three separate occasions over 10 days by two raters using the same interview. Interrater reliability for the total BPRS score was high (intraclass correlation coefficient [ICC]=.98, df=27). Both the total and individual BPRS item scores used in subsequent analyses were the means of both raters for the 3 days. In addition to the BPRS, a Clinical Global Impression (CGI) rating, based on a 7-point scale, was used to allow for the assessment of severity and was particularly useful with subjects whose symptoms precluded meaningful use of the BPRS, such as those whose catatonia or severe thought disorder made information difficult to obtain. The CGI scores were based on the same interviews as the BPRS scores and were highly correlated with them (r=.69, df=19, p=.001). Because the CGI was introduced after this study began, scores were unavailable for the first eight subjects.

The severity of positive and negative symptoms was determined with a modified version (9) of the Scale for the Assessment of Negative Symptoms (10). These ratings represent the total severity of symptoms grouped into positive and negative categories. Negative symptoms included affective blunting, psychomotor retardation, inappropriate affect, lack of vocal inflections, poverty of speech, poverty of content of speech, thought blocking, increased latency, poor grooming, lack of persistence at work, subjective complaints of inattention, uninvolvement in recreational activities, inability to feel intimacy, and deficient relationships with friends and peers. Positive symptoms were delusions, hallucinations, bizarre behavior, and positive formal thought disorder. Each rating was the average of two raters, who showed a high degree of interrater reliability (ICC=.91 for both negative and positive scores). The negative symptom scores ranged from 10 to 48 (possible scores=0–80) and the positive symptom scores ranged from 4 to 17 (possible scores=4–24).

### *Determination of Ventricle-Brain Ratio*

CAT scans of the head were obtained without contrast on a high-resolution Technicon 2020 scanner. The slices scanned were 1 cm apart, parallel to the orbitomeatal line. The cut that displayed the lateral

ventricles most prominently was used to determine the VBR. After adjustment of the image window and center to standard settings, the ventricular margins were outlined by means of an operator-controlled joystick, with the enclosed area automatically displayed, for the individual right and left lateral ventricles. Likewise, the area of the brain on that slice was also determined. The averages of the left and right lateral ventricular areas were summed and divided by the brain area, and the result was mutiplied by 100 to yield the VBR for that rater. Each VBR was determined twice by each of two raters, blind to the age and diagnosis of the subject. The final VBRs used in subsequent analyses were the numerical averages of these two raters' two measurements. Intrarater reliability was strong (ICC=.99) for both raters, and interrater reliability was also high (ICC=.96). These outlines were photographed and reviewed later by a neuroradiologist (I.S.S.) to ensure that the lateral ventricles were correctly identified.

In addition to the VBR, a measure of ventricular symmetry was calculated. The mean area of the left ventricle for each rater was divided by the mean area of the right ventricle, resulting in the left-to-right lateral ventricular ratio for each rater. The mean of the ratios for both raters was used in subsequent calculations.

*Neuroleptic Treatment Response*

Determinaton of neuroleptic responsivity was assessed in those chronic schizophrenic patients who were classed as having acute exacerbations or Kraepelinian schizophrenia on the basis of their clinical histories. Nineteen of the 23 subjects eligible for this protocol completed the study. Two subjects were studied before the neuroleptic protocol was instituted, and two subjects required emergency treatment because of their clinical states. Briefly, this study involved a 6-week fixed-dose regimen of oral haloperidol. The patients received 10 mg b.i.d. during the first 4 weeks, then 15 mg b.i.d. for 1 week, and 20 mg b.i.d. for the final week, independent of clinical response. Treatment response was assessed by means of both the BPRS change and CGI change over the course of the study. Baseline ratings were performed by two independent raters on 3 separate days, as already described, and the mean of both raters for all 3 days was used as the basis to determine response. Ratings continued weekly throughout the study with two raters, usually different individuals for each rating to minimize rater accommodation to the subjects' symptoms. The raters were not blind to treatment or its duration, and no placebo controls were used.

## RESULTS

The schizophrenic subjects showed significantly higher VBRs as a group than the normal control subjects. The mean±SD VBR of the schizophrenic patients was 6.17±2.48, while the normal control subjects had a VBR of 4.4±2.2 (analysis of variance: F=6.17, df=48, p=.017). No ventricle was too small to measure. The distribution of VBRs among the schizophrenic subjects is presented in figure 1. This distribution did not significantly deviate from normal (Kolmogorov-Smirnov [11] Z statistic=.59, two-tailed p=.88). In the schizophrenic sample a significant age effect was seen (r=.38, df=27, p=.05) (older subjects had higher VBRs), while no age effect was found in the normal subjects.

The lack of relationship between the severity of positive symptoms, severity of negative symptoms, and VBR in this sample of chronic schizophrenic patients is shown in a three-dimensional projection plot (figure 2). The positive and negative symptom scores did not correlate with the VBR or with each other. There is no distinct cluster of subjects with high VBRs and a preponderance of negative symptoms, and higher VBRs are not notably absent among the subjects with a preponderance of positive symptoms. In light of the chronic nature of this study group, which as a whole had enlarged ventricles, the absence of individuals clearly representing the type II syndrome is striking.

**FIGURE 1. Distribution of Ventricle-Brain Ratios (VBRs) in 28 Chronic Schizophrenic Patients**

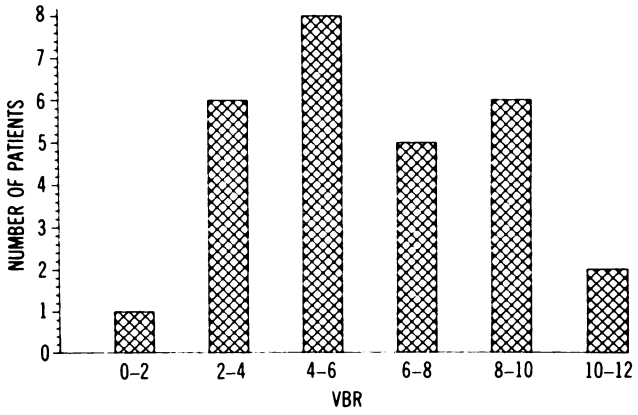
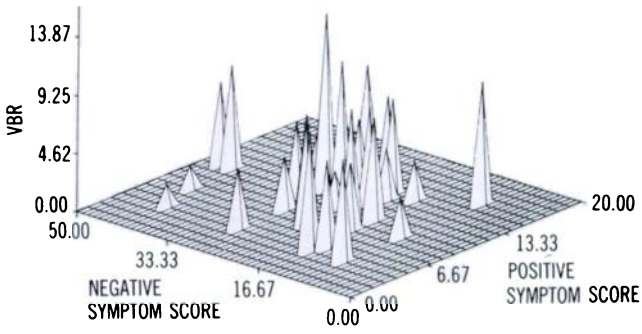



**FIGURE 2. Relationship of Negative and Positive Symptom Scores and Ventricle-Brain Ratio (VBR) in 28 Chronic Schizophrenic Patients**



Since these symptom severity scores were the sum of many different items, which individually may be related to each other only tenuously, a more detailed analysis of the more narrowly defined BPRS item scores and VBR was performed. None of the BPRS item scores was significantly related to ventricular size. Total BPRS and CGI scores were also unrelated to VBR in this sample. Individual item scores for the individual elements of the positive and negative symptom scores were also unrelated to VBR.

This cohort of chronic schizophrenic patients showed relatively little response to neuroleptics. Because an excellent response was infrequent, criteria were developed to separate patients into two groups on the basis of their relative improvement on haloperidol. Those patients who showed a decline of at least 12 points or 20% from baseline BPRS scores or a CGI improvement of 1.5 points or more after 4 weeks were considered neuroleptic responders. Only seven of the 19 subjects completing this study showed sufficient improvement to be considered responsive even by these generous criteria. The responders actually showed a trend toward a higher VBR than the nonresponsive group (mean±SD=7.1±1.9 versus 5.3±2.2; t=1.74, df=18, p=.10), probably because they were older as a group (mean ages=44.4 and 35.3 years), although the difference in ages was not statistically significant. There was no difference between responders and nonresponders in the mean±SD pretreatment scores for severity of negative symptoms (31.8±8.7 versus 29.1±9.4) or positive symptoms (12.9±3.3 versus 11.3±3.0). Of the 19 subjects completing the haloperidol study, two had VBRs higher than 2 SD above the control mean. One was a good neuroleptic responder and the other was not affected by medication. However, two of the four candidates for the haloperidol study who did not enter this protocol had VBRs 2 SD above the control mean, and both subjects were clinically considered to be nonresponders. The fifth subject with enlarged ventricles according to this criterion was only examined while in remission and was clinically felt to be a neuroleptic responder.

Because of recent reports implicating decreased caudate function in the left hemisphere (12), diminished left parahippocampal gyrus width (13), and a trend toward ventricular asymmetry (14), the possibility of a larger left ventricle in some schizophrenic patients was examined. This was done by using the ratio of the area of the left to the area of the right ventricle to minimize effects of head size. In most subjects, there was little difference in size between the left and right ventricles. However, the original cohort of the four most chronically ill patients, classed as Kraepelinian, did show significantly larger ventricles on the left side than on the right; they had a mean±SD left-to-right ventricular ratio of 1.24±0.19, as opposed to 0.98±0.19 for the rest of the schizophrenic study group (t=2.43, df=26, two-tailed p=.022). There was no significant difference in age between the Kraepelinian and non-Kraepelinian groups, and the left-to-right ventricular ratio did not correlate with VBR and correlated very weakly with age (r=.33, df=27, p=.09). To further explore whether this ventricular asymmetry was merely a chance finding, another five Kraepelinian subjects were recruited just for CAT studies. Although these additional subjects were somewhat older than the original four Kraepelinian patients (mean±SD age=48.2±10.3 versus 43.5 ±8.1 years), the difference was not significant. These five subjects also showed significant asymmetry (mean±SD left-to-right ratio=1.31±0.21), suggesting that this finding did not occur by chance. The mean±SD left-to-right ratio of these nine Kraepelinian subjects was 1.28±0.20, which differed highly significantly from both the rest of the schizophrenic study group (t=3.86, df=31, two-tailed p=.001) and the normal sample (t=−2.44, df=27, two-tailed p=.021), whose left-to-right ratio was 1.03±0.27. There was no difference between the normal subjects and the non-Kraepelinian schizophrenic patients in the left-to-right ratio of their ventricles.

## DISCUSSION

This study does not support the validity of clinical subdivision of chronic schizophrenic patients on the basis of the VBR. Neither negative nor positive symptoms, as defined by two different rating systems, were related to VBR in this sample of drug-free male veterans with schizophrenia. Negative and positive symptoms were unrelated to each other and did not predict treatment response. Ventricular size was also not related to response to antipsychotics. However, the nine severely deteriorated (Kraepelinian) schizophrenic patients did differ from the other schizophrenic patients in ventricular asymmetry; their left ventricles were 28% larger than the right.

The absence in this sample of a cluster of subjects with larger ventricles and a predominance of negative symptoms is striking. Although the total sample did have larger lateral ventricles than those of matched control subjects, the distribution of VBRs was not notably bimodal. While perhaps merely reflecting a small sample size, this distribution is more consistent with a continuum of ventricular sizes, in which ventricular enlargement is simply a statistical definition without, at this point, biological validity. Furthermore, these results suggest that few subjects, if any, in this sample of severely ill chronic schizophrenic patients, manifest a pure syndrome of type II schizophrenia. This is particularly surprising in light of the very low neuroleptic response rate in this group.

Considering the widespread currency of the negative-positive symptom dichotomy, relatively few data address the distribution among chronic schizophrenic patients of syndromes characterized by 1) predominantly positive symptoms with good treatment response, 2) predominantly negative symptoms with

**TABLE 1. Previous Studies of the Relationship of Ventricle-Brain Ratio (VBR) to Positive and Negative Symptoms in Chronic Schizophrenic Patients**

| Study | N | Diagnostic Criteria | Clinical Setting | Drug-Free Status[a] | Significant Relationships to VBR | |
|---|---|---|---|---|---|---|
| | | | | | Negative Symptoms | Positive Symptoms |
| Johnstone et al., 1976 (15) | 13 | Feighner | Long-term institutionalization | No | No | No |
| Andreasen et al., 1982 (3) | 52 | *DSM-III* and RDC | Hospital admission | No | No | Yes |
| Bishop et al., 1983 (16) | 46 | RDC (acute and chronic) | Hospital admission and discharge | No | No | No |
| Nasrallah et al., 1983 (17) | 55 | *DSM-III* and Feighner | Hospital admission | No | No | No |
| Luchins et al., 1984 (18) | 45 | RDC | Hospital admission | Yes (1 week) | No | Trend |
| Pearlson et al., 1984 (19) | 19 | *DSM-III* | Remission | No | Yes | — |

[a]At the time of symptom assessment.

**TABLE 2. Previous Studies of the Relationship of Ventricle-Brain Ratio (VBR) to Neuroleptic Response in Chronic Schizophrenic Patients**

| Study | N | Diagnostic Criteria | Clinical Setting | Significant Relationship of VBR to Treatment Response | Response Criterion |
|---|---|---|---|---|---|
| Weinberger et al., 1980 (2) | 20 | RDC and Feighner | Long-term institutionalization | Yes | BPRS change |
| Weinberger et al., 1982 (unpublished) | 26 | RDC and Feighner | Hospital admission | No | BPRS change |
| Nasrallah et al., 1983 (17) | 55 | *DSM-III* and Feighner | Hospital admission | No | Clinical history |
| Schulz et al., 1983 (20) | 12 | *DSM-III* | Hospitalized adolescents | Yes | BPRS change |
| Luchins et al., 1984 (18) | 35 | RDC | Hospital admission | Yes | GAS change |

high VBRs and poor treatment response, or even 3) a mixed picture. Table 1 summarizes the results of six major studies (3, 15–19) that have examined the relationship between enlarged lateral ventricles and symptom picture, using various definitions of the positive-negative symptom dichotomy. Although individual schizophrenic patients with enlarged ventricles and a predominance of negative symptoms may exist, only one study (19) of the six found significantly higher negative symptom scores in schizophrenic patients with enlarged ventricles. That study used a group of neuroleptic-treated patients between episodes of decompensation and could reflect differences in sensitivity to side effects of neuroleptics (18). Since neuroleptics produce effects such as akinesia and severe sedation, which are very difficult to distinguish from some negative symptoms, interpretation of studies on medicated subjects is problematic. In these same studies, a significant relationship between normal VBRs and more positive symptoms was reported only once (3), and there was a trend in another study (18). Our finding that psychopathology in drug-free subjects shows no relationship to VBR is consistent with most previous work and provides no support for the existence of two clinically distinct syndromes of schizophrenia.

A potential relationship between poor neuroleptic treatment response and enlarged ventricles in schizophrenic patients has received more support in the literature, as summarized in table 2. Three of five studies with diverse samples (2, 17, 18, 20, and unpublished work of D.R. Weinberger et al.) showed that subjects with high VBRs (defined as 2 SD above the control mean) did not as a group improve after neuroleptic treatment, whereas schizophrenic patients with smaller ventricles did improve. One of the negative studies (17) used a retrospective chart review to determine response, and the other negative study (unpublished work of Weinberger et al.) included very few neuroleptic-responsive subjects. The study reported in this paper is also limited in this respect; there were few subjects with enlarged ventricles, defined as patients whose VBRs were 2 SD above the mean, and a rather limited response among the entire cohort. It should be noted, however, that the group of responders actually had a somewhat higher mean VBR than the nonresponders and that one of the two subjects with enlarged ventricles did show a definite response. This study suggests that VBR should not be used to affect decisons about neuroleptic treatment.

Perhaps the most intriguing finding is also the most sensitive to mere chance occurrence. The presence of an asymmetric enlargement of the lateral ventricles, affecting the left more than the right, was found in the subgroup characterized by the most unrelenting, debilitating clinical course (i.e., Kraepelinian). This ven-

tricular asymmetry may result from an asymmetric degenerative process in the periventricular structures. If confirmed in a larger series of patients, this finding would suggest a need for a carefully designed postmortem study to examine left-right differences in periventricular degenerative processes, especially in subjects whose clinical histories showed the greatest deterioration. Although probably unresponsive to medications, this subgroup appears to have many positive and negative symptoms (unpublished work of R.S.E. Keefe et al.) and would not clearly fit into either predominantly positive or negative symptom syndromes. Nevertheless, the degenerative process on the left may be etiologically relevant.

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